Systematic review of the care of children with diarrhoea in the community-based management of severe acute malnutrition

Mark Manary[1]
Lora Iannotti[2]
Indi Trehan[3]
Ariana Weisz[4]

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[1] Helene B. Roberson Professor of Pediatrics, Washington University in St. Louis;
Senior Lecturer in Community Health, University of Malawi
[2] Assistant Professor, Institute of Public Health, George Warren Brown School of Social Work, Washington University in St. Louis
[3] Assistant Professor of Pediatrics, Washington University in St Louis;
Visiting Lecturer in Paediatrics and Child Health, University of Malawi
[4] Research Assistant, Department of Pediatrics, Washington University in St. Louis

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Abbreviations

AIDS	acquired immunodeficiency syndrome
CI	confidence interval
CMAM	Community Management of Acute Malnutrition
F-75	therapeutic milk used in stabilization phase of the treatment of SAM
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAZ	height-for-age z-score
HIV	human immunodeficiency syndrome
L/R ratio	lactulose-rhamulose test
NCHS	National Center for Health Statistics
ORS	oral rehydration salts
PICO	Population, Intervention, Comparator and Outcomes
RCT	randomized controlled trial
RDA	recommended daily allowance
ReSoMal	Rehydration Solution for Malnutrition
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition

UNICEF	United Nations Children's Fund
WAZ	weight-for-age z-score
WHO	World Health Organization
WHZ	weight-for-height z-score

Measurements

cal	calorie
d	day
hr	hour
g	gram
kg	kilogram
k/J	kilojoule
m	metre
mg	milligram
ml	millilitre
mmol	millimole
n	number
yr	year

Background

Severe acute malnutrition (SAM) and diarrhoea are major causes of morbidity and mortality among children in the developing world *(1,2).* When SAM and diarrhoea are coincident, they place the child at increased risk of death and disability. Diarrhoea reduces nutrient and fluid absorption, while SAM creates a vulnerable fluid and nutrition homeostasis. The etiology and management of diarrhoea, therefore, raises concern in SAM outpatient treatment regimens in order to decrease mortality, improve growth outcomes, and enhance the success of community-based programmes.

The relationship between malnutrition and diarrhoea is bidirectional – malnutrition predisposes children to a greater incidence and duration of diarrhoea *(3)*, and malnutrition can be triggered or worsened by significant diarrhoea. Diarrhoea leads to reduced absorption of carbohydrates, protein, potassium, zinc and other nutrients, further contributing to malnutrition *(4)*. Significant water losses from diarrhoea can lead to dehydration, electrolyte imbalance, shock, decreased mental status and ultimately death *(*5). Episodes of prolonged diarrhoea are also associated with increased morbidity and mortality from other diseases, adverse neurodevelopment and growth stunting *(6*).

Treatment of diarrhoea with oral rehydration therapy and zinc is well established in children *(7)*. Zinc and oral rehydration salts (ORS) are standard therapies in the treatment of acute diarrhoea and recommended in World Health Organization (WHO) guidelines (*1*). Micronutrient supplementation, treatment with antibiotics and antiparasitic drugs, antimotility agents and modified feeding strategies are other potential therapies that could conceivably be effective in the treatment of diarrhoea. No specific WHO guidelines exist to provide guidance on the diagnosis and treatment of diarrhoea in children with SAM treated as outpatients, an especially vulnerable population. The effectiveness of a variety of therapies for the treatment of diarrhoea in the specific context of the community-based management of SAM is thus reviewed here.

For children with SAM and acute or persistent diarrhoea without moderate or severe dehydration receiving community-based management of acute malnutrition:

- What are the most effective strategies to determine the etiology?
- What are the most effective therapeutic measures, including:
    - antibiotics
    - antiparasitics
    - ORS
    - modified feeding strategies
    - glutamine and zinc supplementation?

Methodology

A search of computerized databases for all studies from 1950 to 2011 was carried out. Databases searched included Medline, Embase and Google Scholar, and clinical trial registries at clinicaltrials.gov, pactr.org and apps.who.int/trialsearch. Both observational and randomized studies

were included. Key words for the searches included “malnutrition”, “severe malnutrition”, “kwashiorkor”, “marasmus”, “therapeutic food”, “CMAM”, “outpatient”, “OTP”, “community-based care”, “diarrhea”, “zinc”, “glutamine”, “oral rehydration solution”, “ORS”, “prebiotics”, “probiotics” and “antibiotics”. A number of outcome measures were sought including mortality, weight gain, nutritional recovery, resolution of diarrhoea and duration of therapy. Further terms were added iteratively to the search based on results obtained from the initial searches. Searches were also conducted to identify relevant publications and study documents produced by international health organizations such as the WHO, the United Nations Children’s Fund (UNICEF) and Médecins Sans Frontières. Included studies were limited to those published in English, French or Spanish.

