GUIDELINE

UPDATES ON THE MANAGEMENT OF SEVERE ACUTE MALNUTRITION IN INFANTS AND CHILDREN

World Health Organization

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Contents

Acknowledgements

Abbreviations

CI	confidence interval
eLENA	electronic Library of Evidence for Nutrition Actions
FEAST	Fluid Expansion as Supportive Therapy (trial)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	haemoglobin
IM	intramuscular
IMCI	Integrated Management of Childhood Illness
IV	intravenous
MDG	Millennium Development Goal
NCHS	National Center for Health Statistics, Centers for Disease Control and Prevention
PICO	patient/population, intervention, control, outcomes
SD	standard deviation
TB	tuberculosis
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Executive summary

Purpose of the guideline[1]

Severe acute malnutrition affects nearly 20 million preschool-age children, mostly from the World Health Organization (WHO) African Region and South-East Asia Region. Malnutrition is a significant factor in approximately one third of the nearly 8 million deaths in children who are under 5 years of age worldwide *(1)*. WHO established guidelines for the treatment of severe acute malnutrition in 1999 and Member States have requested WHO to update their 1999 document *Management of severe malnutrition: a manual for physicians and other senior health workers (2)*. This guideline presents the updated evidence and practice for key interventions and will also serve to inform revisions of the manual. This guideline does not reflect all WHO recommendations related to the management of children with severe acute malnutrition but only those related to areas that were prioritized by the guideline development group: the WHO Nutrition Guidance Advisory Group – Subgroup on Nutrition in the Life Course and Undernutrition 2010–2012. This group reviewed the previously published guidelines and indicated the areas of care and specific recommendations that should be revised first in the process of updating all WHO recommendations. Relevant standing recommendations are included adjacent to updated recommendations, to contextualize updated recommendations. Other WHO recommendations will be addressed in future guideline updates.

Guideline development methodology

WHO has developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development (3)*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment of the quality of evidence and synthesis of the findings; (iv) formulation of recommendations, including future research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews. The WHO Nutrition Guidance Advisory Group – Subgroup on Nutrition in the Life Course and Undernutrition 2010–2012, comprised content experts, methodologists, representatives of potential stakeholders and consumers. These experts, together with external resource people, participated in three WHO technical consultations, held in Geneva,

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[1] This publication is a WHO guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. A full guideline is one that provides complete coverage of a health topic or disease. It is expected to include recommendations in relation to all aspects of the topic (e.g. surveillance, diagnosis, public health and clinical interventions) and to be fully based on systematic reviews of the evidence for each aspect. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Switzerland, on 2–4 June 2010, 14–16 March 2011 and 1–3 February 2012, to scope questions for the systematic reviews, review and discuss the evidence, draft the recommendations, and vote on their strength, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; and (iii) values and preferences related to the intervention in different settings. The cost of options available to health-care workers in different settings was not formally assessed, owing to lack of primary data in the literature or elsewhere. However, cost implications were considered as part of general discussion by the guideline development group, namely the Nutrition Guidance Advisory Group members and the external resource people. Members of the external experts' and stakeholders' panel were identified through a public call for comments and peer reviewed the guideline. Everyone involved in the development of this guideline submitted declarations of interests. All guideline development group members submitted them before each meeting and also made verbal declarations of interest at the beginning of meetings.

Available evidence

The evidence, available for the development of recommendations, was in general of very low quality, as defined in the *WHO handbook for guideline development (3)*. This was due to the limited availability of randomized controlled trials, trials comparing existing WHO recommendations with new treatment options, or trials documenting comparisons of diagnosis and treatment methods identified by the guideline development group as requiring review. Where direct evidence was not available, indirect evidence from different population groups, or different intervention strategies has been noted, if appropriate. The need for future research directly addressing several of the areas of concern was highlighted. Owing to the scarcity of data on the cost of proposed recommendations, it is not possible to directly estimate the financial implications of implementation of these recommendations.

Recommendations

1. **Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition**

   Criteria for identifying children with severe acute malnutrition for treatment

   1.1   In order to achieve early identification of children with severe acute malnutrition in the community, trained community health workers and community members should measure the mid-upper arm circumference of infants and children who are 6–59 months of age and examine them for bilateral pitting oedema. Infants and children who are 6–59 months of age and have a mid-upper arm circumference <115 mm, or have any degree of bilateral oedema, should be immediately referred for full assessment at a treatment centre for the management of severe acute malnutrition (***strong recommendation, low quality evidence***).

   1.2   In primary health-care facilities and hospitals, health-care workers should assess the mid-upper arm circumference or the weight-for-height/weight-for-length status of infants and children who are 6–59 months of age and also examine them for bilateral oedema. Infants and children who are 6–59 months of age and have a mid-upper arm circumference <115 mm or a weight-for-height/length <–3 Z-score[1] of the WHO growth standards *(4)*, or have bilateral oedema, should be immediately admitted to a programme for the management of severe acute malnutrition (***strong recommendation, low quality evidence***).

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   [1]   A Z-score equates to one standard deviation.

Criteria for inpatient or outpatient care[1]

1.3 Children who are identified as having severe acute malnutrition should first be assessed with a full clinical examination to confirm whether they have medical complications and whether they have an appetite. Children who have appetite (pass the appetite test) and are clinically well and alert should be treated as outpatients. Children who have medical complications, severe oedema (+++), or poor appetite (fail the appetite test), or present with one or more Integrated Management of Childhood Illness (IMCI) danger signs[2] should be treated as inpatients (***strong recommendation, low quality evidence***).

Criteria for transferring children from inpatient to outpatient care[3]

1.4 Children with severe acute malnutrition who are admitted to hospital can be transferred to outpatient care when their medical complications, including oedema, are resolving and they have a good appetite, and are clinically well and alert. The decision to transfer children from inpatient to outpatient care should be determined by their clinical condition and not on the basis of specific anthropometric outcomes such as a specific mid-upper arm circumference or weight-for-height/length (***strong recommendation, low quality evidence***).

Criteria for discharging children from treatment

1.5. a. Children with severe acute malnutrition should only be discharged from treatment when their:

— weight-for-height/length is ≥–2 Z-score and they have had no oedema for at least 2 weeks, or

— mid-upper-arm circumference is ≥125 mm and they have had no oedema for at least 2 weeks.

b. The anthropometric indicator that is used to confirm severe acute malnutrition should also be used to assess whether a child has reached nutritional recovery, i.e. if mid-upper arm circumference is used to identify that a child has severe acute malnutrition, then mid-upper arm circumference should be used to assess and confirm nutritional recovery. Similarly, if weight-for-height is used to identify that a child has severe acute malnutrition, then weight-for-height should be used to assess and confirm nutritional recovery.

c. Children admitted with only bilateral pitting oedema should be discharged from treatment based on whichever anthropometric indicator, mid-upper arm circumference or weight-for-height is routinely used in programmes.

d. Percentage weight gain should not be used as a discharge criterion

(***strong recommendation, low quality evidence***).

Follow-up of infants and children after discharge from treatment for severe acute malnutrition

1.6. Children with severe acute malnutrition who are discharged from treatment programmes should be periodically monitored to avoid a relapse (***strong recommendation, low quality evidence***).

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[1] Necessary resources and services need to be in place if children are referred to outpatient care.
[2] Danger signs: unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now.
[3] Necessary resources and services need to be in place if children are referred to outpatient care.

2. Where to manage children with severe acute malnutrition who have oedema

2.1 Children with severe acute malnutrition who have severe bilateral oedema (+++),[1] even if they present with no medical complications and have appetite, should be admitted for inpatient care (***strong recommendation, very low quality evidence***).

3. Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

3.1 Children with uncomplicated severe acute malnutrition, not requiring to be admitted and who are managed as outpatients, should be given a course of oral antibiotic such as amoxicillin (***conditional recommendation, low quality evidence***).

3.2 Children who are undernourished but who do *not* have severe acute malnutrition should *not* routinely receive antibiotics unless they show signs of clinical infection (***strong recommendation, low quality evidence***).

4. Vitamin A supplementation in the treatment of children with severe acute malnutrition

4.1 Children with severe acute malnutrition should receive the daily recommended nutrient intake of vitamin A throughout the treatment period. Children with severe acute malnutrition should be provided with about 5000 IU vitamin A daily, either as an integral part of therapeutic foods or as part of a multi-micronutrient formulation (***strong recommendation, low quality evidence***).

4.2 Children with severe acute malnutrition do not require a high dose of vitamin A as a supplement if they are receiving F-75, F-100[2] or ready-to-use therapeutic food that complies with WHO specifications (and therefore already contains sufficient vitamin A), or vitamin A is part of other daily supplements (***strong recommendation, low quality evidence***).

4.3. Children with severe acute malnutrition should be given a high dose of vitamin A (50 000 IU, 100 000 IU or 200 000 IU, depending on age) on admission, only if they are given therapeutic foods that are not fortified as recommended in WHO specifications and vitamin A is not part of other daily supplements (***strong recommendation, low quality evidence***).

5. Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

5.1 Children with severe acute malnutrition who present with either acute or persistent diarrhoea, can be given ready-to-use therapeutic food in the same way as children without diarrhoea, whether they are being managed as inpatients or outpatients (***strong recommendation, very low quality evidence***).

5.2 *In inpatient settings, where ready-to-use therapeutic food is provided as the therapeutic food in the rehabilitation phase (following F-75 in the stabilization phase)*

Once children are stabilized, have appetite and reduced oedema and are therefore ready to move into the rehabilitation phase, they should transition from F-75 to ready-to-use therapeutic food over 2–3 days, as tolerated. The recommended energy intake during this

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[1] + Mild: both feet; ++ moderate: both feet, plus lower legs, hands, or lower arms; +++ severe: generalized oedema including both feet, legs, hands, arms and face. Source: Module 2. Principles of care. In: *WHO training course on the management of severe malnutrition*. Geneva: World Health Organization; 2002 (updated 2009).

[2] F-75 and F-100 are formula diets used for the management of children with severe acute malnutrition in inpatient care. F-75 (75 kcal or 315 kJ/100 mL) is used during the initial phase of treatment, while F-100 (100 kcal or 420kJ/100 mL) is used during the rehabilitation phase.

period is 100–135 kcal/kg/day. The optimal approach for achieving this is not known and may depend on the number and skills of staff available to supervise feeding and monitor the children during rehabilitation (***strong recommendation, very low quality evidence***). Two options for transitioning children from F-75 to ready-to use therapeutic food are suggested:

a. start feeding by giving ready-to-use therapeutic food as prescribed for the transition phase. Let the child drink water freely. If the child does not take the prescribed amount of ready-to-use therapeutic food, then top up the feed with F-75. Increase the amount of ready-to-use therapeutic food over 2–3 days until the child takes the full requirement of ready-to-use therapeutic food, or

b. give the child the prescribed amount of ready-to-use therapeutic food for the transition phase. Let the child drink water freely. If the child does not take at least half the prescribed amount of ready-to-use therapeutic food in the first 12 h, then stop giving the ready-to-use therapeutic food and give F-75 again. Retry the same approach after another 1–2 days until the child takes the appropriate amount of ready-to-use therapeutic food to meet energy needs.

5.3 *In inpatient settings where F-100 is provided as the therapeutic food in the rehabilitation phase*

Children who have been admitted with complicated severe acute malnutrition and are achieving rapid weight gain on F-100 should be changed to ready-to-use therapeutic food and observed to ensure that they accept the diet before being transferred to an outpatient programme (***strong recommendation, very low quality evidence***).

6. Fluid management of children with severe acute malnutrition

6.1 Children with severe acute malnutrition who present with some dehydration or severe dehydration *but who are not shocked* should be rehydrated slowly, either orally or by naso-gastric tube, using oral rehydration solution for malnourished children (5–10 mL/kg/h up to a maximum of 12 h) (***strong recommendation, low quality evidence***).

6.2 Full-strength, standard WHO low-osmolarity oral rehydration solution (75 mmol/L of sodium) should not be used for oral or nasogastric rehydration in children with severe acute malnutrition who present with some dehydration or severe dehydration. Give either ReSoMal or half-strength standard WHO low-osmolarity oral rehydration solution with added potassium and glucose, unless the child has cholera or profuse watery diarrhoea (***strong recommendation, low quality evidence***).

Dissolve one sachet of standard WHO low-osmolarity oral rehydration solution in 2 L water (instead of 1 L). Add 1 level scoop of commercially available combined minerals and vitamins mix[1] or 40 ml of mineral mix solution (5), and add and dissolve 50 g of sugar. In some countries, sachets are available that are designed to make 500 mL of standard WHO low-osmolarity oral rehydration solution. In this situation, dilution can be revised to add 1 L.

6.3 ReSoMal[2] (or locally prepared ReSoMal using standard WHO low-osmolarity oral rehydration solution) should not be given if children are suspected of having cholera

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1   A specific electrolyte–micronutrient product formulated according to WHO specifications for use in the management of children with severe acute malnutrition.

2   ReSoMal (short for rehydration solution for severely malnourished children) is the generic name for a powder for the preparation of an oral rehydration solution exclusively for oral or nasogastric rehydration of people suffering from severe acute malnutrition. It must be used exclusively under medical supervision in inpatient care, and must not be given for free use to the mother or caregiver.

or have profuse watery diarrhoea.[1] Such children should be given standard WHO low-osmolarity oral rehydration solution that is normally made, i.e. not further diluted (***strong recommendation, low quality evidence***).

6.4 Children with severe acute malnutrition and signs of shock or severe dehydration and who cannot be rehydrated orally or by nasogastric tube should be treated with intravenous fluids, either:

   a. half-strength Darrow's solution with 5% dextrose, or

   b. Ringer's lactate solution with 5% dextrose.

   If neither is available, 0.45% saline + 5% dextrose should be used (***conditional recommen-dation, very low quality evidence***).

7. Management of HIV-infected children with severe acute malnutrition

7.1 Children with severe acute malnutrition who are HIV infected and who qualify for lifelong antiretroviral therapy should be started on antiretroviral drug treatment as soon as possible after stabilization of metabolic complications and sepsis. This would be indicated by return of appetite and resolution of severe oedema. HIV-infected children with severe acute malnutrition should be given the same antiretroviral drug treatment regimens, in the same doses, as children with HIV who do not have severe acute malnutrition. HIV-infected children with severe acute malnutrition who are started on antiretroviral drug treatment should be monitored closely (inpatient and outpatient) in the first 6–8 weeks following initiation of antiretroviral therapy, to identify early metabolic complications and opportunistic infections (***strong recommendation, very low quality evidence***).

7.2 Children with severe acute malnutrition who are HIV infected should be managed with the same therapeutic feeding approaches as children with severe acute malnutrition who are not HIV infected (***strong recommendation, very low quality evidence***).

7.3 HIV-infected children with severe acute malnutrition should receive a high dose of vitamin A on admission (50 000 IU to 200 000 IU depending on age) and zinc for management of diarrhoea, as indicated for other children with severe acute malnutrition, unless they are already receiving F-75, F-100 or ready-to-use therapeutic food, which contain adequate vitamin A and zinc if they are fortified following the WHO specifications (***strong recom-mendation, very low quality evidence***).

7.4 HIV-infected children with severe acute malnutrition in whom persistent diarrhoea does not resolve with standard management should be investigated to exclude carbohydrate intolerance and infective causes, which may require different management, such as modification of fluid and feed intake, or antibiotics (***strong recommendation, very low quality evidence***).

8. Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

8.1 Infants who are less than 6 months of age with severe acute malnutrition and any of the following complicating factors should be admitted for inpatient care:

   a. any serious clinical condition or medical complication as outlined for infants who are 6 months of age or older with severe acute malnutrition;

   b. recent weight loss or failure to gain weight;

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[1] Three or more loose or watery stools in a day, for more than 14 days.

c. ineffective feeding (attachment, positioning and suckling) directly observed for 15–20 min, ideally in a supervised separated area;

d. any pitting oedema;

e. any medical or social issue needing more detailed assessment or intensive support (e.g. disability, depression of the caregiver, or other adverse social circumstances)

(*strong recommendation, very low quality evidence*).

8.2 Infants who are less than 6 months of age with severe acute malnutrition should receive the same general medical care[1] as infants with severe acute malnutrition who are 6 months of age or older:

a. infants with severe acute malnutrition who are admitted for inpatient care should be given parenteral antibiotics to treat possible sepsis and appropriate treatment for other medical complications such as tuberculosis, HIV, surgical conditions or disability;

b. infants with severe acute malnutrition who are not admitted should receive a course of broad-spectrum oral antibiotic, such as amoxicillin, in an appropriately weight-adjusted dose

(*strong recommendation, very low quality evidence*).

8.3 Feeding approaches for infants who are less than 6 months of age with severe acute malnutrition should prioritize establishing, or re-establishing, effective exclusive breast-feeding by the mother or other caregiver (*strong recommendation, very low quality evidence*).

8.4 Infants who are less than 6 months of age with severe acute malnutrition and who are admitted:

a. should be breastfed where possible and the mothers or female caregivers should be supported to breastfeed the infants. If an infant is not breastfed, support should be given to the mother or female caregiver to re-lactate. If this is not possible, wet nursing[2] should be encouraged;

b. should also be provided a supplementary feed:

— supplementary suckling approaches should, where feasible, be prioritized;

— for infants with severe acute malnutrition but no oedema, expressed breast milk should be given, and, where this is not possible, commercial (generic) infant formula or F-75 or diluted F-100[3] may be given, either alone or as the supplementary feed together with breast milk;

— for infants with severe acute malnutrition and oedema, infant formula or F-75 should be given as a supplement to breast milk;

c. should not be given undiluted F-100 at any time (owing to the high renal solute load and risk of hypernatraemic dehydration);

d. if there is no realistic prospect of being breastfed, should be given appropriate and adequate replacement feeds such as commercial (generic) infant formula, with relevant support to enable safe preparation and use, including at home when discharged.

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[1] Recommendations regarding vitamin A, zinc and other micronutrients were not reviewed in this guideline process.
[2] All potential wet-nurses should be tested for HIV.
[3] Prepared F-100 should be further diluted by adding 30% water.

In addition:

e. assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided

(*strong recommendation, very low quality evidence*).

8.5. Infants who are less than 6 months of age and have been admitted to inpatient care can be transferred to outpatient care when:

a. all clinical conditions or medical complications, including oedema, are resolved, and

b. the infant has good appetite, is clinically well and alert, and

c. weight gain on either exclusive breastfeeding or replacement feeding is satisfactory, e.g. above the median of the WHO growth velocity standards or more than 5 g/kg/day for at least 3 successive days, and

d. the infant has been checked for immunizations and other routine interventions, and

e. the mother or caregiver is linked with needed community-based follow-up and support

(*strong recommendation, very low quality evidence*).

8.6 Infants who are less than 6 months of age can be discharged from all care when they are breastfeeding effectively or feeding well with replacement feeds, and

a. have adequate weight gain, and

b. have a weight-for-length ≥–2 Z-score

(*strong recommendation, very low quality evidence*).

8.7 For infants who are less than 6 months of age with severe acute malnutrition and who do not require inpatient care (Recommendation 8.1), or whose caregivers decline admission for assessment and treatment:

a. counselling and support for optimal infant and young child feeding should be provided, based on general recommendations for feeding infants and young children, including for low-birth-weight infants;

b. weight gain of the infant should be monitored weekly to observe changes;

c. if the infant does not gain weight, or loses weight while the mother or caregiver is receiving support for breastfeeding, then he or she should be referred to inpatient care;

d. assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided

(*strong recommendation, very low quality evidence*).

Research priorities

Guideline group members and stakeholders identified several research priorities to improve the body of evidence at the basic, clinical, epidemiological and operational levels on the management of severe acute malnutrition in infants and children. Major research gaps were identified in each of the sections covered. See **Annex 7** for a compiled list.

Scope and purpose

This guideline provides global, evidence-informed recommendations on a number of specific issues related to the management of severe acute malnutrition in infants and children. In conjunction with other World Health Organization (WHO) recommendations,[1] it provides evidence-informed guidance on the care of infants and children with severe malnutrition, including in the context of HIV.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions for severely malnourished children, and contribute to achieving the Millennium Development Goals (MDGs), particularly reduction in child mortality (MDG 4). It will also support Member States in their efforts to achieve global targets on the maternal, infant and young child nutrition comprehensive implementation plan, especially global target 1, which entails achieving 40% reduction by 2025 of the global number of children under 5 years who are stunted and global target 6, which aims to reduce and maintain childhood wasting to less than 5%. *(6)*. The guideline is intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff in organizations involved in the design, implementation and scaling-up of nutrition actions for public health. The guideline will form the basis for a revised manual on the management of severe malnutrition for physicians and other senior health workers), a training course on the management of severe malnutrition and other training materials.

This document presents the key recommendation and a summary of the supporting evidence.

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[1] This guideline does not reflect all WHO recommendations related to the management of children with severe acute malnutrition but only those related to areas of care that were prioritized by the guideline development group advising WHO for this guideline. Relevant standing recommendations are included adjacent to updated recommendations, to contextualize updated recommendations.

Background

It is estimated that 19 million preschool-age children, mostly from the WHO African Region and South-East Asia Region, are suffering from severe wasting *(7)*. Childhood undernutrition is a major global health problem, contributing to childhood morbidity, mortality, impaired intellectual development, suboptimal adult work capacity, and increased risk of diseases in adulthood *(7)*. Of the 7.6 million deaths annually among children who are under 5 years of age *(1)*, approximately 35% are due to nutrition-related factors and 4.4% of deaths have been shown to be specifically attributable to severe wasting *(7)*. Severe acute malnutrition remains a major cause of child mortality worldwide. While pneumonia and diarrhoea are often the final steps in the pathway, severe wasting is estimated to account for around 400 000 child deaths each year *(7)*. For this reason, the improved management of severe acute malnutrition is an integral part of the *World Health Resolution on Infant and Young Child Nutrition* (WHA 63.23), to improve child survival and to reduce the global burden of disease.

In 2006, WHO released new growth standards for children aged 0–5 years *(8)*. These represent the standards on which all WHO definitions and estimates of malnutrition, including moderate and severe acute malnutrition, and obesity are now based. In children who are 6–59 months of age, severe acute malnutrition is defined as weight-for-height less than –3 Z-score[1] of the median of the WHO growth standards, or clinical signs of bilateral oedema of nutritional origin, despite other measures being above specified cut-off values *(9)*. Since publication of the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers (2)*, a joint statement by the World Health Organization, World Food Programme, United Nations Standing Committee on Nutrition and United Nations Children's Fund (UNICEF) in 2007 *(10)* acknowledged the feasibility of community health workers or volunteers identifying children affected by severe acute malnutrition, using simple coloured plastic strips that are designed to measure mid-upper arm circumference. In children who are 6–59 months of age, a mid-upper arm circumference less than 115 mm also indicates severe acute malnutrition, allowing early identification of affected children within the community before the onset of complications.

Major challenges remain to implementation of effective use of growth monitoring in primary health-care settings, to identify the most at-risk infants and children who need medical and nutritional interventions to prevent serious morbidity and mortality. The importance of this is highlighted by the strong epidemiological evidence that low weight-for-height, weight-for-length or mid-upper arm circumference are highly associated with a 5–20-fold increased risk of mortality *(11)*. At the same time, it is necessary to examine the implications of very low anthropometry in different epidemiological settings, especially South East Asia, and to establish the equivalent anthropometric thresholds for older children and adolescents.

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[1] A Z-score (or standard deviation score) is the deviation of the value for an individual from the median value of the reference population, divided by the standard deviation for the reference population. We refer herein to the median of the WHO growth standards.

Malnutrition in children typically develops during the period from 6 to 18 months of age, when growth velocity and brain development are especially high. Young children are particularly susceptible to malnutrition if complementary foods are of low nutrient density and have low bioavailability of micronutrients. In addition, children's nutritional status will be further compromised if complementary foods are introduced too early or too late, or are contaminated.

The nutritional status of children can also be affected by chronic infections such as HIV. It is estimated that over 2 million children worldwide are living with HIV, 90% of them in sub-Saharan Africa *(12)*. In a report describing children admitted to hospital in southern Africa, the prevalence of HIV in children with severe acute malnutrition was 29% and these children were more likely to die than malnourished children who were not infected with HIV *(13)*. Higher HIV prevalence, i.e. up to 50%, has been reported among children with severe acute malnutrition *(14)*.

Children with severe acute malnutrition have profoundly disturbed physiology and metabolism, such that if intensive refeeding is initiated before metabolic and electrolyte imbalances have been corrected, mortality rates are high. For this reason, WHO developed clinical guidance *(2)* on the management of the child with severe acute malnutrition. This guidance was updated in part through subsequent WHO publications on the outpatient management *(10)* and inpatient treatment of children with severe acute malnutrition *(15, 16)*. Outpatient treatment of uncomplicated severe acute malnutrition is increasingly provided, using ready-to-use therapeutic foods *(10)*. These are high-energy, fortified, ready-to-eat foods that have a nutrient content/100 kcal similar to that of F-100, the therapeutic diet used to treat children with severe acute malnutrition in hospital settings. Unlike F-100, however, ready-to-use therapeutic foods are not water based, meaning that bacteria are less likely to grow in them. These foods can therefore be used safely at home or in hospital without refrigeration and even in areas where hygiene conditions are not optimal. Ready-to-use therapeutic food can be consumed easily by children from the age of 6 months and have been shown to be effective in treating children with severe acute malnutrition in communities or in hospital after the stabilization phase. The technology to produce ready-to-use therapeutic food is simple and can be transferred to any country with minimal industrial infrastructure, while still complying with the *Recommended international code of hygienic practice for foods for infants and children* of the Codex Alimentarius Standard CAC/RCP 21-1979 *(17)*.

These significant advances have not been matched by research and development in other key areas of clinical management of children with severe acute malnutrition. Furthermore, the HIV epidemic has produced a number of new research questions related to the basic science and clinical management of undernutrition in children infected with HIV. While some of the basic principles and lessons for managing children without HIV can be extended to HIV-infected children, there is little empirical evidence to guide management of this specific population.

Increasingly, severe acute malnutrition is being documented among infants who are less than 6 months of age. However, there are few data describing to what extent the pathophysiology in this population is the same as that in older children and how to approach therapeutic feeding, including the support and/or supplementation of breastfeeding. The lack of epidemiological and intervention data in young infants is common also for children who are older than 5 years. WHO has commissioned systematic reviews and convened a guideline development group to formulate guidelines for this important age group.

Lastly, the epidemiological and clinical implications of the WHO child growth standards and the populations that will be defined as having severe acute malnutrition need to be examined. While increased mortality has been reported among children with severe acute malnutrition in several African countries and Bangladesh, the burden of disease based on the revised growth standards has not been estimated, especially in India and other settings in South Asia.

