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Lessons learned from ready-to-use therapeutic foods

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Developing food supplements for moderately malnourished children: Lessons learned from ready-to-use therapeutic foods

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Abstract

Ready-to-use therapeutic foods (RUTFs) are solid foods that were developed by changing the formulation of the existing liquid diet, F-100, recommended by the World Health Organization (WHO) for the rapid catch-up phase of the treatment of children suffering from severe acute malnutrition (SAM). The resulting products proved highly effective in promoting weight gain in both severely and moderately wasted children and adults, including those infected with HIV. The formulation of the existing RUTFs, however, has never been optimized to maximize linear growth, vitamin and mineral status, and functional outcomes. The high milk content of RUTFs makes it an expensive product, and using lower quantities of milk seems desirable. However, the formulation of alternative, less expensive but more effective versions of RUTF faces difficult challenges, as there are uncertainties regarding the effect in terms of protein quality, antinutrient content, and flatulence factors that will result from the replacement of current dairy ingredients by less expensive protein-rich ingredients. The formulation of alternative RUTFs will require further research on these aspects, followed by efficacy studies comparing the future RUTFs to the existing formulations.

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Ready-to-use therapeutic foods (RUTFs) are highly effective in promoting rapid weight gain in children recovering from severe acute malnutrition (SAM). The physiology of weight gain is not fundamentally different in children with moderate acute malnutrition (MAM), and standard RUTF could be used in theory and was used to treat successfully large numbers of children with MAM [1]. Standard RUTF, however, was designed to be given as the only food that a child consumes while being treated for SAM. This approach may not be appropriate, or likely to happen in practice in children with MAM, unless the household is severely food insecure. When special nutritious foods are required for treating children with MAM, cost considerations usually also prevent the use of standard RUTF, as the number of children with MAM is considerably higher than the number of children with SAM. Current estimates based on prevalence data (which underestimate the number that suffer from MAM or SAM in a year) suggest that globally there are about 32.8 million children with MAM, compared with about 18.7 million with SAM [2]. So there is a need to adapt the RUTF formulation to lower its cost by using less expensive ingredients. Using locally available ingredients is another important factor to consider. Arguably, the cost of ingredients is only one part of the final cost of the product, and local ingredients are not always less expensive than those found on the international market. Local production, however, is always better politically accepted and seems desirable, even if its impact on the final cost of the product is often uncertain. So the use of local ingredients should be discussed when designing food supplements for children with MAM.

When trying to further adapt the current RUTF formulation for children with MAM, two important aspects of RUTF development should be taken into account. First, it should be acknowledged that the current RUTF formulation has not been fully optimized

and may need improvement. Second, cost reduction by using less expensive ingredients may lead to less effective formulations, for reasons that are not fully understood. The goal of this paper is to highlight the questions remaining in RUTF development and research, which may also be relevant for development of effective foods for children with MAM. This paper complements existing reference documents on management of MAM in children* [3–5].

Need for RUTF optimization

When RUTF was developed, it was derived from the existing liquid F-100 diet recommended by the World Health Organization (WHO) for the treatment of children with SAM; at that time F-100 had already been used successfully to treat hundreds of thousands of these children. The first RUTF (Plumpy'Nut®) was formulated by replacing about half of the dried skimmed milk in the F-100 formula with peanut paste. This resulted in a food that looked like a paste and could be used without the addition of water, which eliminated the risk of bacterial proliferation in case of contamination after opening the container or sachet. To minimize the difference between the first RUTF and the existing F-100 diet, whey powder was introduced in the recipe so that the final diet contained an equivalent level of lactose. In the same manner, maltodextrins, which were part of the industrially produced F-100 diet at that time to reduce its osmolarity, were kept in the formulation of RUTF. This approach, aiming at reproducing as closely as possible the existing reference diet, minimized the risk of not obtaining similar results when programs started to replace the traditional liquid milk-based product with this new solid diet, which still had some substantial formulation differences.