The titles and abstracts from these search results were scanned to identify relevant studies. The full texts of relevant studies were obtained and the list of relevant articles for inclusion were further optimized. Reference lists in relevant articles were also scanned manually and electronically (Google Scholar, Web of Science) to identify prior citations that may have been missed by the original searches. Publications that cite those previously identified articles were similarly sought.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (www.GradeWorkingGroup.org) approach to evaluating studies was then used to guide the assessment of identified studies. A number of criteria were applied to retrieved studies in order to evaluate their methodological quality: type of study (observational vs randomized), study quality, relevant choice of study population, appropriate choice of interventions and outcomes, and methods for controlling for confounders. Subjectivity arising from possible conflicts of interest was also assessed. Evidenced-based Population, Intervention, Comparator and Outcomes (PICO) review tables for each source were created and thoroughly reviewed by other investigators.

Results

After initial screening of abstracts, none was identified as studies that encompassed etiologic diagnosis or management of diarrhoea in children with SAM being treated as outpatients or in a community-based programme.

The finding of no direct evidence relevant to these questions regarding community-based management of SAM and diarrhoea without dehydration was disappointing and, therefore, the search was broadened: 1644 abstracts were identified as having keywords diarrhoea and malnutrition. After review of the abstracts, 121 were selected for full review as they might be relevant to the question under consideration. Of these, 32 were designated *medium to high quality* based on GRADE criteria and thus, discussed below. Question 1 is addressed in two parts: (a) most effective etiologic *diagnostic* strategies; and (b) most effective *therapeutic* strategies.

Question 1a. For children with SAM and acute or persistent diarrhoea, without moderate or severe dehydration, receiving community-based management of acute malnutrition, what are the most effective diagnostic strategies?

No evidence was identified that directly answers the PICO question.

Diagnosing diarrhoea in children with SAM

Children with SAM and diarrhoea are at increased risk for morbidity and mortality compared to those without diarrhoea, making accurate and prompt diagnosis essential. An observational, case-controlled study conducted in Bangladesh among SAM children hospitalized with diarrhoea found that clinical

septicaemia (AOR 8.8, 95% CI 3.7-21.1), hypothermia (AOR 3.5, 95% CI 1.3-9.4) and bronchopneumonia (AOR 3.0, 95% CI 1.2-7.3) increased the risk of mortality significantly among SAM children <3 years with diarrhoea *(8)*.

While diarrhoea occurs frequently and often severely in the population of children who suffer most often from SAM, particular clinical presentations may occur more frequently in children with SAM and may be useful as diagnostic strategies for SAM. Diarrhoeal episodes of longer duration are associated with poor short-term and long-term outcomes in children with SAM. Persistent diarrhoea (≥3 liquid or semi-liquid stools per day for ≥14 days) was the most commonly used indicator of longer duration diarrhoea, but prolonged diarrhoea (≥3 liquid or semi-liquid stools per day for 7–13 days) could more consistently be applied in the context of SAM in Community Management of Acute Malnutrition (CMAM). A 10-year cohort study in Brazil found prolonged diarrhoea to be prevalent in 12% of children *(6)*. Prolonged diarrhoea increased the risk of persistent diarrhoea later in childhood, and resulted in significant reductions in weight-for-height z-scores (HAZ) and weight-for-age z-scores (WAZ). Prolonged diarrhoea was frequently associated with cryptosporidium and shigella infection.

Pathogens associated with diarrhoea and SAM

Several studies have examined the diarrhoeal pathogens found in children with SAM. One review article focused on parasitic infections found that diarrhoea caused by *Giardia lamblia, Strongyloides sterocoralis* and Cryp*tosporidium* were common and severe in malnourished children *(9)*. *Giardia lamblia* and *Strongyloides* may be detected in duodenal fluid and not stools and thus are harder to diagnose. Malnourished children with profuse diarrhoea may, therefore, need routine antiparasitic treatment *(9)*. One study in Bangladesh found that of the 12 pathogens examined, *Escherichia coli, Cryptosporidium spp*. and *Entamoeba histolytica* were significantly more prevalent in malnourished children 2–5 years old *(10)*. In Ghana, malnourished children with diarrhoea were more likely to be coinfected with *Escherichia coli and Cryptosporidium (11)*.

