The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review

J Picot,[1] D Hartwell,[1] P Harris,[1] D Mendes,[1] AJ Clegg[1]* and A Takeda[1,2]

[1]Southampton Health Technology Assessments Centre, University of Southampton, Southampton, UK
[2]Centre for Primary Care and Public Health, Barts and the London School of Medicine and Dentistry, London, UK

*Corresponding author

Executive summary

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Executive summary

Background

Undernutrition (referred to here as malnutrition) makes a major contribution to the global disease burden, accounting for more than one-third of child deaths worldwide. Acute malnutrition arises as a consequence of a sudden/sharp period of food shortage and is associated with loss of body fat and wasting of skeletal muscle. Malnutrition can be classified as mild, moderate or severe based on anthropometry (measurement of the size, weight and proportions of the human body), biochemistry and clinical assessment. The focus of this report is on severe acute malnutrition (SAM). A defining feature of SAM is severe wasting. In developing countries, some 19 million children < 5 years old are severely wasted. In 2004, approximately 310,000 deaths among these children in Africa, Asia and Latin America were attributed to severe wasting. Forms of SAM include kwashiorkor, marasmus and marasmic kwashiorkor.

Standard and accepted methods for defining and/or classifying SAM in children < 5 years of age have been established by organisations such as the World Health Organization (WHO) and the United Nations, although a variety of definitions exist, differing in the specific criteria and thresholds used. In addition, differences in treatment practices have been found to be a key factor in the large variation in mortality rates of severely malnourished children during treatment. To try and improve identification and treatment of SAM, WHO introduced guidance in 1999 that provided a 10-step ordered approach through three treatment phases. In the first phase of initial treatment, the focus is on stabilising the child's condition. The second phase of rehabilitation involves increasing the energy content and volume of the feeds to recover lost weight. The third phase begins after discharge and focuses on following up the child and his or her family at home, and providing support in order to prevent relapse and ensure the continued development of the child. However, implementation of this guidance in the 20 countries that are home to 80% of the world's undernourished children is variable. As a result of this, and many other factors, mortality from SAM remains unacceptably high.

Objectives

The objective of this report was to systematically review the evidence assessing interventions, programmes and/or guidelines to treat infants and children aged < 5 years of age who have SAM. The effects that factors such as the setting (e.g. hospital, community, emergency) or different comorbidities [e.g. human immunodeficiency virus (HIV) infection] have on their effectiveness have also been examined.

Methods

Data sources

A sensitive search strategy was designed and applied to eight electronic bibliographic databases, including MEDLINE (1950 onwards), EMBASE (1980 onwards) and The Cochrane Library (from inception to November/December 2010). Bibliographies of included articles and grey literature sources were searched, and the project expert advisory group was contacted to identify additional published and unpublished references.

Study selection

Titles and abstracts were screened independently by two reviewers. Inclusion criteria were defined a priori and applied to the full text of retrieved papers by one reviewer and checked independently by a second. The inclusion criteria were as follows.

- Study design: randomised controlled trials (RCTs), controlled clinical trials (CCTs), cohort studies (with control group) and case–control studies were eligible for inclusion. Evidence from studies with the most rigorous designs was prioritised based on the hierarchy evidence. Studies without a comparator group or those with a comparator group that did not have SAM (e.g. healthy individuals) were excluded.
- Interventions: any intervention for treating SAM (either an entire treatment plan or any individual treatment step).
- Comparators: any alternative treatment strategy (including no intervention and placebo).
- Population: infants and children < 5 years of age with SAM. The set of criteria for the definition/classification of SAM were agreed following consultation with the expert advisory group and included WHO's and the United Nations Children's Fund's reference standards, the Wellcome working party's, Gómez and colleagues' and the Indian Academy of Paediatrics' classifications, mid-upper arm circumference < 115 mm, clinical oedema and diagnoses of marasmus, kwashiorkor or marasmic kwashiorkor.
- Outcomes: studies were included providing they reported on measures of mortality or weight change.

