Inpatient management of children with severe acute malnutrition: a review of WHO guidelines
Kirkby D Tickell & Donna M Denno

Introduction

Each year, severe acute malnutrition – defined as a weight-for-height z-score of less than −3 or a mid-upper arm circumference of less than 115 mm – is the direct cause of an estimated 540 000 child deaths and an important underlying contributor to many other child deaths, especially those due to pneumonia and diarrhoea. The prevalence of – and case fatality rate for – malnutrition are particularly high in infants. Severe acute malnutrition without medical complications can now be effectively managed in the community, with ready-to-use therapeutic foods. The presence of complications such as anorexia, infections or metabolic dysfunction still warrants inpatient management. The World Health Organization (WHO) indicates that, by following its inpatient management guidelines, less than 10% of children with complicated severe acute malnutrition should die.

However, despite reported compliance with these guidelines, health centres in sub-Saharan Africa have reported mortality rates of 10–40% among severely malnourished hospitalized children. The corresponding published rates in Asia tend to be lower, possibly because: Asian health systems are generally stronger than their African counterparts; therapeutic innovations have been introduced in some Asian facilities that have not yet been used in Africa; and children with uncomplicated severe malnutrition are sometimes admitted to Asian health facilities – but not, generally, to African health facilities. In sub-Saharan Africa, human immunodeficiency virus (HIV) is believed to contribute greatly to malnutrition-related mortality – although, a recent meta-analysis demonstrated an overall case fatality rate of 15% among paediatric inpatients with severe malnutrition without HIV infection.

It is unlikely that severe acute malnutrition will be eliminated in the foreseeable future, as preventative interventions would have to reach the 52 million children who have moderate acute malnutrition. Optimizing the management of complicated severe malnutrition therefore remains an important strategy for reducing malnutrition-related mortality.

WHO’s first guidelines on the management of malnutrition – published in 1981 and focused on protein-energy malnutrition – were replaced in 1999 by guidelines on the management of severe acute malnutrition. These two documents summarized decades of clinical experience and described the achievement of low malnutrition-related case fatality rates in some specific settings. Further guideline revisions were made in 2003 and 2013. Relevant joint statements from WHO and other United Nations agencies were issued in 2007 and 2009. The combination of these joint statements, the 1999 guidelines and the revisions of 2003 and 2013 constitute the current WHO severe acute malnutrition guidelines and underpins WHO’s related training material.

Although weak health systems and the inadequate implementation of guidelines undoubtedly contribute to the high number of preventable deaths attributed to complicated severe acute malnutrition, this condition causes high case fatality even in relatively well resourced centres that report full implementation of the WHO guidelines. This review attempts to identify evidence gaps within the guidelines on inpatient management of severe acute malnutrition that, if filled, may help reduce mortality below the levels that can be accomplished solely by adherence to existing guidelines. We reviewed each individual recommendation contained within current WHO guidelines – including those relating to the post-discharge...
care that forms an integral extension of hospital management. We traced the lineage and quantified the evidence cited in support of each recommendation. We also searched trials registries systematically, to determine which evidence gaps may be closed by the results of ongoing or recently completed trials.

**Methods**

We identified WHO’s recommendations for severe acute malnutrition management by searching Google Scholar – using “severe acute malnutrition” and “author:WHO” as the search terms – and by downloading the publications on the WHO nutrition website in December 2015.15 Full texts were reviewed if they represented a relevant guideline – as classified by WHO’s guideline review committee – or guideline update.16 Documents specific to humanitarian crises and those without inpatient or post-discharge management recommendations – e.g. the 2007 and 2009 joint statements15,16 – were excluded. Each included guideline was parsed into individual recommendations. We excluded diagnosis and admission criteria and care principles that are applicable to all hospitalized children – e.g. the monitoring of blood glucose after treatment of hypoglycaemia.

We traced each recommendation’s evolution through the development of the guidelines and noted any modifications and references cited in support of the recommendation. The full texts of all potentially relevant citations were reviewed. To determine the origins of each recommendation further, we reviewed three documents predating the current guidelines: WHO’s 1981 severe protein-energy malnutrition recommendations,9 and two textbooks commonly used before the publication of WHO’s first severe malnutrition guidelines in 1999.17,18

According to formal GRADE (grading of recommendations, assessment, development and evaluation) assessment, each of the recommendations we investigated was of low, very low or unclassifiable quality. We evaluated each recommendation using GRADE’s directness assessment, as this provided meaningfully differentiated categories of evidence quality.19 Recommendations that were not supported by any cited evidence were considered to be based entirely on expert opinion. Recommendations were defined as indirectly supported if all of the cited studies were either among populations other than children with complicated severe acute malnutrition – e.g. HIV care guidance derived from studies of HIV-infected children without concurrent malnutrition – or only based on a treatment that was similar, but not identical, to the WHO recommended treatment – e.g. commercial ready-to-use therapeutic foods recommended on the basis of trials of locally produced versions of such foods. If at least one study concerning the endorsed intervention in a population of children with complicated severe acute malnutrition was cited in support of a recommendation, then that recommendation was considered to be directly supported. Direct evidence was further categorized as an observational study or a randomized trial.