A study in Nepal focused on etiologies of persistent diarrhoea found that protozoal infections (35.5%) were more prevalent than helminthic (24.9%) and bacterial (12.6%) infections. Among protozoal infections, *Giardia lamblia* and *Entamaeba histolytica* were most common *(12)*. Among HIV-infected children and severely malnourished children, persistent diarrhoea was most commonly associated with *Cyclospora cayetanensis* and *Cryptosporidium spp*. infection (*12*). In a study in Tanzania, a higher percentage of children with cryptosporidiosis-related diarrhoea was malnourished than those without cryptosporidiosis *(13)*. These same pathogenic etiologies were found in other studies reviewed in association with persistent diarrhoea and malnutrition. In Uganda, microsporidiosis or infection with *Enterocytozoon bieneusi*, were shown to be associated with reduced weight gain rates among children with persistent diarrhoea, after adjusting for sex, HIV status and concurrent cryptosporidiosis (p=0.014) *(14)*.

Question 1b. For children with SAM and acute or persistent diarrhoea without moderate or severe dehydration receiving community-based management of acute malnutrition, what are the most effective therapeutic measures, including:

- antiparasitics
- ORS
- modified feeding strategies
- glutamine
- zinc supplementation?

No direct evidence was found for the second PICO question of this review, although 24 studies of therapeutic strategies with relevance to the question in an indirect manner were identified and are presented.

Antiparasitics

As discussed previously, *Cryptosporidium parvum* is commonly found in children with SAM and diarrhoea. Metronidazole has been first-line therapy for the treatment of *Giardia lamblia* and *C. parvum* for many years. More recently, nitazoxanide has been shown to be active against these pathogens in children with diarrhoea *(15,16)*. In Zambia, 100 children (half with HIV) with cryptosporidial diarrhoea were randomized to receive nitazoxanide 100 mg/day for three days or placebo (*15*). Significant differences in resolution of diarrhoea (33% reduction, 95% CI 7%–59%; p=0.037) and eradication from the stool (38% reduction, 95% CI 14%–63%; p=0.007) were found in the HIV-negative children only. In a subgroup analysis, baseline WAZ did not alter responses to nitazoxanide. Another study in Egypt found that nitazoxanide reduced duration of diarrhoea (p<0.001) and oocyte shedding (p<0.001) among children aged 1–11 years with *Cryptosporidium (16).*

ORS

Because malnourished children with dehydration often have different electrolyte imbalances than children without malnutrition, WHO guidelines currently recommend Rehydration Solution for Malnutrition (ReSoMal) *(17)* to correct dehydration, hypokalaemia, and hyponatraemia in malnourished children. No studies were identified that directly answered the question regarding the optimal ORS formulation in the community-based management of SAM. Two trials conducted in Bangladesh, however, have relevance to the question. First, a study compared the efficacy of ReSoMal with standard ORS among malnourished children 6–36 months old with acute diarrhoea (*18*). Basal hypokalaemia was corrected in a significantly higher proportion of children on ReSoMal than standard ORS by 24 hours (36% vs 5%, p=0.0006) and by 48 hours (46% vs 16%, p=0.004). Hyponatraemia, however, did persist in children on ReSoMal, especially for those with *V. cholerae* and *Enterotoxigenic E. coli.*

Another study in Bangladesh used a historical control to examine the differences between a standardized protocol of slow rehydration with emphasis on oral rehydration and a non-protocol conventional treatment among hospitalized severely malnourished children with diarrhoea (*19*). The primary differences in the protocols were the use of oral (standardized) vs intravenous (conventional) rehydration and timing of refeeding, immediately (standardized) vs delayed (conventional). Mortality was lower in the standardized treatment arm compared to the conventional treatment arm, with an odds ratio of 0.49, (95% CI 0.3- 0.8; p=0.003). Rehydration success was higher in the standardized protocol than the conventional (59.9% vs 29%, p<0.0001) and hypoglycaemia episodes were lower (15 vs 30, p=0.005) (*19*).