Given developments in treatment options for severely malnourished children and the increasing prevalence of HIV as an adjunct to undernutrition, certain aspects of the existing guidelines on the management and treatment of severe acute malnutrition needed updating and revision. Following the review *(18)* of the existing recommendations *(2, 9, 10)*, WHO identified the eight following major areas where revision of guidelines was needed:

1. Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition

   — Admission cut-off values for the respective screening indicators

   — Discharge cut-off values for the different admission indicators

   — Admission criteria for inpatient care and outpatient care

   — Transition from inpatient care to outpatient care after stabilization

2. Where to manage children with severe acute malnutrition who have oedema

   — Which children with severe acute malnutrition who also have oedema should be managed in hospital compared to at home?

3. Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

   — Do children with uncomplicated severe acute malnutrition need to be treated with antibiotics and, if so, then which antibiotic should be used?

4. Vitamin A supplementation in the treatment of children with severe acute malnutrition

   — What is the effectiveness and safety of giving high-dose vitamin A supplementation to children with severe acute malnutrition when they are receiving a WHO-recommended therapeutic diet containing vitamin A?

   — How does the timing of high-dose vitamin A supplementation (i.e. at the beginning, after stabilization or after rehabilitation) affect the effectiveness and safety of the management of children with severe acute malnutrition?

5. Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

   — Does ready-to-use therapeutic food given to children with severe acute malnutrition as outpatients increase the incidence of acute diarrhoea or worsen acute diarrhoea if already present?

   — Do children with severe acute malnutrition and acute diarrhoea who are managed as outpatients require modification of therapeutic feeding approaches?

   — Does ready-to-use therapeutic food given to children with severe acute malnutrition in the rehabilitation phase, as either inpatients or outpatients, increase the prevalence of diarrhoea or worsen diarrhoea if already present, in comparison to F-100?

   — Can ready-to-use therapeutic food be given safely to children with severe acute malnutrition who have persistent diarrhoea?

   — What is the most appropriate "transition" feeding approach for changing from F-75 to F-100, or from F-75 to ready-to-use therapeutic food, for children with severe acute malnutrition who are managed in hospital?

6. Fluid management of children with severe acute malnutrition

   — What is the most effective and safest fluid-management approach for children with severe acute malnutrition diagnosed with dehydration but without shock?

   — What is the most effective and safest fluid-management approach for children with severe acute malnutrition with shock?

7. Management of HIV-infected children with severe acute malnutrition

   — What is the optimal timing for initiating and dosing of antiretroviral drug treatment?

   — What are the optimal feeding regimens for HIV-infected children with severe acute malnutrition and do these differ from those for uninfected children with severe acute malnutrition?

   — What is the value (effectiveness and safety) of vitamin A supplementation?

   — What are the most effective therapeutic strategies for managing diarrhoea?

8. Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

   — What are the criteria for defining severe acute malnutrition in infants who are less than 6 months of age?

   — What are the criteria for hospital admission of infants who are less than 6 months of age with severe acute malnutrition?

   — What are the essential interventions, especially feeding approaches, for infants who are less than 6 months of age with severe acute malnutrition?

   — What are the criteria for transferring infants who are less than 6 months of age and have been treated in hospital for severe acute malnutrition to outpatient care, or discharging them from treatment?

Recommendations

1. Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition

Preamble

Severe malnutrition in children who are 6–59 months of age was defined in previous publications *(2)* as weight-for-height (or length) less than –3 Z-score, or less than 70% of the median National Center for Health Statistics (NHCS)/WHO reference values, or the presence of oedematous malnutrition. The manual recommended admitting children with severe acute malnutrition to hospital for initial treatment and rehabilitation, and to continue treatment as outpatients (transfer to a nutritional rehabilitation centre) when children have completed the initial phase of the treatment, have no complications, and are eating satisfactorily and gaining weight *(2)*. Since ready-to-use therapeutic food became available in the 1990s, reports have demonstrated that most children with severe acute malnutrition can be treated safely without admission to hospital *(19)*. Consequently, in 2007 a joint United Nations statement endorsed outpatient care of children who are 6–59 months of age with severe acute malnutrition and who present with no medical complications and with good appetite *(10)*. The same statement also endorsed the use of mid-upper arm circumference measurements as an independent criterion for screening.

The transition from the NCHS growth reference to the WHO growth standards in 2006 *(4)* prompted the revision of cut-off values for indicators of severe acute malnutrition. A 2009 joint United Nations statement endorsed a low mid-upper arm circumference less than 115 mm as a criterion for diagnosing severe acute malnutrition in children, in light of the high predictive value for mortality *(9)*. Mid-upper arm circumference is measured using simple arm bands that are marked in millimetre graduations and are sometimes colour coded. These armbands can be used and interpreted by health-care workers who receive appropriate training. The statement also noted the programmatic advantage of using a single mid-upper arm circumference cut-off value to identify children with severe acute malnutrition in this age group *(9)*. However, mid-upper arm circumference and weight-for-height indicators do not always correlate when used to identify children with severe acute malnutrition *(20–22)*. About 40% of children who are classified as having severe acute malnutrition using one of these indicators are similarly classified using the other indicator *(8)*. The agreement between these criteria varies considerably between settings and geographic location *(9, 23)*. Comparison of the sensitivity–specificity curves (receiver operating characteristic curves) in community studies shows that mid-upper arm circumference is better at identifying children with a high risk of death *(24)*.

The 1999 recommendations included discharging children from hospital care when they achieved a weight-for-height ≥–1 Z-score or ≥90% of the median NCHS/WHO reference values *(2)*. The 2009 joint

United Nations statement proposed using a single discharge criterion of 15% (or 20%, depending on the local context) weight gain over oedema-free weight on enrolment, for children admitted based on weight-for-height or mid-upper arm circumference, as well as absence of oedema for 2 weeks *(9)*. Data from children treated for severe acute malnutrition in outpatient care in Malawi and Ethiopia have suggested that 15% weight gain would result in 50% of children with severe acute malnutrition meeting or exceeding 80% of the median weight-for-height of the NCHS reference *(25)*. However, while some programmes adopted this approach, there was concern about its validity as an indicator of nutritional recovery, and in many settings only the mid-upper arm circumference cut-off value of ≥125 mm was applied *(26)*. The discharge cut-off value for mid-upper arm circumference of ≥125 mm was based on historical cohort studies from Bangladesh, Malawi and Uganda that suggested that mortality risk at this cut-off value did not exceed 1/10 000 per day *(25)*. The safety of using changes in mid-upper arm circumference as an indicator of progress of recovery during nutritional rehabilitation, and a single cut-off value to indicate "recovery", has not been validated.

In light of these experiences, WHO, with support from the guideline development group aimed to provide guidance on the following:

◼ Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition:

— Admission cut-off values for the respective screening indicators

— Discharge cut-off values for the different admission indicators

— Admission criteria for inpatient care and outpatient care

— Transition from inpatient care to outpatient care after stabilization

Summary of the evidence

A systematic review was conducted to examine admission and discharge criteria for severe acute malnutrition in children who are 6–59 months of age *(27)*. The search identified 11 relevant epidemiological studies. Three of the 11 studies used cut-off values for admission that did not correspond to the WHO definition of severe acute malnutrition, namely mid-upper arm circumference <120 mm *(28)*, mid-upper arm circumference <130 mm *(29)* and weight-for-height <–2 Z-score *(30)*. However, these three studies reported stratified results from which outcomes of children with severe acute malnutrition could be extracted. All studies, except one, were conducted in African countries and five out of the 11 studies took place in the same setting in Malawi where there was a high proportion of children with oedema. The majority of studies involved uncomplicated cases of severe acute malnutrition that were managed in an outpatient programme. Five of the studies used mid-upper arm circumference as an inclusion criterion, and the other seven used weight-for-height for enrolling children, but reported on gain in mid-upper arm circumference during nutritional rehabilitation.

Low values of weight-for-height and mid-upper arm circumference both identify children with an increased risk of mortality, but the children identified by each indicator may be different. In one study including 34 937 children aged 6–59 months from Afghanistan, Angola, Burkina Faso, Burundi, Chad, Ethiopia, Malawi, Sierra Leone, Niger and India, the criterion of mid-upper arm circumference <115 mm did not detect severe acute malnutrition in up to 75% of children who were identified as having severe acute malnutrition defined by weight-for-height <–3 Z-score in the WHO growth standards *(31)*. In two smaller studies, this proportion was around 40% *(32, 33)*. The proportion of cases identified by a low weight-for-height that were undetected by a low mid-upper arm circumference was higher in males than in females and increased with age.

No randomized studies were identified that compared the outcomes of nutritional rehabilitation of children with severe acute malnutrition admitted on the basis of mid-upper arm circumference versus weight-for-height Z-score. Only one study compared the mortality risk of hospitalized children according to their mid-upper arm circumference versus their weight-for-height Z-score *(32)*. The mortality risk was similar for children presenting with a weight-for-height ≤–3 Z-score or with a mid-upper arm circumference ≤115 mm, i.e. 10.1% and 10.9%, respectively. The highest risk for mortality (25.4%) was observed in children who had both weight-for-height ≤–3 Z-score or a mid-upper arm circumference ≤115 mm. Children with a mid-upper arm circumference ≤115 mm presented more frequently with signs of recent or current oedematous malnutrition, stunting and subcostal indrawing, and were more frequently girls and of younger age than those admitted with a weight-for-height ≤–3 Z-score *(32)*. Bipedal oedema was present in 38.0% of children with a low mid-upper arm circumference versus 13.9% in those with a weight-for-height ≤–3 Z-score.

Four studies, including an unpublished report, reported on outcomes of children diagnosed on the basis of mid-upper arm circumference only and managed in outpatient care without a comparison group admitted on the basis of weight-for-height *(25, 28, 29, 33)*. The mortality risk for children with severe acute malnutrition was reported in three of the studies and was overall relatively low (≤2.1 %). The median recovery times ranged from 44.4 ± 29.7 days *(33)* to 50.5 ± 25.8 days *(28)*. The daily gain of mid-upper arm circumference ranged from 0.17 ± 0.16 mm in children admitted with a mid-upper arm circumference <110 mm and treated in a supplementary feeding programme *(25)* to 0.51 ± 0.3 mm in Burkina Faso in children with a mid-upper arm circumference ≤110 mm and receiving ready-to-use therapeutic food *(28)*. Two of the studies stratified the results by level of mid-upper arm circumference at admission *(28, 29)*. In both studies, children admitted with a lower mid-upper arm circumference displayed a greater daily gain in weight and mid-upper arm circumference. Furthermore, in Burkina Faso, mortality was greater among children with a lower mid-upper arm circumference at admission and referral for inpatient care was more common. This latter study also reported that the daily gain in mid-upper arm circumference was higher in older and taller children, and in boys *(28)*.

Six additional studies also reported on gain in mid-upper arm circumference during nutritional rehabilitation, but admission was based on a weight-for-height Z-score of <–3. The daily gain in mid-upper arm circumference was in the same range as in studies that admitted children on the basis of a low mid-upper arm circumference only. Overall, mid-upper arm circumference increased by 0.2 to 0.4 mm/day during rehabilitation, with no obvious differences among studies admitting children on the basis of mid-upper arm circumference or weight-for-height. In all studies, the increase in mid-upper arm circumference paralleled the daily weight gain, which ranged between 3.0 and 6.5 g/kg.

Two observational studies reported outcomes when mid-upper arm circumference was used as a discharge criterion for malnourished children from nutritional rehabilitation programmes *(28, 29)*. In Burkina Faso, the time to discharge of children with mid-upper arm circumference <120 mm from an outpatient programme (*n* = 5689) was reported for the period April to December 2008 when discharge was based on 15% weight gain, and then for the period April to December 2009 when discharge was based on achieving mid-upper arm circumference ≥124 mm (without consideration of weight gain). When 15% weight gain was used as the discharge criterion, the mean time to discharge of children was 53 ± 25 days; in the later period when discharge was based on achieving a mid-upper arm circumference ≥124 mm, children were discharged after an average duration of 36 ± 20 days. In children whose mid-upper arm circumference was initially ≤114 mm, the average duration of treatment to achieve at least 15% weight gain was 48 ± 23 days, whereas for children whose mid-upper arm circumference was initially between 115 mm and 119 mm, the average duration of treatment was 55 ± 26 days. In contrast, when mid-upper arm circumference ≥124 mm was used as the discharge criterion, the average duration of treatment for the more malnourished children

(mid-upper arm circumference initially ≤114 mm) was 47 ± 25 days, which was longer than for the less malnourished children (initial mid-upper arm circumference between 115 mm and 119 mm) who were discharged on average after 33 ± 16 days. These observations provide indirect evidence that 15% weight gain is not an appropriate discharge criterion, because it results in the more severely malnourished children getting the shortest duration of treatment and being discharged when still malnourished. In this study, the mortality risks up until the end of treatment when using 15% weight gain versus mid-upper arm circumference ≥124 mm as a discharge criterion were comparable and were 1.5 %. The second study in Guinea-Bissau used a mid-upper arm circumference ≥130 mm as a discharge criterion but did not separate outcomes for children who were admitted with severe acute malnutrition from those with moderate acute malnutrition *(29)*.

No published data were found that reported the final outcome status of children with severe acute malnutrition following discharge from treatment programmes, e.g. relapse rates; subsequent mortality when discharged was based on a mid-upper arm circumference measurement compared to other indicators such as weight-for-height Z-score, mid-upper arm circumference-for-age Z-score, or mid-upper arm circumference-for-height Z-score.

The overall quality of evidence was rated as low for the relationship between anthropometry and mortality risk on admission. There was no evidence available informing the relationship between anthropometry and the risk of mortality post discharge. The quality of evidence for other important outcomes, including time to recovery, growth and daily weight gain was rated very low or low, owing to methodological and reporting issues. A Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of the evidence was not developed, as the published data were epidemiological reports rather than comparative studies.

Only one of the studies reported outcomes in children identified, monitored or discharged based on mid-upper arm circumference and also by weight-for-height, and this was carried out among hospitalized children. Few of the studies addressed the precision and accuracy of anthropometric measurements, which may affect reliability. The fact that most of the studies were done in Malawi, where the majority of cases are oedematous and the prevalence of HIV infection is high, may affect the external validity *(30, 34–38)*. No studies were retrieved reporting on a number of important outcomes, i.e. costs, adverse effects and population coverage.

Discussion

■ The guideline group noted that the development of ready-to-use therapeutic food has made outpatient management of children with severe acute malnutrition more feasible and safer. Active community screening makes it possible to identify and treat these children early as outpatients. It also allows children to be appropriately managed while avoiding the risk and problems of inpatient care, such as nosocomial infections, patient transport and costs and disruptions to families. Screening in the community has been facilitated by the feasibility of using mid-upper arm circumference to identify severely malnourished children.

■ Depending on the age group, and excluding consideration of oedematous malnutrition, anthropometric assessments based on weight-for-height using the WHO growth standards *(8)* are likely to identify a larger population with severe acute malnutrition than NCHS growth reference values. This has a major implication for countries in South and South-East Asia, where large numbers of infants and young children would be defined as having severe acute malnutrition, using the WHO growth standards.

■ The guideline group noted that while weight-for-height and mid-upper arm circumference are good methods to assess wasting, both require training and methodical implementation to

achieve reliable assessments. Even after training, significant variation has been noted in health-care workers' measurements and classification during standardization tests.

■ The guideline group agreed that children with severe acute malnutrition identified using weight-for-height do not consistently have a mid-upper arm circumference <115 mm, and vice versa. The group discussed the importance of each indicator for screening and admission of children for treatment in different settings. The evidence shows that the two indicators do not always identify the same populations.

■ It is doubtful that health-care workers could detect the small incremental changes of between 1.4 mm and 2.8 mm per week of mid-upper arm circumference during the first month of treatment for monitoring recovery *(39)*.

■ There is limited evidence on the most appropriate cut-off value for mid-upper arm circumference to indicate nutritional recovery. The 2006 WHO growth standards *(4)* indicate that a mid-upper arm circumference of 125 mm corresponds to a mid-upper arm circumference-for-age Z-score <–3 for males older than 33 months and for females older than 44 months. So using this single cut-off value may result in children who still have severe acute malnutrition being discharged, especially older male children. At younger ages, this problem is less significant, though a proportion of children may be discharged while still being moderately malnourished. Adopting a higher cut-off value for mid-upper arm circumference would avoid this problem, though it would result in children being kept in treatment for significantly longer. Using mid-upper arm circumference-for-age or mid-upper arm circumference-for-height Z-scores ≥–2 would allow discharge of children who are no longer malnourished, and avoid inappropriate treatment of young children.

■ The guideline group noted that simple and uniform cut-off values are programmatically helpful, but that the evidence suggests that the sensitivity and specificity of measurements of mid-upper arm circumference compared to weight-for-height differ significantly at both upper and lower age (and/or height) ranges and by sex. Examining the clinical relevance and programmatic feasibility of different cut-off values for mid-upper arm circumference for these age (and/or height) groups is an important area for future research, possibly by re-analysing existing data sets.

■ The simplicity of mid-upper arm circumference and its superior correlation to risk of death makes it an attractive diagnostic tool for severe acute malnutrition. However, a single cut-off value for mid-upper arm circumference for admission and discharge of all children aged 6–59 months may not adequately reflect the variability and associated mortality risks of all children in this age range.

■ The 1999 WHO manual does not refer to "*visible severe wasting*" as a diagnostic criterion for severe malnutrition, although visible severe wasting is included in the *Integrated management of childhood illness (40, 41)* and versions of the WHO *Pocket handbook (42)* and the 2007 joint United Nations Statement *(10)*. Evidence does not support using *visible severe wasting* as a stand-alone criterion for children who are less than 5 years of age. However, the guideline group endorsed the principle that a trained clinician should always undress children identified with severe acute malnutrition and examine them naked to identify other medical complications.

■ The guideline group noted that triaging of children with severe acute malnutrition to treatment as outpatients or inpatients should be guided primarily by the children's clinical condition, including appetite, and social circumstances, such as whether children are disabled or there are other mitigating circumstances, including significant social or access issues.

■ The guideline group noted that the decision to transfer children from inpatient care to outpatient care (i.e. discharge from hospital) after the initial phase of stabilization should be guided primarily by the children's clinical condition, including appetite and response to treatment, and also social circumstances.

■ The guideline group noted that percentage weight gain should no longer be used as a criterion for discharge from treatment.

■ The guideline group noted that correlations of anthropometric indicators with risk of death and response to treatment are urgently needed to inform clinical recommendations and guidelines for managing severe acute malnutrition in infants less than 6 months old and in children 5 years and older, especially in the context of HIV.

Relevant standing recommendations

The recommendations below were confirmed as current in the context of existing WHO recommendations included in WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*; joint United Nations statement on *Community-based management of severe acute malnutrition*, 2007 *(10)*; *WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund*, 2009 *(9)*; and WHO *Integrated management of childhood illness: caring for newborns and children in the community*, 2011 (IMCI) *(41)*, noting in particular that:

■ in children who are 6–59 months of age, severe acute malnutrition is defined as:

— weight-for-height ≤–3 Z-score, or

— mid-upper-arm circumference <115 mm, or

— presence of bilateral oedema;

■ visible severe wasting is not included as a diagnostic criterion *(2)*. However, all malnourished children should be clinically examined when undressed, as part of routine management;

■ all anthropometric indicators are assumed to be derived from the WHO growth standards *(8)*;

■ children with severe acute malnutrition with medical complications or failed appetite test[1] should be admitted to hospital for inpatient care;

■ admission may also be warranted if there are significant mitigating circumstances such as disability or social issues, or there are difficulties with access to care;

■ children with severe acute malnutrition and without these signs or mitigating circumstances can be managed as outpatients by providing appropriate amounts of ready-to-use therapeutic food.

Recommendations

Criteria for identifying children with severe acute malnutrition for treatment

1.1   In order to achieve early identification of children with severe acute malnutrition in the community, trained community health workers and community members should measure the mid-upper arm circumference of infants and children who are 6–59 months of age and examine them for bilateral pitting oedema. Infants and children who are 6–59 months of

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[1]   Appetite test from http://www.fantaproject.org/downloads/pdfs/CMAM_Training_Mod4_ENGLISH_Nov2008.pdf

age and have a mid-upper arm circumference <115 mm, or who have any degree of bilateral oedema should be immediately referred for full assessment at a treatment centre for the management of severe acute malnutrition.

strong recommendation, low quality evidence

1.2   In primary health-care facilities and hospitals, health-care workers should assess the mid-upper arm circumference or the weight-for-height/weight-for-length status of infants and children who are 6–59 months of age and also examine them for bilateral oedema. Infants and children who are 6–59 months of age and have a mid-upper arm circumference <115 mm or a weight-for-height/length <–3 Z-scores of the WHO growth standards *(8)*, or have bilateral oedema, should be immediately admitted to a programme for the management of severe acute malnutrition.

strong recommendation, low quality evidence

Criteria for inpatient or outpatient care[1]

1.3   Children who are identified as having severe acute malnutrition should first be assessed with a full clinical examination to confirm whether they have medical complications and whether they have an appetite. Children who have appetite (pass the appetite test) and are clinically well and alert should be treated as outpatients. Children who have medical complications, severe oedema (+++), or poor appetite (fail the appetite test) or present with one or more IMCI danger signs[2] should be treated as inpatients.

strong recommendation, low quality evidence

Criteria for transferring children from inpatient to outpatient care[1]

1.4   Children with severe acute malnutrition who are admitted to hospital can be transferred to outpatient care when their medical complications, including oedema, are resolving and they have good appetite, and are clinically well and alert. The decision to transfer children from inpatient to outpatient care should be determined by their clinical condition and not on the basis of specific anthropometric outcomes such as a specific mid-upper arm circumference or weight-for-height/length.

strong recommendation, low quality evidence

Criteria for discharging children from treatment

1.5   a.   Children with severe acute malnutrition should only be discharged from treatment when their:

—   weight-for-height/length is ≥–2 Z-score and they have had no oedema for at least 2 weeks, or

—   mid-upper-arm circumference is ≥125 mm and they have had no oedema for at least 2 weeks.

b.   The anthropometric indicator that is used to confirm severe acute malnutrition should also be used to assess whether a child has reached nutritional recovery, i.e. if mid-upper arm circumference is used to identify that a child has severe acute malnutrition, then mid-upper arm circumference should be used to assess and confirm nutritional recovery.

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[1]   Necessary resources and services need to be in place if children are referred to outpatient care.

[2]   Danger signs: unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now.

Similarly, if weight-for-height is used to identify that a child has severe acute malnutrition, then weight-for-height should be used to assess and confirm nutritional recovery.

c. Children admitted with only bilateral pitting oedema should be discharged from treatment based on whichever anthropometric indicator, mid-upper arm circumference or weight-for-height is routinely used in programmes.

d. Percentage weight gain should not be used as a discharge criterion.

strong recommendation, low quality evidence

Follow-up of infants and children after discharge from treatment for severe acute malnutrition

1.6 Children with severe acute malnutrition who are discharged from treatment programmes should be periodically monitored to avoid a relapse.

strong recommendation, low quality evidence

Rationale

The guideline development group noted that the quality of evidence was low for the relationship between anthropometry and mortality risk on admission and very low/low for the relationship between anthropometry and time to recovery, growth and weight gain. However, the guideline group agreed that the recommendation should be strong. The group recognized that the associations between anthropometric outcomes and high mortality risks originated largely from observational or population-based studies rather randomized trials. Other evidence informing the recommendations was also based on programmatic experience and this characteristically downgrades the quality of evidence. However, it was felt that examining these issues through randomized trials would be very difficult and possibly unethical. The guideline group also considered that there is high biological plausibility for the associations between poor anthropometry and mortality. The benefits of identifying and treating children with severe acute malnutrition through screening with mid-upper arm circumference were determined to far outweigh the possible disadvantage of overdiagnosing malnutrition and causing children to be further assessed. The recommendations were considered to be feasible and sustainable in low-resource settings, even though there were no cost data available. As has been reported in a limited number of settings, community screening does increase the rate of identification of children with severe acute malnutrition. This will result in increased costs to the health system as treatment, either as inpatients or in the community. However, it is also likely that earlier identification will enable children to be successfully treated at home without the costs of hospitalization or complications associated with later presentation, or through nosocomial infection. Community-based management will also probably reduce transportation costs to the family and time away from home. The guideline group viewed the other recommendations in a similar way and that their overall benefits far outweighed any potential harm. However, there are several important research questions that need to be addressed to give greater certainty to these recommendations.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ To refine cut-off values of mid-upper arm circumference to identify severe acute malnutrition in children who are 6–11 months, 12–23 months and 24–59 months of age, through assessment of treatment outcomes.

■ To test strategies to improve active community screening and routine health-facility screening, and investigate barriers to service access and uptake, to enhance treatment coverage.

Other issues (no specific order)

■ To evaluate the validity of mid-upper-arm circumference values versus weight-for-height Z-score as discharge criteria for end of treatment (in relation to response to treatment, relapse and mortality) and determine the appropriate cut-off values.

■ To assess the sensitivity and specificity of mid-upper-arm circumference measurements at the lower and higher age ranges of children who are 6–59 months of age, controlled for stunting and the presence of oedema.

■ To establish mid-upper-arm circumference thresholds to identify severe acute malnutrition in infants who are less than 6 months of age and children who are 5 years of age and older.

■ To assess the response to treatment according to initial anthropometric criteria and clinical and biochemical characteristics.

■ To assess the correlation of anthropometric indicators with risk of death and response to treatment of severe acute malnutrition in infants who are less than 6 months of age and children who are 5 years of age and older, especially in the context of high and low HIV prevalence.

2. Where to manage children with severe acute malnutrition who have oedema

Preamble

The standard recommendation for the management of severe acute malnutrition has been inpatient care during the stabilization phase and the first part of the rehabilitation phase, and then transfer to a nutrition rehabilitation centre (when they exist) for the rest of the rehabilitation phase *(42)*. However, inpatient treatment is resource intensive *(43)*, disrupts the family and places children at risk of nosocomial infections. Reports of children with severe acute malnutrition being effectively treated at home *(34, 35, 44)* have prompted categorization of severe acute malnutrition as being with or without medical complications *(43, 45)*. Cases are uncomplicated if there are no signs of severe clinical illness and the child has a good appetite. Using this classification, WHO, UNICEF and the World Food Programme recommend treating children with uncomplicated severe acute malnutrition as outpatients whenever possible *(10)*. Children with severe acute malnutrition who have severe bilateral oedema (+++) have an increased risk of mortality compared to children with severe acute malnutrition but with lesser degrees of oedema. For this reason, it is unclear whether the severity of oedema, in the absence of other complications and with adequate appetite, should independently influence where to treat children with severe acute malnutrition.

The guideline development group aimed to review the evidence and provide guidance on the following question:

■ Which children with severe acute malnutrition who also have oedema should be managed in hospital compared to at home?