Delphi process and map of the evidence base

A Delphi process was used in order to gain an understanding of the priority order of the research questions relating to the WHO 10-step plan. A 'map' of the evidence base was created, as each study was mapped to the prioritised research question(s) it primarily addressed by one reviewer. The decision was checked by a second reviewer. After the available evidence had been mapped, the final decision on how many questions would be addressed by the systematic review was taken, based on the extent of the evidence and the resources available for the research.

Data extraction and assessment of validity

Data were extracted and study quality was assessed by one reviewer and checked by a second. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Included studies that mapped to questions that could not be assessed in the systematic review, and studies that did not map to any question were not data extracted or quality assessed.

Data synthesis

Studies were synthesised through a narrative review with tabulation of results of included studies.

Results

Quantity and quality of studies

A total of 8954 records were identified. Seventy-four references describing 68 studies met the general review inclusion criteria. The available evidence mapped against 9 of the 15 questions prioritised in the Delphi process. For one other question, very limited evidence was available in two studies. No evidence was found to inform the remaining five questions. Project resources were available to review the evidence for the first six questions for which any evidence was available. Only the best available evidence was reviewed and, for all but one question, this meant that only RCTs and CCTs were included.

Summary of benefits and risks

What methods are effective for treating severe acute malnutrition among infants <6 months old?

No research focused on treating SAM in infants <6 months old. Two cohort studies included this age group within their study populations. However, baseline data were not reported separately for this subgroup and only a very limited quantity of separate outcome information was provided. No formal quality assessment was undertaken.

Which form of intravenous fluid administration is most effective for treating shock?

One RCT of moderate methodological quality compared the efficacy of three fluid resuscitation solutions for treating hypovolaemic shock in children with SAM. The principal comparison was between Ringer's lactate isotonic fluid (RL) and the WHO hypotonic fluid solution [half-strength Darrow's in 5% dextrose (HSD/5D)] because few participants received 4.5% human albumin solution (HAS). Hypotonic HSD/5D was given according to the WHO recommendation, whereas similar volumes and rates of the isotonic RL and HAS solutions were administered to a different schedule. Other aspects of management in all groups followed WHO guidelines. The study found that neither the standard WHO hypotonic HSD/5D nor the RL isotonic resuscitation fluids were effective in reducing mortality or adequately treating shock after 48 hours of treatment. However, it should be noted that the study was prematurely terminated because of high overall mortality and inadequate correction of shock in all study arms.

What are the best treatments for children with severe acute malnutrition who have diarrhoea?

Five RCTs of strong or moderate methodological quality focused on children with acute diarrhoea and three RCTs of strong or weak methodological quality focused on children with persistent diarrhoea.

Acute diarrhoea

Four of the five RCTs compared oral rehydration solutions (ORSs). The fifth RCT investigated standard WHO-ORS alongside a zinc-containing syrup compared with WHO-ORS and placebo. Children with acute diarrhoea benefited from the use of hypo-osmolar oral rehydration solution compared with the standard WHO-ORS on measures of frequency, duration and recovery from diarrhoea and consumption of ORS. In contrast, weight gain was significantly higher in those receiving WHO-ORS (one study). WHO-ORS was not significantly different from rehydration solution for malnutrition (ReSoMaL) for mortality or adequacy of hydration, although ReSoMal may pose safety concerns. A rice-based ORS was more beneficial at 72 hours in promoting weight gain and reducing diarrhoeal output than glucose-based ORSs, whereas the provision of zinc and a WHO-ORS had a favourable impact on diarrhoeal outcomes and reduced the need for ORS.

Persistent diarrhoea

These studies compared different diets and had conflicting findings. Although a comparison in one study of an elemental diet with a skimmed milk and soy-based diet showed significant benefits on anthropometric measures for the elemental diet, two other studies either showed no difference between an elemental diet, soy-based diet and a chicken-based diet on mortality, weight gain, frequency of diarrhoea and recovery, or showed a significant benefit on anthropometric measures and ORS consumption from a soy-based diet compared with a khitchri and yoghurt-based diet.

What methods are effective in treating infection?