Modified feeding strategies

Two home-based therapeutic feeding trials in Malawi provided evidence for the effectiveness of ready-to-use therapeutic food (RUTF) for children with SAM (*20,21*). The studies were not limited to malnourished children with diarrhoea, but did examine differences in prevalence of diarrhoea post-treatment.

Using a quasi-experimental design, a controlled effectiveness trial was conducted in Malawi comparing standard hospital-based therapy with home-based therapy with RUTF *(20)*. The mothers of 745 out of 940 children (82%) in the RUTF group reported no diarrhoea, compared to 124/176 (70%) in the standard therapy group (p<0.05*).*

Another trial in Malawi compared three different feeding regimens for home-based therapy of severe malnutrition *(21)*. The three comparison groups were: RUTF (23 kJ/g); micronutrient-fortified RUTF

(26 kJ/g); and a maize (80%)/soy (20%) (4 kJ/g) + micronutrient supplement. Longitudinal prevalence of diarrhoea differed significantly among different dietary regiments: RUTF group (74/1959 days, 3.8%); RUTF supplement (181/2565 days, 5.6%); and maize/soy + micronutrient supplement group (74/3228 days, 2.3%) ($p<0.01$ by x^2 test). Among Malawian children with kwashiorkor, a standard milk-based diet was associated with improved permeability ratios (lactulose-rhamulose test [L/R ratio]) by a mean of 6.4 compared to a maize–soya–egg diet that declined by 6.8 (p=0.001) (*22*). There was a higher percentage of hospital days with diarrhoea in the milk group, but a lower prevalence of clinical sepsis and greater weight gain for children in the milk group compared to the maize group.

The Kingston Project in Jamaica from 1985 to 1986 was a multifactorial randomized controlled trial (RCT) to determine whether adding a high-energy nutrient supplement (milk-based gruel) or an antibiotic (metronidazole) would improve outcomes in the community-based care of malnourished children. While the study found greater gains in weight and height for groups taking the supplement and the antibiotic, similar advantages for morbidity outcomes were not observed, specifically the number and duration of diarrhoeal episodes. There was significantly higher prevalence of dysentery in both the standard care and the supplement groups compared to the metronidazole groups (p=0.01) *(23)*.

A small body of evidence exists regarding the issue of lactose intolerance among children with SAM and enteric infection. F-75 is a low-lactose formula. Studies confirm that following diarrhoeal disease, there is lactose malabsorption and intolerance, but evidence is mixed regarding the benefits of removing lactose from the diet. One trial in Peru investigated the differences in recovery from persistent diarrhoea in children receiving a milk-based diet (6 g/kg/day lactose) vs the same diet with prehydrolyzed β-galactosidase. Results showed no differences in treatment failure, but demonstrated a benefit for the hydrolyzed milk group in terms of reduced stool output ($p<0.01$) *(24)*. A study in Australia among hospitalized Aborginal children compared three formulas differing in osmolality and protein hydrolysis (*25*). The two lactose-free formulas (De-Lact and O-Lac) showed a reduced duration of diarrhoea compared to the partially hydrolyzed formula (Alfare). De-Lact, the low osmolality and lactose-free formula, also demonstrated an improved L/R ratio compared to Alfare. An older study in Canadian children hospitalized with severe gastroenteritis found that those fed a lactose regimen had longer duration of diarrhoea, higher frequency of relapse and greater stool output than those given glucose regimen (*26*).

Other studies have not replicated these advantages, though the heterogeneity in study design and sample anthropometry and morbidity (acute diarrhoea vs persistent) is problematic for making comparisons. An RCT in Peru compared four dietary regimens for nutritional management of children 3–24 months old with diarrhoea. Lactose content of milk in the different diets was not significant for any clinically relevant outcomes. The study did find that when the two wheat noodle and milk product groups were combined and compared with each other, treatment failure rates were lower and diaarhoeal outcomes better (shorter duration and lower faecal output) in the wheat groups than the milk product alone (*27*). In India, an RCT compared two diets: group 1 (milk-free diet of rice, lentil, sugar and coconut oil) vs group 2 (spray dried commercial cow's milk formula) in children with acute diarrhoea *(28)*. No differences in duration of diarrhoea were found, but mean energy intake and weight gain were both higher in the milk group ($p<0.05$). Another older study in Guatemala found a decreased stool frequency among malnourished children given β-galactosidase-treated milk compared to those receiving intact, untreated cow's milk, but all other outcomes, including recovery, growth and various intestinal functions, were not significant (*29*).

