Recent Issues in Energy-Protein Malnutrition in Children

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Abstract

Thirty years ago, protein deficiency was perceived to be the major nutritional problem of children in developing countries. Later on increasing the energy intake of young children during the complementary feeding period became a priority. Early studies on the pathophysiology of malnutrition are now turned into strategic and practical consequences for the prevention and treatment of severe malnutrition, four of which are presented. (1) Almost half of the deaths worldwide are due to being underweight. Nowadays, well-defined preventive and curative interventions have been identified. (2) An efficient and rigorous technique based on linear programming is now available to design a diet suitable for the complementary feeding period using locally available foods with a minimum budget to cover the nutritional requirements of at least 97% of the children. (3) Managing acute malnutrition in emergencies has greatly improved by the use of a spread that a child can eat directly without the addition of water (often called Ready-to-Use Therapeutic Food) and Community Therapeutic Care that treats the majority of severely malnourished children at home. (4) Recent data strongly suggest that it is possible to avoid death due to careful and rapid rehydration despite the high purging rate even if many of the risk factors for mortality are present in these severely malnourished children. Recovery from malnutrition was achieved in 7 days.

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Thirty years ago protein deficiency was perceived to be the major nutritional problem of children in developing countries. This idea was later challenged when it became clear that the protein requirements were overestimated and that protein deficiency was almost always associated with an insufficient energy intake [1–3]. The term ‘protein malnutrition’ was subsequently replaced, first by ‘protein-calorie malnutrition’ and later by ‘energy-protein malnutrition’ [4]. Increasing
the energy intake of young children during a complementary feeding period then became a priority. In the meantime, kwashiorkor and marasmus, the two main clinical forms of severe malnutrition, were found to be associated with a change in body composition: essentially loss of fat, muscle and cellular proteins; changes in body water distribution (increased extracellular but decreased intracellular water), and potassium and magnesium deficiency. It is remarkable that in the 1960s the Tropical Metabolism Research Unit in Jamaica obtained a small whole body counter with which total body potassium could be determined from the radiation of the natural isotope $^{40}\text{K}$. This is how it was firmly established that potassium deficiency is a common and important feature of energy-protein malnutrition [5–7]. Then trace element deficiencies, essentially vitamin A and zinc, were also recognized. Thus, energy-protein malnutrition is by far the most lethal form of malnutrition.

In addition to the deficit in food intake, other factors can also contribute to malnutrition. They could broadly be classified as medical and environmental. In the medical or nutritional category one can include: associated diseases which are essentially bacterial, viral or parasitic infections, and a selective deficit in nutrients in the daily monotonous diet. It is not uncommon that the food found in the local market does not provide all the nutrients required for child growth. Therefore a protein and energy deficit is often associated with a deficit in minerals and vitamins, and an imbalance between the nutrients is also common.

In the environmental category the list is long, including a lack of hygiene and clean water, overcrowding, illiteracy, poverty, an unstable political situation, and war. Malnutrition has been known to affect a large population of children throughout the history of humanity. In Europe, until the end of the 19th century, it was one of the leading causes of mortality, even though breastfeeding was the rule [8]. One of the most appalling accounts of malnutrition can be found in the celebrated lecture of Dickens who for the benefit of the Great Ormond Street Hospital described an Edinburgh slum [9]. In the rest of the world, the epidemic was later ‘discovered’ by Europeans.

The nutritional and medical aspects of infantile malnutrition have been studied in detail and presented in reference books [9–13] and journal articles in the case of famine [14, 15]. Furthermore, in 1999 the World Health Organization published a manual for physicians and health workers on the management of severe malnutrition [10].

The aim of this presentation is not to repeat what has already been communicated on infantile malnutrition, rather I would like to stress four recent issues of practical importance for preventing and treating malnutrition: (1) assessment of the magnitude of the problem; (2) assessment of the nutrients in food markets; (3) home-based therapy for malnutrition, and (4) rehydration therapy in dehydrated and malnourished children. It appears that the early studies on the pathophysiology of malnutrition have now turned into strategic and practical consequences for the prevention and treatment of severe malnutrition.
The Magnitude of the Problem

More than 10 million children younger than 5 years of age die every year. When facing such statistics it seems that malnutrition is beyond the nutritionists’ reach. In the last 5 years an overall estimate of the determinants of child mortality has been published with specific targets identified [16, 17]. To summarize, it is notable that six countries account for 50% of worldwide deaths and 42 countries for 90%, this implies that national or regional policies should be implemented. Even if the causes of death differ substantially among countries, almost half the deaths are due to being underweight, which indicates that malnutrition is a key determinant, in addition to genetics and the infectious environment. It is well known that malnutrition alters the immune response, which leads to two main groups of diseases, respiratory infection and diarrhea (20% each), with neonatal disorders taking approximately 35% of the death toll. Also according to the prevalence of other diseases, essentially malaria, measles and AIDS, five different main profiles emerge in the 42 countries with 90% of global child deaths.

