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[Intervention Review]

Early versus Delayed Refeeding for Children with Acute Diarrhoea

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ABSTRACT

Background

Acute diarrhoea is one of the principal causes of morbidity and mortality among children in low-income countries. The cornerstone of treatment is oral rehydration therapy and dietary management. However, there is a lack of data and studies on both the timing and type of feeding that should be adopted during the course of the illness.

Objectives

To compare the efficacy and safety of early and late reintroduction of feeding in children with acute diarrhoea.

Search methods

In May 2011, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2011, Issue 1), MEDLINE, EMBASE, LILACS, and *m*RCT. We also contacted researchers and organizations, and searched reference lists.

Selection criteria

Randomized controlled trials of early versus late refeeding among children less than 10 years old with acute diarrhoea. Early refeeding was defined as within 12 hours of start of rehydration and late refeeding was defined as more than 12 hours after start of rehydration.

Data collection and analysis

Two authors independently assessed the search results and the risk of bias, and extracted data. We present risk ratios for dichotomous outcomes and mean differences for continuous outcomes. We combined the results of the trials using meta-analysis when heterogeneity was not substantial.

Main results

Twelve trials involving 1283 participants wereincluded; 1226 participants were used in the analysis (724 in the early refeeding group and 502 in the late refeeding group). Nine trials described their allocation sequence, but only two used concealed allocation. One trial reported single-blinding but did not clearly identify the person who was blinded. Early refeeding meant intake during or immediately after start of rehydration, while late refeeding meant intake only 20 hours to 48 hours after start of rehydration. Significant heterogeneity was noted in the data for the duration of diarrhoea. There was no significant difference between the two refeeding groups in the number of participants who needed unscheduled intravenous fluids (six trials with 813 participants), who experienced episodes of vomiting (five trials with 466 participants), and who developed persistent diarrhoea (four trials with 522 participants). The mean length of hospital stay was also similar (two trials with 246 participants).

Authors' conclusions

There was no evidence that early refeeding increases the risk of unscheduled intravenous fluid use, episodes of vomiting, and development of persistent diarrhoea. No conclusion could be made regarding the duration of diarrhoea.

23 March 2018

No update planned

Research area no longer active

This research area is no longer active.

PLAIN LANGUAGE SUMMARY

Reintroducing a normal diet following acute diarrhoea

Many children in developing countries die from acute diarrhoea. Although it is usually caused by infectious viruses or bacteria, the exact organism is rarely known, as it is impractical to test for the organism. Treating the diarrhoea is thus standard therapy, with the recommended policy of using oral rehydration therapy and dietary supplements. Because the gut can be damaged by the infection, many doctors recommend a period of fasting followed by gradual reintroduction of food, although the evidence for when exactly a “normal” diet should be reintroduced is lacking. The authors here looked at children who received ‘early’ refeeding (within 12 hours of the start of rehydration) or ‘late’ refeeding (after 12 hours from the start of rehydration). The authors identified 12 trials that met their inclusion criteria, with a total of 1283 children under 5 years; of these, 1226 were used in the analysis (724 given early refeeding; 502 given late refeeding). There was no significant difference between the two refeeding groups in the number of participants who needed unscheduled intravenous fluids (813 participants, 6 trials), who experienced episodes of vomiting (466 participants, 5 trials), and who developed persistent diarrhoea i.e. greater than 14 days in duration (522 participants, 4 trials). The mean length of hospital stay was also similar (246 participants, 2 trials).There is therefore no evidence to suggest that early refeeding increases the risk of complications after acute diarrhoea such as the need for IV fluids, or increases the risk of developing persistent diarrhoea. Further studies are needed to fully examine other parameters such as duration of diarrhoea, and effect on weight gain.

BACKGROUND

Acute diarrhoea remains one of the major causes of morbidity and preventable deaths among children, especially in the developing world (WHO/UNICEF 2004). A review of 27 prospective studies from 20 countries published between 1990 and 2000 estimated the incidence of diarrhoea at 3.2 episodes per child per year for children under five years of age (Kosek 2003). Although there was a declining trend, it was still estimated that diarrhoea claimed 1.4 million to 2.5 million lives in 2000 (Kosek 2003). Acute diarrhoea is conventionally defined as increased frequency of defecation (three or more times in 24 hours) (WHO 1995) and faeces that are sufficiently liquid to take the shape of the container in which they are placed (Keusch 2006). Persistent diarrhoea is defined as diarrhoea lasting for 14 days or longer (WHO 1995).

The most common causes of acute diarrhoea in children are infectious agents (viruses, bacteria, and parasites) (Podewils 2004). Most cases of acute diarrhoea in infants and young children have viral causes and are usually short-lived; antibiotics are not routinely prescribed for viral diarrhoea. Transmission may occur through faecal-oral routes (transmitted from the stool of one individual to the mouth of another), respiratory secretions, or fomites (inanimate objects such as kitchen utensils) (Keusch 2006). Aetiologic diagnosis of acute diarrhoea is more important epidemiologically and from a public health perspective than for clinical management. Standard diagnostic tests, such as microbiological culture and microscopy, are not cost-effective or practical for managing individual cases (Keusch 2006). Most cases of acute diarrhoea are managed clinically, especially in developing countries where resources are limited.

Acute diarrhoea may be accompanied by nausea, vomiting, abdominal cramping, clinically significant systemic symptoms or malnutrition. Acute watery diarrhoea is rapidly dehydrating and can be life-threatening unless fluid therapy is instigated , especially for the very young. Prevention of complications among affected children depends on an accurate assessment of the hydration status and timely instigation of appropriate oral rehydration therapy (ORT), and dietary and zinc supplements (WHO 1995; WHO/UNICEF 2004).

Children used to be starved during and after the diarrhoeic episode for fear of exacerbating the symptoms and worsening the course of the illness (WHO 1999). Although oral hydration therapy has been studied and recommended for the past 30 years, there is a lack of data and studies on the timing and type of feeding that should be adopted during the course of diarrhoea. Early refeeding has been recommended as part of the management of acute diarrhoea (Walker-Smith 1997). Non-clinical studies have shown that early refeeding may induce digestive enzymes, improve absorption of nutrients, enhance enterocyte regeneration, and promote recovery of the brush border disaccharidase (Hageman 1977; Hirshhorn 1980; Isolauri 1989; Williamson 1978).

Early studies showed that early refeeding has a significant nutritional advantage, especially among malnourished children (Brown 1988). Some cohort and non-blinded studies have shown that early refeeding has the potential to reduce stool frequency and volume, and hasten recovery (Chung 1948; Nanulescu 1995; Sarker 1983). Controlled non-randomized studies assessing the reintroduction of milk formula at different times and concentrations showed no significant difference in the duration of hospitalization (Rees 1979) or the duration of diarrhoea between the different feeding regimens (Santosham 1991; Soeprapto 1979), although vomiting was more frequent among those who had higher concentrations of milk formula (Rees 1979).

A meta-analysis of 29 randomized clinical trials compared the effects of continuous feeding with lactose-containing versus lactose-free diets to young children suffering from acute diarrhoea (Brown 1994). There was a significantly higher treatment failure rate among those receiving lactose-containing diets: this was noted among patients with initial severe dehydration and in studies conducted before 1985. The authors thus concluded that routine dilution of milk and use of lactose-free milk formulas are unnecessary for mildly dehydrated cases, especially when ORT and early feeding (in addition to milk) are already part of the routine management. In a controlled clinical trial, a formula containing soy fiber improved the consistency of stools during diarrhoea, with no effect on stool volume (Brown 1993). Adding soy to formula also decreased the duration of antibiotic-associated diarrhoea among older children (Burks 2001). Continued breastfeeding during diarrhoea was also found to cause a significant decrease in the volume and number of stools (Khin-Maung-U 1985). But despite these studies and the quoted clinical recommendations, nutritional management during diarrhoea still varies among health practitioners (Bezerra 1992; Chongban 2005; Santosham 1997).

Since there is still uncertainty and incomplete information on the use of early refeeding in the management of acute diarrhoea in children, this review clarifies and reviewes the clinical evidence to support early refeeding. We define early refeeding as within 12 hours from start of rehydration and define late refeeding as more than12 hours after start of rehydration. The division between early and late refeeding was arbitrary but was guided by the authors' knowledge of the subject. This review only covers children, as the aetiologic distribution, clinical course and approach to management is different for adults. The main outcomeswere clinically-relevant endpoints such as duration of diarrhoea, total stool output, percentage weight gain at resolution of illness, unscheduled use of intravenous fluids, and episodes of vomiting. These outcomes addressed the common concerns and doubts harbored by most health practitioners, mothers and caregivers with regard to early refeedings.