Summary of the evidence

A systematic review examined the evidence on the effectiveness of managing children who are more than 6 months of age with uncomplicated oedematous malnutrition grade +/++,[1] in ambulatory settings *(46)*. No randomized controlled trials comparing the outcomes achieved in inpatient and outpatient care for this specific group were identified. However, eight reports were found that described outcomes of children with severe acute malnutrition who had bilateral oedema and who were treated as outpatients. The data were from case-series that did not have control groups and so comparisons were not therefore possible.

Among uncomplicated cases of oedematous malnourished children, recovery rates exceeded 88% and case-fatality rates remained below 4%. Oedema classification varied among the studies and in some studies it was not clear whether children with severe oedema were excluded from outpatient treatment. These outcomes are consistent with those recommended in the Sphere guidelines *(47)* and the Prudhon index for case-fatality rates *(48)*. However, complicated cases were associated with high case-fatality rates during the first 4 days of inpatient stabilization, especially in the context of HIV infection *(49)*. The weight gain of children with oedema who were treated as outpatients was reported in only two studies and the time to nutritional recovery was prolonged and did not meet the minimum Sphere standards *(47)*. Authors suggested that this was due to sharing of ready-to-use therapeutic food at home or absence of food supplementation in the home-based treatment group *(51)*. Methods to assess weight gain were not, however, uniform across the studies. No association was reported between the severity of oedema and the likelihood of nutritional recovery or not.

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[1] + Mild: both feet; ++ moderate: both feet, plus lower legs, hands, or lower arms; +++ severe: generalized oedema including both feet, legs, hands, arms and face. Source: Module 2. Principles of care, in ref *(50)*.

The quality of the evidence was rated as very low, as the absence of a control group in the reports of outpatient treatment of children with severe acute malnutrition and oedema make it difficult to make conclusions about the effectiveness and safety of outpatient treatment for children with oedema +/++. As a result, no GRADE table for this evidence base was developed.

Discussion

■ The guideline development group considered that the systematic review supported the general principle that severely malnourished children with oedema, but no other medical complications, can be effectively and safely treated as outpatients.

■ It was also noted that the severity of oedema reported in children is influenced by the familiarity of the staff with seeing oedematous cases. Inexperienced staff have been observed to overestimate the extent of oedema.

■ While data were not available to comment on the severity of oedema and the safety and effectiveness of managing children with severe malnutrition and oedema at home, the association of increased mortality risk with more severe oedema (independent of site of care) was noted by the guideline group.

■ The guideline group considered that evidence from inpatient settings supported managing children with severe malnutrition who have oedema +++ as inpatients and those with oedema +/++ as outpatients.

■ The guideline group noted, however, that caution is required in interpretation of these results, as there are limitations in the quality of the design of the included studies.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* and Joint United Nations statement on *Community-based management of severe acute malnutrition*, 2007 *(10)*, noting in particular that:

■ infants and children who have only + or ++ bilateral pitting oedema but present with medical complications or have no appetite should be admitted for inpatient care;

■ infants above 6 months of age and children who have + or ++ bilateral pitting oedema but who have no medical complications and have appetite should be managed as outpatients;

■ children with bilateral pitting oedema who are admitted for inpatient care should transition from the stabilization to the transition phase when appetite returns and oedema is reducing.

Recommendations

2.1 Children with severe acute malnutrition who have severe bilateral oedema +++,[1] even if they present with no medical complications and have appetite, should be admitted for inpatient care.

strong recommendation, very low quality evidence

Rationale

The guideline group noted that the quality of evidence was very low but was in consensus that the recommendation should be strong. The recommendation essentially makes explicit what is presently implicit in existing WHO recommendations. The recommendation is therefore not new but clarifies where children with severe bilateral oedema should be treated, i.e. in hospital. The recommendation prioritizes the safety of children with this complication. The recommendation is feasible, as, in previous guidelines, all children with severe acute malnutrition were admitted. Hence, this recommendation places no additional cost burden on health systems than previously.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ What is the predictive value of different degrees of oedema (+, ++ or +++) on recovery of children with severe acute malnutrition managed as inpatients or outpatients?

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[1] Mild: both feet; ++ moderate: both feet, plus lower legs, hands, or lower arms; +++ severe: generalized oedema including both feet, legs, hands, arms and face *(50)*.

3.   Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

Preamble

Epidemiological and clinical studies have documented the high prevalence of pneumonia, bacteraemia and urinary tract infections in children with severe acute malnutrition, which often may not be symptomatic.

The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 recommended that all children with severe acute malnutrition should be admitted to hospital and treated with a course of antibiotics *(2)*. If clinical complications were present, then parenteral antibiotics were recommended, depending on local resistance patterns and availability. For children without obvious clinical sepsis, oral antibiotics were recommended. Because severe acute malnutrition suppresses the immune response, it is hard to detect infection.

The availability of ready-to-use-therapeutic foods now allows large numbers of children who have severe acute malnutrition and are over 6 months of age, but who do not have medical complications, to be treated as outpatients. These children were previously treated in hospital because ready-to-use therapeutic foods that could be safely used in the community were not available. The 2007 joint United Nations statement on *Community-based management of severe acute malnutrition (10)* recommends that, in addition to the provision of ready-to-use therapeutic food, children with severe acute malnutrition receive a short course of basic oral medication to treat infections.

In 2007, however, the evidence to support the use of oral antibiotics in children without signs of clinical sepsis was limited. The emergence of successful outpatient management of children who have severe acute malnutrition but do not demonstrate clinical complications, has raised the question of whether these children would benefit from a course of oral antibiotics as part of routine management – in line with WHO's 1999 recommendation for treatment in hospitals *(2)*.

The choice of antibiotic, for either inpatient or outpatient management, should consider patterns of antibiotic resistance, which vary between countries *(52, 53)*; high rates of resistance to second-line antibiotics such as chloramphenicol, gentamicin and cephalosporins have been reported *(52)*, while sensitivity to ciprofloxacin remains generally high. In vitro resistance, however, does not necessarily reflect clinical efficacy.

The guideline development group aimed to update guidance on the following question:

■ Do children with uncomplicated severe acute malnutrition need to be treated with antibiotics and, if so, then which antibiotic should be used?

Summary of the evidence

A systematic review was conducted to examine the clinical safety and efficacy of antibiotic inter-ventions among children with uncomplicated severe acute malnutrition *(54)*.

One study reported outcomes in hospitalized children with severe acute malnutrition who all received antibiotics. In a randomized controlled trial (2002–2003), there were no significant differences in any of the efficacy outcomes among Sudanese children with severe acute malnutrition (complicated and uncomplicated) who were treated with either 5 days of oral amoxicillin or 2 days of intramuscular (IM) ceftriaxone *(55)*. Given that the study population was restricted to hospitalized children and there was no control group, this study did not provide direct evidence on the safety and efficacy of antibiotics in children with uncomplicated severe acute malnutrition.

Two studies provided evidence on the efficacy of antibiotics in children managed as outpatients. In a retrospective analysis of children in Malawi with uncomplicated severe acute malnutrition managed as outpatients, outcomes in one cohort who received 7 days of oral amoxicillin in addition to ready-to-use therapeutic food were compared with those of a cohort who received ready-to-use therapeutic food only. At 12 weeks' follow-up, mortality rates were less than 5% in both cohorts and rates of nutritional recovery were similar *(56)*. However, these two cohorts of children were quite different at baseline and therefore the results are difficult to interpret.

In a prospective, randomized, double-blind trial in southern Malawi, children with uncomplicated severe acute malnutrition managed as outpatients were randomized to receive either 1 week of amoxicillin 80–90 mg/kg/day, cefdinir 14 mg/kg/day or placebo *(57)*. The rate of nutritional recovery of children who received antibiotics was significantly better than that of those who received placebo (amoxicillin 89.0%, cefdinir 91.4%, placebo 85.1%, $P < 0.0002$). This result was consistent among both children with bilateral oedema (amoxicillin 91.6%, cefdinir 92.9%, placebo 88.3%, $P < 0.007$) and those with severe wasting (amoxicillin 78.9%, cefdinir 85.1%, placebo 73.7%, $P < 0.03$). Mortality rates were significantly lower in the groups that received antibiotics (amoxicillin 4.63%, cefdinir 3.86%, placebo 7.48%, $P < 0.002$). When analysed by type of malnutrition, mortality was reduced in children who had bilateral oedema (amoxicillin 3.49%, cefdinir 3.56%, placebo 7.48%, $P < 0.0006$). However, the study was not specifically powered to undertake the latter analysis.

One before-and-after study of ampicillin and gentamicin as second-line antibiotics was also identified. The design of the study was such that it was not possible to estimate the relative effect of the introduction of the antibiotic regimen independently of an algorithm for managing hypoglycaemia that was introduced in parallel *(58)*.

No studies of ceftriaxone, ciprofloxacin or co-trimoxazole as a first-line treatment for children with severe acute malnutrition were identified.

The overall quality of this evidence was rated as low, owing to methodological and reporting bias. See **Annex 1**, **Table 1** for details of the GRADE assessment of the evidence.

Discussion

■ The guideline group considered that the use of broad-spectrum antibiotics such as amoxicillin for children with severe acute malnutrition is supported by epidemiological data demonstrating a high prevalence of infections in these children, including children with uncomplicated severe acute malnutrition receiving outpatient management.

■ It is possible that providing antibiotics will result in some adverse events such as diarrhoea, skin reactions and hypersensitivities. However, it is unlikely that the frequency of such complications will be significantly more than in well-nourished children.

■ However, it was noted that the one randomized trial that specifically examined outcomes in this population was in a setting where the pattern of severe acute malnutrition is predominantly oedematous and HIV is also prevalent.

■ Increased antimicrobial resistance is a potential consequence of prescribing broad-spectrum antibiotics for the outpatient treatment of children with severe acute malnutrition.

— However, children with severe acute malnutrition are at high risk of mortality – higher for example, than infants with fast breathing, where antibiotics are also currently recommended.

— The reported reduction in mortality in children with uncomplicated severe acute malnutrition treated with antibiotics as outpatients (7.48% to 4.63%) is significant and the guideline group thought it was justified to recommend this intervention to this population, even at the risk of increasing antimicrobial resistance in the community.

— Community-level antimicrobial resistance is not a certain consequence of providing antibiotics to children as part of outpatient care but will depend on factors that include the prevalence of uncomplicated severe acute malnutrition, the quality of health-care worker counselling and adherence to medications at home.

— Antimicrobial resistance of community-acquired infections may be already present and the consequence of antibiotic use for other reasons.

— Research is needed to examine these issues.

■ It was noted that small bowel bacterial overgrowth is common in children with severe acute malnutrition and affects intestinal function.

■ The mechanism by which oral antibiotics may benefit children with uncomplicated severe malnutrition is unclear but may include reducing excessive proliferation of small bowel flora, translocation of gut bacteria into the bloodstream, or modification of the microbiome.

■ The cost of providing oral antibiotics to all children with uncomplicated severe acute mal-nutrition as outpatients would be about US$0.45 to US$0.60 per child for 5 days' treatment *(59)*. WHO guidelines previously recommended that all children with severe acute malnutrition should be admitted and all children given appropriate antibiotics *(2)*. Hence, while guidelines have changed to provide treatment for these children in outpatient care, treating all children with antibiotics has been the standard of care. While the budget to pay for antibiotics may be different between hospital and primary health-care facilities, the total cost to the national health authority would theoretically not be different. It is likely that all children in hospital are indeed given antibiotics and hence this cost is real. Reports from programmes indicate that the introduction of community-based screening has increased the identification of children with severe acute malnutrition – both those requiring hospital care and those that can be managed as outpatients. The funds required for antibiotics have therefore increased because of community-based screening improving coverage and service uptake. Managing children as outpatients is likely to be cheaper than hospital care, even if oral antibiotics are included as part of standard care. No cost analysis of these approaches was available.

■ While providing antibiotics would increase the transaction time between health-care workers and mothers/caregivers of children, and highlights the importance of reliable supply-chain management, the potential reduction in mortality justifies these opportunity costs.

■ WHO endorses the principle that antimicrobials should only be given to patients when infection is present. In the context of severe acute malnutrition, "uncomplicated" should not be understood to mean that infection is not present. Rather "uncomplicated" implies the absence of symptoms for infection and that the child can be otherwise managed as an outpatient.

■ The guideline group noted that research is urgently needed to examine outcomes in populations where wasting predominates, such as in South-East Asia, and where HIV is less common.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, noting in particular that:

■ children admitted with severe acute malnutrition and complications such as septic shock, hypoglycaemia, hypothermia, skin infections, or respiratory or urinary tract infections, or who appear lethargic or sickly, should be given parenteral (IM or intravenous [IV]) antibiotics;

■ children admitted with severe acute malnutrition and with no apparent signs of infection and no complications should be given an oral antibiotic.

Recommendations

3.1   Children with uncomplicated severe acute malnutrition, not requiring to be admitted and who are managed as outpatients, should be given a course of oral antibiotic such as amoxicillin.

conditional recommendation, low quality evidence

3.2   Children who are undernourished but who do not have severe acute malnutrition should not routinely receive antibiotics unless they show signs of clinical infection.

strong recommendation, low quality evidence

Rationale

The guideline group noted that the quality of evidence regarding the efficacy of antibiotics in children with uncomplicated severe acute malnutrition was low and agreed that the first recommendation should therefore be conditional. However, the guideline group acknowledged that there is an extensive evidence base highlighting the adverse consequences of indiscriminate use of antibiotics, including antibiotic resistance and, though this evidence was not directly reviewed in the meeting, the group considered the evidence to be of high quality and that the second recommendation should be strong.

A conditional recommendation indicates that a decision by a national or local health authority to include, or not to include, an intervention into local protocols is context sensitive and should be based on consideration of local circumstances.

The guideline group considered the findings from the one randomized controlled trial to be informative and robust. The reduced mortality associated with the intervention was significant and such benefit should be offered to this group of very high-risk children.

The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* recommends oral antibiotics for children with severe acute malnutrition but without overt signs of sepsis. The classification "uncomplicated" that is now applied to children with severe acute malnutrition who can be managed at home, identifies the same children referred to in the 1999 manual, who previously received oral antibiotics in hospital.

It should be noted that the classification "uncomplicated" should not be interpreted to mean that infection is not necessarily present but that the overall condition of the child means that outpatient management can be considered.

Furthermore, providing antibiotics to the specific population of children with uncomplicated severe acute malnutrition does not mean that any child with some degree of undernutrition – e.g. low weight-for-age, moderate stunting or moderate wasting (weight-for-height <–2 Z-score but >–3 Z- score; mean upper-arm circumference <125 mm but >11.5 cm) – should also be routinely given antibiotics.

Providing antibiotics to children with uncomplicated severe acute malnutrition is unlikely to cause them harm, e.g. anaphylaxis or other hypersensitivities. It may, however, contribute to antimicrobial resistance in the community.

Monitoring of antimicrobial resistance in the population should be routine practice when broad-spectrum antibiotics are used for any community treatment of children with life-threatening conditions. Outpatient treatment with a broad-spectrum antibiotic is already recommended for specific conditions, e.g. treating children with fast breathing. Future adaptations of national policies and guidelines to give oral antibiotics to children with uncomplicated severe acute malnutrition intensifies the need to monitor patterns of antibiotic resistance at population level.

The strength of the first recommendation is conditional for two main reasons:

1. the magnitude of population-based antimicrobial resistance that may follow implementation of the recommendation among the target population is unknown. It is also not known whether implementation of the recommendation will result in significant reductions in the therapeutic efficacy of antibiotics, through antimicrobial resistance, when used for treating other patients with life-threatening conditions;

2. there were significant contextual factors regarding the evidence underpinning the recommendation, namely, most children in the study had bilateral oedema and a significant proportion were HIV exposed. These factors may limit the generalizability of the recommendation. Despite these concerns, the guideline group considered that it would be inappropriate and unethical to deny children with a high mortality risk access to an intervention that may significantly reduce mortality.

Further research is essential to:

■ establish the efficacy of routine antibiotics in children with uncomplicated severe acute malnutrition living outside southern Africa, and therefore the generalizability of the recommendation;

■ monitor the effect of this intervention on population-based antimicrobial resistance;

■ establish the cost effectiveness of the intervention in different regions.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ What is the clinical effect and cost effectiveness of giving oral antibiotics to children and infants with severe acute malnutrition who do not require inpatient management in:

   — settings with predominantly wasting (e.g. West Africa, South Asia); and

   — non-HIV settings (randomized controlled trial with mortality as main outcome)?

■ What is the effect of giving broad-spectrum antibiotics to infants and children with severe acute malnutrition without complications, who do not require inpatient management, on:

   — the prevalence of population-based antimicrobial resistance;

   — therapeutic efficacy.

Other issues (no specific order)

■ What clinical algorithms or point-of-care technologies can identify the presence of significant bacterial infections in infants and children with uncomplicated severe acute malnutrition?

■ What is the positive and negative predictive value of the appetite test for identifying children with severe acute malnutrition and clinically important infection?

■ What are the most effective antibiotics for managing children with complicated severe acute malnutrition who are admitted for inpatient care:

   — stratified by HIV status, complications, type of severe acute malnutrition (oedematous versus wasting) and age;

   — taking account of in vivo and in vitro resistance versus effectiveness?

4. Vitamin A supplementation in the treatment of children with severe acute malnutrition

Preamble

Globally, between 100 and 140 million children are vitamin A deficient, 4.4 million of whom are estimated to have xerophthalmia *(7, 60)*. Many children living in low-resource settings have a marginal deficiency because of poor intake of either preformed vitamin A, or its precursor, carotene, from the diet. Vitamin A is essential to maintain mucosal barriers and for normal humoral and cellular immune responses. In response to infections, inflammatory processes may disrupt vitamin A metabolism and the release of vitamin A from body stores.

In addition to impairing immune responses, vitamin A deficiency causes the epithelial lining to produce less mucus, which enables bacterial adherence and thereby the invasion of pathogenic microbes *(61)*. Untreated vitamin A deficiency in all children, including severely malnourished children, leads to blindness and increased susceptibility to infection *(2)* and mortality. There is, however, evidence from randomized trials of vitamin A toxicity and adverse health outcomes in certain settings, such as in patients with pneumonia *(62)*.

Several observational studies have reported the association between severe acute malnutrition and vitamin A deficiency. In Brazil, low serum retinol (less than 0.70 μmol/L) was more prevalent among hospitalized children with severe acute malnutrition than well-nourished hospitalized children, after controlling for several important factors *(63)*. In a subgroup analysis, lower serum retinol concentrations in children with severe acute malnutrition were associated with increased diarrhoeal morbidities (P = 0.021). Among hospitalized Egyptian children with oedematous malnutrition and wasting, plasma vitamin A concentrations were significantly reduced (P < 0.05) *(64)*. A study from Bangladesh that aimed to examine predictors and outcomes associated with shigellosis versus other forms of dysentery, also described the relationship between vitamin A and diarrhoea in children *(65)*. Lower serum retinol concentrations (0.8 μmol/L) were reported in children with shigellosis, especially those with more severe disease and also those with low weight-for-age Z-score. Infection with the more virulent strain, *Shigella dysenteriae* type 1, showed the lowest serum retinol concentrations. A case-control study in Bangladesh showed that longer duration of diarrhoea (10–14 days and more than 14 days) and weight-for-age less than 60% of the reference median (adjusted odds ratio = 3.8; 95% confidence interval [CI] = 1.8 to 8.0) were independently associated with xerophthalmia, whereas weight-for-age of 60–70% of the expected median showed no association *(66)*.

The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 recommends giving a high dose of vitamin A (50 000 to 200 000 IU, according to age) to all children with severe acute malnutrition on admission, even if they have no signs of vitamin A deficiency. Children with eye signs of vitamin A deficiency or recent measles should receive a second high dose on the following day and a third high dose 2 weeks later *(2)*.

Commercially available therapeutic formulas (F-75 and F-100) and ready-to-use therapeutic food that complies with the WHO specifications are fortified with vitamin A. This raised questions as to whether it is both safe and necessary to routinely give a high dose of vitamin A to children with severe acute malnutrition, especially those with oedema or signs of hepatic dysfunction, when they are fed with therapeutic foods that already contain vitamin A, and whether there is any risk associated with receiving a single high dose.

There is no question that all children with low, or potentially low, vitamin A status/intake need an increased intake of this nutrient. In resource-poor settings, this is most commonly achieved

by supplementation, in particular among children with malnutrition, measles, severe or persistent diarrhoea and other forms of impaired absorption. The question being addressed concerns only the appropriate dose and timing of supplementation.

The guideline development group aimed to review and provide guidance on the following questions:

■ What is the effectiveness and safety of giving high-dose vitamin A supplementation to children with severe acute malnutrition when they are receiving a WHO-recommended therapeutic diet containing vitamin A?

■ How does the timing of high-dose vitamin A supplementation (i.e. at the beginning, after stabilization or after rehabilitation) affect the effectiveness and safety of the management of children with severe acute malnutrition?

Summary of the evidence

A systematic review examined the effectiveness and safety of giving single high-dose vitamin A supplementation as part of management of children with severe acute malnutrition who are receiving low doses of vitamin A (several times higher than the recommended nutrient intake) through the daily therapeutic diet *(67)*. The review examined the effect of the timing of high-dose vitamin A supplementation (i.e. at the beginning of treatment or after rehabilitation) on treatment outcomes for children with severe acute malnutrition.

Three randomized controlled trials conducted in sub-Saharan Africa and Bangladesh compared daily low-dose (5000 IU) versus single high-dose vitamin A supplementation (100 000 IU for children who were less than 1 year of age, 200 000 IU for children who were aged 1 year or older) in children with severe acute malnutrition *(68, 69)*. The first trial in the Democratic Republic of the Congo found no differences in mortality, acute lower respiratory tract infections, or duration of diarrhoea between malnourished children who received low-dose and high-dose vitamin A supplementation compared with placebo *(69)*. However, children with bilateral pitting oedema who received low-dose vitamin A supplementation had a lower incidence of diarrhoea (relative risk = 0.21; 95% CI = 0.07 to 0.62) compared with placebo; no effect was shown in the high-dose group. Furthermore, severely malnourished children without oedema who received the high-dose supplementation had a two-fold increased risk of severe nosocomial diarrhoea compared with children who received placebo *(69)*. The second trial, in Senegal, gave hospitalized children with severe acute malnutrition either high-dose vitamin A supplementation at admission, or the low-dose supplements daily until discharge *(68)*. The incidence and duration of respiratory infection were lower in the low-dose group than in the high-dose group. In children with oedema on admission, mortality was significantly lower in the low-dose group (adjusted odds ratio = 0.21; 95% CI = 0.05 to 0.99). No differences were detected for diarrhoea morbidity or mortality. The third trial in Bangladesh compared the efficacy of a single high dose (200 000 IU) of vitamin A in addition to a daily low dose (5000 IU) in the management of children with severe acute malnutrition who also had diarrhoea with or without acute lower respiratory tract infections *(70)*. The addition of high-dose vitamin A to daily low-dose supplements did not modify the time to resolution of diarrhoea, recovery from acute lower respiratory tract infections or mortality. No adverse effects were seen with high-dose supplementation of vitamin A.

No direct evidence was available on whether the timing of high-dose vitamin A supplementation, given either early or later in the treatment of children with severe acute malnutrition, influences nutritional recovery, including weight gain, mortality, signs of symptomatic vitamin A deficiency or biological indicators of vitamin A status. Subgroup analyses from the two studies comparing high-dose and daily low-dose vitamin A supplements suggested that, in severely malnourished children

with oedema, low-dose vitamin A is more protective than high-dose vitamin A supplementation against diarrhoea incidence *(69)* and mortality *(68)*. Other trials compared different high-dose vitamin A supplementation with placebo but did not select children on the basis of being malnourished. Several studies gave children vitamin A supplements once at enrolment *(71–75)*, and two studies tested the effect of high-dose supplementation over multiple days *(62, 76)*. Because these studies were heterogeneous and were not done exclusively in children with severe acute malnutrition, it was not possible to draw conclusions about the timing of high-dose supplementation. However, one study among hospitalized children who did not have severe acute malnutrition did observe adverse effects of high-dose vitamin A supplementation on children with respiratory tract infection *(62, 76)*.

In summary:

■ low-dose (5000 IU) vitamin A supplementation given daily to children with severe acute malnutrition, from the time of admission until discharge from treatment, is more effective in reducing the mortality of children with oedema, the incidence of severe diarrhoea, and the incidence and duration of respiratory infection than single high-dose vitamin A supplementation (100 000 IU for children who are less than 1 year of age; 200 000 IU for children aged 1 year or older) on day 1 of admission;

■ high-dose vitamin A supplementation appears to confer some benefit (compared to receiving no supplementation at all) in children with severe acute malnutrition who present with severe diarrhoea or shigellosis or have clear signs of vitamin A deficiency;

■ the evidence for the efficacy and safety of vitamin A supplementation in children with severe acute malnutrition with non-measles pneumonia and other acute lower respiratory tract infections is inconclusive;

■ high-dose vitamin A supplementation reduces mortality in children with severe acute malnutrition complicated by measles-specific respiratory infections.

The overall quality of this evidence was rated as low, owing to methodological and reporting bias. See **Annex 1**, **Table 2** for details of the GRADE assessment of the evidence.

Discussion

■ The vitamin A intake of children who are fed therapeutic food (F-75, F-100 or ready-to use therapeutic foods) that complies with WHO specifications exceeds the recommended nutrient intake for well-nourished children and seems adequate for malnourished children; there is no clear rationale for giving a single high-dose vitamin A supplement, unless children have eye signs of vitamin A deficiency or have had measles or diarrhoea recently.

■ Clarifying the recommendations to avoid double provision of vitamin A (through therapeutic foods and as supplements) unless absolutely required (e.g. eye signs of deficiency or recent measles) reduces opportunity costs and simplifies the work for health-care providers.

■ Avoiding double dosing with vitamin A will be cost saving, though the savings were not estimated in any of the studies.

■ There may be some programmatic advantages in giving a single high dose of vitamin A, for example in families that are unable to give their children regular therapeutic foods or multi-vitamin supplements, once the children are taken home.

■ Even healthy children may experience adverse effects such as irritability, vomiting, blurred vision and raised intracranial pressure from high-dose vitamin A supplements; these effects

may be more pronounced in children with severe acute malnutrition, especially those with bilateral pitting oedema or with compromised liver function. Clarifying and rationalizing the use of vitamin A in this population will help to avert such adverse events, while still identifying the children who will benefit most in terms of reducing mortality.