To determine the aims and extent of any recently completed, ongoing, or pending trials relevant to the management of complicated severe acute malnutrition, we searched the WHO International Clinical Trials Registry Platform, the United States National Institutes of Health’s clinicaltrials.gov database and the Controlled Trials metaRegister systematically, using the search terms “malnutrition” and “wasting”. We completed this search on 10 August 2015. We fully reviewed all records with relevant or non-specific titles and included interventional trials among children with complicated severe acute malnutrition. We excluded trials already cited in WHO guidelines and those stopped before subject enrolment. We investigated the publication status and results of relevant trials by searching PubMed for the corresponding registration numbers.

**Results**

Eight documents containing 33 current recommendations met our inclusion criteria (Fig. 1).2,3,13–17,20 The lineage of the 33 recommendations is summarized in Table 1. Expert opinion, in the absence of published evidence, was the basis for 16 (48.5%) of the recommendations. Three (9.1%) and six (18.2%) of the recommendations were drawn from direct observational or indirect evidence, respectively. The remaining eight recommendations (24.2%) were each supported by at least one direct randomized trial.

---

**Fig. 1. Flowchart of the search for guidelines and recommendations on the inpatient management of severe acute malnutrition, 2015**

379 records identified through search:
- 279 from WHO nutrition publication list
- 100 from Google Scholar

368 records excluded:
- 13 duplicates
- 350 not addressing SAM
- 5 specific to humanitarian crisis

14 full-text records reviewed for eligibility

8 records included – covering 216 recommendations

33 recommendations included in qualitative analysis

SAM: severe acute malnutrition.
Table 1. Ancestry of evidence cited in support of the World Health Organization’s recommendations on the inpatient management of children with severe acute malnutrition

| Recommendation | History | Evidence base, year published |  |
|----------------|---------|-----------------------------|---|
| **Micronutrients** | | | |
| 200 000 IU of vitamin A for patients with eye signs of deficiency\(^a\) | 1981 | 1998, 2007, 2012 | – | – |
| 200 000 IU of vitamin A for patients with measles\(^1\) | 2003 | – | 1998, 2007, 2012 | – | – |
| 200 000 IU of vitamin A for patients not receiving vitamin A via feeds or other supplements\(^1\) | 2013 | – | 1998, 2007, 2012 | – | – |
| 5000 IU of vitamin A per day\(^1\) | 2013 | – | 1998, 2007, 2012 | – | – |
| Zinc for patients with diarrhoea unless receiving zinc-fortified feeds | 2013 | – | – | – | – |
| No difference in zinc and vitamin A dosing based on HIV status\(^3\) | 2013 | – | – | 2010 | – |
| Copper, folic acid, iron, magnesium and potassium to be given daily for at least 2 weeks | 1992 | 1996 | – | – | – |
| **Feeding** | | | |
| Feed immediately on admission, then every 2–3 hours. Transition from F-75 therapeutic milk feed to RUTF when patient stable, with appetite and decreasing oedema\(^2\) | 2003 | – | – | 1998 | 1989, 1998, 1998, 2009 |
| Transition from F-100 therapeutic milk feed to RUTF when weight gain is rapid and patient accepting diet\(^2\) | 2003 | – | – | 1998 | 1989, 1998, 1998, 2009 |
| For patient aged < 6 months, support breastfeeding – or relactate – with supplementary feeds and do not give undiluted F-100\(^1\) | 1981 | 2013 | 2009 | 2000 | 2009 |
| No difference in feeding approach based on HIV status | 2013 | – | – | – | – |
| Can give RUTF in acute or persistent diarrhoea cases | 2013 | – | – | – | 1994, 1995, 1997, 2002, 2005 |
| **Fluid management** | | | |
| Give ReSoMal for mild–moderate dehydration in non-cholera cases | 1999 | – | 2003 | 2000 | 1999, 2000, 2001 |
| Give standard low-osmolarity ORS for mild–moderate dehydration in suspected cases of cholera | 2013 | – | 2009 | – | – |
| For shock or severe dehydration, give intravenous Ringer’s lactate solution or half-strength Darrow’s solution, each supplemented with 5% dextrose\(^1\) | 1999 | 2013 | 2010 | – | – |
| Every 5–10 minutes, monitor patients receiving intravenous fluids to check for overload | 1999 | – | – | – | – |
| Give blood transfusion, at 10 ml/kg, for shock if no improvement after 1 hour of intravenous therapy, and for severe anaemia | 1999 | – | – | – | – |
| Do not give blood transfusions > 24 hours post-admission | 2013 | – | – | 2006 | – |
| **ART** | | | |
| Start lifelong ART if patient aged < 24 months\(^1\) | 2013 | – | – | – | 2009, 2010 |
| Start lifelong ART, based on CD4 counts or clinical staging, if patient aged ≥ 24 months\(^1\) | 2013 | – | – | – | 2009, 2010 |
| Start ART after stabilization of complications | 2013 | – | – | – | 2009, 2011, 2012 |
| **Hypoglycaemia and hypothermia** | | | |
| If patient conscious, give 50 ml bolus of 10% dextrose – by mouth or nasogastric tube – then F-75 every 30 minutes for 2 hours | 1996 or before | 1996 | – | – | – |
| If patient unconscious, lethargic or convulsing, give 10% dextrose intravenously, at 5 ml/kg, and then 50 ml of 10% dextrose by mouth | 1996 or before | 1996 | – | – | – |

