Severe Anaemia and Invasive Non-Typhoidal *Salmonella* Bacteraemia in Kenyan Children

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Anaemia – A global problem

Source: GBD anaemia collaborators, Lancet Haemat, 2023
Severe anaemia is associated with bacteraemia

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>OR (95% CI)</th>
<th>n/N</th>
<th>Severe anaemia aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen et al.</td>
<td>Ghana</td>
<td>2.5 (1.3, 4.5)</td>
<td>28/46</td>
<td>Children with malaria</td>
</tr>
<tr>
<td>Moon et al.</td>
<td>Mozambique</td>
<td>3.9 (1.7, 9.0)</td>
<td>14/39</td>
<td>HIV-infected adults</td>
</tr>
<tr>
<td>Were et al.</td>
<td>Kenya</td>
<td>1.6 (0.9, 3.0)</td>
<td>30/59</td>
<td>Children with malaria</td>
</tr>
<tr>
<td>Nadjm et al.</td>
<td>Tanzania</td>
<td>1.6 (1.1, 2.1)</td>
<td>N/A</td>
<td>Severe anaemia overall</td>
</tr>
<tr>
<td>Sigauque et al.</td>
<td>Mozambique</td>
<td>1.1 (0.9, 1.4)</td>
<td>96/1,550</td>
<td>Severe anaemia overall</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>Kenya</td>
<td>26.3 (14.5, 47.6)</td>
<td>108</td>
<td>Sickle cell anaemia</td>
</tr>
<tr>
<td>Calis et al.</td>
<td>Malawi</td>
<td>5.3 (2.6, 10.9)</td>
<td>54</td>
<td>Severe anaemia overall</td>
</tr>
<tr>
<td>Bachou et al.</td>
<td>Uganda</td>
<td>2.3 (0.5, 10.2)</td>
<td>2/56</td>
<td>Malnourished children</td>
</tr>
<tr>
<td>Lackritz et al.</td>
<td>Kenya</td>
<td>1.0 (0.6, 1.7)</td>
<td>37/303</td>
<td>Severe anaemia overall</td>
</tr>
</tbody>
</table>

- Small sample sizes
- Single causes of severe anaemia
- Reverse causality?

n = Severe anaemia with bacteraemia
N = Total bacteraemia
Severe anaemia might increase risk of iNTS

1. Increased gut permeability

2. Increased erythropoietic drive

3. Increased haemolysis

4. Impaired immune function

Abuga et al. 2021, IJMS
Approaches

1. Epidemiological associations between severe anaemia and iNTS.

2. Assays of iron and immune-mediated biomarkers.

3. Bacterial growth assays.

4. Effects of anaemia on NTS vaccine responses.
Anaemia is prevalent among children living in Kilifi, Kenya.

Community surveys (N=6,717)

Hospital admissions (N=102,559)

Anaemia classified based on age-dependent World Health Organization (2011) and GBD anaemia collaborators (2023, Lancet Haemat.) cut-offs

Overall 47.5%
iNTS remains an important cause of paediatric admissions

Bacteraemia, n=5,050 (4.9%)

- Salmonella Enteritidis: 154 (32.5%)
- Salmonella Typhimurium: 149 (31.4%)
- Not typeable: 39 (8.2%)
- Not tested: 132 (27.8%)

In-hospital iNTS mortality = 21.4% (vs 8.2% overall)

Abuga et al., haematologica, 2022; Muthumbi et al., CID, 2015
Severe anaemia associated with 4-fold increased risk of iNTS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Odds Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Bacteraemia</td>
<td>2.18 (2.03–2.34)</td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2.51 (2.19–2.88)</td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0.96 (0.76–1.20)</td>
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<tr>
<td><em>Escherichia coli</em></td>
<td>3.59 (2.98–4.33)</td>
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<tr>
<td>Non-typhoidal <em>Salmonella</em></td>
<td>4.64 (3.81–5.65)</td>
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<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1.34 (0.98–1.85)</td>
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<tr>
<td><em>Acinetobacter</em> species</td>
<td>1.14 (0.86–1.50)</td>
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<tr>
<td><em>Haemophilus influenzae</em></td>
<td>3.84 (3.00–4.89)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2.00 (1.38–2.89)</td>
</tr>
<tr>
<td>Other Gram Negatives</td>
<td>1.53 (1.18–1.97)</td>
</tr>
<tr>
<td>Other Gram Positives</td>
<td>1.28 (1.01–1.62)</td>
</tr>
</tbody>
</table>

*Odds ratios adjusted for age, sex, year of admission and number of readmissions*
Risk of iNTS was not age-dependent, but increased with each 1g/dL decrease in haemoglobin levels

*Odds ratios adjusted for age, sex, year of admission and number of readmissions
iNTS risk in severely anaemic children with and without malaria

*B: Odds ratios adjusted for age, sex, year of admission and number of readmissions
Low hepcidin and high plasma iron levels in severe anaemia

SA – severe anaemia (n=52); NTS – non-typhoidal Salmonella (n=44); SA+NTS (n=29)
High iron levels associated with bacterial growth in-vitro
Severe anaemia doesn’t impair cytokine production in children with iNTS

SA – severe anaemia (n=52); NTS – non-typhoidal Salmonella (n=44); SA+NTS (n=29)
Why this work is important

• Anaemia and iNTS are important causes of hospitalization and death

• Strategies to manage iNTS remain ineffective.

• Understanding underlying risk factors for iNTS (such as severe anaemia) ⇒ better interventions.
Summary

• Anaemia and iNTS are prevalent among Kenyan children.

• Severe anaemia is associated with a four-fold increased risk of iNTS.

• The risk is independent of malaria parasitaemia.

• Severe anaemia may increase iNTS risk through iron-dependent mechanisms.
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