■ It is not clear whether there is a risk of vitamin A toxicity in children who receive a high-dose vitamin A supplement before discharge from treatment for severe acute malnutrition and later receive another high dose during a national vitamin A campaign. The recommendation should follow the WHO guidance for all children, which is not to give the child their age-appropriate high dose more frequently than once a month.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, the joint United Nations statement on *Community-based management of severe acute malnutrition*, 2007 *(10)* and the WHO publication, *The treatment of diarrhoea: manual for physicians and other senior health workers*, 2005 *(77)*, noting in particular that:

■ a high dose (50 000 IU, 100 000 IU or 200 000 IU, depending on age) of vitamin A should be given to all children with severe acute malnutrition and eye signs of vitamin A deficiency on day 1, with a second and a third dose on day 2 and day 15 (or at discharge from the programme), irrespective of the type of therapeutic food they are receiving;

■ a high dose (50 000 IU, 100 000 IU or 200 000 IU, depending on age) of vitamin A should be given to all children with severe acute malnutrition with recent measles on day 1, with a second and a third dose on day 2 and day 15 (or at discharge from the programme), irrespective of the type of therapeutic food they are receiving.

Recommendations

4.1   Children with severe acute malnutrition should receive the daily recommended nutrient intake of vitamin A throughout the treatment period. Children with severe acute malnutrition should be provided with about 5000 IU vitamin A daily, either as an integral part of therapeutic foods or as part of a multi-micronutrient formulation.

   strong recommendation, low quality evidence

4.2   Children with severe acute malnutrition do not require a high dose of vitamin A as a supplement if they are receiving F-75, F-100[1] or ready-to-use therapeutic food that comply with WHO specifications (and therefore already contain sufficient vitamin A), or vitamin A is part of other daily supplements.

   strong recommendation, low quality evidence

4.3   Children with severe acute malnutrition should be given a high dose of vitamin A (50 000 IU, 100 000 IU or 200 000 IU, depending on age) on admission, only if they are given therapeutic foods that are not fortified as recommended in WHO specifications and vitamin A is not part of other daily supplements.

   strong recommendation, low quality evidence

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[1] F-75 and F-100 are formula diets used for the management of children with severe acute malnutrition in inpatient care. F-75 (75 kcal or 315 kJ/100 mL) is used during the initial phase of treatment, while F-100 (100 kcal or 420 kJ/100 mL) is used during the rehabilitation phase.

Rationale

The guideline group noted that the quality of evidence was low because there were serious differences in the criteria used to define study populations, and that one study included, a priori, children with diarrhoea. Also, two of the three studies were published by the same principal investigator. However, the guideline group agreed that the recommendation should be strong. The recommendations clarify the role of vitamin A in the management of children with severe acute malnutrition and this was considered an important safety measure. They reduce the likelihood of double dosing with vitamin A and therefore should reduce opportunity costs and the likelihood of adverse events related to vitamin A. Vitamin A supplementation has been feasible in standard care of children with severe acute malnutrition. Vitamin A is widely available and studies in non-malnourished children have found vitamin A supplements to be a cost-effective child-survival intervention. Mortality reductions in this high-risk group of children are likely to be similarly cost effective. While additional randomized trials are warranted (see below), the guideline group agreed that it was justified to assign the recommendations as strong, in order to avoid the potential harm of children receiving too much vitamin A.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

- What is the efficacy of daily low-dose vitamin A supplementation compared to single high-dose vitamin A in the treatment of children with severe acute malnutrition either with bilateral pitting oedema or presenting with severe diarrhoea or shigellosis?

- What is the most effective way to improve and sustain the vitamin A status of children with severe acute malnutrition after discharge from treatment?

- Are there regional differences in the response to, and safety of, vitamin A supplementation in children with severe acute malnutrition?

5.   Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

Three aspects of therapeutic feeding in the management of children with severe acute malnutrition were identified for review by WHO and the guideline development group. These were:

■ therapeutic feeding of children with severe acute malnutrition and acute diarrhoea treated as outpatients;

■ therapeutic feeding of children with severe acute malnutrition and persistent diarrhoea;

■ therapeutic feeding of children during the transition period from initial stabilization to nutritional rehabilitation (in inpatient settings).

Systematic reviews were completed and the guideline development group considered each area separately.

5.1   Therapeutic feeding of children with severe acute malnutrition and acute diarrhoea treated as outpatients

Preamble

The relationship between acute malnutrition and acute diarrhoea is bidirectional – acute malnutrition predisposes children to a greater incidence and duration of diarrhoea (78), while diarrhoea can, in turn, precipitate or worsen acute malnutrition. Diarrhoea leads to reduced absorption of carbohydrates, protein, potassium, zinc and other nutrients, which may contribute to malnutrition *(79)*. Significant water losses from diarrhoea can lead to dehydration, electrolyte imbalance, shock, decreased mental status and ultimately death (80). Episodes of prolonged diarrhoea are also associated with increased morbidity and mortality from other diseases, adverse neurodevelopment and growth stunting *(81)*.

WHO recommends zinc and oral rehydration solution as standard therapies for the treatment of diarrhoea *(77, 82)*. Both the oral rehydration fluid used for malnourished children (ReSoMal) and the therapeutic foods recommended by WHO, namely F-75, F-100 and ready-to-use therapeutic food, contain vitamin A and zinc, together with other vitamins, trace elements and electrolytes, to correct deficiencies associated with severe acute malnutrition. The amounts of zinc included in these therapeutic foods *(2, 10)* are beyond the 10–20 mg of zinc per day recommended for children with diarrhoea (but without severe acute malnutrition). Treatment with antibiotics (for dysentery or cholera), anti-parasitic drugs and modified feeding strategies are other therapies that could be effective in the treatment of diarrhoea.

Osmotic diarrhoea due to carbohydrate intolerance has been identified in children with severe acute malnutrition. This is generally the result of villous atrophy and challenge to the gut from concentrated carbohydrate-rich feeds. The sugars (including glucose) in diets and rehydration fluids may also result in increased fluid losses from the gut in acute malnutrition. While health-care workers can observe this in children with severe acute malnutrition who are admitted to hospital, questions have been raised as to whether therapeutic foods given to children as outpatients increase their susceptibility to diarrhoea and whether modification of therapeutic diets is warranted.

The possibility of therapeutic foods resulting in increased diarrhoea may be influenced by the severity of severe acute malnutrition in the child and may signal the need for additional care. Children with severe acute malnutrition who have additional complications, including concurrent

sepsis, and who are managed as inpatients, may be more susceptible to potential adverse effects of therapeutic diets. Children managed as outpatients who develop a serious complication, such as watery diarrhoea with dehydration, or fail to respond to treatment should be transferred for inpatient care.

The 2005 WHO guidelines in *The treatment of diarrhoea: a manual for physicians and other senior health workers*, including new recommendations for the use of oral rehydration solution and zinc supplementation for clinic-based health-care workers *(77)* do not, however, specifically refer to children with severe acute malnutrition treated as outpatients. the guideline development group therefore reviewed the systematic reviews, with the aim of providing guidance on the following questions:

■ Does ready-to-use therapeutic food given to children with severe acute malnutrition as out-patients increase the incidence of acute diarrhoea or worsen acute diarrhoea if already present?

■ Do children with severe acute malnutrition and acute diarrhoea who are managed as outpatients require modification of therapeutic feeding approaches?

Summary of the evidence

A systematic review examined the management of children with severe acute malnutrition and acute diarrhoea receiving outpatient therapeutic care *(83)*. No randomized trials were identified that reported outcomes when different therapeutic foods were given to this population. Indirect evidence was identified that provides some information for consideration. The review included reports on children with severe acute malnutrition who received modified therapeutic feeding regimens including pre- and probiotics, glutamine supplementation and micronutrient (including zinc) supplementation.

Up to 5% of caregivers report acute diarrhoea in children with severe acute malnutrition treated with ready-to-use therapeutic food as outpatients *(30, 36)*. Treating children with severe acute malnutrition exclusively as outpatients is still relatively recent *(10)* and direct clinical evidence concerning the management of acute diarrhoea in these settings is lacking. The only information currently available to inform recommendations is from studies that included children with severe acute malnutrition and acute diarrhoea treated as inpatients.

In Malawi, two trials examined the use of ready-to-use therapeutic food for children with severe acute malnutrition in outpatient care, but not necessarily with acute diarrhoea. The prevalence of acute diarrhoea, while relatively low in the sample population, was studied in relation to ready-to-use therapeutic food compared with other feeding regimens. In one study, recovery from severe acute malnutrition and rates of weight gain were higher, while diarrhoeal morbidity was lower in hospitalized children with severe malnutrition who were given ready-to-use therapeutic food than in children given standard treatment with F-100, followed by a corn–soy blend porridge diet (80% maize and 20% soy flour) *(84)*. In the other study, there was no reduction in the longitudinal prevalence of diarrhoea (total days with diarrhoea/total days observed) in the groups receiving ready-to-use therapeutic food with or without additional micronutrients, compared with the corn–soy-blend-based diet *(36)*. A study in Jamaica reported benefits for weight and height gains from taking a milk-based gruel supplement and an antibiotic (metronidazole), but no advantage in terms of diarrhoea *(85)*.

Glutamine supplementation had no effect on diarrhoea or weight gain in malnourished children in Brazil but was not evaluated in children with severe acute malnutrition *(86–88)*. More studies are needed to assess the impact of dietary modifications and supplements in children with severe acute malnutrition and acute diarrhoea, to inform recommendations.

While studies in well-nourished children have reported some effect of probiotics on diarrhoeal morbidity *(18)*, findings among malnourished children have been inconclusive. A high-quality study in Malawi provided probiotics to children with severe acute malnutrition in addition to ready-to-use therapeutic food. Neither showed any benefits in terms of nutritional cure. While there were trends towards reduced severe diarrhoea among inpatients and outpatients, diarrhoeal morbidity was otherwise unaffected *(89)*. In a study in India, however, probiotics added to oral rehydration solution did reduce the frequency and duration of diarrhoea, as well as the duration of hospital stay among children admitted with acute diarrhoea, more than half of whom had acute malnutrition *(90)*. No subgroup analysis was undertaken in the malnourished children. It was noted that the medium in which probiotics are delivered may be relevant, but more research is needed.

A Cochrane review examining the effect of zinc on children with diarrhoea concluded that it is effective in reducing the duration of diarrhoea in children with moderate malnutrition but there were no studies of zinc specifically in children with severe acute malnutrition with diarrhoea *(91)*. A trial in Bangladesh reported significantly higher mortality in children with severe malnutrition given 6 mg zinc/kg/day than in children given 1.5 mg zinc/kg/day ($P = 0.033$) *(92)* as part of routine care but not specifically for diarrhoea.

The quality of evidence informing this area is very low, owing to the lack of comparative trials reporting the desired outcomes in the defined population using therapeutic diets currently recommended by WHO. The studies' use of different definitions for diarrhoea, failure to differentiate acute from persistent diarrhoea, and different approaches for reporting also confounded the interpretation of outcomes. As a result, it was not appropriate to develop GRADE tables to assess the evidence.

5.2   Therapeutic feeding of children with severe acute malnutrition and persistent diarrhoea

Preamble

The possible causes of persistent diarrhoea (i.e. three or more loose or watery stools in a day, for more than 14 days) in children with severe acute malnutrition include all those that give rise to "malabsorption syndrome" in all children. Persistent diarrhoea in children living in resource-limited settings may be due to carbohydrate intolerance, though it may also be associated with enteric infections such as cryptosporidiosis, or *Giardia*, *Shigella* or *Salmonella* infection. Carbohydrate intolerance is usually the result of villous atrophy and small bowel bacterial overgrowth, which are common in malnourished patients. Management of persistent diarrhoea in such situations generally involves nutritional interventions, including diets that are rich in essential nutrients, particularly zinc, restricting disaccharides (e.g. low-lactose feeds) *(93–95)*, treating bacterial overgrowth, and, when appropriate, excluding enteric or other systemic infections. Children infected with HIV also commonly develop persistent diarrhoea, sometimes due to cryptosporidiosis or severe carbohydrate intolerance.

Carbohydrate intolerance in children with severe malnutrition may require modified feeding approaches. For children with severe acute malnutrition admitted to hospital because of medical complications such as sepsis or dehydration, it is essential to start therapeutic feeding as soon as possible in the initial phase of treatment. The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* recommends using F-75, a therapeutic milk formula that is low in protein and fat but relatively high in carbohydrate, as the first therapeutic feed. Once children with severe acute malnutrition are stabilized in inpatient care, it is recommended to change the therapeutic diet to F-100 or a ready-to-use therapeutic food, to enable recovery of weight and lean body tissue.

In children with severe acute malnutrition who have persistent diarrhoea or who develop diarrhoea during the course of treatment, it is important to determine the most effective and safest therapeutic feeding approach to resolve diarrhoea while meeting their nutritional needs. The guideline development group aimed in particular to provide guidance on the following questions:

■ Does ready-to-use therapeutic food given to children with severe acute malnutrition in the rehabilitation phase, as either inpatients or outpatients, increase the prevalence of diarrhoea or worsen diarrhoea if already present, in comparison to F-100?

■ Can ready-to-use therapeutic food be given safely to children with severe acute malnutrition who have persistent diarrhoea?

Summary of the evidence

A systematic review examined therapeutic feeding approaches for children with persistent diarrhoea and severe acute malnutrition *(96)*. No trials or studies were identified that specifically addressed the questions identified by WHO and the guideline development group regarding the use of ready-to-use therapeutic food in children with persistent diarrhoea.

Three randomized controlled trials, in inpatient settings, were identified. In Mexico *(97)*, investigators compared a chicken-based diet, a soy-based diet and an elemental diet), all provided by nasogastric tube. There was no significant difference in the time to recovery from diarrhoea or in mortality. In a study in Pakistan *(98)* that compared a full-strength soy diet to half-strength buffalo milk with rice/lentil and yoghurt, there was no difference in the time to recovery, measured as time to cessation of diarrhoea; stool volume and frequency were not different – mortality was not reported. In Zambia *(99)* an amino-acid-based infant formula was compared to a standard skimmed milk diet. This was the only trial that followed WHO guidelines for the treatment of persistent diarrhoea, but it used the Wellcome classification of malnutrition. The other two trials defined malnutrition by weight-for-age ≤80th percentile of the median of the NCHS reference and weight-for-age ≤80th percentile of the median. There was no difference in mortality or diarrhoeal morbidity between the groups but children in the amino-acid-based infant formula group gained more weight. More than half of the children were HIV infected.

The guideline group reviewed the literature on micronutrient supplementation, especially zinc supplementation in children with severe acute malnutrition and diarrhoea. Two studies from India were identified that included both well-nourished and malnourished children in their sample *(100, 101)*. In one study, there was no effect on diarrhoeal morbidity in a small subsample of malnourished children. In the second study, malnourished children who received zinc had a shorter duration of diarrhoea and were less likely to develop persistent diarrhoea than children who did not receive zinc. In one study in Bangladesh, stool output was significantly lower among stunted children supplemented with zinc than among children who received a placebo. In another study, zinc supplementation reduced the duration of illness among underweight children presenting with persistent diarrhoea *(102, 103)*.

In summary, none of the diets evaluated in these trials produced statistically significant improvements in measures of persistent diarrhoea in children with severe acute malnutrition.

The overall quality of this evidence was rated as very low, owing to methodological and reporting issues. Since there were no studies that directly examined the effect of ready-to-use therapeutic foods that meet WHO specifications on diarrhoeal outcomes, no GRADE table was developed.

5.3 Therapeutic feeding of children during the transition period from initial stabilization to nutritional rehabilitation (in inpatient settings)

Preamble

Standard inpatient management of severe acute malnutrition involves two phases: initial stabilization when life-threatening complications are treated, and nutritional rehabilitation when catch-up growth occurs *(2)*. F-75, a low-protein milk-based formula diet, is given as the therapeutic food in the stabilization phase, while F-100, a milk formula with higher protein and energy content, is recommended as the therapeutic food in the rehabilitation phase. WHO recommends changing from F-75 to F-100 once sepsis and metabolic abnormalities are managed effectively, usually indicated by a return of appetite. The transition to F-100 in the rehabilitation phase should be gradual, with F-75 replaced with an equal volume of F-100 over about 2 days, before increasing the amount of therapeutic food offered to the child. For the purpose of this review and discussion, "therapeutic feeding in the transition phase" refers to the feeding regimen offered to children with severe acute malnutrition between initial stabilization and the rehabilitation phase *(104)*. The practice of a transition phase was adopted from successful clinical treatment protocols implemented at established malnutrition treatment centres in the 1980s and 1990s, when diarrhoea resulting in weight loss and refeeding syndrome was observed to cause sudden death attributed to the rapid introduction of large amounts of F-100 *(105–107)*.

Ready-to-use therapeutic food has replaced liquid F-100 in a variety of settings where severe acute malnutrition is treated. Most ready-to-use therapeutic foods are lipid-based pastes combining milk powder, electrolytes and micronutrients to meet recommended nutritional values *(10)*. Ready-to-use therapeutic food offers the malnourished child the same nutrient intake as F-100, with the addition of 10–14 mg/100 g of iron, and without the free water, when consumed in isoenergetic amounts. Children with severe acute malnutrition taking ready-to-use food in the rehabilitation phase therefore do not need additional iron.

Current practice in many units that treat children with severe acute malnutrition is to implement a transition phase of feeding. In these transition phases, the amount of the rehabilitation diet, namely F-100 or ready-to-use therapeutic food, is introduced in carefully restricted amounts for several days, until ad libitum feeding is introduced. However, the optimal approach to transition-phase feeding is unclear from practice.

The guideline development group examined the evidence and aimed to provide guidance on the following question:

■ What is the most appropriate "transition" feeding approach for changing from F-75 to F-100, or from F-75 to ready-to-use therapeutic food, for children with severe acute malnutrition who are managed in hospital?

Summary of evidence

A systematic review was conducted to examine transition-phase feeding approaches *(108)*. No trials or studies were identified that compared a transition-phase approach to therapeutic feeding approaches that did not include a transition phase, nor were any comparative trials identified that examined the composition or amounts of food offered to children who completed the stabilization phase. No direct evidence is thus available to critically examine the practice of transition-phase feeding.

The guideline development group examined indirect evidence to establish the importance and process of transition-phase feeding. The primary risks of introducing high-protein and high-energy food such as F-100 too quickly to children with severe acute malnutrition are refeeding syndrome *(109–112)* and diarrhoea. In refeeding syndrome, cardiac dysrhythmias and failure, respiratory distress and acute renal failure may occur and result in sudden death *(113, 114)*. Practitioners may interpret these effects as sepsis and change the antibiotic regimen. The physiological basis for refeeding syndrome is unclear but is thought to be the secretion of insulin in response to large amounts of dietary carbohydrate *(115, 116)*. In people who are severely malnourished and consuming a diet with limited amounts of carbohydrate, catabolic metabolism predominates. Both amino acids, primarily alanine, and the glycerol part of triglycerides are converted to provide glucose to the brain and kidney. The brain can also use ketone bodies derived from fatty-acid metabolism as fuel *(117)*. Children with severe acute malnutrition who are abruptly fed large amounts of carbohydrate, as would be the case in nutritional rehabilitation, would secrete insulin to move this dietary glucose into cells. This secreted insulin also causes intracellular movement of phosphate, potassium and magnesium, resulting in profound hypophosphatemia, hypokalaemia and hypomagnesaemia *(118–121)*.

Transition-phase feeding between the two milk-based therapeutic foods F-75 and F-100 has been implemented in many treatment units and is part of several national protocols for managing children with severe acute malnutrition. The approach detailed in a previous WHO document *(2)* appears to manage this transition effectively, while reducing the risk of refeeding syndrome. However, it remains unclear from available evidence whether there is scope to improve the approach recommended by WHO, and how best to apply the same principles to ready-to-use therapeutic food or other therapeutic foods that are not liquid formulations. There is no physiological basis for believing that refeeding syndrome occurs more or less frequently with ready-to-use therapeutic food than with F-100.

In light of the common and serious nature of refeeding syndrome, and the risk of overloading the absorptive capacity of the intestine and precipitating osmotic diarrhoea, it is prudent to increase energy intake slowly, transitioning from F-75 to either F-100 or ready-to-use therapeutic food, when moving from stabilization to rehabilitation *(122, 123)*.

Given the lack of direct evidence to critically examine the practice of transition-phase feeding, no GRADE tables were developed.

Discussion

■ The guideline development group noted that no studies compared therapeutic foods recommended in the previous WHO recommendations *(2)* with other feeding approaches. It is therefore difficult to consider changes from the interventions recommended *(2, 10)*. There was no published evidence to inform recommendations about transition feeding. The guideline development group considered programmatic experiences from a range of settings when considering recommendations.

■ It was noted there was no empirical data to suggest that ready-to-use therapeutic food either increases the incidence of diarrhoea or worsens diarrhoea among children with severe acute malnutrition. Experience of members of the guideline group suggests that ready-to-use therapeutic food is not harmful or less effective than F-100 in children with severe acute malnutrition who have diarrhoea. However, research is urgently needed to confirm or refute any concern about efficacy or safety, and in particular to compare outcomes from giving ready-to-use therapeutic food or F-100.

■ The guideline development group considered that children with severe acute malnutrition who present with diarrhoea should be given ready-to-use therapeutic foods in the same way as for children with severe acute malnutrition who do not have diarrhoea, even though studies have not been explicitly conducted in this population.

■ In view of the different therapeutic foods and approaches used during the rehabilitation phase (in either inpatient or outpatient care), the guideline group considered how a child in inpatient care should transition from a milk-based therapeutic food to a ready-to-use therapeutic food. It was agreed that rapid increases in energy intake during this potentially vulnerable time are likely to be harmful.

■ It was noted that, during this period, it is important to monitor significant changes in pulse and respiration, which may indicate adverse physiological changes.

■ However, transition-feeding approaches need to be feasible, particularly in settings with limited staff available to supervise children's food intake and monitor their clinical condition. In these settings especially, transition-feeding approaches need to be defined clearly and formulated as simple stepwise changes that can be safely and simply implemented on a routine basis.

■ It was noted that children with severe acute malnutrition should not be forced to eat, by medical staff, mothers or caregivers. If children do not eat therapeutic foods, they should be assessed for signs of sepsis or other clinical complications. The group affirmed the principles outlined in the 2007 joint United Nations statement *(10)* that children with severe acute malnutrition who are managed at home may consume ready-to-use therapeutic food, directly from a container at any time of the day or night. While a child in the rehabilitation phase may eat ready-to-use therapeutic food without supervision, guided simply by appetite, mothers or other caregivers should feed the children actively and encourage them to eat. However, children should never be force fed.

■ The guideline development group aimed to provide appropriate guidance based on available evidence, but emphasized the need for research into which diets currently recommended by WHO are included for comparison, in order to confirm recommendations and resolve other important clinical issues.

■ It was noted that there are no data describing physiological responses such as intestinal, renal, hormonal or immunological function, or even recovery of lean body tissue in children with severe acute malnutrition who are managed with ready-to-use therapeutic food. Similarly, there are no data on whether physiological changes differ according to children's age or baseline anthropometric measurements.

■ It was noted that the research that has established the effectiveness of ready-to-use therapeutic food has been conducted largely in African settings. Ready-to-use therapeutic food is not widely available in South Asia, especially for use in outpatient programmes. There have been major concerns that commercial interests in South Asia might influence decisions to use one ready-to-use therapeutic food rather than another. Related to this, the group noted the importance of assessing the effectiveness of ready-to-use therapeutic food based on different ingredients, while retaining the recommended nutritional content and formulation approach.

■ The guideline development group noted that no cost data are available to assess whether therapeutic feeding with ready-to-use therapeutic food is more or less cost effective than using F-100, although there are cost data comparing inpatient and outpatient care.

■ WHO recommends that all children who present with diarrhoea should receive zinc as soon as possible, to reduce the duration and severity of the episode and the risk of dehydration. The guideline group pointed out that the 10–20 mg of zinc daily for 10 to 14 days recommended in

the 2005 WHO guidelines for diarrhoea treatment *(77)* is less than the amount already included in either F-75 or ready-to-use therapeutic food. Hence, if children with severe acute malnutrition are admitted to hospital and treated with F-75 and subsequently with ready-to-use therapeutic food, or managed as outpatients with ready-to-use therapeutic food from the beginning, they should not receive oral zinc supplements in addition to F-75 or ready-to-use therapeutic food. The guideline group commented that this should be clarified in future recommendations.

■ The guideline development group considered that the limited evidence of the effect of probiotics on diarrhoeal outcomes reported in well-nourished children could not be extrapolated to children with severe acute malnutrition. The one randomized controlled study in children with severe acute malnutrition showed no effect *(108)*.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, the joint United Nations statement on *Community-based management of severe acute malnutrition*, 2007 *(10)* and the WHO 2005 publication, *The treatment of diarrhoea: a manual for physicians and other senior health workers (77)*, noting in particular that:

■ when there are no medical complications, children with severe acute malnutrition with appetite can be managed as outpatients with ready-to-use therapeutic food and given amounts adjusted to their weight, to provide recommended energy intakes for recovery;

■ the majority of children with severe acute malnutrition who are identified through active or passive case-finding (such as community screening or communities accessing decentralized services, or health-care workers identifying cases through routine services or other contacts), do not need inpatient care but can be treated as outpatients;

■ these children can be treated with ready-to-use therapeutic food until fully recovered;

■ children who fail to respond, or who develop medical complications, should be assessed by an experienced health-care worker and referred for inpatient care;

■ children with severe acute malnutrition who have diarrhoea should receive zinc, in the same way as children who are not severely malnourished. However, children with severe acute malnutrition who are receiving F-75, F-100 or ready-to-use therapeutic food that complies with the WHO specifications should not be given additional zinc supplements even if they have diarrhoea, as these therapeutic foods contain at least the recommended amounts of zinc for management of diarrhoea;

■ because ready-to-use therapeutic food does not contain water, children should also be offered safe drinking water to drink at will. Breastfeeding should be continued and offered *ad libitum*;

■ follow-up of children being managed as outpatients, including monitoring of their response to treatment and provision of the next supply of ready-to-use therapeutic food, should be done, ideally weekly, by a skilled health-care worker in a nearby clinic or in the community.