Regarding the osmolarity of cow's milk, only one study was identified. This was an equivalence trial to examine whether there were any harmful effects associated with giving full-strength cow's milk or formula versus diluted milk to Guatemalan and Brazilian infants 2 weeks to 6 months of age with diarrhoea. No differences were detected for treatment failure, mean stool output or duration of diarrhoea (*30*).

Glutamine

Glutamine has been previously shown to improve intestinal absorptive function and weight gain in adults with HIV *(31)*. In animal models of cholera and *Cryptosporidium* infection, glutamine enhanced intestinal absorption of sodium and water. Only one RCT was identified of low to medium quality testing the addition of glutamine to ORS in malnourished children *(32)*. Conducted in Brazil among hospitalized infant boys, this study showed no improvement with glutamine for diarhoeal stool output, diarrhoeal duration or volume of ORS needed to maintain hydration.

Probiotics and prebiotics

Studies have shown that probiotics (specifically, *Lactobacillus rhamnosus* GG, *Lactobacillus bulgaricus* and *Streptococcus thermophilus)* decrease diarrhoea frequency and duration in relatively well-nourished children (*33,34*), but the evidence is mixed regarding malnourished children. One RCT in Malawi examined the efficacy of Synbiotic2000 Forte (10^{11} colony-forming units of lactic acid bacteria) added to RUTF for the inpatient treatment of SAM (*35*). No differences were found for the primary outcome of nutritional cure (W/H >80% of National Center for Health Statistics [NCHS] on two consecutive outpatient visits) or for secondary outcomes of weight gain, time to cure and morbidity symptoms between the control and interventions groups. There was a significant reduction in severe diarrhoea among inpatients (p=0.01) and a trend among outpatients (p=0.07). A trend towards decreased mortality at outpatient follow-up was observed (p=0.06) (*35*).

In India, one study of children with acute diarrhoea, 56–64% of whom had protein energy malnutrition, tested the efficacy of *Lactobacillus rhamnosus* GG added to ORS in different dosages (10^{10} colony-forming units and 10^{12} colony-forming units) with standard ORS. The frequency and duration of diarrhoea duration, requirement for intravenous therapy and hospital stay were significantly lower in both *Lactobacillus rhamnosus* GG groups compared to the standard ORS group (*36*). No subgroup analyses were conducted for malnourished children. No significant differences in diarrhoea outcomes were found in another study from India comparing a milk to yogurt regimen among malnourished boys with diarrhoea (*37*). The children in the milk group showed greater weight gain at both 72 hours (p=0.04) and recovery (p=0.02) compared to those in the yogurt group.

Zinc supplementation

Zinc is recommended by WHO and UNICEF as adjuvant therapy with ORS in the treatment of diarrhoea (*38*). For inpatient care of children with SAM, zinc supplements are recommended to be given daily for at least two weeks (2 mg/kg/day) (*17*). There is, however, limited evidence on the efficacy of zinc or other micronutrient supplementation for treatment of diarrhoea in SAM. Two RCTs from India examined daily zinc supplementation in children with diarrhoea, not all of whom were severely malnourished (*39,40*). In one study, children who were supplemented over four months with zinc gluconate showed significantly reduced odds of diarrhoeal incidence, prolonged and persistent diarrhoeal episodes and recurrent diarrhoeal episodes (*39*). In a subgroup analysis, however, no effect on incidence of "all diarrhoea" and "episodes >7 days" was shown for children with WHZ <-2, possibly due to the small sample size of this subset.

In the other RCT from India with a strong study design, zinc added to micronutrient supplementation and ORS treatment showed a protective effect in both well-nourished and malnourished children with diarrhoea (*40*). The risk of continued diarrhoea was reduced by 23% (95% CI 12–32%) among children supplemented with 20 mg of elemental zinc. If zinc supplementation was initiated within three days of the onset of diarrhoea, then the risk of prolonged diarrhoea lasting longer than seven days was reduced by 39% (95% CI 7-61%). The effect size for duration and severity of diarrhoea was increased for stunted children.