(continues . . .)
Twenty-three (69.7%) recommendations had been added or revised since the original guideline published in 1999. Only six (26.1%) of these 23 were supported by a directly relevant randomized trial. Three (13.0%) and six (26.1%) were supported by at least one direct observational or indirect study, respectively, while no references were cited in support of the remaining eight (34.8%) recommendations. The 1999 guidelines presented a 10-step management protocol – as originally proposed in the article Ten steps to recovery that was published in 1996. Five (15.2%) of the 33 current recommendations are identical to – or slight modifications of – the recommendations first proposed in this 1996 article. Seven (21.2%) of the current recommendations originated before 1996 – although five of these have since been slightly revised.

**Recommendation age and quality**

The age of the recommendation and quality of supporting evidence varied according to the involved clinical area.

**Micronutrients**

Micronutrient recommendations were largely based on expert opinion, although three randomized trials directly supported two of the recommendations made in the 2013 update: low-dose vitamin A administration, reserving high-dose vitamin A for those with eye signs of deficiency or measles. Collectively, the trials demonstrated that either dose of vitamin A was superior to placebo, and that high-dose vitamin A offered no benefit compared with low-dose and might be associated with nosocomial diarrhoea and pneumonia. The 2013 update also recommended that HIV-infected children receive the same zinc and vitamin A doses as uninfected peers. This recommendation was supported by a systematic review of studies among HIV-infected children and adults without malnutrition, which indicated that HIV infection should not alter zinc requirements. Specific recommendations on the broader micronutrient package, which have remained constant for over 20 years, are all based on expert opinion.

**Feeding**

Indirectly related studies were the predominant reference type cited in support

---

| Recommendation | History | Evidence base, year published |
|----------------|---------|-------------------------------|
|                | First released | Last modified | Direct RCT | Direct observational | Indirect |
| **Infection**  |         |                  |             |                    |          |
| Give empiric ampicillin and gentamicin and then, if no response, chloramphenicol | 1969 or before | 1996 | – | – | – |
| Patients aged < 6 months should receive same antibiotics as older children | 2013 | – | – | – | – |
| Give measles vaccine to non-immunized children aged ≥ 6 months | 1996 | – | – | – | – |
| **Discharge from inpatient or outpatient care** |         |                  |             |                    |          |
| Transfer to outpatient care on clinical condition rather than anthropometry | 2013 | – | – | – | – |
| Move patients aged < 6 months to outpatient care if their daily weight gain exceeds the median growth velocity standard or is > 5 mg/kg/day for 3 days | 2013 | – | – | – | – |
| Discharge from outpatient care when WHZ is ≥ –2 or MUAC is ≥ 125 mm | 2013 | – | – | – | – |
| The anthropometric measure that qualified a child for admission should be used to monitor the child’s outpatient progress | 2013 | – | – | – | – |
| If oedema was the only observed complication, normal anthropometrics can be used to monitor outpatient progress | 2013 | – | – | – | – |
| Discharge from outpatient care should not be based on percentage weight gain | 2013 | – | – | – | – |
| **Emotional support** |         |                  |             |                    |          |
| Provide patient with emotional and sensory support | 1969 or before | – | – | – | – |

ART: antiretroviral therapy, HIV: human immunodeficiency virus, IU: international unit, MUAC: mid-upper arm circumference, ORS: oral rehydration solution, RCT: randomized controlled trial, RUTF: ready-to-use therapeutic foods, WHZ: weight-for-height z-score.

a All vitamin A recommendations are supported by the same randomized trials.

b Citation for vitamin A and zinc dosing in HIV infection is a Cochrane review of five vitamin A and two zinc randomized trials indirectly related to the management of complicated severe acute malnutrition.

c The F-75 and F-100 therapeutic milk feeding recommendations are supported by the same studies.

d If maternal breastfeeding is not possible, wet nursing should be encouraged.

e If neither solution available, use 0.45% saline with 5% dextrose.

f Based on indirect evidence discussed in two sets of World Health Organization guidelines.

g That is, if the diagnosis was made on low MUAC, use MUAC – and not WHZ – to quantify recovery.
of the feeding recommendations. Recommendations for the use of therapeutic milk feeds – i.e. F-75 and F-100 – and the criteria for transition to ready-to-use therapeutic foods were last updated in 2003 and were based on the results of six studies. Five of these studies demonstrated an association between refeeding syndrome and death among adolescents with eating disorders, children with neurological dysphagia, children with parent-imposed starvation, and critically ill adults in high-income settings.27-31 The 2013 update advised against use of undiluted F-100 among young infants, based on a direct study that indicated a possible connection between undiluted F-100 and renal solute overload, hypernatraemia and death.32 Specific advice on breastfeeding has remained largely unchanged for almost half a century.33