Recommendations

5.1   Children with severe acute malnutrition who present with either acute or persistent diarrhoea, can be given ready-to-use therapeutic food in the same way as children without diarrhoea, whether they are being managed as inpatients or outpatients.

strong recommendation, very low quality evidence

5.2 *In inpatient settings where ready-to-use therapeutic food is provided as the therapeutic food in the rehabilitation phase (following F-75 in the stabilization phase)*

Once children are stabilized, have appetite and reduced oedema and are therefore ready to move into the rehabilitation phase, they should transition from F-75 to ready-to-use therapeutic food over 2–3 days, as tolerated. The recommended energy intake during this period is 100–135 kcal/kg/day. The optimal approach for achieving this is not known and may depend on the number and skills of staff available to supervise feeding and monitor the children during rehabilitation. Two options for transitioning children from F-75 to ready-to use therapeutic food are suggested:

a. start feeding by giving ready-to-use therapeutic food as prescribed for the transition phase. Let the child drink water freely. If the child does not take the prescribed amount of ready-to-use therapeutic food, then top up the feed with F-75. Increase the amount of ready-to-use therapeutic food over 2–3 days until the child takes the full requirement of ready-to-use therapeutic food, or

b. give the child the prescribed amount of ready-to-use therapeutic food for the transition phase. Let the child drink water freely. If the child does not take at least half the prescribed amount of ready-to-use therapeutic food in the first 12 h, then stop giving the ready-to-use therapeutic food and give F-75 again. Retry the same approach after another 1–2 days until the child takes the appropriate amount of ready-to-use therapeutic food to meet energy needs.

strong recommendation, very low quality evidence

5.3. *In inpatient settings where F-100 is provided as the therapeutic food in the rehabilitation phase*

Children who have been admitted with complicated severe acute malnutrition and are achieving rapid weight gain on F-100 should be changed to ready-to-use therapeutic food and observed that they accept the diet before being transferred to an outpatient programme.

strong recommendation, very low quality evidence

Rationale

The guideline group noted that the quality of evidence was very low, yet agreed that the recommendations should be strong. The group considered that the recommendations were essentially clarifications of good care rather than defining new interventions, and that it is highly unlikely that randomized clinical trials would be designed and funded to address these areas of clinical management. The guideline group thought that it would be advantageous to provide practical guidance rather than being vague and deferring such decision-making to health-care workers with less clinical experience. There are no data to inform cost implications. Overall, the guideline group was confident that such guidance would provide significant benefit to the child and avert potential harm though poor care practices.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ What are the efficacy and effectiveness of different ready-to-use therapeutic foods that comply with WHO specifications and are made from different ingredients in different regions of the world (using commercially produced ready-to-use therapeutic food as the comparison)?

◼ What is the comparative effectiveness of ready-to-use therapeutic food and F-100 for recovery of children with severe acute malnutrition who have diarrhoea?

Other issues (no specific order)

◼ What are the most effective approaches for managing the transition from F-75 to ready-to-use therapeutic food, or from F-100 to ready-to-use therapeutic food, in children with severe acute malnutrition before discharge from hospital to continued treatment as outpatients?

◼ What is the impact of different feeding approaches to management of severe acute malnutrition in integrated severe acute malnutrition services?

◼ What is the comparative efficacy (in terms of physiological, immunological and body composition recovery) and effectiveness of therapeutic foods made from locally produced food and ready-to-use therapeutic food for management of severe acute malnutrition of children in outpatient care?

◼ What body composition and physiological changes follow management of severe acute malnutrition using different durations of feeding with ready-to-use therapeutic food in children of different ages and according to different criteria for stopping ready-to-use therapeutic food (see Recommendations)?

◼ What is the relative cost effectiveness of managing severe acute malnutrition in children in hospital and community settings, taking into consideration coverage and effectiveness of services at scale?

◼ What are the key indicators of performance for integrated services for the management of severe acute malnutrition? What is an appropriate cost-effective system for standardized and minimal monitoring and reporting of performance of integrated services for the management of severe acute malnutrition? What is an appropriate and cost-effective integrated system for monitoring coverage, barriers to access and service uptake?

◼ What is a cost-effective system to integrate the management of severe acute malnutrition into routine heath systems and monitor this integration with a health-system-strengthening approach?

6.   Fluid management of children with severe acute malnutrition

Children with severe acute malnutrition have profound disturbances of normal physiology, including electrolyte imbalances and altered fluid distribution. Children with bilateral pitting oedema typically have high intracellular sodium and are therefore inclined to retain fluids. By comparison, intracellular potassium is lost to the extracellular space and total body potassium is often very low. These changes at cellular level are part of the overall adaptive responses to repeated infections and damage to cell membranes by free radicals. Children with severe wasting but without oedema also have depleted intracellular and total body potassium and similarly experience adaptive physiological changes such as reduced renal and cardiac output. As a result, they are prone to fluid retention and susceptible to fluid changes and, in particular, have reduced tolerance to rapid changes in circulating blood volume.

For these reasons, fluid management is complex in all children with severe acute malnutrition. WHO recommends a cautious approach to fluid management, especially if children have diarrhoea. It is frequently very difficult to assess and determine the hydration status and circulating volume of severely malnourished children.

6.1   Fluid management in children with severe malnutrition and dehydration without shock

Preamble

Global child mortality rates have decreased significantly over the past 10 years, even in many low-resource countries. Child deaths from diarrhoea have reduced from over 2 million each year in 1990 to about 760 000 in 2011 *(1, 124, 125)*. This is most likely a result of significant reductions in the incidence of persistent diarrhoea, cholera and dysentery over the same time period. WHO recommendations for managing children with diarrhoea have evolved and include giving WHO-standard low-osmolarity oral rehydration solution (sodium 75 mmol/L), zinc and, in cases of dysentery, suspected cholera and laboratory-proven, symptomatic *Giardia duodenalis*, appropriate antibiotics *(77)*. In children with cholera, low-osmolarity oral rehydration solution is as safe, and at least as effective, as the previously recommended WHO standard oral rehydration solution.

Children with severe acute malnutrition who also have diarrhoea and are dehydrated need additional fluids to treat dehydration. Because children with severe acute malnutrition are primed to retain sodium, there is concern that even low-osmolarity oral rehydration solution may still put these children at risk of sodium, and thereby fluid, overload. The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 (written before low-osmolarity oral rehydration solution was developed) recommended the use of a modified oral rehydration solution for malnutrition (ReSoMal), which contains 45 mmol/L sodium and 40 mmol/L potassium *(2)*. ReSoMal is not, however, appropriate for dehydrated children with severe acute malnutrition with cholera or profuse watery diarrhoea. Where ReSoMal is not available for children with severe acute malnutrition with dehydration, dissolving a packet of low-osmolarity oral rehydration solution to make up 2 L of solution instead of 1 L, and including additional potassium and glucose, is recommended *(77)*.

In light of these contextual issues, the guideline development group reviewed the evidence in order to provide guidance on the following question:

■   What is the most effective and safest fluid-management approach for children with severe acute malnutrition diagnosed with dehydration but without shock?

Summary of the evidence

A systematic review examined the management of children with severe acute malnutrition and dehydration from diarrhoea but without shock *(96)*.

Five single-centre randomized controlled trials carried out between 1997 and 2004 in India *(126–128)* and Bangladesh *(130, 131)* were identified. Three of the trials defined severe malnutrition by weight-for-age <70% of the median NCHS reference *(126)* and either weight-for-length <70% of the median NCHS reference, or bilateral pedal oedema *(129, 130)*. One trial defined severe malnutrition by weight-for-age <60% of the median in the Harvard reference, and without oedema *(127)*. Another trial *(128)* included children with different grades of malnutrition according to the Indian Academy of Pediatrics 1972 classification system.

Two trials *(126, 127)* evaluated a hypo-osmolar oral rehydration solution (containing lower concentrations of sodium, chloride and glucose) and one trial *(129)* evaluated ReSoMaL, the modified oral rehydration solution for malnutrition (containing lower concentrations of sodium, chloride and citrate, and higher concentrations of potassium and glucose, as well as other selected minerals) with the previous standard WHO oral rehydration solution (sodium = 90 mmol/L). The fourth trial *(128)* gave either a zinc-supplemented syrup or a placebo syrup in addition to the previous standard WHO oral rehydration solution. The fifth trial *(130)* evaluated three different oral rehydration solutions, to which glucose or glucose plus amylase-resistant starch or rice powder had been added. All trials took place in an inpatient setting and all five trials had similar inclusion criteria.

In summary, one trial found no significant difference in the duration of diarrhoea *(126)*, and another trial found a significantly shorter duration of diarrhoea (41.5 h, standard deviation [SD] = 25.1 h, n = 32, versus 66.4 h, SD = 32.3 h, n = 32, P = 0.001) among children receiving hypo-osmolar oral rehydration solution compared with the standard WHO solution *(127)*. Inclusion of zinc supplementation reduced the duration of diarrhoea significantly (70.4 h, SD = 10.0 h, n = 44 versus 103.4 h, SD = 17.1 h, n = 36, P = 0.0001) *(128)*. The trial comparing glucose oral rehydration solution with one containing additional amylase-resistant starch or rice powder found no significant difference in the duration of diarrhoea *(130)*. Only the second trial mentioned above *(127)* found a significant difference in the time to recovery or rehydration among children receiving the hypo-osmolar oral rehydration solution and the standard oral rehydration solution (36 h versus 53 h, P = 0.001). There was no significant difference in any other group in any of the other trials.

Consumption of oral rehydration solution was significantly lower in the hypo-osmolar group in one trial *(127)*, but not in the other one *(126)*; there was a 38% reduction in the group receiving glucose oral rehydration solution with rice powder compared to oral rehydration solution containing additional amylase-resistant starch *(130)*.

The review identified no studies that directly examined the use of different oral rehydration solution formulations for severe acute malnutrition and diarrhoea in outpatient settings. There was some evidence that ReSoMal can correct hypokalemia but not hyponatraemia *(130)*. An older trial from Bangladesh suggests that providing oral rehydration solution and immediate refeeding can achieve rehydration and reduce hypoglycemia in children with severe acute malnutrition and diarrhoea *(131)*.

The overall quality of this evidence was rated as low for the recovery from diarrhoea and rehydration. See **Annex 1**, **Table 3** for details of the GRADE assessment of the evidence.

Discussion

■ Children with severe acute malnutrition and some dehydration may receive too much sodium and insufficient potassium if treated with the previous standard WHO oral rehydration solution (90 mmol/L sodium). This concern prompted recommendations to further dilute the standard WHO oral rehydration solution or to give additional water to drink, along with potassium supplements. This was the rationale for WHO to include ReSoMal in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*.

■ ReSoMal continues to be recommended for children with severe acute malnutrition with dehydration, even though the sodium content of the recommended WHO low-osmolarity oral rehydration solution has decreased from 90 mmol/L to 75 mmol/L. The guideline group commented that there is no firm evidence of risk of sodium overload if children with severe acute malnutrition with dehydration are carefully managed with the WHO low-osmolarity oral rehydration solution (75 mmol/L sodium).

■ In the context of feeding with F-75 or ready-to-use therapeutic food, adding potassium, zinc and magnesium to an oral rehydration solution (such as is done in ReSoMal) may be less important. Therapeutic foods already include adequate amounts of these minerals and trace elements.

■ The guideline group noted that sodium losses in the stools of children with cholera are usually above 90 mosmol/L. ReSoMal is not adapted to provide the amount of sodium needed to correct losses in cholera or profuse watery diarrhoea. For this reason, it would not be advisable to use, or test the efficacy of, ReSoMal for the management of dehydration in children with severe acute malnutrition and cholera or cholera-like diarrhoea that is profuse and watery.

■ While the guideline group questioned whether low-osmolarity oral rehydration solution could be used safely and effectively without additional dilution, it noted that the ability of health-care workers to evaluate the hydration status of children with severe acute malnutrition accurately, especially when they have inadequate time and information from caregivers, may be impaired. Similarly, health-care workers' skills to monitor changes in circulating volume once treatment has started are equally critical determinants of a child's survival.

■ For these reasons, practical guidance on which signs are most effective for monitoring responses to fluids would be helpful for health-care workers in under-resourced settings.

■ Finally, the guideline group noted that where ReSoMal is not available, low-osmolarity oral rehydration solution that is not further diluted is commonly used to rehydrate children with severe acute malnutrition with some or severe dehydration.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, WHO *Training course on the management of severe malnutrition*, 2002 *(50)*, WHO *Diarrhoea treatment guidelines for clinic-based healthcare workers*, 2005 *(132)*, WHO *The treatment of diarrhoea: a manual for physicians and other senior health workers*, 2005 *(77)*, and WHO *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*, 2005 *(42)*, noting in particular that:

■ children with severe acute malnutrition and who have some or severe dehydration but no shock should receive 5 mL/kg ReSoMal every 30 min for the first 2 h. Then, if the child is still dehydrated, 5–10 mL/kg/h ReSoMal should be given in alternate hours with F-75, up to a maximum of 10 h;

■ signs of improved hydration status and overhydration should be checked every half hour for the first 2 h, then hourly;

■ ReSoMal can either be prepared from a ready-to-dilute sachet (as per supplier's instructions) or prepared with one sachet of WHO low-osmolarity oral rehydration solution plus 2 L of water with an added 50 g sugar and 40 mL mineral mix or one level scoop of combined minerals and vitamins;

■ zinc (10–20 mg per day) should be given to all children as soon as the duration and severity of the episodes of diarrhoea start to reduce, thereby reducing the risk of dehydration. By continuing supplemental zinc for 10–14 days, this will also reduce the risk of new episodes of diarrhoea in the following 2–3 months. (Note, WHO-recommended therapeutic foods already contain adequate zinc, and children with severe acute malnutrition receiving F-75, F-100 or ready-to-use therapeutic food should not therefore receive additional zinc – see **Section 5**.)

Recommendations

6.1   Children with severe acute malnutrition who present with some dehydration or severe dehydration *but who are not shocked* should be rehydrated slowly, either orally or by nasogastric tube, using oral rehydration solution for malnourished children (5–10 mL/kg/h up to a maximum of 12 h).

strong recommendation, low quality evidence

6.2   Full-strength, standard WHO low-osmolarity oral rehydration solution (75 mmol/L sodium) should not be used for oral or nasogastric rehydration in children with severe acute malnutrition who present with some dehydration or severe dehydration. Either ReSoMal or half-strength standard WHO low-osmolarity oral rehydration solution should be given, with added potassium and glucose, unless the child has cholera or profuse watery diarrhoea.

Dissolve one sachet of standard WHO low-osmolarity oral rehydration solution in 2 L water (instead of 1 L). Add 1 level scoop of commercially available combined minerals and vitamins mix[1] or 40 mL of mineral mix solution (5), and add and dissolve 50 g of sugar. In some countries, sachets are available that are designed to make 500 mL of standard WHO low-osmolarity oral rehydration solution. In this situation, dilution can be revised to add 1 L.

strong recommendation, low quality evidence

6.3   ReSoMal[2] (or locally prepared ReSoMal using standard WHO low-osmolarity oral rehydration solution) should not be given if children are suspected of having cholera or have profuse watery diarrhoea.[3] Such children should be given standard WHO low-osmolarity oral rehydration solution that is normally made, i.e. not further diluted.

strong recommendation, low quality evidence

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[1]   A specific electrolyte–micronutrient product formulated according to WHO specifications for use in the management of children with severe acute malnutrition.

[2]   ReSoMal is a powder for the preparation of an oral rehydration solution exclusively for oral or nasogastric rehydration of people suffering from severe acute malnutrition. It must be used exclusively under medical supervision in inpatient care, and must not be given for free use to the mother or caregiver.

[3]   Three or more loose or watery stools in a day, for more than 14 days.

Rationale

The guideline group noted that the quality of evidence was low and agreed that the recommendations should be strong. The group viewed that the recommendations brought clarity to areas of clinical care that were implicit in WHO documents and training materials but were not formulated as recommendations. The body of evidence supported the recommendations and relevant areas for research were identified. Oral rehydration is generally advised for the management of children with some or severe dehydration, and clarifying the same for children with severe acute malnutrition should be feasible. The recommendations should not have any adverse implications for electrolyte disturbances. The recommendations should help to avert the risks of overhydration and hyponatraemia.

6.2 Fluid management of children with severe acute malnutrition and shock

Preamble

Dehydration, usually resulting from profuse watery diarrhoea,[1] is often difficult to diagnose in malnourished children because the clinical signs usually relied on to diagnose dehydration are similar to those found in severe wasting without dehydration. The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* addresses the treatment of dehydration with appropriate caution, given the risk of overhydration and precipitating pulmonary and interstitial oedema, cerebral oedema and heart failure. The risks of overhydration are particularly critical in settings where there is no easy or rapid access to radiography, diuretics, inotropic support or other components of intensive care that are generally available in well-resourced settings. These concerns have gained more attention *(133)* following the multicentre FEAST (Fluid Expansion as Supportive Therapy) trial *(134)*, which reported increased mortality among children with severe illness in Africa who were hospitalized and received fluid boluses. However, children with severe acute malnutrition and gastroenteritis were specifically excluded from participating in that study. Therefore, while dehydrating diarrhoea is still a problem complicating the care of malnourished children, the use of oral rehydration solutions such as ReSoMal for the treatment of dehydration in malnourished children is emphasized to reduce the risks of excessive iatrogenic fluid administration, while intravenous therapy is reserved for children with shock who are lethargic or unconscious (or cannot be fed orally or by nasogastric tube) *(2)*. However, despite agreement on this principle, questions remain about the most appropriate types of fluid (oral and intravenous), the volume and rate at which it should be given and the best way to assess initial hydration status and monitor the response to fluid administration.

When resuscitating children with shock who are not malnourished, isotonic fluids are generally given intravenously to expand the circulating volume. The WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* recommends using half-strength Darrow's solution with 5% dextrose, or Ringer's lactate solution with 5% dextrose or 0.45% saline with 5% dextrose (initially 15 mL/kg/h, while observing for signs of overhydration and congestive heart failure, then changing to oral fluids by mouth or by nasogastric tube when the pulse volume has improved) for resuscitating children with severe acute malnutrition and shock. Of the three options, half-strength Darrow's solution with 5% dextrose was preferred because it has a lower sodium and higher potassium content than either of the other two fluids. However, today half-strength Darrow's solution is not commonly available in many countries. In children without severe

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[1] Three or more loose or watery stools in a day, for more than 14 days.

acute malnutrition, half-strength Darrow's solution is not recommended for resuscitation because of the risk of hyponatraemia.

Another frequently encountered complication among children hospitalized for severe acute malnutrition is severe anaemia, often associated with bacteraemia, frequent bouts of malaria, hookworm infection, HIV infection and micronutrient deficiency *(135, 136)*. Conflicting demands must be balanced when caring for severely malnourished patients with anaemia. These demands include the need to conserve limited blood products in resource-poor settings, the risk of transmission of HIV, hepatitis B, hepatitis C, and other blood-borne pathogens, and the risk of excess fluid compromising cardiac and pulmonary function (as with intravenous fluid infusions for dehydration) on the one hand, and the physiological damage and mortality that results from decreased oxygen perfusion to metabolically active tissues on the other hand. The most recent guidelines for hospitalized children with severe acute malnutrition and anaemia *(42, 137)* recommend blood transfusion for children with haemoglobin (Hb) levels <4 g/dL, or <6 g/dL if the child has respiratory distress. Children with severe acute malnutrition with these findings should only receive blood transfusion within the first 24 h of admission. A blood transfusion is also recommended if a severely malnourished child admitted with (septic) shock does not improve after 1 h of intravenous fluid therapy. Care is needed because respiratory distress can also be a sign of cardiac failure, and inappropriate blood transfusions can exacerbate heart failure, resulting in death. For children with severe acute malnutrition, especially those with shock, it remains important to identify the safest and most effective way to give such transfusions.

The guideline development group reviewed the evidence with the aim of providing guidance on the following question regarding clinical care:

◼ What is the most effective and safest fluid-management approach for children with severe acute malnutrition?

Summary of the evidence

A systematic review examined the efficacy of various fluid-resuscitation solutions for treating hypovolaemic shock in children with severe acute malnutrition *(138)*. One randomized controlled clinical trial was identified *(139)*. This trial compared the standard WHO fluid-resuscitation regimen using either hypotonic half-strength Darrow's solution with 5% dextrose, or Ringer's lactate isotonic fluid. The overall mortality rate was high and there was no statistically significant difference between groups in mortality or time to death. An inadequate correction of shock persisted after fluid-resuscitation treatment, irrespective of which fluid was used. Children who received half-strength Darrow's solution with 5% dextrose had a statistically significantly higher incidence of oligurea and tachycardia, compared with those who received isotonic Ringer's lactate.

No studies were identified that compared different fluid-volume approaches (while giving the same fluid type) or examined different methods for assessing the response to fluid administration. No prospective clinical trials were identified that examined blood or plasma infusion for treatment of shock in children with severe acute malnutrition. Seven observational studies or case-series provided data with some relevance. None were designed specifically to assess the efficacy and safety of infusions or transfusions for treatment of shock in children with severe acute malnutrition.

The principle of limiting infusions and transfusions to the sickest children with severe acute malnutrition, and only within the first 24 h after admission, is consistent with years of experience in managing non-malnourished hospitalized children, especially in settings without resources for close haemodynamic monitoring or the ability to intervene aggressively in cases of pulmonary oedema, cerebral oedema, heart failure and fluid overload. Limited evidence suggests that giving inappropriate intravenous infusions to children with severe acute malnutrition without severe

dehydration, or children who are able to tolerate oral hydration, especially after the first 24 h of admission, and giving inappropriate blood transfusions to children with severe acute malnutrition without very severe anaemia (Hb ≤4 g/dL) or shock increases the likelihood of death. Reducing the rate of these inappropriate transfusions is likely to decrease mortality rates and also help conserve limited resources.

The overall quality of the evidence was rated as very low. See **Annex 1**, **Table 4** for details of the GRADE assessment of evidence.

Discussion

■ WHO recommendations for the choice of fluid for children with severe acute malnutrition and shock, in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, were based on the premise that these children are sodium overloaded and lack potassium. The evidence for this in children with bilateral pitting oedema is strong. Analyses of tissue and cadaver samples and whole-body counting of potassium shows that this is also the case for children with severe wasting but without oedema. This may have implications for fluid-strategy approaches in different populations.

■ International guidelines for managing children without severe acute malnutrition with shock recommend the use of intravenous isotonic fluids such as Ringer's lactate solution. Intravenous fluids are generally given as a bolus of 10–15 mL/kg, repeated after 15–20 min. In many resource-limited settings, equipment is not available to monitor children's cardiorespiratory status, and health-care workers are forced to rely on clinical assessments only. The task of health-care workers is often made more difficult because health-care facilities are understaffed and they may have many other children to care for at the same time.

■ The findings of the FEAST study were discussed, even though it explicitly excluded children with severe acute malnutrition. This study reported increased mortality in children who presented with shock that was not due to dehydration if they were given rapid boluses of intravenous fluids. The guideline group concluded that it was difficult to extrapolate findings from this population to children with severe acute malnutrition.

■ With respect to the choice of intravenous fluids to use when resuscitating children with severe acute malnutrition, the guideline group noted that half-strength Darrow's solution is not available in many countries.

■ It is also complex, especially in emergency settings, to add the correct amount of glucose to make 5% dextrose solution of Ringer's lactate (also recommended for resuscitation).

■ Available evidence is unclear whether a more or less aggressive fluid strategy for treating shock would be beneficial in children with severe acute malnutrition.

■ The guideline development group noted that children with severe acute malnutrition who present with shock have an extremely high risk of mortality. It is therefore extremely difficult to undertake high-quality comparative research in this group. The group recognized that, for the same reason, many more lives could be saved by intervening earlier to prevent severe dehydration rather than being forced to manage children with shock.

■ It was also noted that future WHO guidelines should emphasize other general principles of resuscitation, in particular providing oxygen and improving breathing.

■ The guideline development group commented on the importance of treating very severe anaemia in children with severe acute malnutrition, especially if the children present with shock. Whole-blood transfusion is recommended within the first 24 h of admission in severely malnourished children presenting with severe anaemia and shock, if there is no improvement

with the first 15 mL/kg of IV fluid, even without checking haemoglobin levels. No research studies were identified that reported findings in severely malnourished children in whom alternative resuscitation approaches were used.

■ The guideline development group noted that blood for transfusion should be screened for HIV, hepatitis B and C and other blood-borne pathogens. Safe blood-transfusion services should be prioritized in all settings, to reduce the risks of inadvertently transmitting these pathogens.

■ The lack of sufficient trained staff to manage oral and intravenous fluids safely was noted as a serious limitation in many resource-limited settings. While clear protocols are important for patient care, appropriate numbers of skilled staff and adequate equipment are essential to correctly manage, and reduce mortality among, children with severe acute malnutrition.

■ The guideline development group noted that there is no evidence to demonstrate the clinical benefit of giving albumin to children with severe acute malnutrition with shock.

■ The guideline development group noted that, in addition to identifying the most effective and safest type of intravenous fluid for resuscitating children, research is urgently needed to establish the optimal fluid-volume strategy, the best way to identify children with severe acute malnutrition with severe dehydration before shock develops, and the best way to monitor clinical condition in response to resuscitation and to clarify the role of blood transfusions in the management of children with severe malnutrition, with or without shock.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, WHO *Training course on the management of severe malnutrition*, 2002 *(50)*, WHO *Diarrhoea treatment guidelines for clinic-based healthcare workers*, 2005 *(132)*, WHO *The treatment of diarrhoea: a manual for physicians and other senior health workers*, 2005 *(77)*, and WHO *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*, 2005 *(42)*, noting in particular that:

■ the general principles of resuscitation, in particular providing oxygen and improving breathing, similarly apply to children with severe acute malnutrition;

■ the only indication for intravenous infusion in a child with severe acute malnutrition is circulatory collapse caused by severe dehydration or septic shock when the child is lethargic or unconscious (excluding cardiogenic shock);

■ all children with severe acute malnutrition with signs of shock with lethargy or unconsciousness should be treated for septic shock. This includes especially children with signs of dehydration but no history of watery diarrhoea, children with hypothermia or hypoglycaemia, and children with both oedema and signs of dehydration;

■ in case of shock with lethargy or unconsciousness, intravenous rehydration should begin immediately, using 15 mL/kg/h of one of the recommended fluids;

■ it is important that the child is carefully monitored every 5–10 min for signs of overhydration and signs of congestive heart failure. If signs of overhydration and congestive heart failure develop, intravenous therapy should be stopped immediately;

■ if a child with severe acute malnutrition presenting with shock does not improve after 1 h of intravenous therapy, a blood transfusion (10 mL/kg slowly over at least 3 h) should be given;

■ children with severe acute malnutrition should be given blood if they present with severe anaemia, i.e. Hb <4 g/dL or <6 g/dL if with signs of respiratory distress;

■ blood transfusions should only be given to children with severe acute malnutrition within the first 24 h of admission.

Recommendations

6.4   Children with severe acute malnutrition and signs of shock or severe dehydration and who cannot be rehydrated orally or by nasogastric tube should be treated with intravenous fluids, either:

a.   half-strength Darrow's solution with 5% dextrose, or

b.   Ringer's lactate solution with 5% dextrose.