OBJECTIVES

To compare the efficacy and safety of early and late reintroduction of feeding in children with acute diarrhoea.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Children less than 10 years old with acute diarrhoea, including both breastfed and non-breastfed. Acute diarrhoea was defined as increased frequency of defecation (three or more times in 24 hours) and faeces that are sufficiently liquid to take the shape of the container in which they are placed, with a duration of 14 days or less at the time of presentation.

Types of interventions

Intervention: Early refeeding group

Feeding was reintroduced *within 12 hours* from start of rehydration; continuous breastfeeding during rehydration was included in this group.

Control: Late refeeding group

Feeding was reintroduced more than *12 hours after* start of rehydration.

Types of outcome measures

Primary

- Duration of diarrhoea (hours) from admission until cessation of diarrhoea.

Secondary

- Total stool output (ml/kg) during the first 24 hours and 48 hours after start of rehydration.
- Percentage weight gain 24 hours after start of rehydration and at resolution of diarrhoea.
- Unscheduled intravenous (IV) fluid therapy.
- Cases of vomiting.

Adverse events

- All adverse events, including hyponatraemia (low sodium; serum sodium level ≤130 mmol/L), hypokalaemia (low potassium; serum potassium level ≤3 mol/L) (), and development of persistent diarrhoea.

Search methods for identification of studies

All relevant trials regardless of language or publication status (published, unpublished, in press, and ongoing).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (May 2011); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2011, Issue 1); MEDLINE (1966 to May 2011; EMBASE (1974 to May 2011; and LILACS (1982 to May 2011). We also searched the*meta*Register of Controlled Trials (*m*RCT) using 'diarrhoea', 'refeeding', 'breastfeeding' and 'feeding' as search terms.

Researchers and organizations

To help identify unpublished and ongoing trials, we searched (May 2007 to Dec 2009) the web sites of the following organizations: World Health Organization (www.who.int); Child Health and Nutrition Research Initiative (CHNRI) (www.chnri.org); International Clinical Epidemiology Network (INCLEN) (www.inclen.org); USAID (www.usaid.gov); Asian Development Bank (www.adb.org); World Bank (www.worldbank.org); and the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) (www.icddrb.org). We also questioned individual researchers working in the field of general paediatrics and gastroenterology, and the members of local and international societies for paediatric gastroenterology, hepatology and nutrition (such as the Philippine Society of Pediatric Gastroenterology and Nutrition and the Asia Pacific Society of Pediatric Gastroenterology, Hepatology and Nutrition), about whether they had conducted trials relating to feeding in acute diarrhoea.

We checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Trial selection

The first two authors (GV Gregorio and LF Dans) independently assessed the results of the literature search to determine the eligibility of the trials. We then retrieved the full reports of all trials considered by one or both authors to be potentially relevant, as well as trials with unclear treatment allocation. We used a standard eligibility form based on the inclusion criteria to independently assess the trials. We resolved disagreements through discussions or by consulting the third author (MAA Silvestre). If eligibility was unclear due to inadequate data, or if a multiple publication of the same trial was observed, we attempted to contact the trial authors for clarification. We appraised each of the trials to ensure that multiple publication was not an issue. We listed the excluded studies and the reasons for the exclusion.

Assessment of risk of bias

The first two authors (GV Gregorio and LF Dans) independently assessed the risk of bias of each trial using six components: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other biases. Using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, a judgment of yes, no or unclear to indicate a low, high, or unclear/unknown risk of bias, respectively, was used to describe each component. Although trial participants or care providers might be impossible to blind, we noted if other study personnel were blinded. The percentage of missing outcome data was reported in the risk of bias tables.

We classified the trials as having a high or low risk of bias and included studies with a low risk of bias in a sensitivity analysis. A high risk was defined as trials with unclear sequence generation or allocation concealment, and trials where less than 90% of randomized participants completed the trial. Disagreements over the risk of bias assessment were resolved by a third author. A ‘risk of bias summary’ and ‘risk of bias graph; in addition to the risk of bias tables, were completed. .

Data extraction and management

The first two authors (GV Gregorio and LF Dans) independently extracted data from the trials using pre-tested data extraction forms. We extracted the number of participants who were randomized and the number who were analyzed for all outcomes for each treatment arm in each trial to determine loss to follow-up, whether loss was comparable across treatments, and the type of analysis used. For continuous outcomes, we extracted arithmetic means and standard deviations for each treatment group and noted the number of participants in each group. In trials with multiple interventions (where two or more types of feeding were used as treatment groups), we pooled the means and standard deviations of the different feeding groups across the treatment arms. We used as our unit of analysis the mean duration of diarrhoea in hours and the total stool output as ml/kg.

For data that reported the outcome as a median, we extracted the ranges and presented the data in a separate table.

For dichotomous outcomes, we recorded the number of participants experiencing the event and the number of participants in each treatment group. For trials with multiple treatment arms, we combined the numbers experiencing the outcome in two or more experimental interventions and also combined the total number of participants in the combined treatment arms, whenever appropriate. We then compared collectively with the identified control group.

We resolved any disagreements over data extraction by referring to the trial report and through discussion, or, if that failed, by consulting with another author. Where data were insufficient or missing, we attempted to contact the trial authors. LF Dans entered the data into Review Manager 5.

Data analysis

The first two authors (GV Gregorio and LF Dans) analyzed the data using Review Manager 5 and all results were presented with a 95% confidence interval (CI). We combined trials that compared early versus late feeding using meta-analysis. We analyzed data using an available case approach (i.e. all patients for whom an outcome was measured and reported are included in the analysis). We aimed to include all the originally randomized patients in the analysis, including protocol-violators

We compared dichotomous data using risk ratio. The mean difference was used to combine continuous data summarized by arithmetic means and standard deviation.

We checked for features of a normal distribution by calculating the ratio of the mean and standard deviation. If the ratio (mean/SD) was less than two, then it was likely that the data were skewed. We considered the skewed data in the primary analysis but excluded it in the sensitivity analysis.

For continuous outcomes reported in medians and ranges, the results were reported in a table. Similarly, when the outcome was reported using a different unit (e.g. ml/kg/patient or ml/patient rather than ml/kg/day), the results were tabulated.

Some of the data reported by the trials could not be used in the meta-analysis. One trial reported the duration of diarrhoea as a median instead of a mean (Hoghton 1996; Table 2); another compared the data of those who did not (considered a success) and did (considered a failure) require IV fluids (Shaikh 1991; Table 3).

Subgroup analysis and investigation of heterogeneity

We evaluated the presence of statistical heterogeneity among the interventions by inspecting the forest plot and by performing a Chi^2 test for heterogeneity using a P value of 0.10 to determine statistical significance. Also, we used a I^2 value of >50% as an indication of moderate heterogeneity. If there was statistically-significant heterogeneity, we used the random-effects model (DerSimonian and Laird method) to combine data, otherwise we applied a fixed-effect model.

We used subgroup analysis to investigate the effect of age , nutritional status (normal and mild malnutrition versus moderate and severe malnutrition), breastfeeding (breastfed and non-breastfed infants) and type of food reintroduced (diluted versus full-strength milk formula, lactose-free versus lactose-containing). When there was substantial statistical heterogeneity, we did not combine the trials in the meta-analysis.

Sensitivity analysis

We planned to conduct a sensitivity analyses to assess the robustness of the meta-analysis by excluding trials with high risk of bias. The number of studies judged as having a high/low/unclear risk of bias were reported. Trials with skewed data were excluded from the analysis.

Assessment of reporting bias

A funnel plot was constructed to look for evidence of reporting bias

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

We assessed the abstracts of 98 references uncovered in the primary search up until 27 May 2011 and retrieved the full papers for 22 potentially relevant trials. A total of 12 trials met the inclusion criteria (see Characteristics of included studies). Ten trials were excluded: five studies did not satisfy the definition of early or late refeeding used in this review (Armistead 1989; Chew 1993; Fox 1990; Haffejee 1990; Soeprapto 1979); three trials were unclear about when the refeeding started (Haque 1983; Hjelt 1989; Ransome 1984); and two were not randomized controlled trials (Parker 1981; Nanulescu 1995).

No additional or unpublished trials were identified from searching organization web sites or from questioning individual researchers.

Included studies

The 12 included trials enrolled a total of 1283 participants (757 for early refeeding and 526 for late refeeding), all of whom were children. However, only 1226 were used in the final analysis (724 for early refeeding and 502 for late refeeding) as some of the randomized patients were withdrawn or were considered as drop-outs. All available data up to the time of withdrawal were included. All trial reports were in English. All trials were published between 1979 and 1997, and there were no multiple publications.