Fluid management

Three of the six recommendations on fluid management – including the specification of low-osmolarity salts for cholera – had been revised in the 2013 update.34 Recommendations for the treatment of shock or severe dehydration underwent a relatively minor re-ordering in the preference of intravenous fluids, based on a direct randomized trial of 62 children, in which Ringer’s lactate solution with 5% dextrose was compared with half-strength Darrow’s solution with 5% dextrose. Neither of these fluids was found to correct shock sufficiently and the choice of fluid had no significant effect on mortality.35 Finally, the study that was cited in support of limiting the timing, indications and infusion rates for transfusions demonstrated a strong association between mortality and transfusion – although adjustment for confounding by indication may have been insufficient.36

Antiretroviral treatment

Although three recommendations on antiretroviral treatment were added in the 2013 update, none was supported by direct evidence. Antiretroviral initiation recommendations referenced WHO’s guidelines on the management of childhood HIV infection.21,22 The advice to initiate antiretrovirals after clinical stabilization cited two pharmacokinetic studies among children with varying degrees of malnutrition37,38 and one retrospective study that demonstrated faster recovery when antiretroviral treatment was initiated within 21 days of the diagnosis of uncomplicated severe malnutrition.39

Fig. 2. Flowchart of the search for recent or current trials relevant to the inpatient management of severe acute malnutrition, 2015

---

Other clinical problems

Recommendations on the management of hypoglycaemia, hyperthermia and acute infections – including specifics related to antimicrobial treatment – were made in the Ten steps to recovery article.41 They remain unchanged and are not supported by any cited evidence.

Discharge and follow-up

Six recommendations on discharge from hospital and outpatient care were added in the 2013 update and were almost exclusively drawn from expert opinion. Supporting citations were limited to two indirect retrospective studies demonstrating that mid-upper arm circumference was an adequate measure of outpatient progress.42,43 The results of these studies led to the recommendation to eliminate percentage weight gain as a criterion for discharge from outpatient follow-up.

Ongoing or recent trials

Our search of trials registries yielded the full records of 58 trials – after review of trial titles (Fig. 2). Twenty of these trials met our inclusion criteria (Table 2). Fifteen of the 20 trials had been completed – and the results of four had been published – by the time of our search.44-50 Two had reported statistically significant results; one demonstrated that community follow-up increased linear growth and clinic attendance45 and the other that long-chain n-3 polyunsaturated fatty acid in erythrocytes increased among severely malnourished children who were given ready-to-use therapeutic food enriched with polyunsaturated fatty acid.42 The other two published trials, which detected no significant differences, compared alternative formulations of ready-to-use therapeutic food with standard formulations. Of the 16 unpublished trials, nine and two had been designed to investigate alternative feeding regimens and the use of probiotics, respectively. One each had been designed to investigate pancreatic enzyme replacement, antioxidants, intravenous rehydration, stool output assessment, and antiretroviral pharmacokinetics. Three unpublished antibiotic trials – completed between 2008 and 2014 – examined ciprofloxacin pharmacokinetics, ceftriaxone for concurrent pneumonia, and post-discharge prophylaxis with co-trimoxazole (Table 2).

Discussion

The 2013 update stated that “major research gaps were identified in each of the sections covered.”4 Our analysis shows that such gaps persist and extend across the entire spectrum of guidance on the management of complicated severe acute malnutrition. The absence of relevant published data has forced a reliance on expert opinion. The evidence that was cited in support of many recommendations was of very low quality and often did not specifically pertain to the recommended treatment. These deficits demonstrate that guideline reforms have been driven by an overwhelming clinical need – rather than by a body of compelling evidence. This is not criticism of WHO or the guidelines’ authors, who should be commended for creating pragmatic management documents by threading together the little solid evidence available and expert opinion.
It should be noted that recommendations supported by weak evidence or expert opinion are not necessarily incorrect. Many of the recommendations are grounded in the results of basic science research and careful clinical observations, much of which was made before the 1996 seminal Ten steps to recovery article. However, the population of paediatric inpatients with severe malnutrition has dramatically changed in the last 10–20 years. Over that period, HIV has emerged as an important contributing problem, younger infants have come to represent an increasing proportion of malnourished children and, for cases without complications, outpatient care has eclipsed hospital management.\(^a\) Data from previous eras may therefore not be generalizable to the modern child with complicated severe acute malnutrition.

In some areas the absence of clinical data is particularly concerning. For example, given that the largest burden of mortality from malnutrition is in sub-Saharan Africa, where the prevalence of HIV infection is relatively high, the lack of evidence to guide the management of HIV-infected children with malnutrition is worrying.\(^a\) A 2009 meta-analysis found that, among severely malnourished children, HIV infection was associated with a threefold increased risk of mortality.\(^b\) In a cohort study of severely malnourished children admitted to Queen Elizabeth Hospital in Malawi, HIV-infected children represented 64% of the deaths. The same study found that 67% of infants died.\(^a\) In the absence of data addressing these two populations – i.e. young infants and HIV-infected children with complicated severe malnutrition – the guidelines’ authors have been forced to generalize the management practices from other populations, without evidence that this is optimal or even appropriate.\(^a\)

Furthermore, in the Malawian study, 25% of the children who were discharged died in the following 12 months and these deaths represented 44% of the total recorded mortality.\(^a\) Post-discharge mortality rates are high and their causes are poorly understood. This knowledge gap warrants urgent attention.

