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PERSPECTIVE

Thiamine content of F-75 therapeutic milk for complicated severe acute malnutrition: time for a change?

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Since community-based management of severe acute malnutrition has become the standard of care, the clinical profile of severe acutely malnourished patients admitted to hospitals or inpatient therapeutic feeding centers has changed significantly. These patients are usually very ill and often present with several comorbidities, such as shock, sepsis, and pneumonia. Complicated severe acute malnutrition patients are at risk of thiamine insufficiency, and critically ill patients have higher thiamine requirements. The thiamine content of F-75, the therapeutic milk formula used in the early stabilization phase of refeeding in patients with severe acute malnutrition, seems insufficient. Here, we discuss the need and rationale for a substantial increase in the thiamine content of F-75.

Keywords: thiamine deficiency; thiamine insufficiency; F-75 therapeutic milk; SAM; beriberi

Introduction

Severe acute malnutrition (SAM) is defined by a below –3 weight for height Z score of the median World Health Organization (WHO) growth standards, by the presence of nutritional edema, or by mid–upper arm circumference less than 115 mm. It is a life-threatening condition requiring urgent treatment, because the median under-five case-fatality rate is around 15%.[1] It is associated with thiamine depletion, although data are limited.[2–4] It is now well known that the metabolic requirements for thiamine increase during severe illnesses. Today, community-based management of SAM is the rule. Therefore, the majority of patients with SAM admitted to hospitals or to inpatient therapeutic feeding centers are usually very ill and often present with several comorbidities, such as shock, sepsis, respiratory distress, malaria, diarrhea, and severe anemia. The early phase of inpatient nutritional treatment for SAM is based on low-protein therapeutic milk known as F-75, which is given to improve metabolic homeostasis before the second phase of refeeding to achieve catch-up growth. Despite advances in nutritional science, specific recommendations on F-75 micronutrient content (besides vitamin A and zinc) have remained unchanged for over 20 years, and are mainly based on expert opinion.[5] F-75 was conceived for use in general SAM patients, but its current thiamine content does not reflect the changes that have occurred in the management of the SAM population, with less severely affected patients being managed in the community with ready-to-use therapeutic food (RUTF).[5] Therefore, F-75 is now only used for critically ill patients, for whom its thiamine content could be insufficient. Here, we present a rationale to substantially increase the thiamine content of F-75.

Conditions and risk factors leading to thiamine deficiency in malnutrition

Thiamine deficiency principally affects precarious communities, where children are most vulnerable and where dietary habits rely on refined processed cereals or tubers, such as rice, wheat, and cassava, notably in Southeast Asia,[6–12] Africa,[2,13,14] and the Americas.[3] The reports on thiamine deficiency

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prevalence vary from 13.4% of children admitted to hospital without signs of beriberi in Laos to 30% of Laotian children with uncomplicated malaria and 40% of severely malnourished children from Jamaica and Ghana. The majority of infants in parts of Cambodia are thiamine deficient,[9] and 45% of infant deaths in rural Cambodia could be related to thiamine deficiency.[15]

Thiamine can be lost from food secondary to precooking and food processing (e.g., repetitive rice washing, soaking).[16] Other risk factors include the ingestion by breastfeeding mothers or older children of antithiamine agents, such as tea leaves, betel nuts, and coffee, and the ingestion of thiaminases in raw fish and some insect larvae that inactivate thiamine.[17,18] Some bacteria, such as *Clostridium* species, have been identified as producing thiaminases.[19,20]

Reduced intestinal absorptive capacity during environmental enteropathy and malnutrition may also lead to thiamine insufficiency (subclinical low vitamin B_1 levels).[21] Gut microbiota is also affected in malnourished children, which might affect thiamine-uptake capacity.[22–24]

A relative inadequacy of thiamine content to caloric ratio, such as is found in individuals on high-carbohydrate diets, is also a common precipitating factor of thiamine insufficiency (e.g., pure cassava or milled rice).[25] This very same imbalance can contribute to the onset of thiamine deficiency when dextrose-based fluids are administered without thiamine supplementation in critically ill patients.[26] Excessive digestive (chronic diarrhea) or renal (loop diuretics) losses of thiamine from the body can also precipitate thiamine deficiency.[25,27]