Fortunately, well-defined preventive and curative interventions exist for a large series of identified causes of death [18]. Those interventions can be delivered through the health sector with maternal education or birth control. In addition to immunization and specific treatments, nutritional interventions include appropriate use of breastfeeding and complementary feeding, and supplementation such as a pharmacological dosage of zinc and vitamin A. It is of note that other nutritional interventions are not considered in the analysis, and for this reason they will be discussed below. As a result of extensive analysis, 23 interventions were proven to be effective in a context of middle or low income countries identified. They were then put into an economic model where 18 contacts between the child or mother and a health care provider were incorporated into a delivery timetable from birth to 5 years of age [19]. The conclusion was that approximately USD 5 billion in new resources is required to save the lives of 6 million children annually in the 42 countries where 90% of the deaths occur. The average cost per life saved is USD 900.

Assessment of Nutrients in the Food Market

Ideally malnutrition should be prevented by using locally available food. However, this approach is restricted to the availability and cost of food. Even in industrialized nations the recommended daily allowances in toddler diets, especially for iron, is difficult to achieve [20]. During complementary feeding, children require a nutrient-dense diet to meet their high nutritional requirements. In addition, the cost of food may also limit proper feeding. Traditionally, research was conducted using a trial-and-error approach or by expert
guessing. Nowadays, an efficient and rigorous technique based on linear programming offers solutions to previous questions [21]. This method operates on widely available programs, including Microsoft Excel, and it aims to answer the following question: is it possible to design a diet suitable for complementary feeding periods using locally available foods? If this is possible, what is the minimum budget for designing a diet covering the nutritional requirements for at least 97% of children?

To understand the principle of this method one can look at a simple example, though nonrealistic and theoretical: a complementary diet based on cow’s milk and maize flour. Any nutritionist would say that the calcium requirement could be met, but not iron. However, linear programming further indicates graphically how far iron is out of the present regimen, and if designing a proper diet is feasible (fig. 1).

The second question is the determination of a maize flour and cow’s milk combination that provides enough energy for a 12- to 23-month-old breastfed child (746 kcal/day according to FAO table and 196 of calcium at the lowest cost). Linear programming again presents a basic and immediate answer. It can help design a graphic solution for a local diet problem taking into account both the availability of food and its cost (fig. 2).

Linear programming is much more efficient than the empirical trial-and-error approach currently used for formulating diets. It could become an indispensable tool for pediatricians and nutrition program planners. Several examples are already available [22, 23] and short courses on linear programming are available on the internet: http://www.nutrisurvey.de/lp/lp.htm

Fig. 1. Graphical illustration representing no solution for the diet problem. From Briend [personal commun.].
Home-Based Therapy for Malnutrition and Ready-to-Use Therapeutic Food

A review of the literature over the past 5 decades indicates that the median case fatality from severe malnutrition has remained unchanged over this period and was typically 20–30%, with the highest levels (50–60%) being among those with edematous malnutrition [24]. The authors indicated that a likely cause of this continuing high mortality was faulty case management. In the 1990s, malnutrition was revisited. Most recently, the management of severe acute malnutrition in refugee camps has been examined. It was proposed that a formula containing 100 kcal/100 ml, and called F100, was used in a well-defined setting called the therapeutic feeding center (TFC) [11, 25]. This diet is prepared as a liquid formula by mixing together dried skimmed milk, oil, sugar, and a vitamin and mineral complex. Similar diets have been used in relief operations for more than 25 years. In this case the practice was tested with striking results on several hundred children in refugee camps situated in sub-Saharan regions [26], and the mortality was often found to be below 5%. In its 1999 manual, the WHO recommended the use of F100 during the rehabilitation phase of severe malnutrition [10].