Antimicrobial therapy for severely malnourished inpatients represents another conspicuous knowledge gap. Empiric antibiotics have been recommended since at least 1969\(^a\) and the currently endorsed regimen has remained unchanged since it was standardized to ampicillin and gentamicin in 1996.\(^a\) A 1996 trial demonstrated the superiority of ampicillin and gentamicin compared with previously endorsed protocols relying on co-trimoxazole or penicillin and gentamicin.\(^a\) We are not aware of any subsequent studies comparing the currently recommended regimen with other antimicrobials. In the care of severe acute malnutrition, fluid man-

### Table 2. Registered clinical trials addressing the inpatient or post-discharge management of children with complicated severe acute malnutrition, 2015

| Topic, title, country | Registry identifier | Date of last update\(^a\) | Status\(^a\) |
|-----------------------|---------------------|---------------------------|------------|
| **Antibiotics**       |                     |                           |            |
| Antibiotics in concurrent pneumonia, Bangladesh | NCT00968370 | 14 July 2013 | Complete |
| Post-discharge co-trimoxazole prophylaxis, Kenya | NCT00934492 | 15 August 2014 | Complete |
| Oral ciprofloxacin, Kenya | ISRCTN31079753 | 2 February 2009 | Complete |
| **Antiretrovirals**   |                     |                           |            |
| Steady-state pharmacokinetics in concurrent HIV infection, Uganda, United Republic of Tanzania and Zimbabwe | NCT01818258 | 5 August 2015 | Not yet recruiting |
| **Feeding**           |                     |                           |            |
| Comparison of RUTF with 10% and 25% milk, Malawi | ISRCTN54186063 | 4 June 2009 | Complete\(^b\) |
| Reformulated F-75 therapeutic milk feed, Kenya and Malawi | NCT02246296 | 6 January 2015 | Ongoing |
| Rehabilitation with undiluted F-100 or diluted F-100, Bangladesh | NCT01558440 | 26 July 2015 | Complete |
| RUTF based on sorghum, soybean and maize, Malawi | PACTR201505001101224 | 15 April 2015 | Not yet recruiting |
| RUTF based on soybean, Bangladesh | NCT01634009 | 4 March 2015 | Ongoing |
| RUTF enriched with n-3 PUFA, Kenya | NCT01593969 | 15 August 2014 | Complete\(^b\) |
| Three dietary regimes, Malawi | ISRCTN13916953 | 14 January 2013 | Complete |
| Three new formulations of RUTF, Malawi | ISRCTN19364765 | 23 July 2009 | Complete\(^b\) |
| Whole milk during initial management, India | CTRI/2011/07/001853 | 3 May 2012 | Complete |
| **Fluids**            |                     |                           |            |
| Slow versus rapid rehydration, Bangladesh | NCT02216708 | 20 August 2014 | Complete |
| **Follow-up**         |                     |                           |            |
| Community-based follow-up, Bangladesh | NCT01157741 | 7 July 2010 | Complete\(^b\) |
| **Stool output**      |                     |                           |            |
| Stool frequency, Malawi | ISRCTN11571116 | 15 January 2014 | Complete |
| **Supplements**       |                     |                           |            |
| Antioxidants and oxidants, Jamaica | NCT00069134 | 27 January 2015 | Ongoing |
| Pancreatic exocrine replacement therapy, Malawi | ISRCTN57423639 | 14 April 2014 | Complete |
| Probiotics in recovery, Uganda | ISRCTN16454889 | 12 May 2014 | Complete |
| Spirulina supplementation, Niger | PACTR201406000810205 | 9 April 2014 | Complete |

HIV: human immunodeficiency virus; PUFA: polyunsaturated fatty acids; RUTF: ready-to-use therapeutic food.

\(^a\) As recorded on 10 August 2015.

\(^b\) Results published before 10 August 2015.
Inpatient management of severe acute malnutrition

Kirkby D Tickell & Donna M Denno

The paucity of relevant research may arise from a misconception that treatment failure among children with severe pneumonia while the Global Enteric Multicentre Study demonstrated Cryptosporidium, enterotoxigenic Escherichia coli, rotavirus and Shigella to be leading causes of childhood diarrhoeal death. These findings have spurred interventional trials that hopefully will improve management and save lives. A few studies have evaluated the causes of infection or death among children admitted for severe acute malnutrition. However, we are aware of no recent or robustly sampled investigation of the causes – including non-infectious etiologies – of mortality among such children during hospitalization or post-discharge. The failure of many trials to find statistically significant results may stem from a superficial understanding of the contemporary etiologies of such mortality. For example, if children with environmental enteric dysfunction require specific treatment more than children who are affected by food insecurity alone, then including both groups of children in trials of ready-to-use therapeutic foods could lead to attenuated estimates of efficacy and reduced statistical power. An improved understanding of the epidemiology of complicated severe acute malnutrition will facilitate the efficient design of clinical trials and catalyse the discovery of new and effective interventions.

This paper is not a detailed systematic review but rather a tracing of the lineage of each recommendation and its supporting citations. We did not review evidence that was not referenced in the relevant WHO guidelines. Early guidelines were published at a time when evidence citation was uncommon. Any relevant evidence available to these guidelines’ authors will not have been captured by our review unless cited in subsequent updates. Additionally, it is impossible to quantify the cumulative clinical experience of the many experts who have contributed to the guidelines. This paper does not address why severely malnourished children admitted to Asian hospitals seem to experience different mortality rates to their counterparts in African facilities. It would be useful to determine, in various settings, the proportion of cases of severe malnutrition that present with complications.