If neither is available, 0.45% saline + 5% dextrose should be used.

conditional recommendation, very low quality evidence

Rationale

The guideline group noted that the quality of evidence was very low and considered that the recommendation should be conditional. The updated recommendation revises the guidance included in the 1999 manual *(2)* and changes the order of preference of recommended intravenous fluids; no new types of fluids were introduced or omitted. While not formally examined, the new recommendation should not have cost implications or altered opportunity costs, as all three fluids were similarly included in previous recommendations. Discussion highlighted the physiological difference between children who are shocked and who have or do not have severe acute malnutrition. There was uncertainty whether recent data from managing shock in children without severe acute malnutrition could be extrapolated to children with severe acute malnutrition. It was agreed that this aspect of care is very complex and research is urgently needed to inform clinical recommendations and care.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ What is the efficacy and safety of ReSoMal compared with that of 75 mosmol/L oral rehydration solution in severely malnourished dehydrated children with non-cholera diarrhoea?

■ What are the most effective ways to assess and monitor the hydration status of children with severe acute malnutrition who present with some dehydration (but no shock)?

■ What are the most appropriate fluid strategy (type, volumes, rate) and monitoring approaches for managing children with severe acute malnutrition, with or without oedema, who present with severe dehydration or shock?

■ How can the diagnosis and severity of dehydration in children with severe acute malnutrition be improved and how can the types of shock, especially hypovolaemic, septic and cardiogenic, be differentiated better, in order to guide the most appropriate management?

■ What is the best way to monitor the clinical condition in response to resuscitation for severe dehydration or shock in children with severe acute malnutrition?

■ What is the role of blood transfusions in the management of children with severe malnutrition, with or without shock?

7.   Management of HIV-infected children with severe acute malnutrition

Preamble

HIV-infected children commonly present with moderate or severe acute malnutrition *(13)*. The exact cause of wasting in these children is probably multifactorial but includes altered glucose and lipid metabolism, raised basal metabolic rate, especially when opportunistic infections are present, multiple micronutrient deficiencies, higher rates of diarrhoea and malabsorption, frequent co-infections and higher rates of food insecurity and poverty. The health and survival of HIV-infected children also suffer when their mothers become ill or die and cannot provide care as usual. As a result of being immune compromised, HIV-infected children suffer high mortality rates, even without the added complication of severe acute malnutrition *(140)*. However, HIV-infected children with severe acute malnutrition are nearly three times more likely to die while on nutritional rehabilitation therapy, compared to their HIV-negative counterparts *(13)*.

HIV-infected children are susceptible to higher rates of persistent diarrhoea and to opportunistic infections such as tuberculosis (TB), cryptosporidiosis, disseminated candidiasis and cryptococ-cosis. Yet, despite these well-recognized clinical patterns, there has been little research on the management of HIV-infected children with severe acute malnutrition.

The effectiveness of antiretroviral drug treatment to significantly reduce the frequency of opportunistic infection and improve the survival of HIV-infected adults and children provides cause for hope. WHO recommends that all infants below 24 months of age should be started on antiretroviral drug treatment, irrespective of clinical condition, and that children who are 24 months of age or older should start if, among other criteria, there is unexplained malnutrition *(141)*. For these reasons, WHO recommends screening of children to determine HIV status where there are any clinical signs consistent with HIV infection, and to assess eligibility for antiretroviral drug treatment. In the context of severe acute malnutrition, children who are known to be HIV exposed should be tested for HIV status, in order to determine their status and eligibility for antiretroviral drug treatment. In settings where HIV infection is common (HIV prevalence more than 1%), children with malnutrition should be tested for HIV, in order to establish their HIV status and to determine their need for antiretroviral drug treatment. WHO provides simplified dosing schedules for antiretroviral drugs based on weight bands.

In many settings, individuals and families who are infected or affected by HIV are the target of marketing of commercial products claiming to provide specific benefit to persons infected with HIV. These products, frequently nutritional products, have generally not been tested to demonstrate efficacy or not. In light of this influence, it is important to clarify which interventions provide clinical benefit to adults and children infected with HIV *(142)*.

Four key issues related to the care of HIV-infected children with severe acute malnutrition, for which guidance should be developed were identified:

■ What is the optimal timing for initiating and dosing of antiretroviral drug treatment?

■ What are the optimal feeding regimens for HIV-infected children with severe acute malnutrition and do these differ from those for uninfected children with severe acute malnutrition?

■ What is the value (effectiveness and safety) of vitamin A supplementation?

■ What are the most effective therapeutic strategies for managing diarrhoea?

Summary of the evidence

A systematic review was conducted to examine these aspects of the treatment of HIV-infected children with severe acute malnutrition *(143)*. No randomized controlled trials in HIV-infected children with severe acute malnutrition were identified that directly addressed any of the prioritized questions. Indirect evidence was available from other randomized trials and observational studies that reported outcomes of HIV-infected children who were undernourished, of whom some were severely malnourished. However, relevant anthropometric indices were not generally reported to determine whether any of the children fulfilled WHO definitions of severe acute malnutrition.

Nine observational studies reported outcomes of HIV-infected children started on lifelong antiretroviral drug treatment. Low weight-for-age was associated with increased mortality *(144–146)*, and the development of immune reconstitution inflammatory syndrome *(147)*. One retrospective study among malnourished children admitted for therapeutic feeding reported improved recovery when antiretroviral drug treatment was started within 21 days of admission compared to children who had delayed initiation of, or who were not considered eligible, for antiretroviral drug treatment *(148)*. There were no data regarding the use of different antiretroviral regimens and their relative outcomes in HIV-infected children with severe acute malnutrition. Two studies reported pharmacokinetic data on HIV-infected children. Suboptimal dosing was not found when dosing was based on weight-band tables compared to requirements estimated using calculations of surface area *(149)*. One study from India reported no difference in trough or 2-h nevirapine concentrations in children with weight-for-age Z-score <–2, compared to weight-for-age Z-score ≥–2, though stunted children had significantly lower median 2-h nevirapine concentrations compared to non-stunted children *(150)*.

For HIV-infected children with severe acute malnutrition, there were no controlled comparative trials examining the effect of WHO-recommended therapeutic feeding approaches compared with other therapeutic feeds. Observational studies reported clinical recovery when ready-to-use therapeutic food was given *(151, 152)*, but these did not compare outcomes with other therapeutic feeds such as F-100. One randomized trial examined the effect of a combination prebiotic and probiotic included as part of a therapeutic feeding approach. There was no benefit evident from inclusion of the combination product *(89)*.

No studies directly tested the value of vitamin A in the care of HIV-infected children with severe acute malnutrition. However, indirect evidence from studies evaluating the effect of vitamin A supplements (200 000 IU every 4 months) in HIV-infected children who were 15–36 months of age without severe acute malnutrition reports improved growth and decreased all-cause mortality when children are regularly given supplements of vitamin A *(153)*. There were no reports of adverse effects of vitamin A in HIV-infected children and there is currently no reason to believe that vitamin A might have an adverse effect in HIV-infected children with severe acute malnutrition.

Although diarrhoea is common in both HIV-infected children and children with severe acute malnutrition, there were no controlled studies identified that directly investigated diagnostic strategies or clinical interventions for HIV-infected children with severe acute malnutrition and diarrhoea. Indirect evidence suggests that *Cryptosporidium* is a common pathogen causing diarrhoea and that disaccharide intolerance is also common. While one study examined clinical outcomes following therapeutic feeding with either an elemental milk diet or a skimmed milk and soya diet, there is not even indirect evidence about the use of F-100 in children with HIV infection and diarrhoea.

There was similarly no direct evidence about the effect of zinc supplements in HIV-infected children with severe acute malnutrition who have diarrhoea. Zinc has been found to be safe in HIV-infected children without severe acute malnutrition *(153)*. However, the effect of zinc on prevention or

management of diarrhoea in HIV-infected children, with or without severe acute malnutrition, is yet to be established. Given that there are no reported adverse effects of giving zinc to children with HIV infection, there appears to be no basis to omit zinc from the routine management of HIV-infected children with severe acute malnutrition.

The overall quality of this evidence has been rated as very low, owing to indirectness and imprecision. A GRADE table was not developed as there were no studies that directly reported the outcomes of interest in HIV-infected children with severe acute malnutrition.

Discussion

■ The former WHO recommendations on severe malnutrition *(2)* did not recommend HIV testing of children with severe acute malnutrition, even in settings of high HIV prevalence. At that time, there was little experience with the use of antiretroviral drugs in children, nor was there significant coverage of antiretroviral drugs as an intervention. Circumstances today are very different.

■ There is high-quality evidence that antiretroviral drug treatment significantly improves the survival of children who are infected with HIV. WHO recommends that children are tested for HIV, especially in high-prevalence settings, when there are clinical signs consistent with HIV infection, or when there is known exposure *(141)*. In the context of severe acute malnutrition, there is strong justification for routinely testing all children for HIV, in order to identify a population that would benefit from a highly effective intervention, namely antiretroviral drug treatment.

■ There remains little direct evidence on the management of HIV-infected children with severe acute malnutrition. The questions identified by the guideline development group remain largely unanswered and recommendations are largely based on extrapolations of evidence in other populations and personal experience. There are several studies currently ongoing examining the pharmacokinetics of antiretroviral drugs in HIV-infected children with severe acute malnutrition. They are also designed to examine some of the mechanisms and risk factors for children developing immune reconstitution inflammatory syndrome. However, other important issues remain unexamined and research is urgently needed. Apart from prioritizing the initiation of antiretroviral drug treatment, the guideline group considered there was no basis, either from indirect evidence or on the grounds of biological plausibility, to recommend management approaches for HIV-infected children with severe acute malnutrition that differed significantly from what is recommended for uninfected children.

Relevant standing recommendations

The recommendations below were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)*, WHO *Diarrhoea treatment guidelines for clinic-based healthcare workers*, 2005 *(132)*, WHO *Guidelines for an integrated approach to the nutritional care of HIV-infected children*, 2009 *(142)*, WHO guidelines on *Antiretroviral therapy for HIV infection in infants and children*, 2010 *(141)*, and WHO *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*, 2011 *(154)*, noting in particular that:

■ all HIV-exposed infants and children (including those with severe acute malnutrition) should be tested for HIV status;

■ in settings where HIV infection is common (HIV prevalence more than 1%), children with severe acute malnutrition should be tested for HIV, in order to establish their HIV status and to determine their need for antiretroviral drug treatment;

- ■ all HIV-infected infants and children who are less than 24 months of age should be initiated with lifelong antiretroviral drug treatment, irrespective of clinical staging (including severe acute malnutrition) and CD4 count. Co-trimoxazole prophylaxis should also be initiated;

- ■ all HIV-infected children who are over 24 months and less than 5 years of age should be started on lifelong antiretroviral drug treatment based on their CD4 count (≤750 cells/mm³) or CD4 percentage (≤25%), or if they have WHO clinical staging 3 or 4 (including severe acute malnutrition). A new recommendation is due to be published in 2013;

- ■ children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions.

Recommendations

7.1 Children with severe acute malnutrition who are HIV infected and who qualify for lifelong antiretroviral therapy should be started on antiretroviral drug treatment as soon as possible after stabilization of metabolic complications and sepsis. This would be indicated by return of appetite and resolution of severe oedema. HIV-infected children with severe acute malnutrition should be given the same antiretroviral drug treatment regimens, in the same doses, as children with HIV who do not have severe acute malnutrition. HIV-infected children with severe acute malnutrition who are started on antiretroviral drug treatment should be monitored closely (inpatient and outpatient) in the first 6–8 weeks following initiation of antiretroviral therapy, to identify early metabolic complications and opportunistic infections.

strong recommendation, very low quality evidence

7.2 Children with severe acute malnutrition who are HIV infected should be managed with the same therapeutic feeding approaches as children with severe acute malnutrition who are not HIV infected.

strong recommendation, very low quality evidence

7.3 HIV-infected children with severe acute malnutrition should receive a high dose of vitamin A on admission (50 000 IU to 200 000 IU depending on age) and zinc for management of diarrhoea as indicated for other children with severe acute malnutrition, unless they are already receiving F-75, F-100 or ready-to-use therapeutic food, which contain adequate vitamin A and zinc if they are fortified following the WHO specifications.

strong recommendation, very low quality evidence

7.4 HIV-infected children with severe acute malnutrition in whom persistent diarrhoea does not resolve with standard management should be investigated to exclude carbohydrate intolerance and infective causes, which may require different management, such as modification of fluid and feed intake, or antibiotics.

strong recommendation, very low quality evidence

Rationale

The guideline group agreed that the recommendation should be strong, while noting that the quality of evidence was very low. No studies reported on the effect of the timing of starting antiretroviral drug treatment and mortality. Initiation of antiretroviral drug treatment and rates of recovery and weight gain were, however, noted. Initiation of antiretroviral drug treatment is already recommended for HIV-infected children who have severe acute malnutrition on clinical criteria.

The first recommendation above aims to clarify how quickly treatment should be started, not whether it should be started. The guideline group considered that it is feasible to start antiretroviral drug treatment when appetite returns and, even though cost data were not presented or formally estimated, this timing would not have significant cost implications compared to starting 1–2 weeks later. The guideline group considered that the other recommendations serve to clarify relevant care and appropriately promote consistency of care for the three populations, namely HIV-infected children, children with severe acute malnutrition and HIV-infected children with severe acute malnutrition. The guideline group considered there to be major advantages, e.g. for training and supply-chain management, and little risk of harm in harmonizing recommendations.

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

- Does early initiation of antiretroviral drug treatment (as soon as metabolic complications are stabilized and sepsis is treated) in HIV-infected children with severe acute malnutrition improve outcomes and reduce adverse events such as immune reconstitution inflammatory syndrome or dyslipidaemia, compared with later initiation?

- Are the pharmacokinetic characteristics of HIV-infected children with severe acute malnutrition being started on antiretroviral drug treatment different from those of HIV-infected children who do not have severe acute malnutrition? Is there any need to modify the dose of antiretroviral drugs in HIV-infected children who are severely malnourished, to either avoid toxicity or ensure adequate therapeutic levels?

- Are the pharmacokinetic characteristics of HIV-infected children with severe acute malnutrition receiving other drugs, such as isoniazid, different from those of HIV-infected children who do not have severe acute malnutrition?

- What is the optimal dosing of antiretroviral drug treatment in HIV-infected children with severe acute malnutrition, to optimize clinical recovery and viral suppression and avoid the development of metabolic complications such as immune reconstitution inflammatory syndrome?

- What is the most effective therapeutic feeding approach for HIV-infected children with severe acute malnutrition who have persistent diarrhoea?

- Are the pathophysiological abnormalities of HIV-infected children with severe acute malnutrition, with or without oedema, the same as those of children with severe acute malnutrition but without HIV?

8. Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

Preamble

Severe acute malnutrition is increasingly being recognized in infants who are less than 6 months of age (155). In addition to aetiologies such as low birth weight, persistent diarrhoea and recurring sepsis or chronic underlying diseases or disability, the development of severe acute malnutrition in this age group commonly reflects suboptimal feeding practices, especially breastfeeding practices. Infants who are less than 6 months of age should be exclusively breastfed to gain optimal nutrition and the greatest protection against infections. Yet, rates of exclusive breastfeeding worldwide remain disappointingly low, with only an estimated 25–31% of infants who are 2–5 months of age being exclusively breastfed (7).

Severe acute malnutrition is often associated with higher mortality in young infants than in older infants and children (24). While this is not unexpected, given the greater vulnerability of young infants and the range of possible underlying or contributing pathologies, the magnitude of this excess mortality risk and how much of it is avoidable are unknown. Few studies have examined the risk factors for young infants developing severe acute malnutrition; similarly, there are few reports describing approaches to managing severe acute malnutrition in this age group. Risk factors for increased mortality are likely to include recent weight loss, failure to gain weight, failure to feed effectively and the presence of bilateral oedema (24). To date, management of severe acute malnutrition in this age group has focused on establishing, or re-establishing exclusive breastfeeding, and, where this has not been possible, there are some reports of using formula feeds and early introduction of complementary foods to treat these infants (24).

However, there are important physiological differences between young infants and older children that justify separate consideration of the management of severe acute malnutrition in this age group. Before 6 months of age, physiological processes, including thermoregulation and renal and gastrointestinal functions, are relatively immature compared with those of older children and may require modified management approaches or clinical interventions. Clinical signs of infection and hydration status may also be more difficult to identify and interpret in the younger infant. As a result, criteria for admitting and discharging infants with severe acute malnutrition have not been adequately defined. Furthermore, it is unclear whether criteria and management approaches for older children with severe acute malnutrition, including outpatient care, can be appropriately extended to this population.

The guideline development group aimed to provide guidance on the following questions:

■ What are the criteria for defining severe acute malnutrition in infants who are less than 6 months of age?

■ What are the criteria for hospital admission of infants who are less than 6 months of age with severe acute malnutrition?

■ What are the essential interventions, especially feeding approaches, for infants who are less than 6 months of age with severe acute malnutrition?

■ What are the criteria for transferring infants who are less than 6 months of age and have been treated in hospital for severe acute malnutrition to outpatient care, or discharging them from treatment?

Summary of the evidence

Systematic reviews were conducted to review the admission and discharge criteria for the management of infants who are less than 6 months of age with severe acute malnutrition *(156)*, and inpatient treatment of severe acute malnutrition in infants who are less than 6 months of age *(157)*.

No studies were identified that directly examined admission and discharge criteria using the WHO growth standards *(8)*. No studies were found in the peer-reviewed literature that reported outcomes when WHO therapeutic feeding recommendations for children who are over 6 months of age with severe acute malnutrition are applied to severely malnourished infants who are less than 6 months of age.

Infants who are less than 6 months of age with severe acute malnutrition were included in some studies *(158–161)* examining therapeutic feeding approaches. Subgroup analyses were not possible however, because of small sample sizes or inadequate detail of treatment for this subgroup. A randomized controlled trial in the Democratic Republic of the Congo *(37, 162)* recruited 161 infants who were less than 6 months of age with severe acute malnutrition defined as weight-for-length less than 70% of the median NCHS reference values, and who did not have oedema. However, infants who were not gaining weight at home or were too weak to breastfeed, or where the mother reported an inability to breastfeed, were also included. Infants were randomized to receive either diluted F-100 therapeutic milk (73.11 kcal/100 mL) or an isocaloric standard generic infant formula milk (76.7 kcal/100 mL). Infants were otherwise given the same treatment, which included support for continued breastfeeding, supplemental suckling when needed and vitamins, folic acid and antibiotics. The volumes of dilute F-100 or generic infant formula milk supplement were decreased by half when the infant was gaining at least 20 g/day for three consecutive days and were completely stopped when the infant maintained 10 g/day weight gain. No differences were found in weight gain, total duration of treatment, or treatment outcome (death, recovery or default).

A doctoral thesis, however, reported the use of WHO therapeutic feeding protocols for children who were 6–59 months of age when they were applied to infants who were less than 6 months of age. Infants from 13 countries in Africa were admitted for treatment of severe acute malnutrition, having been identified by weight-for-length <70% of the median reference value (NCHS). Infants who were less than 6 months of age had a higher mortality rate, particularly those who were not breastfed, than children with severe acute malnutrition who were older but treated with the same protocol. Attempts to put the infants to the breast up to 24 times a day were abandoned because of rapid weight loss *(107)*. The supplemental suckling technique was subsequently successfully introduced to feed such infants *(38)*. The increased mortality was considered to be due to the use of undiluted F-100, which resulted in a high renal solute load.

No studies examined feeding approaches in the transition and rehabilitation phases of treatment of severe acute malnutrition in infants who were less than 6 months of age. In some national guidelines that include supplemental suckling treatment as part of care for these infants, the volume of supplemental milk is gradually stepped down and ultimately stopped, as the infant improves and the supply of breast milk is re-established *(24)*. However, this practice has not been referred to as "transitioning" to a rehabilitation phase. No references were found regarding the use of cup or spoon feeding in the context of young infants with severe acute malnutrition, although their effectiveness has been shown in young children without severe acute malnutrition in other settings.

The overall quality of this evidence has been rated as very low, owing to indirectness and imprecision. As no studies were found in the peer-reviewed literature to address the specific questions identified by the guideline group, it was not possible to develop GRADE tables for the assessment of evidence.

Discussion

■ There is little empirical evidence available to inform recommendations on the management of severe acute malnutrition in infants who are less than 6 months of age. However, the guideline group acknowledged that programmatic guidance is important for health-care workers treating severe acute malnutrition in this age group. However, a summary of case-reports on how infants who are less than 6 months of age with severe acute malnutrition are being managed in some settings is available *(24)*.

■ The guideline development group placed value on highlighting general nutritional and infant feeding principles and their application to young infants with severe acute malnutrition.

■ It was also agreed that general principles on the care of sick neonates and infants, such as identifying and referring infants who are seriously ill for other reasons, can reasonably be extended to infants with severe acute malnutrition.

■ The group highlighted the relevance and value of other existing recommendations, even though they are not explicitly for infants with severe acute malnutrition. These include WHO *Guiding principles for feeding non-breastfed children 6–24 months of age*, 2005 *(163)*, or the WHO *Infant and young child feeding counselling: an integrated course*, 2006 *(164)*.

■ It was considered that the use of the recently published 2011 WHO growth velocity standards *(8)* and the assessment of growth velocity (weight) was equally important as, or even more important than, a single weight-for-length value. This highlights the value of maintaining and examining growth-monitoring charts at primary health-care level for infants and young children.

■ As with older children, severe acute malnutrition in infants who are less than 6 months of age can be "uncomplicated" or "complicated". These infants should be managed in outpatient or inpatient settings respectively. The potential benefits of inpatient treatment should be carefully considered against the potential risks, especially nosocomial infections.

■ The guideline development group acknowledged that generic infant formula milk can be provided safely in some inpatient settings. However, mothers or caregivers, who are expected to give formula milk to their infants after they are discharged from inpatient care, need clear guidance on safe preparation and use of such replacement feeds. This information is included in the WHO integrated course on infant and young child feeding *(164)*.

■ The guideline development group also emphasized that when programmes provide formula milk as part of case-management of infants with severe acute malnutrition, it should be implemented appropriately and not confuse or compromise the wider public health message concerning exclusive breastfeeding for infants who are less than 6 months of age.

■ There is limited evaluated experience and evidence on managing infants who are less than 6 months of age with bilateral oedema, especially regarding the use of F-75 and diluted F-100. The question was considered by participants of a WHO meeting held in 2004 to review programmatic data and theoretical considerations on the management of severe acute malnutrition in young infants. The participants concluded that young infants with oedema should be fed with F-75 during the stabilization phase *(164)*.

■ In contrast, participants of the same meeting concluded that F-75 would not be appropriate for infants with severe acute malnutrition who are severely wasted and without oedema *(165)*. Rather, generic infant formula or dilute F-100 would be appropriate and safer. However, there were no data presented at the meeting to substantiate these conclusions.

■ The meeting report described the diversity of opinions on the feeding strategy for the rehabilitation phase. However, there was consensus that children who are less than 6 months of age with severe acute malnutrition should not be given *undiluted* F-100, owing to high renal solute load and risk of insufficient water intake and hypernatraemic dehydration *(165)*.

■ Infants who are less than 6 months of age have small daily weight gains that cannot easily be assessed with standard spring scales. Health-care workers taking care of infants with severe acute malnutrition should use scales with at least a 20 g precision.

■ It was noted that, in some sites, ready-to-use therapeutic food is being given to infants who are 5–6 months of age, sometimes as a pragmatic response to situations where exclusive breastfeeding is either not possible or difficult for a variety of reasons. Participants recognized that there is no evaluated experience or evidence to indicate the effectiveness and safety of this approach.

■ As with several other aspects of care, an urgent research agenda was identified.

Relevant standing recommendations

The recommendations were confirmed as current in the context of existing WHO recommendations included in the WHO *Management of severe malnutrition: a manual for physicians and other senior health workers*, 1999 *(2)* and *Management of the child with a serious infection or severe malnutrition. Integrated Management of Childhood Illness* (IMCI) 2000 *(16)*, noting in particular that:

■ severe acute malnutrition in infants who are 0–5 months of age is defined as:

— weight-for-length less than –3 Z-score, or

— presence of bilateral pitting oedema;

■ infants who have been identified to have poor weight gain and who have not responded to nutrition counselling and support (IMCI) should be admitted for further investigation and treatment;

■ any infant or child with a general danger sign as defined by the IMCI *(16)*[1] should be admitted for urgent treatment and care.

Recommendations

8.1   Infants who are less than 6 months of age with severe acute malnutrition with any of the following complicating factors should be admitted for inpatient care:

a. any serious clinical condition or medical complication as outlined for infants 6 months of age or older with severe acute malnutrition;

b. recent weight loss or failure to gain weight;

c. ineffective feeding (attachment, positioning and suckling) directly observed for 15–20 min, ideally in a supervised separated area;

d. any pitting oedema;

e. any medical or social issue needing more detailed assessment or intensive support (e.g. disability, depression of the caregiver, or other adverse social circumstances).

strong recommendation, very low quality evidence

[1]   Danger signs: unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now.

8.2   Infants who are less than 6 months of age with severe acute malnutrition should receive the same general medical care[1] as infants with severe acute malnutrition who are 6 months of age or older:

   a.   infants with severe acute malnutrition who are admitted for inpatient care should be given parenteral antibiotics to treat possible sepsis and appropriate treatment for other medical complications such as TB, HIV, surgical conditions or disability;

   b.   infants with severe acute malnutrition who are not admitted should receive a course of broad-spectrum oral antibiotic, such as amoxicillin, in an appropriately weight-adjusted dose.

   strong recommendation, very low quality evidence

8.3   Feeding approaches for infants who are less than 6 months of age with severe acute malnutrition should prioritize establishing, or re-establishing, effective exclusive breastfeeding by the mother or other caregiver.

   strong recommendation, very low quality evidence

8.4   Infants who are less than 6 months of age with severe acute malnutrition who are admitted:

   a.   should be breastfed where possible and the mothers or female caregivers should be supported to breastfeed the infants. If an infant is not breastfed, support should be given to the mother or female caregiver to re-lactate. If this is not possible, wet nursing[2] should be encouraged;

   b.   should also be provided a supplementary feed:

      —   supplementary suckling approaches should, where feasible, be prioritized;

      —   for infants with severe acute malnutrition but no oedema, expressed breast milk should be given, and, where this is not possible, commercial (generic) infant formula or F-75 or diluted F-100[3] may be given, either alone or as the supplementary feed together with breast milk;

      —   for infants with severe acute malnutrition and oedema, infant formula or F-75 should be given as a supplement to breast milk.

   c.   should not be given undiluted F-100 at any time (due to the high renal solute load and risk of hypernatraemic dehydration);

   d.   if there is no realistic prospect of being breastfed, should be given appropriate and adequate replacement feeds such as commercial (generic) infant formula, with relevant support to enable safe preparation and use, including at home when discharged.

