

# **Systematic review of transition phase feeding of children with severe acute malnutrition as inpatients**

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February 2012

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This work was commissioned by the World Health Organization.

Authors declare that they have no conflict of interest.

## **Abbreviations**

AGREE	Appraisal of Guidelines for Research and Evaluation
F-75	therapeutic milk used in stabilization phase of the treatment of SAM
F-100	therapeutic milk used in transition and recovery phases of the treatment of SAM
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
PICO	Population, Intervention, Comparator and Outcomes
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
WHO	World Health Organization

## **Measurements**

g	gram
kcal	kilocalorie
kg	kilogram

## Background

Standard inpatient treatment of severe acute malnutrition (SAM) involves two phases: initial stabilization, during which life-threatening complications are treated; and nutritional rehabilitation, when catch-up growth occurs (1). The first phase uses F-75, a low-protein, low-energy milk-based formula diet, as a therapeutic food, while the second phase uses F-100, a liquid milk that has higher protein and energy content. The World Health Organization (WHO) describes the stabilization phase as complete when the child is hungry. WHO further instructs that the transition to the rehabilitation phase should be gradual and accomplished by replacing F-75 with an equal volume of F-100 for two days, before increasing the amount of therapeutic food offered to the child. Transition phase feeding refers to the feeding regimen offered to children with SAM between stabilization and rehabilitation (2). The practice of a transition phase was adopted from successful clinical treatment protocols at established malnutrition treatment centres in the 1980s and 1990s (3,4).

Ready-to-use therapeutic food (RUTF) has replaced liquid F-100 in a variety of settings where SAM is treated. RUTF is a lipid paste containing large amounts of peanut paste and oil in addition to milk powder. RUTF offers the malnourished child the same nutrient intake as would be received from F-100, without the free water, when consumed in isoenergetic amounts. RUTF has been used in inpatient and outpatient settings during transition phase feeding without explicit instructions as to the amount to be consumed.

It is common practice in some malnutrition treatment centres to add an intermediate phase of treatment, known as a transition phase, where a mixture of F-75, F-100 and/or RUTF is fed to the malnourished child. It is unclear from practice reports what might be the optimum formulation of transition phase feeding. A review of evidence to determine whether or not this practice is effective or beneficial is necessary in order to determine the optimal feeding regimen for children with SAM.

Given the paucity of data and diversity in standard practice and outcomes regarding transitional phase feeding and the increasing need to understand the effectiveness of treatment strategy in the context of community-based management of SAM, a systematic review of the available literature on the subject was carried out. The following specific Population, Intervention, Comparator and Outcomes (PICO) question was identified:

1. For hospitalized children with SAM who have successfully completed the initial stabilization phase feeding with F-75 milk, does a transitional phase feeding approach, i.e. feeding with a formula of intermediate nutrient density (between F-75 and F-100/RUTF) or using a graduated transition approach, result in better weight gain or less adverse events (including mortality), than transitioning directly from F-75 to F-100/RUTF?

## Methodology

A search of computerized databases for all studies from 1950 to 2011 for both observational and randomized studies was carried out. Databases searched included Medline, Embase and Google Scholar and clinical trial registries at [clinicaltrials.gov](http://clinicaltrials.gov), [pactr.org](http://pactr.org), and [apps.who.int/trialsearch](http://apps.who.int/trialsearch). Key words for the searches included “malnutrition”, “severe malnutrition”, “kwashiorkor”, “marasmus”, “transition”, “feeding”, “refeeding syndrome”, and “hypophosphataemia”. A number of outcome measures included mortality, weight gain, nutritional recovery and duration of therapy. Further terms were added iteratively to the search based on results obtained from the initial searches. Searches were also conducted to identify relevant publications and study documents produced by international health organizations such as WHO, the United Nations Children’s Fund and Médecins sans Frontières. Included studies were limited to those published in English, French or Spanish.

The titles and abstracts from these search results were scanned to identify relevant studies. The full texts of relevant studies were obtained and the list of relevant articles for inclusion was further

optimized. Reference lists in relevant articles were also scanned manually and electronically (Google Scholar; Web of Science) to identify prior citations that may have been missed by the original searches. Publications that cite those previously identified articles were similarly sought.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach ([www.GradeWorkingGroup.org](http://www.GradeWorkingGroup.org)) to evaluating studies was then used to guide the evaluation of identified studies. A number of criteria were applied to retrieved studies in order to assess their methodological quality: type of study (observational vs randomized); study quality; relevant choice of study population; appropriate choice of interventions and outcomes; and methods for controlling for confounders. In the GRADE approach, randomized controlled trials constitute high-quality evidence. Observational studies without important limitations constitute low-quality evidence. Quality of evidence may be decreased if there are study limitations, inconsistent results, publication bias or the evidence is indirect. Quality of evidence may also be increased if there is a large magnitude of effect, plausible confounding that would reduce the demonstrated effect or a dose-response gradient. Subjectivity arising from possible conflicts of interest was also assessed. Evidenced-based PICO review tables for each source were created and thoroughly reviewed by other investigators.