Location

The 12 trials were conducted in 16 different countries (see details in Characteristics of included studies). There was one multicenter study involving 11 European countries (Sandhu 1997), including hospitals in the United Kingdom, Italy, Finland, the Netherlands, Croatia, Slovenia, Czechoslovakia, Belgium, Portugal, Poland, and Israel. Two trials each were conducted in the United Kingdom (Conway 1989; Rees 1979); the United States (Santosham 1985; Santosham 1991); Burma (Khin-Maung-U 1985, Khin-Maung-U 1986); and Israel (Gazala 1988; Rees 1979); and one trial each in Egypt (Santosham 1990), Pakistan (Shaikh 1991), and Peru (Brown 1988).

Ten trials were conducted in a hospital setting, while two studies (Gazala 1988; Santosham 1991) enrolled patients from an out-patient clinic.

Source of Funding

Three trials were funded by milk companies (Santosham 1985; Santosham 1990; Santosham 1991); two trials were partially supported by the Department of Medical Research in Burma (Khin-Maung-U 1985; Khin-Maung-U 1986); two trials were supported by a grant from the US Agency for International Development (Brown 1988; Shaikh 1991), but one had additional support from the Diarrheal Disease Control Programme of the World Health Organization and the Nestle Milk Company (Brown 1988). Five trials did not state the source of funding (Conway 1989; Gazala 1988; Hoghton 1996; Rees 1979; Sandhu 1997), including the multicenter study (Sandhu 1997), which was conducted on behalf of the European Society of Paediatric Gastroenterology and Nutrition.

Participants

Diagnosis of diarrhoea

All trials included children with acute diarrhoea of 14 days or less in duration. Six trials included children with diarrhoea of between five and seven days duration (Gazala 1988; Rees 1979; Hoghton 1996; Santosham 1985; Santosham 1990; Santosham 1991). Another four trials included children with diarrhoea of less than 72 hours in duration (Brown 1988; Khin-Maung-U 1985; Shaikh 1991).

Age

All trials included children less than five years old. In six trials, the children were less than two years old (Gazala 1988; Khin-Maung-U 1985; Sandhu 1997; Santosham 1985; Santosham 1990; Santosham 1991); in two trials, they were between three months and three years old(Brown 1988; Hoghton 1996); in three trials, they were between 1.5 months and four years old(Conway 1989; Rees 1979; Shaikh 1991); and in one trial they were between one and five years old (Khin-Maung-U 1986). Only two trials considered the nutritional status of the participants (Brown 1988; Shaikh 1991).

Type and timing of feeding

For those in the early refeeding group, the feeding consisted of either half- or full-strength cow's milk formula (four trials) (Brown 1988; Rees 1979; Santosham 1985; Santosham 1991); boiled rice or the child's usual diet (three trials) (Hoghton 1996; Khin-Maung-U 1986; Sandhu 1997); soy-based milk formula (two trials) (Santosham 1985; Santosham 1991); or breast milk or cow's milk formula (one trial) (Gazala 1988). One trial randomized the patients into either a soy- or rice-based formula or pre-cooked rice (Santosham 1990). Another trial allocated patients to receive either oral rehydration solution and breastfeeding during the rehydration phase or oral rehydration alone for 24 hours (Khin-Maung-U 1986).

For those in the late refeeding group, feeding after start of rehydration was allowed either after 24 hours (seven trials) (Conway 1989; Gazala 1988; Khin-Maung-U 1985; Khin-Maung-U 1986; Santosham 1990; Santosham 1991; Shaikh 1991); 48 hours (two trials) (Brown 1988; Santosham 1985); 20 hours (one trial) (Sandhu 1997); or between 24 and 48 hours (one trial) (Hoghton 1996). One trial allowed feeding only after the diarrhoea had stopped (Rees 1979).

Duration of follow-up

The patients were monitored either until resolution of diarrhoea (six trials) (Conway 1989; Hoghton 1996; Khin-Maung-U 1985, Khin-Maung-U 1986; Santosham 1990; Shaikh 1991); two weeks after hospital discharge (five trials) (Brown 1988; Gazala 1988; Sandhu 1997; Santosham 1985; Santosham 1991); or once full strength milk formula could be tolerated (one trial) (Rees 1979).

Outcomes reported

Most of the trials reported the overall mean duration of diarrhoea from admission to resolution (seven trials) (Conway 1989; Hoghton 1996; Khin-Maung-U 1985; Khin-Maung-U 1986; Santosham 1990; Shaikh 1991) and the number who required unscheduled use of IV fluids (six trials) (Conway 1989; Hoghton 1996; Santosham 1985; Santosham 1990; Santosham 1991; Shaikh 1991). A few trials also reported the total stool output in the first 24 hours (three trials) (Brown 1988; Santosham 1985; Santosham 1991); oral intake in the form of ORS, formula or rice between 24 and 48 hours (six trials) (Khin-Maung-U 1985; Khin-Maung-U 1986; Santosham 1985; Santosham 1990; Santosham 1991; Shaikh 1991); mean percentage weight gain at the 24th hour after start of rehydration (three trials) (Santosham 1985; Santosham 1991; Shaikh 1991) and at the resolution of diarrhoea (three trials) (Santosham 1985; Santosham 1990; Santosham 1991); the number of participants with vomiting (four trials) (Conway 1989; Hoghton 1996; Rees 1979; Santosham 1985;); the development of persistent diarrhoea (four trials) (Conway 1989; Santosham 1985; Santosham 1990; Santosham 1991); and the length of hospital stay (two trials) (Conway 1989; Rees 1979;). Three trials monitored patients for development of hyponatraemia or hypokalaemia.

Some of the data reported by the trials could not be used in the meta-analysis. For the duration of diarrhoea, one trial reported it as a median instead of a mean (Hoghton 1996; Table 2). For the mean total stool output in the first 24 hours, two trials reported it as either ml/kg/patient (Khin-Maung-U 1985) or ml/patient (Khin-Maung-U 1986) rather than ml/kg. Another compared data for the mean stool output of those who did (considered a failure) and did not (considered a success) require IV fluids (Table 3; Shaikh 1991).

Risk of bias in included studies

No trial reported appropriate procedures for all the components used to assess risk of bias (allocation concealment, generation of the allocation sequence, blinding of either the care providers, participants or outcome assessors, inclusion of all randomized participants, selective outcome reporting and other biases). No trial was identified as having selective outcome reporting or other biases.

Allocation

Nine trials had adequate allocation sequence, with either the use of random-number tables (eight trials) or coin toss (one trial) (Gazala 1988). Three trials were randomized but did not describe the allocation method (Conway 1989; Hoghton 1996; Rees 1979).

Of the 12 included trials, ten had unclear allocation concealment. One trial used sealed envelopes (Brown 1988), while another assigned groups to treatment allocations by flipping a coin (Gazala 1988).

Blinding

Only one trial reported single-blinding, but it is unclear who was blinded (Hoghton 1996). The participants of all other trials were not blinded and it is unclear if the caregivers or outcome assessors were blinded.

Incomplete outcome data

The number of participants followed up was complete for five trials (Conway 1989; Khin-Maung-U 1985; Khin-Maung-U 1986; Rees 1979; Shaikh 1991); adequate (90% to 99%)for at least one outcome in five trials (Brown 1988; Hoghton 1996; Sandhu 1997; Santosham 1985; Santosham 1991); and 89% for two trials (Gazala 1988; Santosham 1990).

Effects of interventions

Duration of diarrhoea (hours) from admission until cessation of diarrhoea

A shorter duration of diarrhoea was observed with early refeeding in two trials (Santosham 1985; Santosham 1991) and with late refeeding in one trial (Khin-Maung-U 1986), while for four trials the outcome was similar in both groups (Conway 1989; Gazala 1988; Khin-Maung-U 1985; Santosham 1990). Overall, the late refeeding group showed longer duration compared with the early refeeding group, although the mean difference was not significant (MD -6.90 hrs, 95% CI -18.70 to 4.91; 685 participants, seven trials, Analysis 1.1). Considerable heterogeneity among the limited number of trials was observed (Chi^2 test, P=0.11, I^2 = 82%). There were only two trials where the data were not skewed (Santosham 1990; Santosham 1991), but similar results were seen (Chi^2 test, P = 0.04; I^2 = 77%). Subgroup analysis could not be done because of the limited number of trials.

Total stool output (ml/kg) during the first 24 and 48 hours after start of rehydration

Three trials each reported the total stool output in the first 24 hours (Brown 1988; Santosham 1985; Santosham 1990) and 48 hours (Khin-Maung-U 1985; Santosham 1985; Santosham 1990) after start of rehydration. One trial favoured early refeeding (Santosham 1985) and another favoured late refeeding at both periods of observation (Santosham 1990). Less stool output was also shown on the 24th hour and the 48th hour with early and late refeeding, respectively (Khin-Maung-U 1985). All but one study (Khin-Maung-U 1985) showed skewed results.