A mismatch between cellular thiamine availability and the increased endogenous metabolic demands in hypermetabolic states during critical illnesses, such as severe infections, shock, burns, and fever, can trigger clinical thiamine deficiency in patients with preexisting thiamine insufficiency.[24] Thiamine deficiency is a common finding in pediatric intensive care units, particularly in critically ill children who are unable to eat and have no access to advanced parenteral nutrition in resource-limited settings.[25,26,28–31]

Lastly, humanitarian emergencies due to conflicts, population displacements, and drought leading to poor or no access to food can precipitate major outbreaks of thiamine deficiency.[4,14,32] It is worthwhile to note that, in most resource-limited settings, thiamine is not routinely administered to pediatric intensive care patients, which may further increase the risk of thiamine deficiency.[33]

Refeeding syndrome is a potentially fatal complication of patient mismanagement and is often neglected, as it can be misinterpreted as cardiac failure, pneumonia, or sepsis.[34–36] Refeeding syndrome is characterized by electrolyte imbalances caused by intracellular shifts secondary to refeeding-induced insulin secretion (e.g., hypophosphatemia, hypokalemia, and hypomagnesemia). Insulin production and the resulting increase in glucose utilization and thiamine body requirements may also lead to thiamine deficiency.[36]

Thiamine insufficiency (subclinical low vitamin B_1 levels) or thiamine deficiency (with clinical signs and/or low thiamine levels well below reference values) may be present in children with SAM for many reasons, as mentioned above. Rapid initiation of nutritional rehabilitation during refeeding increases intracellular thiamine turnover, which, in a background of preexisting low whole-body thiamine stores, can precipitate the onset of true thiamine deficiency and may contribute to the nonnegligible mortality of hospitalized SAM patients.[34–37]

Consequences of thiamine deficiency in critically ill patients

Critically ill patients in intensive care units are more likely to be or to become thiamine deficient.[29,31,38–40] Intensive care patients with thiamine deficiency may experience worse outcomes than other critically ill patients.[29] However, recent evidence suggests that thiamine administration to thiamine-deficient adults with septic shock may significantly increase the survival rate.[38] In a small randomized controlled trial conducted in 2016 by Donnino *et al.*, 35% of patients had thiamine deficiency upon admission, and this subgroup had a 72% reduction in mortality when thiamine was included in their therapy.[38]

Long-term consequences of thiamine deficiency in infancy

In 2003, there was an outbreak of acute thiamine deficiency in Israel secondary to the consumption of a thiamine-deficient soya-based infant formula, with severe consequences in infants.[41] The follow-up of the survivors group demonstrated that the initial acute thiamine-deficiency insult, even in

apparently asymptomatic patients, could have significant long-term neurological consequences. This was especially significant on the children's language development, producing alterations in the syntactic and lexical modalities of language acquisition, but they could also present years later with psychomotor impairment and seizures.[42–46] These data highlight the importance of early intervention when thiamine deficiency is suspected in order to limit long-term sequelae. It also suggests encouraging the use of pharmacological doses of thiamine in critically ill and severely malnourished children at high risk of thiamine deficiency.

Thiamine in F-75 milk

There are two major therapeutic preparations currently used in the treatment of patients with SAM. F-75 (75 kcal/100 mL) is used in the initial phase of refeeding (also called stabilization phase), and F-100 (100 kcal/100 mL) is used in the transitional and rehabilitation phase, when RUTFs are not available or the child is not yet ready (refusal or intolerance of RUTF).

For the prevention of refeeding syndrome, the Cape Town Pediatric Interest Group[47] and the Sydney Children's Hospital[48] suggest the administration of 1–2 mg/kg of thiamine daily during the first week of SAM treatment. However, according to the current recommendations for refeeding syndrome published at the end of 2016 in an official journal of the American Academy of Pediatrics,[36] thiamine should be administered in a dose of 50–100 mg intravenously or 100–300 mg orally during the first 3 days of refeeding, which is similar to the thiamine dosage recommended during the first few days of refeeding by Stanga *et al.*,[49] 200 times higher than the recommended daily intake (RDI) of thiamine in the adult population (200–300 mg).[36,49]

Although current international therapeutic feeding guidelines are designed to provide optimal SAM management and avoid complications, high-dose thiamine at initiation of treatment is not the current practice in humanitarian settings.[50] Since it has been shown that children with complicated SAM have borderline thiamine stores,[2,3,51] even a very cautious introduction of feedings may induce thiamine deficiency in the absence of a considerable thiamine supplementation.

