Antiretroviral pharmacology in children: How malnutrition impacts clinical management

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Prevalence of under nutrition in regions of the world, 2008

Note: The trend analysis is based on a subset of 83 countries with trend data, covering 88% of the under-five population in the developing world. For CEE/CIS, data availability was limited for the period around 1990. Prevalence estimates for CEE/CIS are calculated according to the NCHS reference population, as there were insufficient data to calculate trend estimates according to WHO Child Growth Standards.
Malnutrition and HIV

• AIDS was recognized in Uganda as “slim disease” because of the severe wasting noted in infected adults

• Both stunting and wasting are common in infected children

• Children present with varying degrees of malnutrition
  – 30-50% of children with severe acute malnutrition (SAM) are HIV infected

Definition of severe acute malnutrition

• Weight-for-height z score $\leq -3$SD expected for age

• Mid upper arm circumference $\leq 11.5$ cm

• Weight-for-age z score $\leq -3$ SD = wasting

• Height-for-age z score $\leq -3$ SD = stunting
HIV infected children with malnutrition

- Non-edematous malnutrition more prevalent

- Associated micronutrient deficiencies
  - Vitamin A, iron, selenium and zinc

- Mortality higher despite nutritional rehabilitation
  - 4 fold higher mortality when compared to uninfected children

- Initiation of antiretroviral therapy required to prevent HIV disease progression

Mortality: severe acute malnutrition

- 220 Ugandan children hospitalized
  - Mortality of 24% (52 children died)
  - 70% of the deaths occurred in the 1st week
  - Increased risk of death
    - transfused or received IV fluids

- 454 Malawi Cohort of children with SAM
  - Overall mortality 14.8%
  - 35.45 HIV-infected vs 10.4% HIV-negative
  - Highest mortality (75%) in those under 24 months

Bachou H et al BMC Pediatr 2006
Baseline characteristics: children initiating antiretroviral therapy

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>30 Africa studies (n=100-4000)</th>
<th>MSF Cohort N=3936</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (median)</td>
<td>5</td>
<td>&lt;5 (50% 1-3yrs)</td>
</tr>
<tr>
<td>CD4% (median)</td>
<td>6 -15% (53%&lt;10%)</td>
<td>90%*Severe immune suppression/age</td>
</tr>
<tr>
<td>WAZ</td>
<td>- &lt;2.0</td>
<td>- &lt;2.0</td>
</tr>
<tr>
<td>(Weight-for-age z score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ</td>
<td>- &lt;2.0</td>
<td>ND</td>
</tr>
<tr>
<td>(Height-for-age z score)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Children started on ART: Older, lower CD4%, wasted and stunted

Sutcliffe CG et al Lancet Infect Dis 2008 ; Sauvagoet D et al Pediatr 2010
Management of severe acute malnutrition

• No complications: manage as outpatient, use plumpy nut

• Complications: hospitalize and stabilize
  – WHO ten step approach

• Stabilize with F75 milk
  – milk fortified with vitamins, electrolytes & micronutrients
    (75kcal/100mLs and 0.9g protein)
  – Antibiotics
  – Monitor for complications

• Rehabilitation phase – switch to F100 milk (100kcal/100mLs)

WHO recommends starting ART after nutritional stabilization
Response to antiretroviral therapy in severe acute malnutrition
An 8 year old female prior to ART and one year later (MUJHU)
WAZ and HAZ on antiretroviral therapy by treatment response

**Figure 1a.** Mean WAZ scores in the different treatment outcome groups during 48 weeks of HAART

**Figure 1b.** Mean HAZ scores in the different treatment outcome groups during 48 weeks of HAART

Note error bar type = 1 standard error

Musoke P et al  BMC Ped  2010
Response to antiretroviral therapy – UK vs Uganda

A. Viral load
B. CD4
C. Height
D. Weight

Kekitiinwa A et al JAIDS 2008
CD4% decline despite nutritional recovery in HIV infected children with SAM

**FIGURE 1**
Percentage of HIV-infected children with severe immunosuppression (CD4% < 15%). □, children with SM and edema; ■, children with SM and without edema.

Hughes SM et al. Pediatr 2009
Survival among Malnourished children started on HAART: Early and Late – 345 malnourished children

By one year only 6% of the children who started late would have died cf to 15% of those that started early
Pharmacokinetic data of antiretroviral therapy in moderate and severe malnutrition
Effect of Malnutrition on drug pharmacokinetics

• Disease states may affect PK by disrupting drug absorption, protein binding or metabolism.