We used an I^2 value of >50% as an indication of moderate heterogeneity. Overall, the comparison of the mean total stool in the first 24 hours and 48 hours (Analysis 1.2 and Analysis 1.3) after start of rehydration showed significant heterogeneity: I^2 of 85% and 87%, respectively.

Percentage weight gain at the 24th hour after start of rehydration and at resolution of diarrhoea

No difference was observed in the mean percentage weight gain at the 24th hour after start of rehydration (Analysis 1.4) and at resolution of illness (Analysis 1.5) . Skewed data were observed for the results of the mean percentage weight gain at the 24th hour (Santosham 1985; Santosham 1991; Shaikh 1991) and at cessation of diarrhoea (Santosham 1985; Santosham 1990; Santosham 1991; Shaikh 1991).

Unscheduled intravenous fluid therapy

There was no significant difference in both groups in the number of participants who needed IV fluids (RR 0.87, 95% CI 0.48 to -1.59; 813 participants, six trials, Analysis 1.6, Figure 1).

Figure 1. Figure 1. Forest plot of early versus late refeeding in the outcome of unscheduled use of intravenous fluids

Cases of vomiting

There was no significant difference between the two groups in the number of patients with episodes of vomiting (RR 1.16, 95% CI 0.72 to 1.86; 456 participants, five trials, Analysis 1.7).

Adverse events: development of persistent diarrhoea

There was no significant difference in the number of patients who developed persistent diarrhoea (RR 0.57, 95% CI 0.18 to 1.85; 522 participants, four trials, Analysis 1.8).

Adverse events: development of hyponatraemia

Three trials monitored sodium and potassium concentrations on admission and at different intervals during the illness (Brown 1988; Santosham 1985; Santosham 1990). No patient was reported to have developed hypokalaemia. Hyponatraemia (Analysis 1.9) was reported in four patients: two in the early refeeding group (Santosham 1985) and one in the late refeeding group (Santosham 1990), while another trial (Brown 1988) reported one patient who developed hyponatraemia but did not specify to which group they belonged.

Publication bias

We observed significant heterogeneity in the primary outcomes among the limited trials and therefore we decided to use a funnel plot for the secondary outcome, where the data were homogenous. We constructed a funnel plot of six trials to compare early and late refeeding and measure the outcome of unscheduled use of IV fluid (Figure 2). The funnel plot is symmetrical but the number of studies is limited and so we cannot conclude whether the results are free from publication biases for unscheduled IV fluids.

Figure 2. Figure 2. Funnel plot of early vs late refeeding on the number of unscheduled use of intravenous fluids

DISCUSSION

The present meta-analysis did not provide evidence that early refeeding increases unscheduled use of IV fluids, episodes of vomiting, and development of persistent diarrhoea. The results support existing practice of early refeeding during or after start of rehydration of patients.

Up to the present time, some physicians still recommend variable periods of fasting during acute diarrhoea to allow 'bowel rest' followed by gradual reintroduction of food. The proponents of this practice contend that early refeeding may increase the stool output and lead to more complications, such as unscheduled use of IV fluids, episodes of vomiting, and persistent diarrhoea.

Our results suggest that the number of patients who develop these complications are similar whether early or late refeeding is practiced. However, early refeeding is advocated in order to counteract the transient malabsorption of nutrients that can occur during an episode of acute diarrhoea. This may have a negative influence on growth and contribute to malnutrition, which may, in turn, predispose to persistent diarrhoea. It is for this reason that relevant outcomes in a study of this nature should include the duration of diarrhoeal disease, total stool output, and percentage weight gain at resolution of illness. However, these important outcomes could not be assessed in the present study because of skewed data or heterogeneity among the limited number of trials that reported this information. Heterogeneity in the treatment effect may have been influenced by the way the outcomes were measured (methodological diversity). It was unclear in most of the trials whether the duration of diarrhoea was measured from the initial onset of the disease, before admission to the study, or only from admission up to the time of discharge. Ideally, measurement of stool output should be made by taking the difference in the weight of the diaper before and after use. In some studies where both males and females were included, the urine output may have been inadvertently mixed with the stool, giving an erroneously high stool output. The difference in the type of milk (cow- or soy-based milk) or food that was used to re-feed the patient might also have contributed to the heterogeneity of the different trials.

Since most of the studies were conducted more than 20 years ago, reporting of the methodology of the trials was incomplete. In the majority of the studies, it's unclear how the random allocation of patients to groups was concealed. It was also unclear if blinding was observed, although this was difficult to implement because of the nature of the interventions. Overall, therefore, the quality of these studies was relatively difficult to assess because of incomplete reporting.

Whilst previous clinical practice guidelines imply that early refeeding is acceptable (Bezerra 1992; Chongban 2005; MMWR 2003; Murphy 1998; WHO/UNICEF 2004), this is the first systematic review conducted on this topic to synthesize the available evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review summarize the available evidence on the timing of feeding during cases of acute diarrhoea in children. It reveals that there is little additional risk of unscheduled use of IV fluids, persistent diarrhoea, vomiting or longer hospital stays for children who were re-fed early.

Implications for research

Further studies are needed into whether the timing of refeeding has any effect on the duration of diarrhoea, the total stool output, and weight gain in childhood acute diarrhoea.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brown 1988

Methods	Randomized controlled trial
Participants	Number enrolled: 138 participants (128 were analyzed) Inclusion criteria: 3 to 36 months, male, non-malnourished, diarrhoea for less than 60 hours Exclusion criteria: female, received more than one dose of antibiotics for the diarrhoea, more than one episode of breastfeeding per day, diarrhoea within the last 3 weeks, weight for length <2 SD, presence of edema or serum albumin <2.5 g/dL
Interventions	1. Formula diet composed of casein, sucrose, dextrin with maltose (Dextri-Maltose), and vegetable oil to provide 110 kcal/kg body weight/d (CSO-110): 34 participants 2. CSO to provide 55 kcal/kg/d (CSO-55) for 2 days and then CSO-140: 29 participants 3. Oral glucose-electrolyte solution (GES) for 2 days, CSO-55 for the next 2 days, and then CSO-110: 34 participants 4. Intravenous GES was used for the first 2 days, CSO-55 for the next 2 days, and then CSO-110 : 34 participants
Outcomes	Duration of diarrhoea; apparent absorption of macronutrients and retention of nitrogen; changes in anthropometric indicators of nutritional status monitored at intervals during and after illness.
Setting	Hospital based trial Location: Lima, Peru
Notes	Interventions 1 and 2 were considered early refeeding while 3 and 4 were late refeeding groups The mean duration of the diarrhoea in each group was divided among the treatment success and treatment failures Two patients had prolonged severe diarrhoea on the 8th hospital day but their group assignments were unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to one of four dietary groups by means of a block randomization procedure
Allocation concealment (selection bias)	Low risk	In each sub-stratum, 12 envelopes were filled randomly (three envelopes each) with the numbers of the four dietary groups and sealed. Once all envelopes of a substratum were exhausted, 12 new envelopes were prepared.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded

Brown 1988 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomized were included in the final analysis
Selective reporting (reporting bias)	High risk	Two patients with severe diarrhoea were excluded
Other bias	Unclear risk	No details given in trial report

Conway 1989

Methods	Randomized controlled trial
Participants	Number: 200 enrolled Inclusion criteria: 6 weeks to 12 months, fed on formula feeds, with acute onset of watery or extremely loose stools for less than 14 days, no systemic illness Exclusion criteria: None
Interventions	1. Oral rehydration solution (Dextrolyte, Cow and Gate) for 24 hours, followed by 24 hours of half strength and 24 hours of three-quarter strength SMA Gold Cap (Wyeth) before continued feeding with the full strength formula milk: 50 participants 2. HN25 formula (Milupa) for two days after the stools returned to normal followed, on successive days, by replacement of one, three, and then all HN25 feeds by full strength SMA Gold Cap: 50 participants 3. Continued feeding with full strength SMA Gold Cap from the time of admission: 50 participants 4. Continued feeding with Formula S (Cow and Gate) from the time of admission. 50 participants
Outcomes	Duration of diarrhoea after admission, percentage weight change noted on days 2 and 5 and on discharge
Setting	Hospital based trial Location: Seacroft Hospital admissions, Leeds, UK
Notes	Data from Group 2, 3 and 4 were combined in the early refeeding group Data on weight change was only presented in a graph format Only one patient in Group 2 had persistent diarrhoea but recorded only until day 10 One patient in group 1 had continuous vomiting but it was not clear how long it lasted Location: Seacroft Hospital admissions in Leeds