As a consequence of the wide acceptance of community-based SAM management with RUTF, only complicated or critically ill SAM patients are presently being admitted to inpatient facilities. However, the thiamine content of the F-75 used for the treatment of complicated or critically ill patients with SAM has remained unchanged. As a result, complicated SAM managed in healthcare facilities and uncomplicated SAM managed in the community receive roughly the same amount of daily thiamine, although their thiamine needs are clearly different.

A 600-mL sachet of therapeutic milk (either F-75 (75 kcal/100 mL) or F-100 (100 kcal/100 mL)) contains on average 0.5 mg of thiamine;[50] thus, the average daily intake of thiamine is 1–2 mg at most (Table 1), which is 1–4 times the RDI for this pediatric group[52] (Table 2). This is even more significant in infants under 6 months of age with SAM, who are at greater risk of developing thiamine deficiency. These babies do not receive RUTF or F-100 but only breast milk or diluted F-100 or F-75 infant formula, while their breastfeeding mothers rarely receive thiamine supplements.

For example, a child weighing 10 kg who is in the acute stabilization phase would be given eight F-75 feedings of ∼170 mL/day each (1360 mL in total), which is approximately equivalent to 1.1 mg of thiamine (only twice the RDI). An infant under 6 months of age weighing 3 kg would be offered breast milk and/or diluted F-100 (still the most current practice in humanitarian settings) up to 405 mL, which is approximately equivalent to 0.28 mg of thiamine (just about the RDI). According to the Cape Town guidelines, the thiamine requirements would be 18 times more for the first child and 21 times more for the second child.[47] According to Pulcini *et al.*,[36] these children would require 50 and 180 times more thiamine, respectively, which would also be in line with the Stanga *et al.* recommended thiamine dose of 200 times the RDI.[49]

Summary and recommendations

Therapeutic milk F-75 is exclusively used for the acute stabilization phase of refeeding in inpatient facilities for complicated SAM patients. Its thiamine content has not been revised since the change in WHO SAM protocols. The inpatient SAM clinical population profile has drastically changed, since most patients are now managed in the community, and only complicated or critically ill SAM patients are admitted to inpatient facilities. Critically ill SAM

Table 1. Approximate amount of F-100 specially diluted therapeutic milk (SDTM), infant formula, and F-75 (and equivalent of thiamine content) given as eight meals/day according to refeeding protocols[50] compared with recommendations[36,47,48]

Weight (kg)	F-100 SDTM (<6 months)	Infant formula I (<6 months)	F-75	Cape Town and Sydney guidelines for the prevention of refeeding syndrome (2 mg/kg of thiamine)	Pulcini *et al.* recommendations for the prevention of refeeding syndrome: 50–100 mg of thiamine IV or 100–300 mg orally
2.5	337 mL/day (~0.24 mg thiamine)	337 mL/day (~0.22 mg thiamine)	337 mL/day (~0.28 mg thiamine)	5 mg of thiamine	50 mg IV or 100 mg orally
3	405 mL/day (~0.28 mg thiamine)	405 mL/day (~0.26 mg thiamine)	405 mL/day (~0.34 mg thiamine)	6 mg of thiamine	50 mg IV or 100 mg orally
4	540 mL/day (~0.38 mg thiamine)	540 mL/day (~0.35 mg thiamine)	540 mL/day (~0.46 mg thiamine)	8 mg of thiamine	50 mg IV or 100 mg orally
5			680 mL/day (~0.6 mg thiamine)	10 mg of thiamine	50–100 mg IV or 100 mg orally
7			960 mL/day (~0.8 mg thiamine)	14 mg of thiamine	50–100 mg IV or 100 mg orally
10			1360 mL/day (~1.1 mg thiamine)	20 mg of thiamine	50–100 mg IV or 100–300 mg orally
15			2000 mL/day (~1.7 mg thiamine)	30 mg of thiamine	50–100 mg IV or 100–300 mg orally

Table 2. Thiamine RDI by age[52]

Age	Thiamine RDI
0–6 months	0.2 mg
6 months–1 year	0.3 mg
1–3 years	0.5 mg
4–8 years	0.6 mg

patients are likely to present with low or borderline thiamine reserves that can be rapidly depleted, precipitating acute thiamine deficiency, which can have acute and long-term consequences in critically ill children.[41,45,46] F-75 thiamine content (1.1 mg/1000 kcal = 0.083 mg/100 mL) is significantly below the current recommendations to prevent the refeeding syndrome and does not take into account the new understanding of the role of thiamine pathophysiology, which indicates a higher utilization of thiamine during associated severe illnesses. Thiamine therapy has an excellent safety profile with no known risk of side effects or overdose.