This approach proved successful, as clinical trials showed that this RUTF formula was at least as effective in promoting weight gain as the existing F-100 diet [6, 7]. However, this approach has its limitations. First, weight gain is not the best criterion to assess recovery. Evaluation of the efficacy of RUTF according to other criteria, including functional outcomes, is needed. Second, this comparison with F-100 assumes that F-100 is a gold standard that provides the optimal amount of all nutrients needed for catch-up growth and full recovery. F-100, however, was formally tested in only a small number of children in one setting, and it is possible that its contents of some nutrients are not optimal to reverse stunting, which is often associated with wasting [3].

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* See also: Golden M. Technical considerations in setting specifications for supplementary foods for malnourished children. A paper prepared for World Health Organization Consultation on the management of the moderately malnourished child. 2009.

Quantities of RUTF consumed are not the same as for F-100

F-100 was designed to be consumed as the only food during the nutrition rehabilitation phase; therefore, its mineral and vitamin contents were adjusted to cover requirements of a child consuming 150 to 200 kcal/kg/day of this diet and having a weight gain of up to 15 to 20 g/kg/day. The quantities of added vitamins and minerals were adjusted to take into account preexisting deficiencies and also the additional requirements related to rapid growth.

In most protocols, the quantities of RUTF given to children treated in community settings are around 175 to 200 kcal/kg/day, as recommended previously for F-100, assuming implicitly that RUTF is the only food that children consume during treatment. However, this seems to happen rarely. The average weight gains of children treated with RUTF in the community are usually in the range of 4 to 6 g/kg/day and sometimes even less, well below the 10 to 15 g/kg/day observed in the initial clinical trial of RUTF [6]. This suggests, among the main factors directly related to the product, that children do not consume the supposed amount of RUTF (which may be related to sharing of the RUTF), and/or that RUTF is not the only food consumed by these children, who also eat locally available, less nutrient-dense food. The level of consumption of local foods along with RUTF has never been precisely estimated. If the level is substantial and consistent across children receiving RUTF, this may require increased fortification levels of nutrients not provided in adequate amounts by the local diet.

Absorption of minerals is likely to be lower from RUTF

Adjustments of the concentrations of micronutrients in the F-100 diet were made on the basis of limited clinical studies that were done in children who received a milk-based diet as their only food apart from breastmilk. The most common RUTF contains about 25% peanut paste, which itself contains 1% to 2% phytates and may potentially inhibit the absorption of divalent ions, such as iron, zinc, or calcium [3, 4]. The food matrix also is different. Whereas all nutrients in F-100 are dissolved in water, they are within a lipid matrix in RUTF, with unknown effects on their absorption. This may have an impact in particular on the absorption of iron contained in RUTF. Absorption of iron takes place in the upper part of the gut, where iron in RUTF may well still be within the fat matrix. Phosphorus is also potentially a problem, as part of it in RUTF is provided by peanut paste and is presumably in phytate form and thus is less well absorbed than phosphorus provided by dairy products. The 2007 World Health Organization/UNICEF/World Food Programme/United Nations Standing Committee on Nutrition Joint Statement

requires a minimum of 300 mg of nonphytate phosphorus per 100 g of RUTF, which is equivalent to 520 mg minimum for 1,000 kcal, and substantially less than the 850 mg of phosphorus derived from milk in 1,000 kcal of F-100 and the 850 to 1,400 mg/1,000 kcal recommended by the 2012 WHO technical note on foods for moderately malnourished children [5].

Studies comparing the effect of different fortification levels with minerals, in particular zinc, phosphorus, iron, and calcium, in RUTF used in real-life conditions are needed to optimize RUTF. For some nutrients that have stable isotopes, such as zinc, absorption could be measured and compared with their levels of absorption in F-100 and/or with calculated requirements for lean tissue synthesis. For some other nutrients that do not have stable isotopes, such as phosphorus, this is not possible, and comparison of lean tissue synthesis and linear growth with different formulations is needed.