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report
Allocation concealment (selection bias)	Unclear risk	No details given in trial report

Conway 1989 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomized were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Gazala 1988

Methods	Randomized controlled trial
Participants	Number: 90 enrolled Inclusion criteria: 1 to 12 months, acute (<4 days duration) watery (at least 4 watery stools per day) diarrhoea, mild dehydration
Interventions	1. Refeeding was started after 6 hours of oral rehydration with ORS 2. Refeeding was started after 24 hours of rehydration.
Outcomes	Percentage weight gain, duration of diarrhoea, number of infants admitted to the hospital
Setting	Private out-patient trial Location: Primary care clinic in Rahat, Israel
Notes	Clinical features were assessed at 24 hours and 2 weeks following the initial visit We assumed that the reported number of infants admitted to the hospital are interval numbers between the 2 follow-up evaluations Thirty percent of the infants were lost to follow-up during the 2-week period Percentage weight change was reported but not its SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study started on Sunday and infants were randomly assigned, starting on the last day of the week (Friday), to either group by flipping a coin, then alternated everyday. The daily change was to minimize mothers belonging to one group from influencing other mothers in a different group.
Allocation concealment (selection bias)	High risk	Those assigning will be able to decipher the next treatment allocation for the subsequent days after the initial flipping of the coin
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and caregivers were not blinded, but it was not mentioned if the outcome assessors were blinded

Gazala 1988 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	16 out of 53 and 11 out of 37 in the early and late refeeding group, respectively, were not reported in the assessment of outcome 2 weeks following initial visit
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	High risk	Thirty percent of patients lost to follow up

Hoghton 1996

Methods	Single-blind randomized controlled trial
Participants	Number: 62 enrolled Inclusion criteria: children <3 years of age who had acute gastroenteritis of less than 7 days duration, with liquid stools and increased frequency of defecation but with no other associated illness Exclusion criteria: presence of severe vomiting or in those with >5% dehydration
Interventions	1. Oral rehydration therapy (ORT) with glucose electrolyte solution alone for 24 to 48 hours without food: 33 participants 2. ORT with a modified diet: 29 participants
Outcomes	Duration of diarrhoea (reported as median, range); percentage weight gain; consistency of stool output; vomiting episodes; incidence of lactose intolerance
Setting	Hospital based trial Location: Casualty department of Bristol Children's Hospital, Bristol, UK
Notes	Who was blinded was unclear. There were 62 infants recruited in the study: Group 1 had 33 participants while Group 2 had 29. One in each group was withdrawn by their parents. For the outcome of vomiting, we considered 32 participants for Group 1 and 28 participants for Group 2. We included a participant supposedly withdrawn from Group 2 for severe vomiting who had to be hospitalized. Duration of diarrhoea and percentage change in weight gain were reported as median and therefore were not included in the meta-analysis. Length of follow up was 5 days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias)	Low risk	The study indicated that the patients were randomly allocated into two groups in a single-blinded fashion, although it was unclear who was blinded

Hoghton 1996 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 out of 29 and 32 out of 33 patients in the early and late refeeding group, respectively, were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Khin-Maung-U 1985

Methods	Randomized controlled trial
Participants	Number: 52 enrolled Inclusion criteria: 6 to 24 months, with acute watery diarrhoea <48 hours duration, with moderate or severe dehydration, breastfed Exclusion criteria: presence of systemic illness, clinically evident malnutrition, bottle fed and children who had received antibiotics
Interventions	1. Oral rehydration solution alone: 26 participants 2. Breast feeding plus oral rehydration solution: 26 participants
Outcomes	Total input (oral and intravenous) and total output (stool, urine, and vomitus) every hour and body weights
Setting	Hospital based trial Location: Pediatric wards in Infectious Disease Hospital in Rangoon, Burma
Notes	We converted the SE to SD for the duration of diarrhoea. Follow-up period was only for 48 hours and all the participants had resolution of diarrhoea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each child entered into the study was allocated by random numbers
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding is not possible if patients were monitored every hour
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomized were included in the final analysis

Khin-Maung-U 1985 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Khin-Maung-U 1986

Methods	Randomized controlled trial
Participants	Number: 48 enrolled Inclusion criteria: 2 to 5 years with watery diarrhoea <48 hours duration, with moderate to severe dehydration Exclusion criteria: presence of systemic illness, clinically evident malnutrition, children who had received antibiotics
Interventions	1. Oral rehydration solution (ORS) alone during the first 24 hours of admission: 24 participants 2. ORS with boiled rice feeding: 24 participants
Outcomes	Duration of diarrhoea (hrs), total stool output and volume of vomitus (ml/patient)
Setting	Hospital based trial Location: Pediatric wards in Infectious Disease Hospital in Rangoon, Burma
Notes	We converted SE to SD for the duration of diarrhoea Follow-up period was only for 48 hours and all the participants had resolution of diarrhoea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each child allocated by random numbers
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomized were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Rees 1979

Methods	Randomized controlled trial
Participants	Number: 46 enrolled Inclusion criteria: children between 6 weeks to 4 years, with diarrhoea with or without vomiting of less than 5 days duration, <5% dehydrated; gastroenteritis was the only disease
Interventions	1. Full-strength milk: 16 participants 2. 0.18% sodium chloride and 4% dextrose in water (clear fluids) until the diarrhoea settled, when full-strength milk was reintroduced: 16 participants 3. Clear fluids until the diarrhoea settled when milk was reintroduced in increasing concentrations, by a quarter strength every 8 hours until full strength was reached, unless the diarrhoea recurred: 14 participants
Outcomes	Daily records of weight, stool and vomitus; length of hospital stay
Setting	Hospital based trial Location: Primary care clinic in Rahat, Israel
Notes	The control group was the combined 2nd and 3rd group, which had delayed refeeding of full-strength milk and increasing concentrations of milk No vomiting in any group after day 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were randomized were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Sandhu 1997

Methods	Multicenter randomized controlled trial in twelve European hospitals
Participants	Number: 230 enrolled

Sandhu 1997 *(Continued)*

	Inclusion criteria: <3 years old, weaned children, with acute diarrhoea (≥4 watery stools per day for >1 but <5 days) Exclusion criteria: previous intake of oral rehydration solution or on intravenous fluid; previous treatment with antidiarrhoeal drugs; children with short gut syndrome, chronic inflammatory bowel disease, ileus, associated hepatic or renal disease
Interventions	1. Reguar diet: 134 participants 2. Oral rehydration solution (ORS) for 20 hours and then fed with child's regular diet: 96 participants If a child was breastfed, breast-feeding was to continue throughout, and in addition the child was given ORS (10 ml/kg/watery stool) and regular diet as appropriate
Outcomes	Weight gain (gms) during hospitalization, and on day 5 and 14 of hospitalization; stool frequency and the type of stool (watery, loose, or formed); number of patients with vomiting
Setting	Hospital based trial Location: Multicentre study based in 13 European hospitals in 11 countries: Royal Hospital for Sick Children, Bristol, UK; Ospedale Maria Nuova, Reggio Emilia, Italy; Department of Clinical Sciences, University of Tampere, Finland; Departimento Universita Di Napoli, Napoli, Italy; The Children's AMC, Amsterdam, The Netherlands; Groot Ziekengasthius, `s-Hertogenbosch, The Netherlands; Children's Hospital Zagreb, Republic of Croatia; Maribor Teaching Hospital, Ljubljanska, Slovenia; Department of Paediatrics, Charles University, Czech Republic; Antwerp Children's Hospital, Belgium; Hospital de S. Joao, Porto, Portugal; Katedra Pediatrii Akademii Medycznej, Warszawa, Dzialdowska, Poland; and Soroka Medical Centre, Beer Sheva, Israel
Notes	The figures showed that there were still participants who had diarrhoea and vomiting at Day 5 , although it was unclear how many were the actual counts. However, it was mentioned that none of the participants still had persistent diarrhoea and vomiting by Day 14.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were allocated to the two groups according to random numbers by the 12 centres included in the study
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and caregivers were not blinded, but it was not mentioned if the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	134 out of 134 and 88 out of 96 patients in the early and late refeeding group, respectively, were included in the final analysis
Selective reporting (reporting bias)	High risk	There were still participants who had diarrhoea and vomiting at Day 5, although it was unclear how many were the actual counts
Other bias	Unclear risk	No details given in trial report