   In addition:

   e.   assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided.

   strong recommendation, very low quality evidence

8.5   Infants who are less than 6 months of age and have been admitted to inpatient care can be transferred to outpatient care when:

   a.   all clinical conditions or medical complications, including oedema, are resolved, and

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[1]   Recommendations regarding vitamin A, zinc and other micronutrients were not reviewed in this guideline process.
[2]   All potential wet nurses should be tested for HIV.
[3]   Prepared F-100 should be further diluted by adding 30% water.

b. the infant has good appetite, is clinically well and alert, and

c. weight gain on either exclusive breastfeeding or replacement feeding is satisfactory, e.g. above the median of the WHO growth velocity standards or more than 5 g/kg/day for at least 3 successive days, and

d. the infant has been checked for immunizations and other routine interventions, and

e. the mothers or caregivers are linked with needed community-based follow-up and support.

strong recommendation, very low quality evidence

8.6   Infants who are less than 6 months of age can be discharged from all care when they:

a. are breastfeeding effectively or feeding well with replacement feeds, and

b. have adequate weight gain, and

c. have a weight-for-length ≥–2 Z-score.

strong recommendation, very low quality evidence

8.7   For infants who are less than 6 months of age with severe acute malnutrition and who do not require inpatient care (Recommendation 8.1), or whose caregivers decline admission for assessment and treatment:

a. counselling and support for optimal infant and young child feeding should be provided, based on general recommendations for feeding infants and young children, including for low-birth-weight infants;

b. weight gain of the infant should be monitored weekly to observe changes;

c. if the infant does not gain weight, or loses weight while the mother or caregiver is receiving support for breastfeeding, then he or she should be referred to inpatient care;

d. assessment of the physical and mental health status of mothers or caregivers should be promoted and relevant treatment or support provided.

strong recommendation, very low quality evidence

Rationale

The guideline group noted that the quality of evidence was very low but the group was in agreement that the recommendations should be strong. The majority of recommendations outline care practices that are commonly regarded as standard of care and reflected in other WHO recommendations, especially the IMCI *(16)* and the WHO *Pocket book of hospital care for children (42)*. Others are documented in reviews of clinical practice that are cited above. The guideline group also noted that guidelines have not previously been written for this specific age group of infants with severe acute malnutrition. It is therefore of value to affirm principles for this population that are already accepted for other groups, e.g. establishing effective exclusive breastfeeding by the mother or other caregiver, or assessing the physical and mental health status of mothers. The guideline group regarded the recommendations to be important principles of care that may not be easily subjected to randomized controlled trials. The group considered that recommending these practices, even in the absence of clinical or costing data, would benefit infants with severe acute malnutrition with no risk, or negligible risk, of harm. The guideline group hoped that outlining areas of good practice would highlight the need for research in this population of infants that would begin to build an evidence base for best clinical care, e.g. the most effective and safest therapeutic feeding approaches (see below).

Implications for future research

Discussion with guideline development group members and stakeholders highlighted the limited evidence available in themes related to the priority areas listed next.

■ In infants who are less than 6 months of age, what is the predictive value of population-derived thresholds for weight-for-height, mid-upper arm circumference and reduced growth velocity (weight-for-age) with or without oedema to identify infants at high risk of mortality?

— Consider analysis of published or other existing data.

— Consider the feasibility of each assessment.

■ What are the most effective and safest therapeutic feeding approaches, including different food "recipes" in addition to breastfeeding, for infants who are less than 6 months of age with severe acute malnutrition?

■ How is breastfeeding most effectively re-established among infants with a low weight-for-height/poor weight gain?

Other issues (no specific order)

■ Do infants who are less than 6 months of age with weight-for-length less than –3 Z-score also have reduced growth velocity and is there any difference according to epidemiological setting such as African, South Asian and South-East Asian sites?

■ In infants who are less than 6 months of age, what is the feasibility and accuracy of using weight-for-height, mid-upper arm circumference and reduced growth velocity (weight-for-age) with or without oedema to identify infants in need of therapeutic management?

■ What criteria most effectively identify infants who are less than 6 months of age with the metabolic abnormalities/adaptations associated with severe acute malnutrition in older children?

■ What is the effectiveness, tolerance and safety of ready-to-use therapeutic food as an adjuvant to breastfeeding in infants who are less than 6 months of age with severe acute malnutrition?

— Consider specific subgroups, e.g. with oedema, 4–6months old, those with underlying diseases such as HIV.

■ What is the recommended folic acid supplementation for infants who are less than 6 months of age with severe acute malnutrition?

■ Are there adjustments in the drug dosage or selection of drugs required when managing infants who are less than 6 months of age with severe acute malnutrition?

■ Is there any reason to expect that the efficacy of vitamin A supplementation for infants who are less than 6 month of age with severe acute malnutrition is different from that observed in infants who are 1 to 5 months of age without severe acute malnutrition?

Dissemination, adaptation and implementation

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through the Global Inter-Agency Standing Committee Nutrition Cluster Working Group and United Nations Standing Committee on Nutrition (http://www.unscn.org/) mailing lists or the WHO nutrition web site (http://www.who.int/nutrition/en/). The WHO Department of Nutrition for Health and Development has developed an electronic Library of Evidence for Nutrition Actions (eLENA; http://www.who.int/elena/en/). This library aims to compile and display WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence informing the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners.

Adaptation and implementation

The current guideline, together with other updated guidelines on child health will be the basis for updating the WHO manual *(2)*, as well as the *WHO training course on the management of severe malnutrition (50)*.

Countries have requested this updated guidance in order to revise their national protocols on severe malnutrition and to improve their capacity in the management of severe malnutrition.

Monitoring and evaluation of guideline implementation

The impact of this guideline and the derivative products (the manual and the training course) can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. adoption and adaptation of the guideline globally).

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has a centralized platform for sharing information on nutrition action in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into nutrition actions.

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development (3)*.

In summary, this involved:

1. *Identification of priority questions and outcomes* – the Nutrition Guidance Advisory Group comprised content experts, methodologists, representatives of potential stakeholders and consumers (see **Annex 3**). They met in Geneva, Switzerland on 2–4 June 2010 and formulated the questions to be examined through systematic reviews. The group prioritized the areas of clinical care for which updated guidance is needed and identified what evidence was needed as being critical for decision-making and what other evidence was important or not essential for decision-making.

2. *Systematic reviews* were subsequently commissioned to retrieve relevant evidence for guideline development. Academic groups were identified that were experienced in evidence retrieval, assessment and synthesis. Primary authors provided declarations of interest.

3. *Evidence identified in the systematic reviews for any given outcome was assessed*. In brief, GRADE categorizes the quality of evidence as high, moderate, low or very low. These quality ratings apply to the body of evidence assessed for the PICO question,[1] not to individual studies. In general, evidence based on randomized controlled trials is given a high quality rating and evidence from observational studies is given a low quality rating. These initial ratings can be adjusted by the following factors:

   ■ study limitations such as concealment, blinding, type of analysis;

   ■ consistency, namely whether the results from the different studies are similar and in the same direction of effect;

   ■ directness, namely whether the population, intervention or comparator are the same as for the guideline under consideration;

   ■ imprecision, namely whether data arise from a large or small population;

   ■ reporting bias, namely whether there is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies or selective reporting of outcomes.

Other considerations, such as dose–response gradients, direction of plausible bias and magnitude of effect are also important.

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[1] PICO is an acronym that describes the elements of a well-formed clinical question. These include patient/population, intervention, control, outcomes.

Comments related to the domains that inform the assessment of the quality of evidence for each outcome are presented with respective GRADE tables.

Findings of research identified through this process were synthesized as GRADE tables (see **Annex 1**). GRADE tables were formulated only for outcomes that had been ranked as critical by the Nutrition Guidance Advisory Group. Data related to important outcomes were summarized in the narrative. In view of the paucity of data from randomized trials and the heterogeneity of definitions and interventions, it was not possible in most instance to undertake meta-analyses of results. Instead, findings from relevant studies are included in the tables.

Formulation of recommendations, including future research priorities

Draft recommendations are prepared by WHO staff. Following presentation of the systematic reviews, the Nutrition Guidance Advisory Group reviewed the draft recommendation and determined whether it is supported by the evidence. NUGAG and the external resources people met for this purpose on 2–4 June 2010, 14–16 March 2011 and 1–3 February 2012. In addition, the group considered: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) cost. The cost of options available to health-care workers in different settings was not formally assessed, owing to lack of primary data in the literature or elsewhere. However, cost implications were considered as part of general discussion by the Nutrition Guidance Advisory Group . There were no primary costing data included in the literature reviewed and hence comments were restricted to personal experiences and extrapolations from general cost considerations of programmes. The Nutrition Guidance Advisory Group also allocated a strength of recommendation, strong or conditional, which is reported as part of the guideline.

Advisory groups

A WHO Steering Committee for Nutrition Guidelines Development, led by the Department of Nutrition for Health and Development, was established in 2010, with representatives from all WHO departments with an interest in the provision of scientific nutrition advice. The steering committee guided the development of this guideline and provided overall supervision of the guideline development process (**Annex 2**).

The Nutrition Guidance Advisory Group – Subgroup on Nutrition in the Life Course and Undernutrition (**Annex 3**) included experts from various WHO expert advisory panels and experts in the area of undernutrition and other disciplinary areas of expertise, taking into consideration a balanced sex mix, and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group. The role of the guideline group was to advise WHO on the choice of important outcomes for decision-making and the interpretation of the evidence.

The group of external experts and key stakeholders (**Annex 4**) were identified through a call for public comments and commented on the wording of the recommendations and were asked to highlight any missing evidence.

Scope of the guideline, evidence appraisal and decision-making

A Nutrition Guidance Advisory Group meeting, convened in June 2010 in Geneva, Switzerland, prioritized the need for updating the guideline on the management of severely malnourished children. An initial set of questions to be addressed in the guideline was the critical starting point for formulating the recommendations; the questions were drafted by technical staff of the Department of Nutrition for Health and Development and the Nutrition Guidance Advisory Group, in collaboration with the World Food Programme, UNICEF and the Office of the United Nations High Commissioner for Refugees, based on policy and programme guidance needs of Member States and their partners. A risk–benefit format was used (**Annex 5**).

Two other Nutrition Guidance Advisory Group meetings were held on 14–16 March 2011 and 1–3 February 2012, in Geneva, Switzerland, to review the evidence and discuss the draft recommendation, taking into consideration: (i) desirable and undesirable effects of these formulations; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to programme managers in different settings (**Annex 5**). Consensus was defined as agreement by the simple majority of the guideline group members (**Annex 3**). WHO staff present at the meeting, as well as other external technical experts involved in the collection and review of the evidence, were not allowed to vote. There were no strong disagreements among the Nutrition Guidance Advisory Group members.

A public call for comments on the final draft guideline was then released. All interested stakeholders became members of the External Experts and Stakeholders Panel but were only allowed to comment on the draft guideline after submitting a signed Declaration of Interests form. Respondents were asked to comment on the clarity of the recommendations; on any additional evidence that might not have been included; and whether any of the recommendations were in conflict with the evidence base. Feedback was received from 20 stakeholders and external experts. WHO staff then finalized the guideline and submitted it for clearance by WHO before publication.

Management of conflicts of interest

According to the rules in the WHO *Basic documents (166)*, all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The Declarations of Interest statements from all Nutrition Guidance Advisory Group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a Nutrition Guidance Advisory Group meeting. All Nutrition Guidance Advisory Group members and participants of the guideline development meetings submitted a Declaration of Interests form, along with their curriculum vitae before each meeting. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interests strictly followed the WHO *Guidelines for declaration of interests (WHO experts) (167)*. The potential conflicts of interest declared by members of the guideline group are summarized below.

■ Dr Paluku Bahwere is a medical doctor with over 20 years' experience in the fields of public health, paediatrics, nutrition and HIV/AIDS. He declared being the Valid International's research focal person until August 2010. Through operational research and the development and implementation of evidence-based approaches, Valid International is committed to increasing the impact of humanitarian action. Valid International provides specialized advisers to support programme implementation, evaluate programme impact and research humanitarian and development techniques. He has personally been involved in a wide range of research projects, including the integration of community treatment centres with other child survival strategies; the

use of ready-to-use foods for HIV-positive adults; and the use of community treatment centres for providing HIV services and managing malnutrition in HIV-infected children and adults. Dr Bahwere clarified that through his work with Valid International, he had no connection with Valid Nutrition, an Irish-registered charity that makes a range of ready-to-use therapeutic food in Africa and that is linked to Valid International. It was considered that Dr Bahwere's work with Valid International would be reported in the guideline.

■ Dr André Briend has extensive experience as researcher, programme manager and paediatrician. He was a member of technical staff in the Department of Child and Adolescent Health and Development WHO until 2010 and currently works as an independent consultant. Dr Briend was involved in development of the patent of the ready-to-use therapeutic food plumpy nut. He does not, however, own his product rights, and does not receive any royalties. The patent of the product belongs to Nutriset and Institut de Recherche pour le Développement. It was agreed that this would be reported in the guideline.

■ Dr Mark Manary is Professor of Paediatrics at Washington University St Louis School of Medicine, United States of America. He is also director of the Global Harvest Alliance, a joint venture between the St Louis Children's Hospital and the Donald Danforth Plant Science Center. Dr Manary's research interests focus on different aspects of nutrition in populations of developing countries, especially in Malawi, Africa. He has declared that in the last 3 years he has been in the academic field and is founder of the nongovernmental organization Peanut Butter, which produces ready-to-use therapeutic food for use in programmes in Malawi and Sierra Leone. Peanut Butter is a charitable project, which sells the ready-to-use therapeutic food on a cost-recovery basis to governments and agencies, which in turn distribute it free of charge to malnourished children. It was considered that Dr Manary's work on the humanitarian Project Peanut Butter would be reported in the guideline.

External resource persons were invited to the meetings as observers and to provide technical input, but they did not participate in the decision-making processes.

Plans for updating the guideline

The recommendations in this global guideline are planned to be reviewed in 2020. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners, will be responsible for coordinating the guideline update following formal *WHO handbook for guideline development (3)* procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 1. GRADE summary of findings tables

TABLE 1
Question: Should antibiotics (amoxicillin/cefdinir) be used in children with uncomplicated severe acute malnutrition?
Settings: Community

Number of studies	Quality assessment						Number (%) of patients		Effect		Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid-erations	Antibiotics (amoxicillin/cefdinir)	Control	Relative (95% CI)	Absolute		
Mortality up to 6 weeks (follow-up median 6 weeks)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	82/1847 (4.4)	68/920 (7.4%)	RR 1.46 (1.19 to 1.80)	34 more per 1000 (from 14 more to 59 more) –	+++ MODERATE	CRITICAL
Time to recovery												
1	Randomized trials	Serious[a]	No serious inconsistency[2]	No serious indirectness	No serious imprecision	None	– –	– –	MD –0.50 (–2.11 to 1.11)	– –	+++ MODERATE	CRITICAL
Weight gain (g/kg/day)												
1	Randomized trials	Serious[a]	No serious inconsistency[b]	No serious indirectness	No serious imprecision	None	–	–	MD 0.55 (0.18 to 0.92)	– –	+++ MODERATE	CRITICAL
Mortality up to 12 weeks (follow-up median 12 weeks)												
1	Observational studies	Very serious[c]	No serious inconsistency[b]	No serious indirectness	Serious[d]	None	13/498 (2.6)	34/1955 (1.7)	RR 1.50 (0.80 to 2.82)	–	+ VERY LOW	CRITICAL
Recovery at 12 weeks (follow-up median 12 weeks)												
1	Observational studies	Very serious[c,e]	No serious inconsistency[b]	No serious indirectness	No serious imprecision	None	417/498 (83.7)	1673/1955 (85.6)	RR 0.98 (0.94 to 1.02)	–	+ VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk; MD: mean difference.
[a] Double blind study conducted in a setting of high HIV prevalence and most children had kwashiorkor. The response to antibiotics could be modified by these two factors.
[b] Only one study.
[c] Comparison of two different cohorts from different parts of Malawi. There were also significant differences in baseline characteristics between the cohorts.
[d] Few events and wide confidence intervals.
[e] Participants and researchers not blinded to the interventions.

TABLE 2.
Question: Should high-dose vitamin A supplementation versus low-dose vitamin A supplements be used in children with severe acute malnutrition?
Settings: Hospital

Number of studies	Quality assessment						Number (%) of patients		Effect		Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose vitamin A supplements	Low-dose vitamin A supplements	Relative (95% CI)	Absolute		
Mortality												
3	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness[a]	Serious[a]	None	86/1034 (8.3)	92/1038 (8.9)	RR 1.11 (0.84 to 1.47)	10 more per 1000 (from 14 fewer to 42 more)	++ LOW	CRITICAL
Diarrhoea (duration in days)												
3	Randomized trials	Serious[b,c]	No serious inconsistency	Serious[a,b,c]	Serious[a,c]	None	–	–	Not pooled	Not pooled	+ VERY LOW	CRITICAL
Incidence of lower respiratory infections - not reported												
2	–	–[d]	–	–[f]	–[g]	None	–	–	–	–	+ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

[a] Different criteria were used to define the degree of malnutrition in the study populations and different durations of vitamin A supplementation were used in the trials.
[b] Only two investigators have contributed data.
[c] The authors used different classifications of type of diarrhoea and did not provide data according to a pre-specified definition. Details of the use of reported data are described in the narrative
[d] Only one investigator contributed data (2 trials) to this outcome.
[e] The author used different definitions of lower respiratory tract infections outcomes in the two studies.
[f] The number of cases is not reported; the authors simply state in the articles that there are non-significant differences between the groups.

TABLE 3.

Question: Should low-osmolarity oral rehydration solution versus standard-osmolarity oral rehydration solution be used in children with severe acute malnutrition and dehydration?

Settings: Hospital

Number of studies	Quality assessment						Number (%) of patients		Effect		Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-osmolarity oral rehydration solution	Standard-osmolarity oral rehydration solution	Relative (95% CI)	Absolute	Quality	Importance
Rehydration within 12 h												
4	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	219/233 (94)	273/294 (92.9)	RR 1.01 (0.96 to 1.07)	9 more per 1000 (from 37 fewer to 65 more)	++ LOW	CRITICAL
Recovery from diarrhoea (h)												
3	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None			MD –12.00 (–21.27 to –2.73)		++ LOW	CRITICAL

CI: confidence interval; RR: risk ratio; MD: mean difference.
[a] One out of the included studies has no blinding.
[b] Moderate to high statistical heterogeneity (56%), but the results among studies are consistent.
[c] High statistical heterogeneity (78%), but the results among studies are consistent.

TABLE 4.
Question: Should half-strength Darrows/5% dextrose versus Ringer's lactate be used in children with severe acute malnutrition and shock?
Settings: Hospital

Number of studies	Quality assessment						Number (%) of patients		Effect		Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Half-strength Darrows/5% dextrose	Ringer's lactate	Relative (95% CI)	Absolute		
Mortality until the end of hospitalization												
1	Randomized trials	Very serious[a]	No serious inconsistency[b]	no serious indirectness	Serious[c]	None	15/26 (57.7)	13/29 (44.8)	RR 1.29 (0.76 to 2.17)	130 more per 1000 (from 108 fewer to 524 more)	+ VERY LOW	CRITICAL
Shock unresolved at 8 h												
1	Randomized trials	Very serious[a,d]	no serious inconsistency[b]	No serious indirectness	Serious[c]	None	15/22 (68.2)	14/25 (56)	RR 1.22 (0.78 to 1.91)	123 more per 1000 (from 123 fewer to 510 more)	+ VERY LOW	CRITICAL
Shock unresolved at 24 h												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	14/18 (77.8)	14/25 (56)	RR 1.39 (0.91 to 2.13)	218 more per 1000 (from 50 fewer to 633 more)	+ VERY LOW	CRITICAL
Oliguria at 8 h												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	9/22 (40.9)	3/25 (12)	RR 3.41 (1.05 to 11.03)	289 more per 1000 (from 6 more to 1000 more)	+ VERY LOW	CRITICAL
Oliguria at 24 h												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	8/18 (44.4)	6/25 (24)	RR 1.85 (0.78 to 4.41)	204 more per 1000 (from 53 fewer to 818 more)	+ VERY LOW	CRITICAL

TABLE 4. Continued

Tachycardia at 8 h											
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	7/22 (31.8)	2/25 (8)	RR 3.98 (0.92 to 17.18)	238 more per 1000 (from 6 fewer to 1000 more)	+ VERY LOW	CRITICAL
Tachycardia at 24 h											
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	8/14 (57.1)	4/25 (16)	RR 3.57 (1.31 to 9.77)	411 more per 1000 (from 50 more to 1000 more)	+ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio.

[a] Several limitations: non-blinded, small sample size (61 children), assessment restricted to the hospitalization period without further follow-up. One study arm was dropped.

[b] Only one study.

[c] Wide confidence intervals.

[d] Outcomes only presented for survivors and not for all those randomized.

[e] Very wide confidence intervals.

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Annex 5.
Summary of considerations for determining the strength of the recommendations

1. Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition

Benefit or desired effect

- Identification of high-risk children and provision of a high level of coverage
- Active case-finding allowed, with improved coverage
- Reduced mortality and other adverse outcomes
- Markedly improved outcome for vulnerable children

Potential risks or undesired effects

- Overdiagnosis of children with severe acute malnutrition
- Early discharge of oedematous child who has not fully recovered; a minimum length of stay may be advocated
- May keep children in programme too long

Other values/preferences/acceptability

- They make treatment of severe acute malnutrition a public health intervention

Cost considerations

- Increase in absolute costs of programme, owing to increased number of children being identified, but no change in cost effectiveness of interventions
- Potential savings, with earlier detection and reduced number of children being admitted with complicated severe acute malnutrition

Feasibility of implementation

- Programmes in low-resource settings are already implementing these approaches

2. Where to manage children with severe acute malnutrition who have oedema

Benefit or desired effect

- Avoidance of unnecessary hospitalization and exposure to nosocomial infections of children who do not need hospitalization
- Prioritization of children at high risk of mortality

Potential risks or undesired effects

- Some children with oedema +++ who refuse to go for inpatient treatment, or whose caregivers are unable or unwilling to take them, may miss out on care

Other values/preferences/acceptability

- Recommendations clarify where these children should be managed and serve to complement the recommendation on children with mild oedema being managed as outpatients

Cost considerations

- Reduced cost through outpatient care of children not requiring admission

Feasibility of implementation

- Feasible, if accessibility of inpatient facilities is addressed

3. Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

Benefit or desired effect

- Reduced mortality in children with high mortality risk
- Improved time to recovery and growth

Potential risks or undesired effects

- Increased potential for antibiotic resistance in the community
- Increased cost to programmes

Other values/preferences/acceptability

- Evidence of effect in oedematous malnutrition in settings of high HIV prevalence
- No evidence of effect in wasting
- An inexpensive intervention (less than US$1) that is shown, in one well-conducted study, to reduce mortality
- Only one study

Cost considerations

- Modest cost implication

Feasibility of implementation

■ Feasible, except in countries with high case-load

■ Amoxicillin already widely available

■ Requires minimal additional interaction between health-care workers and caregivers

4. Vitamin A supplementation in the treatment of children with severe acute malnutrition

Benefit or desired effect

■ Reduction of early mortality in children with severe acute malnutrition

■ Prevention of vitamin A morbidity, e.g. eye changes

■ Avoidance of potential toxicity associated with providing too much vitamin A

Potential risks or undesired effects

■ Children miss receiving vitamin A if they are given therapeutic foods that do not meet WHO specifications

Other values/preferences/acceptability

■ Good to harmonize recommendations between guidelines

Cost considerations

■ Likely to be cost saving, as repeat dosing of vitamin A is averted

Feasibility of implementation

■ Should be feasible as interventions (vitamin A supplements and therapeutic foods) are already in place; rationalizing supplementation should make care more efficient

■ Will require training to clarify recommendations

5. Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

Benefit or desired effect

■ Reduced mortality and cost and time in an inpatient facility

■ Improved acceptability

■ Clarification and harmonization of recommendations on therapeutic foods in different populations and medical conditions (e.g. presence of diarrhoea)

Potential risks or undesired effects

■ The process of transitioning between therapeutic foods may appear confusing

Other values/preferences/acceptability

■ Magnitude of the problem of the transition phase is largely undocumented

■ Reduce defaulter rates, improve acceptability

Cost considerations

■ Both approaches to transition feeding are of equal cost

Feasibility of implementation

■ Need experiences from programmes to be reported regarding which approach is most feasible

■ A senior health-care worker is needed to decide which approach will be used in any particular setting

6. Fluid management of children with severe acute malnutrition

Benefit or desired effect

■ Reduced mortality

■ Avoidance of electrolyte abnormalities and overhydration

■ Reduced duration of diarrhoea

Potential risks or undesired effects

■ May be some undesired side-effects

■ Danger of over-aggressive care at too early a stage

■ Case recognition difficulty with the metabolic disturbances of severe acute malnutrition

Other values/preferences/acceptability

■ Good acceptability

Cost considerations

■ Fluids and oral rehydration solution are generally available for care of all children with diarrhoea and dehydration; minimal implication for supply chain and therefore cost

Feasibility of implementation

■ Very feasible; however, it is noted that even for children without malnutrition, the coverage of oral rehydration solution is suboptimal

7. Management of HIV-infected children with severe acute malnutrition

Benefit or desired effect

■ Clarification of the most beneficial interventions for HIV-infected children with severe acute malnutrition, especially the most appropriate timing for the initiation of antiretroviral drug treatment and how management approaches for HIV-infected children differ from those for un-infected children with severe acute malnutrition

■ Rapid identification of HIV-infected children who are eligible for lifelong antiretroviral drug treatment and safe and appropriate initiation of treatment

■ Reduction of the likelihood of families or caregivers of HIV-infected children being exploited for commercial gain, namely by clarifying which interventions have proven efficacy for malnourished HIV-infected children and which provide no benefit

■ Identification of the most significant knowledge gaps that need to be addressed through research

Potential risks or undesired effects

■ Recommendations may not appropriately account for significant differences in the pathophysiology of severe acute malnutrition in HIV-infected children compared to HIV-uninfected children with severe acute malnutrition

■ The lack of pharmacokinetic data from HIV-infected children with severe acute malnutrition may result in antiretroviral drug treatment being implemented at a time that is less safe or in doses that are not appropriate

Other values/preferences/acceptability

■ High value was placed by guideline development group members on the potential of antiretroviral drug treatment to improve the survival of HIV-infected children with severe acute malnutrition. Early experiences are that antiretroviral drug treatment is well tolerated and provides significant clinical benefit with no greater rate of adverse events compared with HIV-infected children who are not severely malnourished

■ The dearth of direct evidence in the population; the guideline development group highly recommended the research agenda

Cost considerations

■ There were no data available on cost considerations

Feasibility of implementation

■ The recommendations are feasible and appropriate to all settings where severe acute malnutrition is prevalent, including areas of high HIV prevalence

8. Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

Benefit or desired effect

■ Reduced mortality and early treatment improves growth outcomes

■ Of major relevance, with epidemiological data indicating significant numbers of infants with severe acute malnutrition who have not previously been recognized and cared for in a way that is appropriate for their age (i.e. physiological differences from older children)

■ Provision of basic guidance in the absence of any prior recommendations

Potential risks or undesired effects

■ May be interpreted as undermining breastfeeding policy

■ May wrongly identify low-birth-weight babies who are actually growing appropriately

- Inadvertent use of formula may increase mortality and morbidity
- Large numbers of infants may be identified as severely malnourished, but with no clear programme to treat
- Risk of nosocomial infections if admitted

Other values/preferences/acceptability

- Young children at risk of being harmed by the inappropriate care in programmes, i.e. being treated the same way as children with severe acute malnutrition who are more than 6 months of age
- Problem currently ignored or not accepted by society
- Difficulties conducting appetite tests in this age group

Cost considerations

- Cost of counselling and support of mothers/caregivers to re-establish breastfeeding or to safely provide formula feeds as part of a suckling method of nutritional care

Feasibility of implementation

- Major training initiative needed to provide skills to health-care workers for this group of children, even if interventions are very simple

Annex 6.
Questions on the management of severe acute malnutrition in population, intervention, control, outcomes (PICO) format[1]

1. Admission and discharge criteria for children who are 6–59 months of age with severe acute malnutrition

Admission criteria for children who are 6 to 59 months of age with severe acute malnutrition

Population:

Children with severe acute malnutrition:

- Children who are more than 6 months of age with a weight for height <–2 Z-score, or
- Children who are 6–59 months of age, with a mid-upper arm circumference <125 mm
- Urban/rural
- Camp/no camps
- Oedema/no oedema
- Prevalence of oedema
- Emergency/non-emergency
- Community/health-care facilities
- Active screening/passive screening.
- HIV/TB prevalence
- HIV/TB individual status

Intervention:

- Standard treatment targeting children with low mid-upper arm circumference

Control:

- Standard treatment targeting children with low weight-for-height

Outcomes:

- Response to treatment assessed by standard outcome for severe and moderate acute malnutrition

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[1] In the Outcomes section of each item, the numbering refers to a ranking in order of priority, where 1 is the most critical.