Adequacy of vitamin fortification in the current formula should be assessed

Studies assessing the efficacy of RUTF have used weight gain as the main outcome. No study has ever assessed the vitamin status of children after treatment with RUTF. Ideally, this should be done in different contexts with children having different preexisting nutritional deficiencies. Since fortification levels are based on the assumption that RUTF will be the only food consumed by these children, they may not be optimal when children consume less RUTF than theoretically assumed and also foods of lower nutrient density along with it.

The vitamin A content of RUTF is a particular concern. Currently, it is added within narrow limits (between 0.8 and 1.1 mg/100 g). Because vitamin A is one of the most unstable components of RUTF, producers add vitamin A to RUTF at the maximum level allowed within good practices to try to keep the content remaining above the minimum level at the end of the shelf life. The level of vitamin A remaining in the RUTF before consumption and the vitamin A status of children treated with RUTF with these fortification levels have never been checked, although the current recommendation is to rely only on RUTF and to no longer provide a high-dose vitamin A capsule as part of treatment of SAM to correct associated deficiency [8].

Assessment of hematological status after RUTF treatment is also lacking. Given the uncertainties regarding iron absorption and the fortification levels of vitamins needed for hemoglobin synthesis, a proper evaluation of the hematological status of children after treatment also seems overdue.

Attempts to simplify the RUTF formula and to use less costly ingredients have given mixed results

Soon after the initial success of RUTF in treating malnourished children, attempts were made to simplify its formulation to make it easier to produce locally. A first step was to remove maltodextrin, which was used in the initial formula and had to be imported, and to replace it with locally available sucrose. This was a success, as the simplified RUTF formulation proved as effective as the formula with maltodextrin [9]. In particular, RUTF with sucrose replacing maltodextrin did not result in a higher incidence of diarrhea.

Attempts to remove or to decrease the proportion of dried skimmed milk, the most expensive ingredient in RUTF, have been less successful. A first attempt in Malawi to replace milk powder by a mixture of roasted chickpea and sesame led to a product that was well accepted by young children in tasting sessions but gave them abdominal pains when given several days in a row, apparently as a result of inadequate starch gelatinization [10]. Two other products in which starch gelatinization was obtained by extrusion cooking were better tolerated. A first study with RUTF in Malawi compared RUTF containing 10% dried skim milk with RUTF containing 25% dried skim milk in the standard formulation [11]. The RUTF with reduced milk content, however, was less successful in treating children with SAM, achieving 57% recovery after 4 weeks, compared with 64% for RUTF with 25% milk. Weight gain, height gain, and increase in mid-upper arm circumference (MUAC) were also higher for the RUTF with 25% milk. A second RUTF made without milk, containing soy, maize, and sorghum (SMS-RUTF), was tested in Zambia and also proved less successful than the milk-based original formula, at least in children under 2 years of age, achieving a 53.3% recovery rate versus 60.8% for the standard RUTF [12].

Several factors could explain the apparent superiority of milk-based products in treating SAM [13, 14]. A better understanding of their respective roles is needed to improve the efficacy of the current formulation, to guide attempts to reduce its costs, or to formulate lower-cost foods to treat children with MAM.

Effect of protein quality

Replacing milk proteins with proteins derived from other sources is likely to have an impact on protein quality. This effect is not clearly quantified, however. A comparison of the protein digestibility-corrected amino acid score (PDCAAS) between RUTFs containing 25% and 10% milk suggested that PDCAAS decreases from 1.11 to 1.00 [14]. For SMS-RUTF, PDCAAS was estimated at 0.86 [15], clearly inferior to that for the reference RUTF. These estimates of RUTF protein quality are based, however, on a method that is no longer recommended by the Food and Agriculture Organization (FAO) and WHO. The recently proposed method is based on true ileal protein digestibility (digestible indispensable amino acid score [DIAAS]),

and not on fecal crude digestibility, which may give different results [16]. The impact of this change on assessment of RUTF protein quality is unknown. Current efforts to measure DIAAS on different RUTF formulations may shed light on potential differences.