However, TFCs are difficult to establish, expensive to operate, and have very limited coverage. They do not build on the capacity of the community, and at times they can undermine traditional coping strategies. Mothers are often required to stay with their malnourished children in the TFC for several weeks. In addition, F100 has some disadvantages as bacteria grow very
rapidly in it and safety becomes an issue when prepared under unhygienic conditions. Plus, before water is added, F100 looks like any milk powder, and may undermine efforts to promote breastfeeding if given to families.

In 2001 a new approach to managing acute malnutrition in emergencies and other situations was proposed by Collins and Sadler [27]. Community therapeutic care (CTC) aims to treat the majority of the severely malnourished children at home, build local capacity to better manage the care of acutely malnourished children, and address repeated cycles of relief and recovery. Recently, the use of the F100 formula has been revised by replacing part of the skimmed milk with peanut butter. Instead of dissolving a powdered product in water, this new recipe gives a spread that a child can eat directly without the addition of water. This is often called ready-to-use therapeutic food (RUTF). The nutritional composition of RUTF in relation to its energy content is very similar to F100. Since its energy density is five times higher (5.4 vs. 1 kcal/g), its micronutrient content in relation (per 100 g) is also five times higher [28] (table 1). It can be prepared locally at approximately USD 15–20/kg. Also, it has been tested against F100 in the TFC and proved to be well accepted and comparable to F100 with regard to weight gain [29].

Together, CTC and RUTF have proved to be a major innovation in the treatment of severe malnutrition. Mainly in Africa, RUTF has increasingly been used in emergency and non-emergency situations. The objective has been to shift the treatment of severe malnutrition from the TFC towards the community. To date, CTC programs have treated over 7,000 children in Africa. Results indicate lower mortality rates (perhaps as a reduction of cross-infection), fewer dropouts and better coverage than standard center-based approaches. As a whole, the CTC program has demonstrated that children suffering from severe acute malnutrition without complications can be safely treated at home. According to these data, a new classification of severe malnutrition has been proposed [30].

### Table 1. Daily energy and macronutrient intakes from F100 and RTUF

<table>
<thead>
<tr>
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<th>F100 group</th>
<th></th>
<th>RTUF group</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>local</td>
<td>total</td>
<td>local</td>
<td>total</td>
</tr>
<tr>
<td>Energy, kJ/kg body weight</td>
<td>275*</td>
<td>573*</td>
<td>557*</td>
<td>808*</td>
</tr>
<tr>
<td>Proteins, g/kg body weight</td>
<td>2.0</td>
<td>5.9</td>
<td>3.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Lipids, g/kg body weight</td>
<td>3.3*</td>
<td>4.9*</td>
<td>8.8*</td>
<td>10.2*</td>
</tr>
<tr>
<td>Carbohydrates, g/kg body weight</td>
<td>7.2</td>
<td>17.2</td>
<td>10.3</td>
<td>19.1</td>
</tr>
</tbody>
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*Significantly different between groups.
Rehydration Therapy in Dehydrated and Malnourished Children

There is a scope to further reduce the case fatality rate and enhance recovery from malnutrition by improving the recovery from common associated illnesses including diarrhea. Malnutrition predisposes to an increased incidence and duration of diarrhea. As it is associated with further loss of weight, early recovery and lessening the severity of diarrhea will help to prevent further weight loss and deficiency of the nutrients in severely malnourished children. In addition to the active secretion and defective absorption of water and electrolytes in the small intestine, colonic dysfunction has also been demonstrated in cholera due to a lack of short-chain fatty acids. Recently, we initiated a clinical study to test the hypothesis that the addition of an amylase-resistant starch to a glucose-based oral rehydration solution would ferment in the colon to stimulate salt and water absorption in order to alleviate the severity of diarrheal illness and enhance recovery from it. Additional energy from the absorption of short-chain fatty acids through the colonic

![Fig. 3. Weight gain in the first 72 h in severely malnourished and dehydrated children receiving one of the three oral rehydration solutions (ORS), containing 40 mEq/l potassium and glucose (G), glucose and amylase-resistant starch (ARS), or rice. Weight gain was significant in all three groups but it was greater in the rice group. From Alam et al. [unpublished data].](image-url)
mucosa would also be supplied to assist nutritional recovery [Alam et al. unpublished] (fig. 3).

