Rationale for the Use of Systematic Thiamine at Pharmacological Dose in Malnourished Children Requiring Hospital Admission

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Background and Aims:
Complicated severe acute malnutrition (SAM) remains a major challenge in MSF programmes and carries significant mortality. As the body has a very limited, diet-dependent store of thiamine (vitamin B1), deficiency is common in malnourished children. Thiamine has many functions, and is an essential component of key metabolic pathways involving glucose, nucleic acids and branched-chain amino acids. It is also involved in the production of neurotransmitters, myelin and nucleic acids. Aside from classic beriberi, thiamine deficiency (TD) is implicated in a large spectrum of clinical and sub-clinical conditions and may have an impact on the prognosis of critically ill children with SAM, however the diagnosis is frequently overlooked.

Method:
Literature review of current knowledge including thiamine function in humans and clinical presentation of TD in the context of SAM (PubMed, Google Scholar).

Fig 1: Thiamine B1 functions (Hiffler et al 2016; Frontiers in Nutrition)

Recent evidence suggests that thiamine administration in TD patients with septic shock significantly increases survival (Graph 1)

In this randomised controlled trial by Donnio et al (2016), 35% of patients had TD on admission, while thiamine treatment in TD patients with septic shock was associated with a lower mortality: 13% vs 46%.

The thiamine content of therapeutic F75 alone is markedly lower than the 2mg/kg recommended for the prevention of refeeding syndrome (Table 2), as well as the treatment doses used in critical illness.

CONCLUSION:
Complicated SAM is often associated with acute conditions such as severe malaria, pneumonia and septic shock. Pre-existing low or borderline thiamine stores in SAM are rapidly consumed in these hypermetabolic states, exacerbated by refeeding. We recommend systematic thiamine for all complicated SAM patients at the pharmacological dose of 25 mg (1/2 tablet) PO, preceded by a loading dose of 100 mg (1 ml) by slow IV infusion for the first 48 hours in severe acute conditions.

RESULTS:
Thiamine has dual coenzymatic and non-coenzymatic functions. It is involved in the production of acetyl-CoA and succinyl-CoA, as a cofactor of pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase complexes respectively, thus is essential for the proper functioning of the Krebs cycle (Fig 1). Consequently, TD is associated with lactic acidosis and reduced ATP production through disruption of the Krebs cycle, and could be considered an acquired mitochondrial disease.

Common risk factors for TD are SAM, monotonous diet, diarrhea and malabsorption, while acute precipitating factors include refeeding-induced cellular hyper-utilisation of thiamine, hypermetabolic states associated with critical illness, and resuscitation with dextrose-based fluids, all of which increase cellular thiamine demand (Table 1).

Table 1: TD prevalence in SAM and in critically ill children

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of TD</th>
<th>Median Age</th>
<th>Severe Illness</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>32%</td>
<td>2 years</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>Jamaica</td>
<td>38%</td>
<td>3 years</td>
<td>30%</td>
<td>5%</td>
</tr>
<tr>
<td>Brazil</td>
<td>24%</td>
<td>1 year</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>USA</td>
<td>20%</td>
<td>2 years</td>
<td>24%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Legend: F75 is the therapeutic milk used during early refeeding (75 kcal/100 ml). As an example, a 7 kg child with complicated SAM would be given 4 meals of 120 ml of F75 on admission. The dose recommended in the above guidelines (third column) would give approximately 14 times more thiamine than the amount found in F75 alone.

Table 2: Thiamine content of therapeutic milk and estimated thiamine needs in children during the acute phase of refeeding in SAM

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Approximate amount of F75 in ml (and equivalent of thiamine content)</th>
<th>South African and Australian guidelines for prevention of refeeding syndrome (2 mg/kg of thiamine/ml below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Kg</td>
<td>8 x 85 ml (~ 0.75 mg of thiamine)</td>
<td>10 mg of thiamine</td>
</tr>
<tr>
<td>7 Kg</td>
<td>8 x 120 ml (~ 1 mg of thiamine)</td>
<td>14 mg of thiamine</td>
</tr>
<tr>
<td>10 Kg</td>
<td>8 x 170 ml (~ 1.5 mg of thiamine)</td>
<td>20 mg of thiamine</td>
</tr>
<tr>
<td>15 Kg</td>
<td>8 x 250 ml (~ 2.25 mg of thiamine)</td>
<td>30 mg of thiamine</td>
</tr>
</tbody>
</table>

References:
- F75/P80/P90/P100 Formulations, 2010/0042/rev04, 28/01/2014.