A study in Bangladesh more directly investigated the efficacy of zinc on diarrhoea in malnourished children (*41*). Findings from this study were not significant for diarrhoea duration or stool output, but greater weight gain was observed in zinc-supplemented children (p<0.03) and again a beneficial effect

for stunted children. Stool output was significantly lower among zinc supplemented stunted children compared to placebo ($p<0.04$) and trended towards reduced duration of diarrhoea. In a similarly designed trial in Bangladesh that examined persistent diarrhoea more specifically, zinc supplementation reduced duration of illness among underweight children (*42*). An RCT in Turkey found that zinc supplementation reduced the prevalence of prolonged and not persistent diarrhoea as well as stool frequency by day 4 among malnourished children with diarrhoea (*43*). No differences by zinc supplementation in diarrhoeal morbidities or anthropometry were observed in an RCT of hospitalized, malnourished children in Pakistan (*44*)

Discussion on clinical management

Direct evidence for the implementation of specific interventions in children with SAM receiving outpatient therapeutic feeding with diarrhoea is non-existent. Therefore, this report has no specific recommendations based on evidence generated from clinical trials.

It is generally safe and absolutely necessary for children with SAM on a diet of RUTF to consume free water, water without electrolytes or solute, and they should be allowed to do so ad libitum. It is never indicated to force children to drink free water.

In the absence of direct evidence, a careful clinician needs to draw on experience from other groups of children and what is known concerning the pathophysiology of SAM. Interventions for children with diarrhoea often involve the administration of sugar and electrolyte containing fluids, orally and parenterally, to prevent or treat dehydration, and these fluids are generally safe in well-nourished children. Therefore, the liberal use of such fluids in well-nourished children with diarrhoea is often advocated. However, liberal use of fluids in children with SAM carries risks because electrolyte containing fluids given by any route can disrupt the fragile homeostasis of the child with SAM, and lead to clinical deterioration and even death. So, the decision to administer such fluids to children with SAM should be made only when objective evidence of dehydration is present.

Most diarrhoea is not associated with dehydration in malnourished children. The diet and, therefore, the stools of malnourished children receiving treatment is changing, and caretakers might report this as diarrhoea. The clinical history is the most important feature of the assessment of the child with SAM and diarrhoea. Dehydrated children with SAM should have a definite history of watery stools of increased number with an abrupt onset. The caretaker should note some change in behaviour or appearance, such as the child is breathing more rapidly, is weaker or sleeping more. When such a history is given, a diagnosis of dehydration in SAM can be made and under the care of a health worker, rehydration fluid should be given. Rehydration is best achieved orally. The low osmolality rehydration solution ReSoMal should be given in a dose of 10 ml/kg/hour, with reassessment of vital signs and weight every two hours. The WHO manual provides more management guidelines for the recognition and treatment of dehydration (*17*).

If dehydration is not present, diarrhoea does not require any change in management of the child with SAM. The caregiver should continue to offer the child as much RUTF as the child has appetite to consume, and the child should drink as much water as desired.

Summary

Children with SAM treated with RUTF as outpatients who develop diarrhoea are commonplace, up to 5% of caretakers report diarrhoea in such children. Yet, the treatment of SAM entirely as an outpatient is still relatively recent, the Joint United Nations agencies made this recommendation in 2007, so direct clinical evidence concerning the management of complications is lacking (*45*). Thus, the review has been expanded to include studies that included similar populations of children with SAM as those who are treated currently as outpatients.

This review applied the GRADE methodology to examine the evidence for effective diagnostic and treatment strategies for SAM and diarrhoea, some of which occurs in the outpatient setting. Of the 84 studies reviewed, 6 were rated as medium to high quality for examining effectiveness of diagnostic strategies, and 18 for therapeutic strategies.

Regarding approaches to the diagnosis of diarrhoea in SAM, observational studies examining a broad spectrum of diarrhoeal morbidities in association with SAM and mortality were first examined. Definitions of diarrhoea varied widely and should be more systematically applied in diagnostic protocols for SAM and diarrhoea. Furthermore, we conclude that *prolonged diarrhoea* (≥3 liquid or semi-liquid stools per day for 7–13 days) be more routinely assessed and treated based on evidence that it increases risk of *persistent* diarrhoea, leads to reductions in HAZ and WAZ, and is associated with cryptosporidium infection common in SAM *(8)*.

The second category of studies reviewed for diagnostic strategies were those identifying pathogens responsible for diarrhoea in children with SAM. This evidence may point to appropriate therapeutic responses such as the routine use of empiric antimicrobials in the absence of laboratory-confirmed diagnoses. A recurring etiologic agent in association with diarrhoea and SAM across several studies reviewed was cryptosporidium. *Giardia lamblia, Entamoeba histolytica, Strongyloides sterocoralis* and *Escherichia coli* were also common pathogens *(9,10)*. In a Nepali study examining persistent diarrhoea etiologies, protozoal infections (35.5%) were most prevalent, followed by helminths (24.9%), and bacterial (12.6%) infections *(12)*. *Cyclospora cayetanensis* and cryptosporidium were the most frequent etiologies of persistent diarrhoea in HIV-positive children with SAM *(12)*.