In a prospective randomized study, 174 children (mean ± SE age = 27.6 ± 0.9 months) were included as severely malnourished (weight/height = 68.5 ± 5.5 with or without pedal edema) and dehydrated because of cholera. After intravenous fluid therapy (602 ± 46 ml) for 84% of them, they were randomly assigned one of the three high potassium (40 mEq/l) oral rehydration solutions containing glucose, rice or amylase-resistant starch. On the main parameters, there was no significant difference among the groups at inclusion. Although the death risk factors were frequently present (55% not breastfed; 84% severe dehydration; 9% severe hypoglycemia), all the children recovered from dehydration. In the first 2 days, stool volume and oral rehydration solution intake were significantly different in the 3 groups, but the number of unscheduled intravenous therapies (15%), duration of diarrhea (66.3 ± 2.2 h), weight gain (0.8 ± 0.1 kg), and time to recover 80% of the weight/height ratio (7.1 ± 0.2 days) were not different.

Despite the high purging rate and although many of the risk factors for mortality were present in these severely malnourished children, in this study we were clearly able to avoid any death by using careful and rapid rehydration. After recovery from life-threatening dehydration, we expected that an amylase-resistant starch would have had a beneficial effect on malnutrition recovery, but this was not found. We are now testing the possibility that the intestinal microflora may not appropriately metabolize starch into short-chain fatty acids in severe malnutrition.

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Recent Issues in Energy-Protein Malnutrition in Children

Dr. Desjeux: Feeding children with a high protein diet could be dangerous especially for kidney function. Therefore, at the suggestion of Prof. John Waterloo, when F100 was initially proposed as treatment in emergency situations, we also added F75 which is less dense, that is 75 kg cal/0 ml. But if you look at the results, F100 already reduces mortality to almost zero. It is of course given progressively. I know that some centers still use F75, but I think it would be extremely difficult to show a beneficial effect of F75 on mortality because, as seen under extreme conditions when there is severe malnutrition and dehydration, none of the children died and they were fed with F100 according to the WHO protocol.

Dr. Dewey: I want to thank you for bringing up linear programming. It is a technique that sounds intimidating to some people but I can testify that it is very simple to use. We have used it extensively for a document on feeding of the non-breastfed child from 6 to 24 months of age that the WHO has published. As you said, it involves is having information on the types of foods consumed and their costs. One of the cautions that I would like to mention is that when you work with the youngest age
group, which is 6–9 months approximately, usually when the local foods are entered into this program there will be no solution. In other words you cannot meet all their nutrient needs with local foods, and that is usually because of iron, sometimes zinc as well. So what you can do is include in the program another entry for supplements and put in a cost that is very high, artificially high, so you minimize how much of the supplement is required in the solution. This is one way we determine what the gaps are and how they need to be met in the diet of any particular local area. I strongly encourage people to go to the website that you mentioned and try it out. The other comment I want to make is that the ready-to-use therapeutic food (RUTF), as you said, was originally developed to treat malnourished children. We have recently used a different formulation of it for complementary feeding of healthy normal children in Ghana, and in this case we used a very strongly fortified concentrated version and we only need 20 g/day, about 4 teaspoons. So far the results look very encouraging for improving growth as well as other outcomes. I think this is one product that deserves a lot more attention.

Dr. Desjeux: Thank you very much for your very appropriate comments. For linear programming, a tutorial can be found at www.nutrisurvey.de/lp/background_info.htm. You can enter what you have bought at the market, together with the cost, and then you get this kind of graph that I showed you. It also shows you how much of the requirements have been covered and, as you mentioned, iron is the most difficult micronutrient to fulfill. You can decide to add iron from a source other than local food and see if the diet is now appropriate according to the recommendations. So it is an extremely simple linear program, and extremely powerful for designing and checking the quality of the diet according to the cost. It goes from food to nutrient and cost, and includes all these items together.

Dr. Telmesani: Some studies suggest adding some lactobacillus or bifidobacteria to the oral rehydration solution (ORS), and report a positive effect in reducing the duration of diarrhea. What is your view?