In conclusion, we found that the evidence base for the management of complicated severe acute malnutrition is heavily reliant on expert opinion in the absence of published data, that the relevant recommendations have undergone very limited substantive revision over the past two or more decades and that few ongoing clinical trials are being conducted in high priority areas. Although enhanced implementation of current guidelines would improve outcomes, a renewed and even modest investment in relevant epidemiological and clinical research is likely to lead to more effective recommendations and lower mortality.

Competing interests: None declared.
En décembre 2015, nous avons recherché les recommandations de l’OMS sur le sujet. Cependant, 33% d’entre eux s’appuyaient uniquement sur une opinion d’expert non étayée par des données publiées. Onze (33,3%) autres étaient corroborées par les résultats de recherches présentant un intérêt direct, c’est-à-dire des essais randomisés (8) ou des études observationnelles (3). Les six dernières (18,2%) reposaient quant à elles sur des études n’ayant pas été menées auprès d’enfants atteints de malnutrition sévère avec complications ou sur des études de traitement non conforme à l’intervention recommandée. Les essais enregistrés incluaient 20 études en lien avec le sujet, dont neuf essais de régimes alimentaires alternatifs. Les études sur la prise en charge médicale urgente et les soins de suivi n’étaient que très peu représentées.

Conclusion Les lignes directrices de l’OMS sur le sujet s’appuient sur des données insuffisantes et n’ont fait l’objet que d’ajustements substantiels limités au cours des dernières décennies. Il est nécessaire de réaliser davantage d’essais afin de rendre cet ensemble de données plus fiable. Pour réduire la mortalité associée à la malnutrition sévère, il est nécessaire de réaliser des essais sur la prise en charge des enfants pendant et après leur hospitalisation, et de les étayer par des études sur les causes de la mortalité.

Résumé

Prise en charge des enfants hospitalisés pour malnutrition aiguë sévère: un examen des lignes directrices de l’OMS

Objectif Comprendre comment renforcer les lignes directrices de l’Organisation mondiale de la Santé (OMS) relatives à la prise en charge des enfants hospitalisés pour malnutrition aiguë sévère avec complications en vue d’améliorer les résultats.

Méthodes En décembre 2015, nous avons recherché les recommandations de l’OMS concernant la prise en charge de la malnutrition aiguë sévère dans Google Scholar et sur le site Internet de l’OMS, puis évalué l’historique et les éléments invoqués à l’appui de ces recommandations. Nous avons systématiquement recherché les essais récemment effectués, en cours ou en attente, jusqu’au 10 août 2015, dans le Système d’enregistrement international des essais cliniques de l’OMS, sur ClinicalTrials.gov et dans le metaRegister of Controlled Trials.

Résultats Les lignes directrices de l’OMS contiennent 33 recommandations à ce sujet. Cependant, 16 (48,5%) d’entre elles s’appuyaient uniquement sur une opinion d’expert non étayée par des données publiées. Onze (33,3%) autres étaient corroborées par les résultats de recherches présentant un intérêt direct, c’est-à-dire des essais randomisés (8) ou des études observationnelles (3). Les six dernières (18,2%) reposaient quant à elles sur des études n’ayant pas été menées auprès d’enfants atteints de malnutrition sévère avec complications ou sur des études de traitement non conforme à l’intervention recommandée. Les essais enregistrés incluaient 20 études en lien avec le sujet, dont neuf essais de régimes alimentaires alternatifs. Les études sur la prise en charge médicale urgente et les soins de suivi n’étaient que très peu représentées.

Conclusion Les lignes directrices de l’OMS sur le sujet s’appuient sur des données insuffisantes et n’ont fait l’objet que d’ajustements substantiels limités au cours des dernières décennies. Il est nécessaire de réaliser davantage d’essais afin de rendre cet ensemble de données plus fiable. Pour réduire la mortalité associée à la malnutrition sévère, il est nécessaire de réaliser des essais sur la prise en charge des enfants pendant et après leur hospitalisation, et de les étayer par des études sur les causes de la mortalité.

Brazilian Journal of Medical and Biological Research 2016;49:1019–1027

Введение детей с тяжелой острой недостаточностью питания в условиях стационара: обзор руководящих принципов ВОЗ

Цель Определить возможные способы усовершенствования руководящих принципов ВОЗ по ведению детей, страдающих тяжелой острой недостаточностью питания с осложнениями, в условиях стационара для улучшения конечных результатов.

Методы В декабре 2015 года авторы статьи провели поиск в системе Google Scholar и на веб-сайте ВОЗ на предмет рекомендаций ВОЗ по ведению тяжелой острой недостаточности питания и проанализировали историю изменений этих рекомендаций и цитируемые факты, лежащие в их основе. До 10 августа 2015 года
Resumen

Gestión hospitalaria de niños con malnutrición aguda grave: un análisis de las directrices de la OMS

Objetivo Comprender cómo deben fortalecerse las directrices de la Organización Mundial de la Salud (OMS) sobre la atención hospitalaria de niños con malnutrición aguda grave complicada con el fin de mejorar los resultados.