Two studies of moderate methodological quality (one RCT and one retrospective cohort analysis) investigated the use of antibiotic therapy in children with SAM, but neither focused on treating diagnosed infection. The retrospective observational evidence indicates that the systematic addition of a broad-spectrum antibiotic to home-based treatment with ready-to-use therapeutic food has a statistically significant detrimental effect on the initial recovery (4 weeks) of children with SAM, although later (12 weeks) the proportion recovered was similar and no effect was shown on mortality. The RCT comparing administration of intramuscular ceftriaxone with orally administered amoxicillin showed no difference in effects on outcomes, apart from ceftriaxone being associated with fewer adverse events.

What is the clinical effectiveness of interventions in different settings (e.g. hospital, community, emergency)?

Four included studies, of moderate or weak methodological quality, investigated the clinical effectiveness of SAM treatment in different settings. There were numerous differences between these trials and, although the inpatient hospital setting was included in all trials, the type of inpatient care provided varied. It appears that children receiving inpatient care do as well as, if not better than, those receiving care in the ambulatory or home setting on anthropometric measures and response time to treatment. Longer-term follow-up showed limited differences between the different settings.

Which methods for correcting micronutrient deficiencies are effective?

Thirteen studies evaluated the effect of supplements to correct micronutrient deficiencies. Of these, 10 RCTs focused on the provision of zinc supplements, whereas the remaining three investigated potassium, nicotinic acid or nucleotides (NTs). Although the methodological quality of studies varied, > 80% were either moderate ($n = 3$) or weak ($n = 8$).

Zinc

The provision of zinc varied in a number of aspects (e.g. when supplementation began, dose or duration of supplementation). In seven trials, the comparator was no zinc/placebo, whereas three compared different doses/duration of zinc. Although studies assessing the effects of supplementary zinc were heterogeneous, those considered of a higher methodological quality showed no significant benefit from the addition of zinc supplementation. If there is a benefit to be obtained from zinc supplementation, the included evidence is insufficient to determine which dose of zinc might represent the optimal balance between maximising benefits and minimising any harms.

Other supplements

Evidence on other micronutrients was limited, with significant benefits from the addition of potassium (i.e. reducing late deaths, sepsis, skin ulcers) and nicotinic acid (i.e. weight gain), but no benefit from the addition of NTs.

Conclusions

Evidence for the first six prioritised questions for which any evidence was available was often lacking or not always conclusive. In addition, the diversity of the interventions made

comparisons between studies difficult. No good-quality evidence or adequately reported studies assessed treatments for SAM in infants < 6 months old and neither of the studies evaluating antibiotic therapy focused on treating diagnosed infection. Neither of the resuscitation fluids was effective in treating children with hypovolaemic shock, and no clear benefit was evident from the addition of zinc supplementation in correcting micronutrient deficiencies. Inpatient care was found to be beneficial, or at least comparable, to the ambulatory or home setting for treating children with SAM, whereas trials of children with both acute and persistent diarrhoea found conflicting results.

Recommendations for further research

- Treatments for SAM in infants < 6 months old was one of the highest ranked questions in the Delphi study and, therefore, more research is needed to fill this gap in the evidence base.
- The high priority given to the question of intravenous (i.v.) fluid administration for treating shock, coupled with the potential to significantly improve survival, indicates that further prospective RCTs of alternative i.v. resuscitation regimens for shock are needed. Any RCT should be informed by an initial pilot study and should include measures of cardiac dysfunction and haemodynamic response to fluid expansion.
- More research in treating diagnosed infections in children with SAM is needed because this topic was also ranked highly, and yet little research was found that met the inclusion criteria of the review.
- Additional research could be conducted on many other aspects of the management of SAM in children < 5 years of age, including areas which were also prioritised in the Delphi study but for which little or no research was identified, e.g. use of multivitamin supplements, optimum dose of vitamin A, management strategies for children with HIV infection, tuberculosis or other comorbidities.
- Future trials should include children identified using the current WHO criteria and ideally should involve more than one centre to generate results with better generalisability to other locations and to aid comparison between different trials.

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