Dr. Desjeux: We already discussed adding amino acids, adding bacteria. Many things can be added, but as you have seen very simple ORSs are quite effective, and a reduction of 6 h in the duration of acute disease that last 2–3 days does not matter. From the clinical point of view I don't think it is very relevant, and therefore I think we have to keep it simple and teach people how to use it, but still there is a need to improve its use all over the world. In my view it is more a matter of marketing than composition [1]. For probiotics there are some clinical trials showing a statistical effect. Now to answer the question that was raised earlier about amino acids; amino acids are provided with ORSs because after 4 h the children are fed so they receive amino acids. That is probably one reason why the addition of amino acids in clinical trials doesn't show any striking effect, if at all. Adding glucose to glucose doesn't help very much and adding glutamine to a protein diet doesn't add very much either.

Dr. Macé: Do you have an idea which of the short-chain fatty acids could be the most efficient? Is it acetate butyrate?

Dr. Desjeux: It depends; if you want to rehydrate it is butyrate that stimulates sodium absorption [2]. But the other amino acids are also important because they would provide energy and could help to improve colon function which is very frequently altered in infectious diseases including cholera, and also in malnutrition [3].

Dr. Noor Khatijah Nurani: How long do you use RUTF and when do you start introducing other proteins from locally available food?

Dr. Desjeux: It starts in the rehabilitation phase, and I am referring to the WHO manual for the definition. It depends on the local circumstances but a weight for height of 80% of the National Center for Health Statistics can be obtained in 7 days, even in severely malnourished children.
Dr. Barclay: You have shown that the higher nutrient density refeeding formulas were useful for malnutrition. I was wondering about the same concept for refeeding during diarrhea. As you probably remember about 10 years ago, based on the results of studies mainly in the Indian subcontinent and some which you cited, we developed an improved rice-based ORS containing about 50 g/l of rice and showed that this rice-based ORS improved diarrhea outcome vs. standard glucose ORS. Nestlé R&D developed a ‘super’ rice-based ORS containing 160 g/l of rice, electrolytes and α-amylase. The product has to be cooked just prior to administration by the caregiver so the product is actually sterilized preventing further microbial contamination. Studies in Ecuador and Columbia showed that children treated with this new rice-based ORS had a significantly shorter duration of diarrhea, a lower number of stools and a greater weight gain during treatment vs. standard glucose ORS [4]. So my question is, do you think that there is any need for more energy-dense, more nutrient-dense ORS, keeping osmolarity below say 280 mosm, or that standard ORS with normal feeding schedules are sufficient?

Dr. Desjeux: First of all you showed very clearly is that it is essential to give enough energy as soon as the child is rehydrated. I don’t know how it is in your country, but in my country the doctors would prescribe no food to the child for 3 or 4 days, which of course would be impossible for the mother to follow. So feeding is really essential in the treatment of diarrhea. Now which type of feeding? I would be a bit reluctant to use RUTF in this condition for two reasons. One is that RUTF has been designed specifically for malnutrition. It is used in different kinds of malnutrition; for instance in mentally retarded children with malnutrition the effect of RUTF is absolutely spectacular. But to have another energetically dense diet for diarrhea could be interesting. This is really a paste and we were a bit afraid that giving such a high energy-dense paste would dehydrate the child, but it does not. I would be afraid of giving that diet to dehydrated children, at least at first.

Dr. Butte: You were focusing on the recovery of weight for height. Is there any new progress being made in treating the stunted child, in recovering linear growth?

Dr. Desjeux: In therapeutic feeding centers growth is faster than in home-based therapy. I would say that growth is really the proper indicator of efficacy, but does it really matter if the gain is 15, 16 or 12 g/day? After all if they are happy and healthy and alive, this is already quite an achievement. Now can we get a better indicator for recovery from malnutrition, does it matter, does the first phase of rehabilitation from malnutrition have long-term consequences? I know there are some people trying to address that question, but it is very difficult to have a follow-up in these populations.

Dr. Huerta: How do you give infants with marasmus, weight for height below 2 standard deviations and a mean age of 13 months, this amount of protein, 6.5/kg/day? How many days do you use it?

Dr. Desjeux: We are often afraid of giving too much protein, but this is not only protein. This diet also contains a high density energy and lipids, carbohydrates, mineral and vitamin mix. I think we have more from the clinical results than the theoretically expected results to base our recommendation on. I am not absolutely sure how it works, but for the time it works. For instance, as a gastroenterologist I am not too much concerned with protein but with fat. We have learned, and it is true, that in severe malnutrition the pancreas does not function well, and although we provide a huge amount of lipids, it works. So there are some discrepancies between what we have learned and what we see now with this treatment. It is a major breakthrough in the treatment of these children.
References