## Results

A total of 938 references were identified through the computerized search. After screening the abstracts and/or articles no trials or studies were identified that compared a transition phase approach to an alternative approach without a transition phase, nor were any comparative trials identified that examined the composition or amounts of food offered upon completion of stabilization phase. No grade or PICO tables were, therefore, created. No evidence is available from which to critically examine the practice of transition phase feeding.

## Discussion

When direct, trial-based evidence is absent, practitioners turn to clinical experience and the understanding of human physiology to guide their practice. It was upon such indirect evidence that the recommendation for transition phase feeding was originally made, and at present should be considered.

The primary risk posed to the malnourished child if feeding is not introduced gradually has been called refeeding syndrome by clinicians (5–8). The physiologic basis for refeeding syndrome is the secretion of insulin in response to large amounts of dietary carbohydrate (9,10). In the severely malnourished state, catabolic metabolism predominates when consuming a diet with limited amounts of carbohydrate. Both amino acids, primarily alanine, and fat in the form of ketone bodies are converted to glucose to provide the brain and kidney with a necessary supply of carbohydrate, primarily glucose. If a child with SAM is abruptly fed ample amounts of carbohydrate, as would be the case in nutritional rehabilitation, the child would secrete insulin to move this dietary glucose into cells. This secreted insulin will also facilitate the movement of phosphate, potassium and magnesium intracellularly (11–13). At times, profound hypophosphataemia, hypokalaemia and/or hypomagnesaemia are the result, precipitating clinical catastrophe (14–17). Using a decrease in serum phosphate as a marker of refeeding syndrome, this has been observed in 20–40% of SAM upon refeeding (18–20). More severely malnourished children are at greater risk of refeeding syndrome.

To the practitioner, refeeding syndrome may present as cardiac failure and shock, an acute arrhythmia resulting in sudden death, hypoventilation and respiratory failure, or acute renal failure; any serious deterioration in clinical condition (21,22). This may be interpreted as sepsis by the practitioner and treated with changes in the antibiotic regimen. Children in the developing world are often cared for in circumstances where monitoring of vital signs is limited and monitoring of serum electrolytes is unavailable. These circumstances hinder the recognition of refeeding syndrome.

Since refeeding syndrome can be provoked by any carbohydrate containing food in SAM, practitioners should be aware of its clinical consequences and whether RUTF, F-100 or another therapeutic food constitutes the diet of the SAM child. There is no physiological basis to suspect that refeeding syndrome occurs more frequently with RUTF or F-100.

In light of the common and serious nature of refeeding syndrome, it is prudent to gradually increase the energy intake when moving from stabilization to rehabilitation (23,24). Foremost, children should not be forced to eat, either by medical staff intent on providing adequate nutrition, or mothers who believe that they are helping their child to recover. We believe it is less likely that a child will intentionally consume food to provoke refeeding syndrome. Second, staff and mothers should be instructed to provide about 100 kcal/kg/day for the first two days after stabilization has been achieved. The following chart estimates the amount of RUTF needed to provide 100 kcal/kg/day, an amount recommended for transition phase feeding.

<b>Child's weight</b>	<b>Weight of RUTF to provide 100 kcal/kg/day</b>	<b>Number of 92 g sachets of RUTF/day</b>
4–5 kg	83g	1
5–6 kg	101g	1
6–7 kg	120g	1
7–8 kg	138g	2
8–9 kg	156g	2
9–10 kg	175g	2
10–11 kg	193g	2
11–12 kg	212g	2

## **Conclusions**

As for treatment of SAM in regard to transition phase feeding, certainly further research is needed to identify risk factors for refeeding syndrome, particularly among children treated exclusively as outpatients for SAM, as well as comparative trials of feeding regimens. Until such evidence is accumulated, the best recommendation is for a gradual increase in dietary energy as the child moves from stabilization to rehabilitation.

## **Further research**

A review of current practice worldwide using a standardized method, such as the Appraisal of Guidelines for Research and Evaluation (AGREE) process should be undertaken regarding transition phase feeding. After this review, clinical trial protocols should be developed, trials undertaken and results reported. This area is devoid of direct trial-based evidence, and clinical practice might well be improved with the addition of such.

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