Santosham 1985

Methods	Randomized controlled trial
Participants	Number: 89 enrolled Inclusion criteria: 0 to 12 months with acute watery diarrhoea (<7 days duration, at least 5 watery stools per day)
Interventions	1. Soy-based lactose-free formula 4 hrs after hospitalization: 43 participants 2. Food was withheld for the first 48 hours of hospitalization: 44 participants
Outcomes	Stool output in the first 24 and 48 hours and during illness (ml/kg); percentage weight gain on the following: 24th and 48th hour, resolution of illness and two weeks after discharge; duration of diarrhoea (hrs); serum sodium and potassium on admission, during and at resolution of illness
Setting	Hospital based trial Location: Indian Health Service Hospital, Whiteriver, Arizona, USA
Notes	One person in each group was excluded because food other than that allowed for the study was taken Persistent vomiting was defined as more than 3 times in an 8 hour interval necessitating intravenous therapy Persistent diarrhoea defined as more than 7 days of diarrhoea

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using block randomization of groups of four
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	43 out of 44 and 44 out of 45 patients in the early and late refeeding group, respectively, were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Santosham 1990

Methods	Randomly assigned
Participants	Number: 200 enrolled Inclusion criteria: children 3 to 18 months with acute watery diarrhoea (<7 days duration, at least 5 watery stools per day)

Santosham 1990 *(Continued)*

	Exclusion criteria: exclusively breastfed, with illness requiring intravenous fluids or antibiotic therapy, <5% dehydration, clinical signs of kwashiorkor
Interventions	1. Glucose oral rehydration solution (G-ORS) for 4 hours followed by soy-based formula (SF): 50 participants 2. G-ORS for 4 hours followed by rice-based formula: 50 participants 3. Rice-based ORS for 24 hours followed by SF: 50 participants 4. G-ORS for 4 hours followed by pre-cooked rice: 50 participants
Outcomes	Stool output during the first 24 hours and during illness (ml/kg); percentage weight gain during illness; duration of diarrhoea (hrs); serum sodium and potassium on admission, during and at resolution of illness
Setting	Hospital based trial Location: Abu El-Reeche Hospital, Cairo, Egypt
Notes	The third group (R-ORS § SF), which continued to receive R-ORS for the first 24 hours of the maintenance period followed by a soy-based lactose-free formula, was considered late refeeding or the control group in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Enrolled infants were randomly assigned in blocks of eight to one of four groups.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	148 out of 150 and 49 out of 50 patients in the early and late refeeding group, respectively, were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	High risk	Eleven percent were lost to follow-up

Santosham 1991

Methods	Randomized controlled trial
Participants	Number: 59 enrolled Inclusion criteria: 2 to 12 months with acute watery diarrhoea (<7 days duration, at least 5 watery stools per day), <7% dehydration

Santosham 1991 *(Continued)*

Interventions	1. Soy-based lactose-free formula and oral electrolyte solution (Resol) on the first 24 hours: 29 participants 2. Oral electrolyte solution (Resol) alternating with water in the first 24 hours; day 2, half-strength soy-based formula alternating with ORS; day 3, full strength soy based formula: 30 participants
Outcomes	Duration of diarrhoea (days); percentage weight gain at 24 hours after entry, at resolution of illness and at 2 weeks after therapy. CBC, serum electrolytes, total proteins and glucose were only monitored on admission
Setting	Out-patient trial Locations: US Public Health Service Hospital in Whiteriver, Arizona; and private and city health clinics in Baltimore, Maryland
Notes	3 dropped out within 24 hours because of non-compliance with the study regimen. No data were obtained for these 3 participants. Persistent diarrhoea lasting for more than 7 days after start of therapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomized to groups of four using the table of random numbers
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded, but it was unclear if the caregivers or the outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	56 out of 59 patients who were randomized in the trial were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Shaikh 1991

Methods	Randomized controlled trial
Participants	Number: 69 enrolled Inclusion criteria: children 9 to 48 months, acute watery diarrhoea <72 hours, moderate to severe dehydration, no previous antibiotic treatment, no complications other those related to dehydration, weaned from mother's milk
Interventions	1. 'Khitchri' and half-strength cow's milk formula in addition to WHO ORS after 4 to 6 hours rehydration: 36 participants

Shaikh 1991 *(Continued)*

	2. WHO ORS with no food in the first 24 hours, then traditional legume-based weaning diet 'khitchri' and half-strength cow's milk formula freely: 33 participants
Outcomes	Stool output (g/kg/day), percentage weight gain after start of rehydration and at 24 hours and 72 hours post-rehydration
Setting	Hospital based trial Location: Civil Hospital, Karachi, Pakistan.
Notes	6 children were withdrawn and did not complete the study due to intercurrent infections and for non-medical reasons (2 from Group A, 4 from Group B) Treatment failures were defined as a need to restart administeringintravenous fluids Data were separated from those who were treatment successes and failures; we were not able to extract the data for appropriate meta analysis Vomiting was monitored only until day 3 11 children in Group A and 15 in Group B had high stool rates on day 3 but it was unclear if this persisted for more than 7 days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to one of the two treatment groups using a random number table
Allocation concealment (selection bias)	Unclear risk	No details given in trial report
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 out of 36 and 31 out of 33 in the early and late refeeding group, respectively, were reported in the final analysis
Selective reporting (reporting bias)	Unclear risk	No details given in trial report
Other bias	Unclear risk	No details given in trial report

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Armistead 1989	This is a randomized controlled trial of 68 hospitalized babies for acute diarrhoea to compare full-strength versus quarter-strength formula. However, both groups were given feedings only after 24 hours of oral rehydration with glucose electrolyte mixture.
Chew 1993	The study assessed the effects on clinical course of two feeding regimens in 159 Guatemalan and Brazilian infant boys aged 2 weeks to 6 months who had acute diarrhoea. They were assigned randomly to one of two feeding regimens: full-strength milk formula (group A), or progressive reintro-

Study	Reason for exclusion
	duction of full-strength milk formula (half-strength for the first 24 hours, two-thirds strength for the second 24 hours, and full-strength thereafter) (group B). Both groups received refeeding after 4 to 6 hours of oral rehydration.
Fox 1990	Sixty-two babies under the age of 6 months who were admitted with gastroenteritis were randomly allocated to gradual refeeding or abrupt refeeding. In both groups, refeeding was started after a period of 12 hours rehydration.
Haffejee 1990	A therapeutic trial of hospitalized children with acute diarrhoea randomized to receive either lactose-free soya formula or their original cow's milk-based formula. However, both comparison groups were re-fed at time of admission.
Haque 1983	One hundred and fifty children with acute enteritis were randomly allocated to three feeding regimens: a. clear fluids (glucose electrolyte solution) then quarter-strength formula; b. clear fluids then full-strength formula; c. continuing full-strength milk. In the first two groups, the initial fluids were given within 6 to 24 hours and therefore it was unclear whether there were children who received refeeding early.
Hjelt 1989	Fifty-two children aged 6 to 46 months who were hospitalized for acute gastroenteritis were randomized after start of rehydration to receive either traditional gradual or rapid refeeding. The gradual refeeding group was allowed to take only syrupy water gruel and apple porridge for at least one day and therefore it was unclear how many in this group would have been re-fed early.
Nanulescu 1995	A quasi-randomized trial compared early versus late re-feeding in the management of acute diarrhoea in the first year of life.
Parker 1981	The participants were 9 infants with protracted diarrhoea and malnutrition and 2 infants with surgically created short bowel. Patients were not selected randomly for allocation to the treatment groups.
Ransome 1984	A blind randomized controlled trial was performed to compare full strength versus graduated milk formula given on the first day of hospital admission for the treatment of acute infantile gastroenteritis.
Soeprapto 1979	The study included babies aged 4 to 24 months with diarrhoea, but it was not clear whether they were suffering from acute watery diarrhoea. Both comparison groups were re-fed after start of rehydration, but the the interval until the participants were given full feeding differed between the groups.