Settings:

■ Programmatic setting in populations with moderate acute malnutrition prevalence >5%

Discharge criteria for children who are 6–59 months of age with severe acute malnutrition

Population:

Children above 6 months of age with severe acute malnutrition:

■ HIV positive/HIV negative/unknown

■ HIV-endemic settings/non-HIV-endemic settings

Intervention:

■ For programme using mid-upper arm circumference: mid-upper arm circumference ≥125 mm or any other discharge criteria

Control:

■ For programme using mid-upper arm circumference: weight gain of 15–20% after oedema disappears

■ For programme using weight-for-height: weight-for-height >–11 standard deviation or weight gain of 15–20% after oedema disappears.

Outcomes:

1. Mortality

2. Relapse

3. Adverse effects

4. Cost of treatment per child treated

Settings:

■ All settings

2. Where to manage children with severe acute malnutrition who have oedema

Population:

Children who are above 6 months of age with severe acute malnutrition:

■ Oedema +/oedema++/oedema +++/no oedema

Intervention:

■ Good appetite or no medical complications and oedema +/oedema++

■ Marasmic kwashiorkor

■ Children who are above 6 months of age and <4 kg

Control:

■ Good appetite or no medical complications as outpatient

Outcomes:

1. Short-term mortality

2. Recovery rate

3. Time to recover

4. Weight gain

5. Use of resources

6. Adverse effects

7. Length gain

Settings:

■ Outpatient

3. Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

Population:

Children who are under 5 years of age with severe acute malnutrition:

■ HIV positive/HIV negative/unknown

■ HIV-endemic settings/non-HIV-endemic settings

■ Under 6 months/above 6 months of age

■ Clinical signs of infection (to be defined)/no clinical signs of infection

■ Local sensitivity

Intervention:

■ Amoxicillin, ampicillin, cephalosporin, chloramphenicol, ciprofloxacin co-trimoxazole, gentamicin, metronidazole

Control:

■ No antibiotics, or

■ Different antibiotics

Outcomes:

1. Mortality rate

2. Recovery rate

3. Adverse effects; relapse

4. Time to recover; weight gain

Settings:

■ Low-resource countries

4. Vitamin A supplementation in the treatment of children with severe acute malnutrition

Effectiveness and safety of vitamin A supplementation in children with severe acute malnutrition

Population:

Children who are under 5 years of age with severe acute malnutrition:

- Presence of oedema/no presence of oedema
- Presence of eye signs/no eye signs
- HIV positive/HIV negative/unknown
- HIV-endemic settings/non-HIV-endemic settings
- Prevalence of vitamin a deficiency in the population
- (+/– other sources of vitamin A, as national/local programmes of supplementation/fortification of vitamin A)
- Under 6 months/above 6 months of age
- Measles diagnosis (outbreak)

Intervention:

Vitamin A single mega dose:

- Admission/rehabilitation/discharge

Control:

- Daily low doses (including therapeutic foods)

Outcomes:

1. Mortality rate
2. Adverse effects (to be specified); morbidity
3. Recovery rate
4. Relapse
5. Time to recover; weight gain

Settings:

- Low-resource countries

5. Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

Feeding outpatient children with severe acute malnutrition and diarrhoea

Population:

Children who are under 5 years of age with severe acute malnutrition and diarrhoea, defined as:

- Diarrhoea based on the mother recall or other definitions
- With vomiting/without vomiting
- Presence of oedema/no presence of oedema
- Under 6 months/above 6 months of age
- Persistent diarrhoea defined as more than 2 weeks
- HIV positive/HIV negative/unknown
- HIV-endemic settings/non-HIV-endemic settings
- Breastfed/ non-breastfed

Intervention:

- Other foods

Control:

- Ready-to-use therapeutic food

Outcomes:

1. Referral to hospitals
2. Recovery from diarrhoea
3. Adverse effects
4. Time to recover from diarrhoea

Settings:

- Outpatient

Feeding inpatient children with severe acute malnutrition and diarrhoea

Population:

Children who are 5 years of age with severe acute malnutrition and diarrhoea, defined as:

- Diarrhoea based on the mother recall or other definitions
- With vomiting/without vomiting
- Presence of oedema/no presence of oedema
- Under 6 months/above 6 months of age
- Persistent diarrhoea defined as more than 2 weeks
- HIV positive/HIV negative/unknown

■ HIV-endemic settings/non-HIV-endemic settings

■ Breastfed/ non-breastfed

Intervention:

■ Other recipes (e.g. lactose-free F-75 formulation)

Control:

■ Cooked cereal-based F-75 or glucose-polymer-based F-75

Outcomes:

1. Use of intravenous fluids

2. Recovery from diarrhoea; duration of diarrhoea

3. Adverse effects

Settings:

■ Inpatient

Feeding children with severe acute malnutrition in the transition phase

Population:

Children who are 6–59 months of age with severe acute malnutrition and return of appetite and most/all oedema disappeared:

■ Presence of oedema/no presence of oedema on admission

■ HIV positive/HIV negative/unknown

■ HIV-endemic settings/non-HIV-endemic settings

Intervention:

■ Combination of F-75/ready-to-use therapeutic food with/without energy restriction, or F-100/ ready-to-use therapeutic food with/without energy restriction, or F-100 without energy restriction, or ready-to-use therapeutic food with/without energy restriction

Control:

■ F-100: 130 mL/kg/day increasing 10 mL/kg/ feed if eaten until drinking 200 mL/kg/day

Outcomes:

1. Mortality rate; recovery rate

2. Cardiac embarrassment

3. Adverse effect (refeeding syndrome)

4. Relapse

Settings:

■ Inpatient

6. Fluid management of children with severe acute malnutrition

Management of dehydration without shock due to diarrhoea (and vomiting) in children with severe acute malnutrition

Population:

Children who are 5 years of age with severe acute malnutrition:

■ Dehydration based on the mother recall of watery diarrhoea or other definitions

■ With vomiting/without vomiting

■ Presence of oedema/no presence of oedema

■ Under 6 months/above 6 months of age

■ Severe watery diarrhoea without signs of shock (e.g. cholera) or hyponatraemia

Intervention:

Treatment with different rehydration solutions:

■ Oral/parenteral/other (F-75/breastfeeding)

Control:

■ Treatment with ReSoMal

Outcomes:

1. Use of intravenous fluids

2. Recovery from dehydration

3. Time to recover from dehydration

4. Adverse effects (convulsions, hyponatraemia, oedema, cardiac embarrassment, shock)

Settings:

■ All settings

Management of shock with intravenous fluids in children with severe acute malnutrition

Population:

Children who are under 5 years of age with severe acute malnutrition and shock:

■ By definition of shock, as:

— Lethargy or unconsciousness and cold hands plus either slow capillary refill or weak or fast pulse

— Cold hands with capillary refill longer than 3 s and weak and fast pulse

— Other definitions including signs of possible septic shock

■ Presence of oedema/no presence of oedema

■ Under 6 months/above 6 months of age

Intervention:

Treatment with isotonic fluids, colloids fluids or crystalloid fluids:

- Quantity/kg/child

- Speed

- Monitoring: frequent/other schemes

Control:

- Treatment with hypotonic fluids as in current guidelines (*1*)

Outcomes:

1. Case-fatality rate

2. Recovery from shock

3. Adverse effects (convulsions, hyponatraemia, hypokalaemia, oedema, cardiac embarrassment)

4. Time to recover from shock

Settings:

- All settings

Blood or plasma transfusion in children with shock after failure of intravenous fluid in children with severe acute malnutrition

Population:

Children who are under 5 years of age with severe acute malnutrition not responding to intravenous fluid treatment of shock:

- By definition of shock, as:
    — Lethargy or unconsciousness and cold hands plus either slow capillary refill or weak or fast pulse
    — Cold hands with capillary refill longer than 3 s and weak and fast pulse
    — Other definitions including signs of possible septic shock

- Presence of oedema/no presence of oedema

- Under 6 months/above 6 months of age

Intervention:

Treatment with blood or plasma transfusion:

- Quantity/kg/child

- Speed

Control:

- No blood transfusion

Outcomes:

1. Case-fatality rate

2. Recovery from shock

3. Adverse effects (convulsions, hyponatraemia, oedema, cardiac embarrassment)

4. Time to recover from shock

Settings:

■ All settings

7. Management of HIV-infected children with severe acute malnutrition

What are the implications of severe acute malnutrition on antiretroviral drug treatment initiation and dosing?

In children who are 0–59 months of age with severe acute malnutrition, at which stage in nutritional recovery should antiretroviral drug treatment be commenced?

Population:

Children who are 0–14 years of age with severe acute malnutrition:

■ Subgroups:

— Age <6 months, age 6 months to 5 years

— Oedema, no oedema

— TB status: positive/negative/unknown

Intervention:

■ Start nutritional therapy plus antiretroviral drug treatment concurrently

Control:

■ Start nutritional therapy and withhold antiretroviral drug treatment for 1 week/2 weeks (within stabilization phase)

■ Start nutritional therapy and withhold antiretroviral drug treatment until rehabilitation phase

Outcomes:

1. Mortality

2. Markers of nutritional status: lean body mass, height gain, body weight, weight-for-height, weight-for-age, body mass index, mid-upper arm circumference

3. Improvements in CD4 %, CD4 counts, viral load; tolerance of antiretroviral drug treatment (adverse effects)

4. Adherence to antiretroviral drug treatment

Timing:

■ From time of initiation of services to first 6 months of treatment

In children with HIV and severe acute malnutrition should antiretroviral drug treatment dosing be adjusted from doses for non-malnourished children?

Population:

Children who are 0–59 months of age with severe acute malnutrition:

■ Subgroups:

— Age <6 months, age 6 months to 5 years

— Oedema, no oedema

— TB status: positive/negative/unknown

Intervention:

■ antiretroviral drug treatment

Comparator:

■ Compare standard antiretroviral drug treatment doses between children with and without severe acute malnutrition of the same weight

■ Compare antiretroviral drug treatment pharmacokinetics (peak levels, clearance) between children of the same age with and without severe acute malnutrition, with weight-appropriate doses

Outcomes:

1. Antiretroviral drug treatment tolerance/adverse events

2. Mortality

3. Measures of pharmokinetics

4. Measures of antiretroviral drug treatment absorption

5. Markers of nutritional status: body weight, weight-for-height, weight-for-age, body mass index, mid-upper arm circumference

6. Change in CD4 counts

Timing:

■ During the first 3 months of antiretroviral drug treatment

8.   Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

Admission and discharge criteria for infants who are less than 6 months of age with severe acute malnutrition

Population:

Children who are less than 6 months of age with severe acute malnutrition:

■ Oedema/no oedema

■ 0–2 months/2–6 months

■ HIV positive/HIV negative/unknown

■ HIV-endemic settings/non-HIV-endemic settings

Intervention:

■ Admission criteria: mid-upper arm circumference, chest circumference, head circumference, weight loss, breastfeeding failure, weight-for-length different cut-off values

■ Discharge criteria: criteria different from those specified for control

Control:

■ Admission criteria: weight-for-length <–3 standard deviations or visible severe wasting (given the lack of gold standard it is advised to compare different criteria)

■ Discharge criteria: there is no standard for this age group; the general recommendation is:

  — for programme using mid-upper arm circumference: weight gain of 15–20% after oedema disappears

  — for programme using weight-for-height: weight-for-height >–1 standard deviation or weight gain of 15–20% after oedema disappears

Outcomes:

1. Short-term mortality

2. Recovery rate; weight gain

3. Adverse effects

4. Time to recover

5. Use of resources

6. Excessive use of breast milk substitute; length gain

Restoration of successful exclusive breastfeeding (added later, not included in the ranking exercise)

Settings:

— Inpatient

Feeding severely malnourished infants who are less than 6 months of age (breastfed or non-breastfed infants)

Population:

Infants less than 6 months of age:

- 0–2 months/2–6 months
- Access to breast milk/no access to breast milk
- Stabilization/rehabilitation
- Presence of oedema/no oedema
- HIV positive/HIV negative/unknown
- HIV-endemic settings/non-HIV-endemic settings

Intervention:

- Different formulation of F-75 (initiation of treatment), breast milk substitute, breast milk substitute specific for premature infants, F-100, F-100 diluted, expressed breast milk, animal milk
- Supplementary suckling method/cup feeding

Control:

- Breast milk if accessible, if not, breast milk substitute

Outcomes:

1. Mortality
2. Recovery rate; weight gain
3. Diarrhoea
4. Restoration of successful exclusive breastfeeding
5. Time to recover
6. Length gain
7. Adverse effects
8. Breast milk output

Settings:

- Inpatient

Annex 7.
Research priorities

1. Admission and discharge criteria for children who are 6–59 months old with severe acute malnutrition

Priority issues

- To refine cut-off values of mid-upper arm circumference to identify severe acute malnutrition in children who are 6–11 months, 12–23 months and 24–59 months of age, through assessment of treatment outcomes.

- To test strategies to improve active community screening and routine health-facility screening, and investigate barriers to service access and uptake, to enhance treatment coverage.

Other issues (no specific order)

- To evaluate the validity of mid-upper-arm circumference values versus weight-for-height Z-score as discharge criteria for end of treatment (in relation to response to treatment, relapse and mortality) and determine the appropriate cut-off values.

- To assess the sensitivity and specificity of mid-upper-arm circumference measurements at the lower and higher age ranges of children who are 6–59 months of age, controlled for stunting and the presence of oedema.

- To establish mid-upper-arm circumference thresholds to identify severe acute malnutrition in infants who are less than 6 months of age and children who are 5 years of age and older.

- To assess the response to treatment according to initial anthropometric criteria and clinical and biochemical characteristics.

- To assess the correlation of anthropometric indicators with risk of death and response to treatment of severe acute malnutrition in infants who are less than 6 months of age and children who are 5 years of age and older, especially in the context of high and low HIV prevalence.

2. Where to manage children with severe acute malnutrition who have oedema

Priority issues

- What is the predictive value of different degrees of oedema (+, ++ or +++) on recovery of children with severe acute malnutrition managed as inpatients or outpatients?

3.   Use of antibiotics in the management of children with severe acute malnutrition in outpatient care

Priority issues

■ What is the clinical effect and cost effectiveness of giving oral antibiotics to children and infants with severe acute malnutrition who do not require inpatient management in:

— settings with predominantly wasting (e.g. West Africa, South Asia); and

— non-HIV settings (randomized controlled trial with mortality as main outcome)?

■ What is the effect of giving broad-spectrum antibiotics to infants and children with severe acute malnutrition without complications, who do not require inpatient management, on:

— the prevalence of population-based antimicrobial resistance;

— therapeutic efficacy.

Other issues (no specific order)

■ What clinical algorithms or point-of-care technologies can identify the presence of significant bacterial infections in infants and children with uncomplicated severe acute malnutrition?

■ What is the positive and negative predictive value of the appetite test for identifying children with severe acute malnutrition and clinically important infection?

■ What are the most effective antibiotics for managing children with complicated severe acute malnutrition who are admitted for inpatient care:

— stratified by HIV status, complications, type of severe acute malnutrition (oedematous versus wasting) and age;

— taking account of in vivo and in vitro resistance versus effectiveness?

■ What are the most effective antibiotics for managing children with complicated severe acute malnutrition who are admitted for inpatient care:

— stratified by HIV status, complications, type of severe acute malnutrition (oedematous versus wasting) and age;

— taking account of in vivo and in vitro resistance versus effectiveness?

4.   Vitamin A supplementation in the treatment of children with severe acute malnutrition

Priority issues

■ What is the efficacy of daily low-dose vitamin A supplementation compared to single high-dose vitamin A in the treatment of children with severe acute malnutrition either with bilateral pitting oedema or presenting with severe diarrhoea or shigellosis?

■ What is the most effective way to improve and sustain the vitamin A status of children with severe acute malnutrition after discharge from treatment?

■ Are there regional differences in the response to, and safety of, vitamin A supplementation in children with severe acute malnutrition?

5. Therapeutic feeding approaches in the management of severe acute malnutrition in children who are 6–59 months of age

Priority issues

◼ What are the efficacy and effectiveness of different ready-to-use therapeutic foods that comply with WHO specifications and are made from different ingredients in different regions of the world (using commercially produced ready-to-use therapeutic food as the comparison)?

◼ What is the comparative effectiveness of ready-to-use therapeutic food and F-100 for recovery of children with severe acute malnutrition who have diarrhoea?

Other issues (no specific order)

◼ What are the most effective approaches for managing the transition from F-75 to ready-to-use therapeutic food, or from F-100 to ready-to-use therapeutic food, in children with severe acute malnutrition before discharge from hospital to continued treatment as outpatients?

◼ What is the impact of different feeding approaches to management of severe acute malnutrition in integrated severe acute malnutrition services?

◼ What is the comparative efficacy (in terms of physiological, immunological and body composition recovery) and effectiveness of therapeutic foods made from locally produced food and ready-to-use therapeutic food for management of severe acute malnutrition of children in outpatient care?

◼ What body composition and physiological changes follow management of severe acute malnutrition using different durations of feeding with ready-to-use therapeutic food in children of different ages and according to different criteria for stopping ready-to-use therapeutic food (see Recommendations)?

◼ What is the relative cost effectiveness of managing severe acute malnutrition in children in hospital and community settings, taking into consideration coverage and effectiveness of services at scale?

◼ What are the key indicators of performance for integrated services for the management of severe acute malnutrition? What is an appropriate cost-effective system for standardized and minimal monitoring and reporting of performance of integrated services for the management of severe acute malnutrition? What is an appropriate and cost-effective integrated system for monitoring coverage, barriers to access and service uptake?

◼ What is a cost-effective system to integrate the management of severe acute malnutrition into routine heath systems and monitor this integration with a health-system-strengthening approach?

6.   Fluid management of children with severe acute malnutrition

Priority issues

■ What is the efficacy and safety of ReSoMal compared with that of 75 mosmol/L oral rehydration solution in severely malnourished dehydrated children with non-cholera diarrhoea?

■ What are the most effective ways to assess and monitor the hydration status of children with severe acute malnutrition who present with some dehydration (but no shock)?

■ What are the most appropriate fluid strategy (type, volumes, rate) and monitoring approaches for managing children with severe acute malnutrition, with or without oedema, who present with severe dehydration or shock?

■ How can the diagnosis and severity of dehydration in children with severe acute malnutrition be improved and how can the types of shock, especially hypovolaemic, septic and cardiogenic, be differentiated better, in order to guide the most appropriate management?

■ What is the best way to monitor the clinical condition in response to resuscitation for severe dehydration or shock in children with severe acute malnutrition?

■ What is the role of blood transfusions in the management of children with severe malnutrition, with or without shock?

7.   Management of HIV-infected children with severe acute malnutrition

Priority issues

■ Does early initiation of antiretroviral drug treatment (as soon as metabolic complications are stabilized and sepsis is treated) in HIV-infected children with severe acute malnutrition improve outcomes and reduce adverse events such as immune reconstitution inflammatory syndrome or dyslipidaemia, compared with later initiation?

■ Are the pharmacokinetic characteristics of HIV-infected children with severe acute malnutrition being started on antiretroviral drug treatment different from those of HIV-infected children who do not have severe acute malnutrition? Is there any need to modify the dose of antiretroviral drugs in HIV-infected children who are severely malnourished, to either avoid toxicity or ensure adequate therapeutic levels?

■ Are the pharmacokinetic characteristics of HIV-infected children with severe acute malnutrition receiving other drugs, such as isoniazid, different from those of HIV-infected children who do not have severe acute malnutrition?

■ What is the optimal dosing of antiretroviral drug treatment in HIV-infected children with severe acute malnutrition, to optimize clinical recovery and viral suppression and avoid the development of metabolic complications such as immune reconstitution inflammatory syndrome?

■ What is the most effective therapeutic feeding approach for HIV-infected children with severe acute malnutrition who have persistent diarrhoea?

■ Are the pathophysiological abnormalities of HIV-infected children with severe acute malnutrition, with or without oedema, the same as those of children with severe acute malnutrition but without HIV?
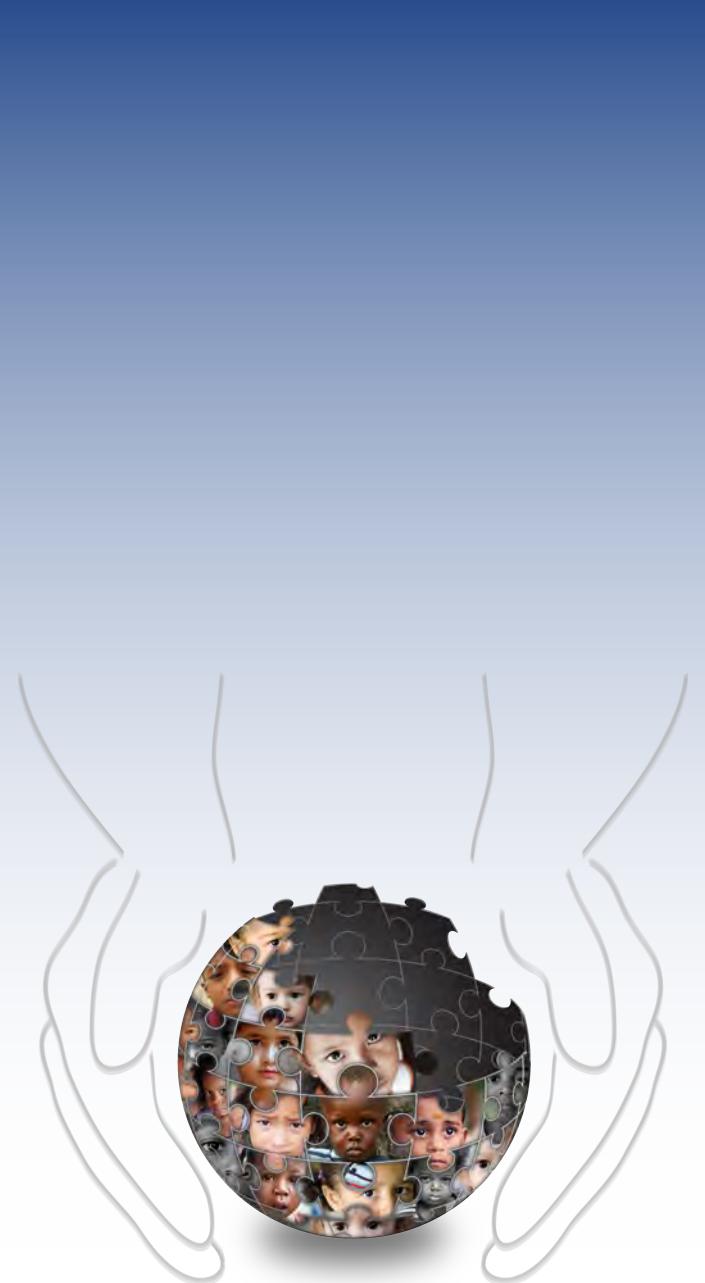
8. Identifying and managing infants who are less than 6 months of age with severe acute malnutrition

Priority issues

■ In infants who are less than 6 months of age, what is the predictive value of population-derived thresholds for weight-for-height, mid-upper arm circumference and reduced growth velocity (weight-for-age) with or without oedema to identify infants at high risk of mortality?

— Consider analysis of published or other existing data.

— Consider the feasibility of each assessment.

■ What are the most effective and safest therapeutic feeding approaches, including different food "recipes" in addition to breastfeeding, for infants who are less than 6 months of age with severe acute malnutrition?

■ How is breastfeeding most effectively re-established among infants with a low weight-for-height/poor weight gain?

Other issues (no specific order)

■ Do infants who are less than 6 months of age with weight-for-length less than –3 Z-score also have reduced growth velocity and is there any difference according to epidemiological setting such as African, South Asian and South-East Asian sites?

■ In infants who are less than 6 months of age, what is the feasibility and accuracy of using weight-for-height, mid-upper arm circumference and reduced growth velocity (weight-for-age) with or without oedema to identify infants in need of therapeutic management?

■ What criteria most effectively identify infants who are less than 6 months of age with the metabolic abnormalities/adaptations associated with severe acute malnutrition in older children?

■ What is the effectiveness, tolerance and safety of ready-to-use therapeutic food as an adjuvant to breastfeeding in infants who are less than 6 months of age with severe acute malnutrition?

— Consider specific subgroups, e.g. with oedema, 4–6months old, those with underlying diseases such as HIV.

■ What is the recommended folic acid supplementation for infants who are less than 6 months of age with severe acute malnutrition?

■ Are there adjustments in the drug dosage or selection of drugs required when managing infants who are less than 6 months of age with severe acute malnutrition?

■ Is there any reason to expect that the efficacy of vitamin A supplementation for infants who are less than 6 month of age with severe acute malnutrition is different from that observed in infants who are 1 to 5 months of age without severe acute malnutrition?

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