Métodos En diciembre de 2015, se realizaron búsquedas de recomendaciones eruditas en Google y en el sitio web de la OMS en relación con la gestión de la malnutrición aguda grave y se evaluó el historial y se citaron las pruebas detrás de estas recomendaciones. De manera sistemática, se realizaron búsquedas de ensayos completados, en proceso o pendientes hasta el 10 de agosto de 2015 en la Plataforma Internacional de Registros de Ensayos Clínicos (International Clinical Trials Registry Platform) de la OMS, en clinicaltrials.gov y en el Metaregistro de Ensayos Clínicos Controlados (Controlled Trials metaRegister).

Resultados Las directrices de la OMS ofrecen 33 recomendaciones sobre el tema. No obstante, 16 (48,5%) de estas recomendaciones se basaron únicamente en opiniones de expertos, sin el respaldo de pruebas publicadas. Otras 11 (33,3%) recomendaciones estaban respaldadas por los resultados de investigaciones directamente relevantes, es decir, ensayos aleatorizados (8) o estudios de observación (3). Las otras 6 recomendaciones (18,2%) se basaban en estudios que no se realizaron en niños con malnutrición aguda grave complicada o en estudios de tratamientos que no eran idénticos a la intervención recomendada.

Conclusiones Las directrices de la OMS sobre el tema tienen una base de pruebas deficiente y han sufrido pocos ajustes importantes durante las últimas décadas. Es preciso realizar más ensayos para que esta base de pruebas sea mucho más firme. Si se pretende reducir la mortalidad asociada a la malnutrición grave, se necesitan ensayos de gestión hospitalaria y tras el alta, con el apoyo de estudios basados en las causas de la mortalidad.

Referencias

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013 Aug 3;382(9890):427–51. doi : http://dx.doi.org/10.1016/S0140-6736(13)60937-X PMID: 23746772
2. Ashworth A, Khamn S, Jackson A, Schofield C. Guidelines for the inpatient treatment of severely malnourished children. Geneva: World Health Organization; 2003. Available from: http://www.who.int/nutrition/publications/guide_inpatient_text.pdf (cited 2016 May 3).
3. Kerac M, Bunn J, Chagaliu G, Bahwere P, Tomkins A, Collins S, et al. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM study): a prospective cohort study. PLoS ONE. 2014 9(6):e96030. doi: http://dx.doi.org/10.1371/journal.pone.0096030 PMID: 24892281
4. Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organisation, 2013. Available from: http://apps.who.int/iris/bitstream/10665/195584/1/9789241506328_eng.pdf (cited 2016 May 3).
5. Community-based management of severe acute malnutrition: a joint statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children’s Fund. Geneva: World Health Organization, 2007. Available from: http://www.who.int/nutrition/topics/Statement_community_based_man_svc_acute_mal_eng.pdf (cited 2016 May 3).
6. Fergusson P, Tomkins A. HIV prevalence and mortality among children undergoing treatment for severe acute malnutrition in sub-Saharan Africa: a systematic review and meta-analysis. Trans R Soc Trop Med Hyg. 2009 Jun;103(6):541–8. doi: http://dx.doi.org/10.1016/trstmh.2008.10.029 PMID: 19058824
7. Sanghvi J, Mehta S, Kumar R. Predicators for weight gain in children treated for severe acute malnutrition: a prospective study at nutritional rehabilitation center. SRN Pediatr. 2014 01 12;2014:800756. doi: http://dx.doi.org/10.1155/2014/800756 PMID: 25060691
8. Singh K, Badgaiyan N, Ranjan A, Dixit HO, Kauhiski A, Kushwaha KP, et al. Management of children with severe acute malnutrition: experience of Nutrition Rehabilitation Centers in Uttar Pradesh, India. Indian Pediatr. 2014 Jan;51(1):21–5. doi: http://dx.doi.org/10.1007/s13312-013-0329-9 PMID: 24277964
9. The treatment and management of severe protein-energy malnutrition. Geneva: World Health Organization, 1981. Available from: http://apps.who.int/iris/bitstream/10665/38925/1/9241541598_eng.pdf (cited 2016 May 3).
10. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva World Health Organization, 1999. Available from: http://apps.who.int/iris/bitstream/10665/41999/1/a57361.pdf (cited 2016 May 3).
11. Ashworth A, Jackson A, Khamn S, Schofield C. Ten steps to recovery: Child Health Dialogue. 1996; (3-4):10–2. PMID: 12292167
12. WHO child growth standards and the identification of severe acute malnutrition in infants and children. Geneva: World Health Organization, 2009. Available from: http://apps.who.int/iris/bitstream/10665/44129/1/9789241598663_eng.pdf?u=1 (cited 2016 May 3).
34. Bachou H, Tumwine JK, Mwadime RK, Tylleskär T. Risk factors in hospital deaths in severely malnourished children in Kampala, Uganda. BMC Pediatr. 2010;10(1):71. doi:10.1186/1471-2431-10-71 PMID: 20925377