There is also an uncertainty regarding the amino acid profile that should be used to assess protein quality in RUTF. Manary used the reference profile recommended for 1- to 2-year-old children [14], and Dibari et al. do not mention the profile used [15]. The amino acid requirements of children depend on those amino acids needed for body maintenance and those needed for new tissue deposition. After the age of 6 to 12 months, in a child growing at normal rates (not sustaining catch-up weight gain), new tissue synthesis is reduced and the amino acids needed are mainly those involved in body maintenance. Arguably, this profile may not be applicable to recovering malnourished children of the same age. During the catch-up growth phase, these children may use a much larger proportion of proteins consumed for new tissue synthesis than do well-nourished children [17].

The availability of sulfur amino acids (cysteine and methionine) may also have an indirect effect on growth, as they represent the main source of sulfur, which is needed for cartilage synthesis during catch-up growth in length [3]. Part of the dried skimmed milk of the F-100 recipe was replaced by peanut paste in RUTF. Peanut paste has a lower sulfur amino acid content, thus reducing the amount of sulfur available for growth. The effect of this reduced availability of sulfur amino acids on linear growth is unknown.

Milk proteins seem to have a specific hormonal effect and to promote the production of insulin-like growth factor 1 (IGF-1), with a possible effect on linear growth. This effect seems mainly due to the casein fraction of milk [18]. A possible hormonal effect of milk on linear growth has never been tested, however, in malnourished children.

Effect of mineral content, in particular phosphorus

Dairy products have high calcium and phosphorus contents, which may also explain their specific effect on growth. Phosphorus is needed for muscle growth, and phosphorus deficiency is associated with bone growth retardation in animals, in contrast with calcium, which is associated with decreased bone mineral density, without a clear effect on linear growth [3]. Phosphorus is also available in plant diets, but in lower concentrations and also in less available form, as some part of it is present in phytates, a form of phosphorus that is hardly absorbed in humans.

An insufficient intake of phosphorus could possibly be corrected by adding phosphorus salts to the fortification formula of these foods with reduced dairy product content. An alternative approach would be to digest phytates at some stage during food production with a specific phytase, which would make the phosphorus more available. Both approaches are used successfully in animal nutrition to promote growth with minimal amounts of dairy products. They have not been tested in foods for malnourished children.

Phytase, like most enzymes, can act only in aqueous solution, which limits its use during the production process in water-free, lipid-based nutrient supplements such as RUTF. Phytase included in lipid-based nutritional supplements mixed with water-containing foods or added directly to food has been used successfully to improve iron absorption [19, 20]. The use of microbial phytase, which is active at low pH levels and acts in the stomach, has been shown to be effective for promoting iron absorption in adult volunteers [21]. In theory, acid-resistant phytase acting in the stomach could be included in water-free RUTF to improve the absorption of iron and other nutrients, but this has never been tested.

Effect of antinutrients

In contrast to dairy products, plant-based foods often contain high levels of antinutrients, which may decrease protein digestibility and have an effect on mineral absorption [22]. A higher content of antinutrients may also explain why attempts to replace dairy products with plant-based sources of protein have given mixed results.

Most antinutrients are destroyed by heating during preparation of foods for infants and young children, but some do persist in currently used foods [23]. Roasting and extrusion cooking are the most commonly used techniques to destroy antinutrients. Extrusion cooking associates mechanical shearing with heating above 100°C for a few minutes in a humid environment and is the most effective method of removing antinutrients [24]. However, there is a limit to the heat treatment that can be applied to foods when attempting to destroy antinutrients, as excessive heat can lead to undesirable chemical reactions with proteins. The Maillard reaction involves the reaction of an amino group of a protein with carbohydrates. Lysine, the main limiting amino acid of cereals and groundnuts, has two amino groups and is particularly reactive, which leads to a decrease of protein quality in case of excessive heating [22]. This sets a limit also on the amount of antinutrients that can be removed by heating. For instance, a study investigating the effect of heating (by extrusion cooking) on phytate in kidney beans showed that at a temperature of 150°C there was a significant decrease in sulfur amino acids, whereas phytates, in contrast to other antinutrients, were not significantly reduced [25].