• Severe malnutrition
  – reduced drug absorption
    • villous atrophy of the intestinal lining
    • reduced gastric acidity
  – low serum albumin
    • reduced binding of some drugs

• Diarrhoea and micronutrient deficiency impacts absorption

Nevirapine drug levels in malnutrition

Normal nutrition ◊ wt for ht > 85%: Mild-moderate malnutrition ◆ wt for ht 70-85%

N=25  N=12

NVP levels dependant on age and not degree of malnutrition

MEC – minimum effective concentration = 3000ng/ml

Pollock L et al  J Antimicrob Chemotherapy
Nevirapine concentrations in Malawi and Zambian children on fixed dose combination

71 Malawian and 56 Zambian children
Median age 8.4 vs 8.5 years
Height for age: - 3.15 vs -1.84
Lower NVP concentrations:
• Lower ht for age (stunting) 0.37mg/ml per unit higher
• Lower prescribed dose/m² + 0.89 mg/ml per 50mg/m2 higher
• Higher BMI for age (lack of wasting) - 0.42mg/ml per unit higher

• Stunted children had lower NVP levels
• Wasted children tended to have higher NVP levels

Ellis JC et al Antivir Ther 2007
Nevirapine (median and range) in children India

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Trough (μg/mL)</th>
<th>n</th>
<th>2 h (μg/mL)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>41</td>
<td>3.6 (0.6–12.6)</td>
<td>39</td>
<td>5.0 (1.5–16.3)</td>
</tr>
<tr>
<td>male</td>
<td>47</td>
<td>3.7 (0.1–10.1)</td>
<td>48</td>
<td>6.0 (1.6–18.9)</td>
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<tr>
<td><strong>Dose</strong></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;300 mg/m²/day</td>
<td>40</td>
<td>3.3 (1.3–10.9)</td>
<td>40</td>
<td>5.3 (2.1–18.9)</td>
</tr>
<tr>
<td>≥300 mg/m²/day</td>
<td>48</td>
<td>4.1 (0.1–12.6)</td>
<td>47</td>
<td>6.2 (1.5–16.3)</td>
</tr>
<tr>
<td><strong>HAZ score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stunted (&lt;−2 HAZ)</td>
<td>55</td>
<td>3.6 (0.6–12.6)</td>
<td>55</td>
<td>5.3 (1.6–14.3)</td>
</tr>
<tr>
<td>normal</td>
<td>33</td>
<td>3.9 (0.1–10.0)</td>
<td>32</td>
<td>6.1 (1.5–18.9)</td>
</tr>
<tr>
<td><strong>WAZ score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>underweight (&lt;−2 WAZ)</td>
<td>51</td>
<td>3.7 (0.6–12.6)</td>
<td>53</td>
<td>5.6 (1.6–18.9)</td>
</tr>
<tr>
<td>normal</td>
<td>37</td>
<td>3.2 (0.1–10.9)</td>
<td>34</td>
<td>5.6 (1.5–16.3)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 years</td>
<td>17</td>
<td>2.5 (0.1–10.9)</td>
<td>14</td>
<td>4.2 (1.5–13.5)</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>71</td>
<td>4.0 (0.6–12.6)</td>
<td>73</td>
<td>5.7 (1.6–18.9)</td>
</tr>
</tbody>
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*P*<0.05.
Research Questions

• What is the effect of severe acute malnutrition on the pharmacokinetics of ARV drugs?

• What is the most appropriate timing for initiation of ART in severe acute malnutrition?
  – Would early or delayed initiation of ART reduce mortality?

• Would nutritional supplementation during ART initiation improve overall outcome?

• Would supplementation of specific micronutrients improve outcome in those who are deficient?
Research priorities identified at the WHO Guideline meeting (1-3 February 2012) to update WHO recommendations on the management of children with severe malnutrition

HIV-INFECTED CHILDREN WITH SEVERE ACUTE MALNUTRITION

• Establish PK characteristics of HIV-infected children being started on ART
• PK of other drugs incl. INH
• The effectiveness (survival and complications) of early vs. late initiation of ART
• In HIV-infected children on ART to establish the relationship between ART regimens including dosing and development of early complications such as acute malnutrition and oedema or later metabolic complications such as IRIS

• To determine the most effective therapeutic feeding approach for HIV infected children with SAM who have persistent diarrhoea
• To determine if the basic physiological abnormalities of HIV-infected children with SAM, with or without oedema, are the same as children with SAM without HIV and to describe significant differences
THANK YOU