DATA AND ANALYSES

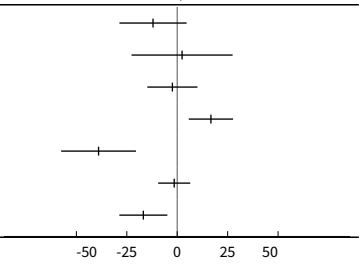
Comparison 1. Early vs late refeeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of diarrhea (hours)	7		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Total stool output during the first 24 hours after start of rehydration, ml/kg	3	394	Mean Difference (IV, Random, 95% CI)	5.86 [-23.66, 35.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Total stool output during first 48 hours after start of rehydration, ml/kg	3	262	Mean Difference (IV, Random, 95% CI)	-19.73 [-55.12, 15.66]
4 Percentage weight gain at 24 hours	3	212	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-1.38, 0.62]
5 Percentage weight gain at resolution of illness	3	322	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.27, 1.47]
6 Unscheduled intravenous fluid therapy	6	813	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.48, 1.59]
7 Cases of vomiting	5	456	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.72, 1.86]
8 Adverse events: Development of persistent diarrhea	4	522	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.18, 1.85]
9 Adverse events: Development of hyponatremaia	2	287	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.06, 7.29]

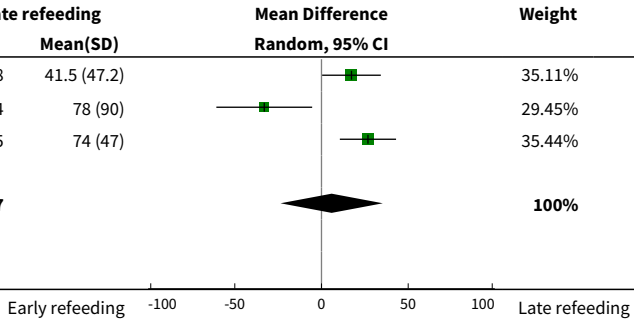
Analysis 1.1. Comparison 1 Early vs late refeeding, Outcome 1 Duration of diarrhea (hours).

Study or subgroup	Early refeeding N	Early refeeding Mean(SD)	Late refeeding N	Late refeeding Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Conway 1989	150	52 (46.6)	50	64 (53.7)		-12[-28.65,4.65]
Gazala 1988	37	88.8 (45.6)	26	86.4 (52.8)		2.4[-22.66,27.46]
Khin-Maung-U 1985	26	43.3 (25.5)	26	45.7 (19.9)		-2.4[-14.83,10.03]
Khin-Maung-U 1986	24	46.3 (15.7)	24	29.6 (22.5)		16.7[5.71,27.69]
Santosham 1985	43	54 (28)	44	93 (56)		-39[-57.54,-20.46]
Santosham 1990	134	45.5 (22.4)	45	47 (24)		-1.5[-9.47,6.47]
Santosham 1991	29	48 (4.8)	27	64.8 (31.2)		-16.8[-28.7,-4.9]



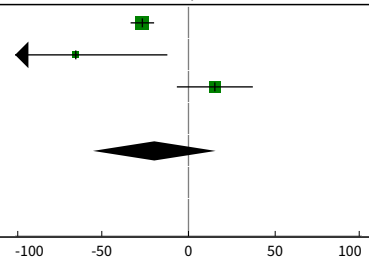
Analysis 1.2. Comparison 1 Early vs late refeeding, Outcome 2 Total stool output during the first 24 hours after start of rehydration, ml/kg.

Study or subgroup	Early refeeding N	Early refeeding Mean(SD)	Late refeeding N	Late refeeding Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Brown 1988	60	58.8 (50)	68	41.5 (47.2)		35.11%	17.3[0.39,34.21]
Santosham 1985	43	45 (25)	44	78 (90)		29.45%	-33[-60.62,-5.38]
Santosham 1990	134	100.8 (50.8)	45	74 (47)		35.44%	26.8[10.6,43]
Total ***	**237**		**157**			**100%**	**5.86[-23.66,35.37]**
Heterogeneity: Tau^2=571.35; Chi^2=13.66, df=2(P=0); I^2=85.36%							
Test for overall effect: Z=0.39(P=0.7)							



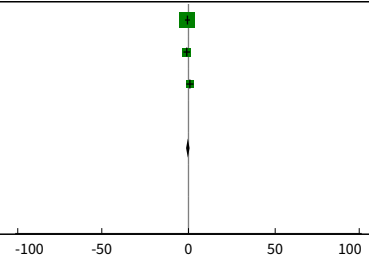
Analysis 1.3. Comparison 1 Early vs late refeeding, Outcome 3 Total stool output during first 48 hours after start of rehydration, ml/kg.

Study or subgroup	Early refeeding N	Early refeeding Mean(SD)	Late refeeding N	Late refeeding Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Khin-Maung-U 1985	26	89.2 (10)	26	115.8 (14.5)		41.73%	-26.6[-33.37,-19.83]
Santosham 1985	43	85 (63)	44	150 (167)		21.8%	-65[-117.82,-12.18]
Santosham 1990	93	78.2 (59.6)	30	63 (51)		36.46%	15.2[-6.7,37.1]
Total ***	**162**		**100**			**100%**	**-19.73[-55.12,15.66]**
Heterogeneity: Tau^2=769.42; Chi^2=15.17, df=2(P=0); I^2=86.81%							
Test for overall effect: Z=1.09(P=0.27)							



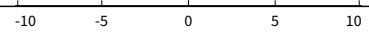
Analysis 1.4. Comparison 1 Early vs late refeeding, Outcome 4 Percentage weight gain at 24 hours.

Study or subgroup	Early refeeding N	Early refeeding Mean(SD)	Late refeeding N	Late refeeding Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Santosham 1985	43	1.8 (3.6)	44	2.4 (3.2)		48.55%	-0.6[-2.03,0.83]
Santosham 1991	29	1.5 (3.5)	27	2.5 (3.7)		27.9%	-1[-2.89,0.89]
Shaikh 1991	36	-0.6 (4.8)	33	-1.4 (3.9)		23.55%	0.8[-1.26,2.86]
Total ***	**108**		**104**			**100%**	**-0.38[-1.38,0.62]**
Heterogeneity: Tau^2=0; Chi^2=1.77, df=2(P=0.41); I^2=0%							
Test for overall effect: Z=0.75(P=0.45)							



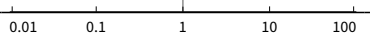
Analysis 1.5. Comparison 1 Early vs late refeeding, Outcome 5 Percentage weight gain at resolution of illness.

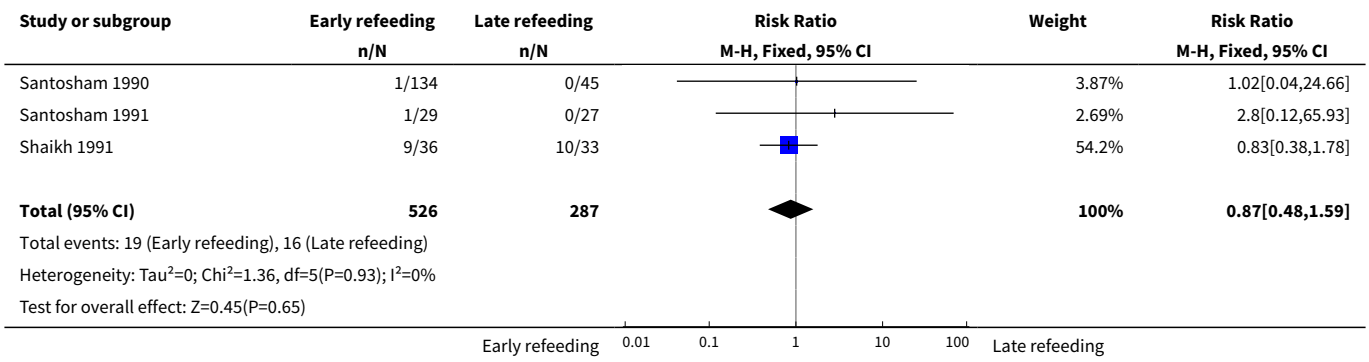
Study or subgroup	Early refeeding N	Early refeeding Mean(SD)	Late refeeding N	Late refeeding Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Santosham 1985	43	3 (4)	44	1.9 (4.3)		25.09%	1.1[-0.64,2.84]
Santosham 1990	134	7.3 (4)	45	7 (4)		41.86%	0.3[-1.05,1.65]
Santosham 1991	29	1.8 (3.5)	27	1.2 (2.2)		33.05%	0.6[-0.92,2.12]
Total ***	**206**		**116**			**100%**	**0.6[-0.27,1.47]**
Heterogeneity: Tau^2=0; Chi^2=0.51, df=2(P=0.78); I^2=0%							
Test for overall effect: Z=1.35(P=0.18)							



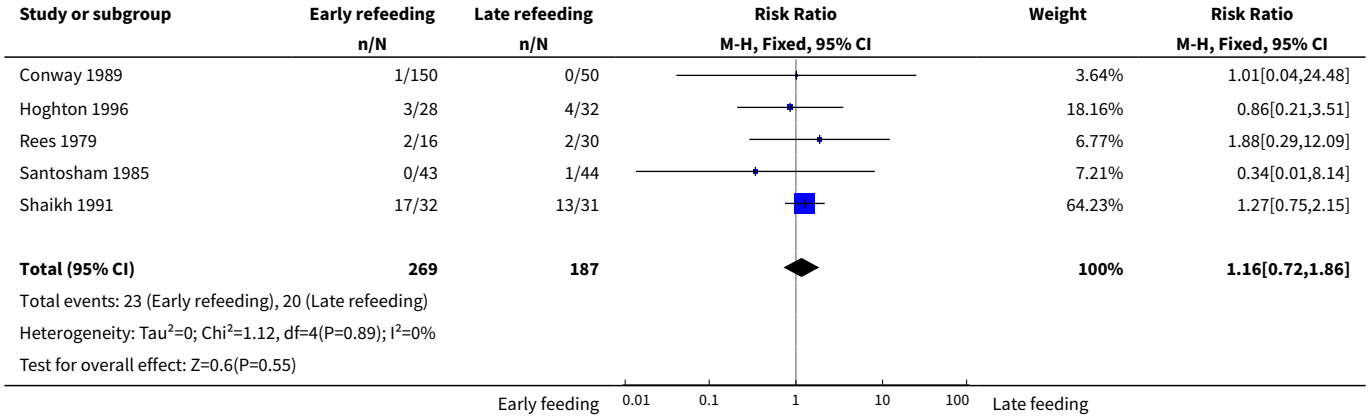
Analysis 1.6. Comparison 1 Early vs late refeeding, Outcome 6 Unscheduled intravenous fluid therapy.