Parameters of the extrusion cooking technique such as temperature, moisture, heating time, and degree of mechanical shearing can be adjusted to maximize

destruction of antinutrients while minimizing the effect on protein quality [24, 26]. This complex optimization work, however, has been done mainly using the rat model, and it is uncertain whether it can be extrapolated to malnourished children.

Effect of flatulence factors

Mature dry legumes may contain up to 30 different soluble carbohydrates. Among those, the raffinose family oligosaccharides (raffinose, stachyose, verbascose) are mono-, di-, and tri-alpha-galactosyl carbohydrates that are not digested by the small intestine [27]. These soluble carbohydrates are digested by the intestinal flora in the colon and may induce flatulence and abdominal discomfort if given in large quantities. This may explain the poor tolerance of early milk-free RUTFs containing legumes to replace dried skimmed milk.

Flatulence factors can be reduced by as much as 47% to 60% by extrusion cooking [28]. Germination reduces flatulence factors by 70% to 80% [29]. The most efficient method of removing these flatulence factors is to use enzymatic methods to split these oligosaccharides [30]. These techniques, requiring an aqueous environment during the production process, are not currently used when preparing foods for malnourished children, either lipid-based nutrient supplements or more traditional blended flours. As a result, attempts to replace dairy ingredients by legumes as a source of protein are likely to result in the presence of flatulence factors that may reduce the acceptability and efficacy of alternative RUTFs. Extrusion cooking may also solubilize some of the dietary fibers and increase flatulence, with a possible negative effect on appetite [31].

Conclusions

The development of RUTF was perceived as a revolution in the treatment of children with SAM, and research focused on how to most rapidly scale up existing programs. So far, optimization of its formulation, which is required because of the change of ingredients compared with F-100 and also because of its use in the community, which likely results in a proportionally greater intake of other, less nutrient-dense foods, has been neglected. We are now in a situation where millions of children are treated every year with RUTF, but without a single evaluation of the vitamin and mineral status of children at the end of treatment. The levels of some nutrients, especially zinc, phosphorus, magnesium, and possibly sulfur, may also be suboptimal [3]. Clinical trials are needed to compare different levels of fortification and their effect on growth and other functional outcomes. Very little is known currently about the effect of RUTF on correction of stunting, which is frequently present in children with SAM. The possibility should be explored of better correcting stunting by treating children with SAM with improved RUTFs containing higher levels of sulfur amino acids, phosphorus, or zinc. This can also provide clues on how to improve the diet to prevent stunting from occurring in the first place, with relevance for improvement of the diets of children between 6 and 23 months of age.

Attempts to reduce the cost of RUTF by using less expensive ingredients, in particular using less dairy products, should be pursued. However, a better understanding of the suboptimal efficacy of alternative formulations tested so far is needed.

A better understanding of the mechanisms limiting the efficacy of RUTF to promote growth of children with SAM would also be useful for the management of MAM; the physiology of SAM and MAM children is not fundamentally different, so findings from children with SAM are also relevant for children with MAM. Studies among children with SAM are more likely to show differences of effect on growth or other functional outcomes between products. Studies on children with SAM aiming at improving RUTF should continue.

Recommendations

RUTF has not been optimized, and research to improve it should continue. This research is relevant for the development of foods for moderately malnourished children, as it can provide clues on how to optimize these foods as well. The following aspects should be especially investigated:

» Determine the amounts of RUTF and of local foods children are typically consuming during treatment and adjust nutrient density accordingly.
» Assess the feasibility of different processing steps to improve nutritional quality of the food, especially by the use of appropriate enzymes.
» Measure nonphytate phosphorus in proposed foods and compare the efficacy of different formulations with different levels of nonphytate phosphorus.
» Determine the vitamin and mineral status of children with MAM after treatment and revise the formulation if needed.

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