Five therapeutic strategies for children with SAM and diarrhoea were evaluated using the GRADE criteria: antiparasitics; ORS; modified feeding regimens; glutamine supplementation; and zinc supplementation. There was, in general, a paucity of evidence with regard to use of antiparasitics. Two studies, however, supported the use of nitazoxanide for treatment of cryptosporidium infection *(15,16)*. This treatment improved resolution of diarrhoea and eradication of the pathogen from the stool, but only for HIV-uninfected children. The review identified no studies directly examining use of different formulations of ORS in home-based therapy for SAM and diarrhoea. There was some evidence that *ReSoMal* can correct for hypokalaemia (depleted potassium), but not hyponatraemia (excess body sodium) *(18)*. An older trial from Bangladesh suggested that ORS and more immediate refeeding could be successful in achieving rehydration and reducing hypoglycaemia in children with SAM and diarrhoea *(19)*.

Very little evidence of medium or high GRADE quality was available regarding modified feeding strategies for SAM and diarrhoea. The trials discussed in this report suggested positive effects for modified feeding strategies on anthropometry, but not diarrhoea necessarily. In Malawi, two trials examined use of RUTF in home-based care of children with SAM. The prevalence of diarrhoea, while relatively low in the sample population, was studied in relation to RUTF treatment compared to other feeding regimens. Recovery from SAM and rates of weight gain were higher and diarrhoea morbidity lower in the RUTF group compared to standard treatment in one study *(20)*. In the other, longitudinal prevalence of diarrhoea (total days with diarrhoea/total days observed) was not reduced in the RUTF groups *(21)*. The multifactoral Kingston Project also showed benefits for weight and height gains associated with taking a milk-based gruel supplement and an antibiotic (metronidazole), but no advantage in terms of diarrhoea *(23)*.

There is only limited evidence to suggest that hydrolyzing lactose in milk-based feeding regimens is beneficial for children with persistent diarrhoea *(24)*. Similarly, glutamine supplementation in malnourished children with diarrhoea has been inadequately tested. More studies to assess the impact of these interventions would be needed in this select population of children with SAM and diarrhoea.

A high degree of heterogeneity was observed in the literature regarding probiotics and prebiotics. Studies in well-nourished children demonstrated positive impacts of probiotics on diarrhoea. Among malnourished children, the findings were mixed. One high-quality study in Malawi added probiotics to RUTF and did not show nutritional cure nor diarrhoea morbidity improvements, with the exception of severe diarrhoea among inpatients *(35)*. However, probiotics added to ORS in India did reduce the frequency and duration of diarrhoea *(36)*. The medium in which probiotics are delivered may be relevant, but more research is needed.

Finally, the literature on micronutrient supplementation was reviewed with particular focus on zinc supplementation in children with SAM and diarrhoea. Only two studies from India were identified with any insight into this question, both of which included well-nourished and malnourished children in their sample *(39,40)* and the use of zinc within the current WHO recommendations was supported.

Further research

- The GRADE criterion of "indirectness" was common across most studies reviewed. Population samples included both well-nourished and malnourished children, with only inadequate subgroup analyses to draw upon. Furthermore, study site or setting was generally hospital based rather than community or home based. More research is needed with study designs explicitly crafted to compare community-based treatment protocols among severely malnourished children with diarrhoea.

- Research is needed to identify antimicrobial treatment of cryp*tosporidium* in HIV-infected children with SAM and diarrhoea. And among children without HIV but with SAM, efficacy trials are needed to identify antimicrobials to treat diarrhoea with *Giardia lamblia, Entamoeba histolytica, Strongyloides sterocoralis, Escherichia coli* and other pathogens.

- In view of the growing use of CMAM, multifactorial trials are needed to examine this feeding regimen for children with SAM and diarrhoea with poor outcomes (dehydration, prolonged diarrhoea or chronic diarrhoea) in combination with other interventions: ReSoMal; intensive breastfeeding support; zinc supplementation; probiotics; and glutamine. Different formulations of RUTF could be introduced, such as one that contains hydrolyzed milk powder.

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