Study or subgroup	Early refeeding n/N	Late refeeding n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Conway 1989	3/150	0/50		3.88%	2.36[0.12,45]
Sandhu 1997	4/134	4/88		25.08%	0.66[0.17,2.56]
Santosham 1985	1/43	2/44		10.27%	0.51[0.05,5.44]

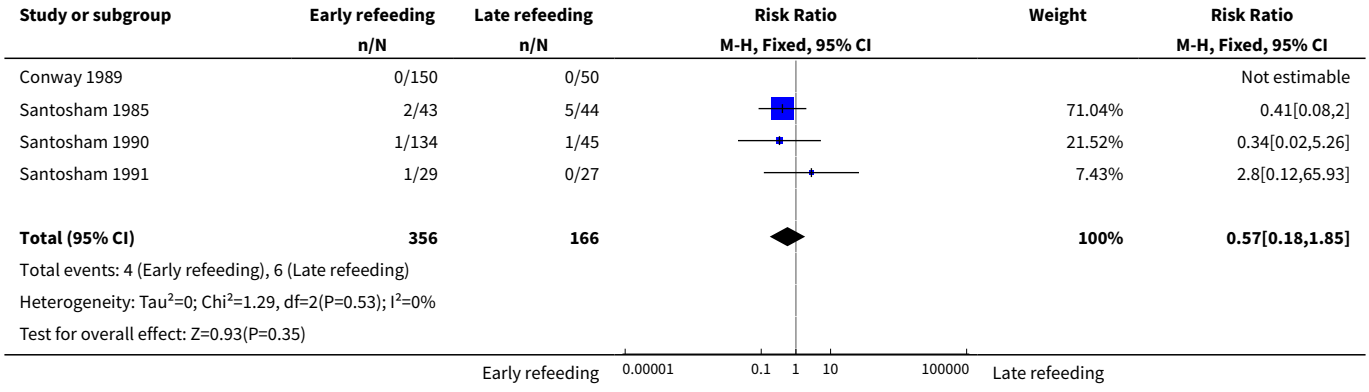




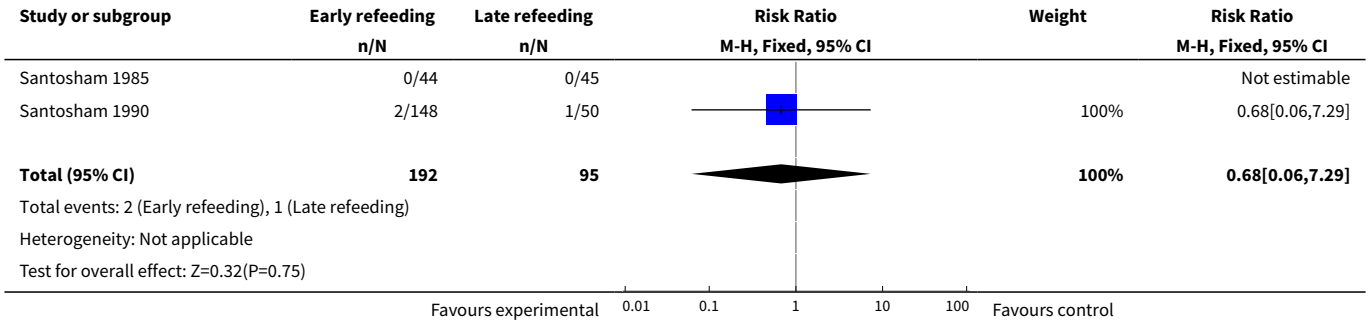
Analysis 1.7. Comparison 1 Early vs late refeeding, Outcome 7 Cases of vomiting.



Analysis 1.8. Comparison 1 Early vs late refeeding, Outcome 8 Adverse events: Development of persistent diarrhea.



Analysis 1.9. Comparison 1 Early vs late refeeding, Outcome 9 Adverse events: Development of hyponatremaia.



ADDITIONAL TABLES

Table 1. Detailed Search Strategies

Search Set	CIDG SR	CENTRAL	MEDLINE	EMBASE	LILACS
1	diarrhoea	diarrhoea	diarrhoea	diarrhoea	diarrhoea
2	diarrhoea	gastroen-teritis	gastroenteritis	gastroenteritis	diarrhoea
3	gastroenteritis	1 or 2	1 or 2	1 or 2	gastroen-teritis
4	1 or 2 or 3	Feed*	Feed*	Feed$	1 or 2 or 3
5	Feed*	Refeed*	Refeed*	Refeed$	Feeding
6	Refeed*	Re-feed*	Re-feed*	Re-feed$	Refeeding
7	Re-feed*	Nutrition*	Nutrition*	Nutrition$	Re-feeding
8	5 or 6 or 7	4 or 5 or 6 or 7	NUTRITIONAL SUPPORT	DIET RESTRIC-TION	5 or 6 or 7
9	4 and 8	3 AND 8	TIME FACTORS	FEEDING BE-HAVIOUR	4 AND 8
10			4-9/OR	4-9/OR	
11			3 AND 10	3 AND 10	
12			Limit 12 to Human	Limit 12 to Hu-mans	
13					
14					
15					

Table 1. Detailed Search Strategies *(Continued)*

Cochrane Infectious Diseases Group Specialized register	Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins); Upper case: MeSH or EMTREE heading; Lower Case: free text term

Table 2. Additional data provided by the studies used in the review

	Outcome and unit of analysis	Early refeeding	Late refeeding
Hoghton 1996	Median (range) of duration of diarrhoea (hours)	66.5 (11-192)	56 (24-216)
Khin-Maung-U 1985	Mean (SE) of total stool output in the first 24 hours, ml/kg/patient	89.2 (10)	115.8 (14.5)
Khin-Maung-U 1986	Mean (SE) of total stool output in the first 24 hours, ml/patient	1447.5 (214.4)	870.6 (152.3)

Table 3. Mean (SD) of stool output at different periods of observation (gm/kg/day)

	Early refeeding		Late refeeding	
Shaikh 1991	Successfully treated	Clinical failure	Successfully treated	Clinical failure
Day 1	195 (116)	300 (111)	256 (157)	354 (156)
Day 2	192 (153)	436 (102)	202 (223)	412 (183)
Day 3	166 (132)	420 (109)	177 (201)	336 (164)

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 7, 2011

Date	Event	Description
1 April 2008	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All the authors wrote the protocol. The first two authors carried out the risk of bias (methodological quality) assessment, data extraction, data analysis, and wrote the final manuscript.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Effective Health Care Research Programme Consortium, UK, Not specified.

External sources

- Department of International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- **Authorship:** GV Gregorio was designated as the principal investigator for the review.
- **Data extraction:** We originally planned to extract data on the number of patients requiring hospitalization. However, most of the trials were conducted in a hospital setting, and the outcome reported by two trials was the mean length of hospital stay. We also intended to obtain count data by determining the total number of episodes in each group (if the episode was rare) or the number of person years in each group for each treatment arm (if the episode was common). However, during our assessment of the trials, we realised that the trials reported the number of participants with vomiting, and thus it was considered to be a dichotomous outcome rather than a count outcome. There were also no studies that reported the mean caloric intake, deaths and all-cause mortality.
- **Data analysis:** In multiple treatment arms with two or more types of feeding as treatment groups, the outcomes were combined as appropriate and compared collectively with the control group.
- **Subgroup analyses:** This could not be done because of the limited number of trials in each outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

*Eating; *Fluid Therapy; Acute Disease; Developing Countries; Diarrhea [diet therapy] [*therapy]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Child; Child, Preschool; Humans; Infant