Considering its exclusive use for in-hospital management of critically ill or complicated SAM patients, we propose that reformulation of F-75 is warranted in order to supply a sufficiently high dose of daily thiamine for either preventative or therapeutic indications. We endorse the recommendations to administer 200 times the RDI thiamine dose in the first few days of refeeding.[36,49] This would translate to a pharmacological dose of thiamine of up to 100 mg of thiamine /1000 kcal (7.5 mg/100 mL) for early refeeding, which is almost 90 times more than the current F-75 content of thiamine (Table 3). Moreover, F-75 should be considered as a pediatric intensive care metabolic resuscitation medicine. Providing 100 mg of thiamine via F-75 daily for approximately 7 days is roughly equivalent to a total thiamine dose of 300–900 mg over 3 days, as recommended by Pulcini *et al.* for the prevention of refeeding syndrome.[36]

For breastfed infants under 6 months who do not receive F-75 but are at high risk of developing thiamine deficiency, both maternal and infant nutrition should be supplemented with thiamine in order to minimize the risk of precipitating thiamine deficiency.

An alternative option would be to maintain the current F-75 thiamine content and treat the complicated SAM patients systematically with

Table 3. Average daily amount of therapeutic milk and equivalent of total thiamine content in specially diluted F-100 (SDTM) and current F-75 and the proposed change to 100 mg/1000 kcal ("new F-75")

			Proposed thiamine content for F-75 reformulation based on 100 mg of thiamine/1000 kcal of a "new F-75" (7.5 mg/100 mL)
Weight (kg)	**F-100 SDTM < 6 months**	**F-75 current recipe > 6 months**	**Total thiamine per day supplying same volumes of F-75**
2.5	337 mL/day (~0.24 mg thiamine)		N/A: give supplement to the breastfeeding mother and the infant in the first days of refeeding (1/2 tablet = 25 mg)
3	405 mL/day (~0.28 mg thiamine)		N/A: give supplement to the breastfeeding mother and the infant in the first days of refeeding (1/2 tablet = 25 mg)
4	540 mL/day (~0.38 mg thiamine)		N/A: give supplement to the breastfeeding mother and the infant in the first days of refeeding (1/2 tablet = 25 mg)
5		680 mL/day (~0.5 mg thiamine)	~51 mg of thiamine
7		960 mL/day (~0.8 mg thiamine)	~72 mg of thiamine
10		1360 mL/day (~1.1 mg thiamine)	~102 mg of thiamine
15		2000 mL/day (~1.7 mg thiamine)	~150 mg of thiamine

oral or intravenous thiamine according to clinical indications and following the recommendations of Pulcini *et al.*[36] However, for operational reasons, it would be reasonable to reserve thiamine tablets and vials for the treatment of clinical thiamine deficiency or as a metabolic resuscitator in non-SAM critically ill patients. In low-resource settings, which rely heavily on humanitarian aid, F-75 would be an optimal vehicle for high thiamine doses to prevent refeeding complications in SAM patients

Many risk factors for thiamine deficiency coexist in tropical pediatrics, making it a highly relevant public health issue. On the basis of current evidence, the thiamine content of therapeutic milk (F-75) should be urgently re-evaluated to minimize the risk for thiamine deficiency during the initial phase of refeeding of hospitalized SAM patients. To date, even though the thiamine requirements in critically ill SAM patients are obviously higher than in community-managed uncomplicated SAM patients, they all receive the same daily amounts of thiamine, regardless of the severity of their condition. Further studies are warranted to validate the recommended thiamine/caloric ratio of 100 mg/1000 kcal as opposed to the current 1.1 mg/1000 kcal. Thiamine has an outstandingly clean safety profile to date, with no upper dose limit, which should encourage clinicians to consider using it. Finally, for both breastfeeding mothers and infants under 6 months who are malnourished, the diet should be supplemented with thiamine in the acute phase and throughout the breastfeeding period.

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Competing interests

The authors declare no competing interests.

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