35. Pollock L, Else L, Poerkisen G, Molyneux E, Moons P, Walker S, et al. Pharmacokinetics of nevirapine in HIV-infected children with and without malnutrition receiving divided adult fixed-dose combination tablets. J Antimicrob Chemother. 2009 Dec;64(6):1251–9. doi: http://dx.doi.org/10.1093/jac/dkp358 PMID: 19812085

36. Swaminathan S, Ramachandran G, Agbogbogbu Kpampah HK, Mahalingam V, Soundararajan R, Perumal Kannabiran B, et al. Factors influencing plasma nevirapine levels: a study in HIV-infected children on generic antiretroviral treatment in India. J Antimicrob Chemother. 2011 Jun;66(6):1354–9. doi: http://dx.doi.org/10.1093/jac/dkr075 PMID: 21393201

37. Kim MH, Cox C, Dave A, Draper HR, Kabue M, Schutze GE, et al. Prompt initiation of ART with therapeutic food is associated with improved outcomes in HIV-infected Malawian children with malnutrition. J Acquir Immune Defic Syndr. 2012 Feb 15;59(2):173–6. doi: http://dx.doi.org/10.1097/QAI.0b013e318204f58F PMID: 22107819

38. Nielsen J, Valentinier-Brand P, Martins C, Cabral F, Aaby P. Malnourished children and supplementary feeding during the war emergency in Guinea-Bissau in 1998–1999. Am J Clin Nutr. 2004 Oct;80(4):436–42. PMID: 15447719

39. Goossens S, Bekele Y, Yun O, Harcz G, Ouannes M, Shepherd S. Mid-upper arm circumference based nutrition programming: evidence for a new approach in regions with high burden of acute malnutrition. PLoS ONE. 2012;7(11):e49230. doi: http://dx.doi.org/10.1371/journal.pone.0049230 PMID: 23189140

40. Bahwere P, Banda T, Sadler K, Nyirenda G, Owino V, Shaba B, et al. Effectiveness of milk whey protein-based ready-to-use therapeutic food in treatment of severe acute malnutrition in Malawian under-5 children: a randomised, double-blind, controlled non-inferiority clinical trial. Matern Child Nutr. 2014 Jul;10(3):436–51. doi: http://dx.doi.org/10.1111/mcn.12112 PMID: 24521353

41. Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, et al. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. Lancet. 2009 Jul 11;374(9684):136–44. doi: http://dx.doi.org/10.1016/S0140-6736(09)60884-9 PMID: 19595348

42. Jones KD, Ali R, Kharsa MA, Odero D, West AL, Koster G, et al. Ready-to-use therapeutic food with elevated n-3 polysaturated fatty acid content, with or without fish oil, to treat severe acute malnutrition: a randomized controlled trial. BMC Med. 2015;13(1):93. doi: http://dx.doi.org/10.1186/s12916-015-0315-6 PMID: 25902844

43. Hossain MI, Nahar B, Hamadadi JD, Ahmed T, Brown KH. Effects of community-based follow-up care in managing severely overweight children. J Pediatr Gastroenterol Nutr. 2011 Sep;53(3):310–9. doi: http://dx.doi.org/10.1097/MPG.0b013e3182093fa6 PMID: 21803567

44. Wilkinson D, Scarce M, Boyd N. Reduction in in-hospital mortality of children with malnutrition. J Trop Pediatr. 1996 Apr;42(2):137–42. doi: http://dx.doi.org/10.1097/0002-8223(199604)42;2[137::AID-JTP1]3.0.CO;2-8 PMID: 9833551

45. Brewster DR. Inpatient management of severe malnutrition: time for a change in protocol and practice. Ann Trop Paediatr. 2011;31(2):97–107. doi: http://dx.doi.org/10.1097/01.TP.0000385139.46687.a3 PMID: 21574313

46. Picot J, Hartwell D, Harris P, Mendes D, Clegg AJ, Takeda A. The effectiveness of nutritional interventions to treat severe acute malnutrition in young children: a systematic review. Health Technol Assess. 2012;16(19):1–316. doi: http://dx.doi.org/10.3310/hta16190 PMID: 22480797

47. McNally LM, Jeena PM, Gajee K, Thula SA, Sturm AW, Cassol S, et al. Effect of age, polycyclic disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. Lancet. 2007 Apr 28;369(9571):1440–51. doi: http://dx.doi.org/10.1016/S0140-6736(07)61603-0 PMID: 17467514

48. Koffol KL, Nataro JP, Blackwelder WC, Nasim D, Farag TH, Panchalingam S, et al. Burden and etiology of diarrhea disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013 Jul 20;383(9928):209–22. doi: http://dx.doi.org/10.1016/S0140-6736(13)60844-2 PMID: 23680352

49. Marland K, Berkley JA, Shebbe M, Peshu N, English M, Newton CR. Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol? PLoS Med. 2006 Dec;3(12):e350. doi: http://dx.doi.org/10.1371/journal.pmed.0030350 PMID: 17194194

50. Page AL, de Rekeneire N, Sayadi S, Aberrane S, Janssens AC, Rieux C, et al. Infections in children admitted with complicated severe acute malnutrition in Niger. PLoS ONE. 2013;8(7):e68699. doi: http://dx.doi.org/10.1371/journal.pone.0068699 PMID: 23874731