Protecting the unprotected: How does HIV infection effect sepsis in children with severe acute malnutrition in Blantyre, Malawi?

J. A. Malone
University of Liverpool
E-mail: joe_anthony_malone@hotmail.co.uk

ABSTRACT

Background: Malnutrition is a preventable cause of a large number of child deaths worldwide. Evidence shows that these children have immunodysfunction putting them at increased risk of bacteraemia and sepsis. HIV reactive children are also at greater risk of infection. There is a deficit in research looking at the combined effect of HIV and malnutrition with regards to sepsis in young individuals.

Method: A structured literature review was carried out.

Results: HIV reactive malnourished children are at increased risk of severe malnutrition, infection and mortality. Among malnourished children with sepsis, the organisms responsible do not differ between HIV-reactive and HIV non-reactive patients. The symptoms may persist for longer with reactive patients.

Conclusion: More research is needed to look at this vulnerable group of patients who pose complex management issues to medical staff. Large sample size comparison of HIV reactive against non-reactive malnourished children with sepsis would be useful to highlight differences in outcome.

Key Words: Malnutrition, HIV infection, Malawi, Paediatrics, Global Health

Introduction

‘More than 10 million children die each year, most from preventable causes and almost all in poor countries’.

Background

Malnutrition contributes to 5.6 million of the 10 million worldwide annual childhood deaths. Severe malnutrition has a 20% mortality rate and this accounts for 1.6 million child deaths per year. Worldwide around 40 million people currently live with HIV/AIDS and 28.1 million of these reside in Sub-Saharan Africa. The majority of paediatric HIV infection occurs via vertical transmission from mother to child with around half of
those infected dying before the age of two\textsuperscript{4}. In Zambia and Malawi more than half of children admitted to nutritional rehabilitation wards are HIV positive\textsuperscript{5}.

**HIV**

Evidence suggests that these HIV positive patients are clinically different from their non-infected counter-parts, including an increased susceptibility to infection\textsuperscript{6,7,8}. It is believed that there is increased immunodysfunction in malnourished HIV positive patients\textsuperscript{9}.

Malnutrition has shown association with:

- **Macrophage, B and T cell lymphocyte functional abnormality**\textsuperscript{10}.
- **Disrupted thymus development**\textsuperscript{11}.

Interestingly, opportunistic infections such as Pneumocystis carinii pneumonia were first described in otherwise well but severely malnourished children in the developing world\textsuperscript{12}. This highlights the similarities of immunodysfunction in HIV and malnutrition as PCP is seen as an AIDS defining illness\textsuperscript{13,14}. With regards to malnutrition, HIV has been found to influence nutrition in a variety of ways:

- **Primary gastrointestinal malabsorption**\textsuperscript{15}.
- **Excessive energy expenditure**\textsuperscript{16}.
- **Poor oral intake**\textsuperscript{17}.
- **Carbohydrate malabsorption specifically**\textsuperscript{15}.

When looking in particular at Malawi it was found that the mortality rate of HIV positive children was over 3 times greater that of non-infected control group\textsuperscript{18}.

**Anti-retroviral therapy**

The availability of ART is increasing in the developing world. With this comes a greater focus on the consequences facing young HIV positive patients\textsuperscript{6}. In Malawi ART was first rolled out in 2005. From speaking to doctors here in QECH it appears there is still a lot of work to be done aside from drug supervision in these patients. As HIV transforms to a chronic disease, much like diabetes and ischaemic heart disease, the management focus is shifting to the management of the complications of the immune deficient state. Malnutrition is a prime example of this and with an increase in the number of severely malnourished children, health professionals need to address methods for effective management\textsuperscript{19}.

**Location of study**

The project took place at Queen Elizabeth Hospital in Blantyre, Malawi. In this country, around 100,000 children die every year and severe acute malnutrition is the most common reason for paediatric hospital admission\textsuperscript{1,20}. The national prevalence of HIV is 24% with 40% of admissions to the paediatric nutritional rehabilitation unit in QECH being HIV positive\textsuperscript{21}.

**A combination of problems**

Malnutrition and opportunistic infections have been found to be highly predictive of death in HIV infected or exposed individuals\textsuperscript{22}. It has been suggested
that HIV may in fact worsen malnutrition in children. With worldwide figures of HIV infected children at 2.1 million and rising, it is clear there is still much work to be done.\textsuperscript{23,24}

\textbf{Sepsis}

Sepsis is common amongst children in the tropics.\textsuperscript{25} It is often undiagnosed in institutions where there are insufficient facilities for blood culture.\textsuperscript{25} With sepsis in severe malnutrition, signs of infection such as fever and inflammation may be absent which can pose significant management problems.\textsuperscript{25} There is a deficit in research looking at the cause, effect and management of sepsis in HIV positive patients.\textsuperscript{26}

\textbf{Organisms}

Gram-negative bacteria are the most common and potentially lethal cause of septicaemia in malnourished children.\textsuperscript{27} They make up between 48.5-55\% of bacteraemia whereas gram-positive organisms make up 35-45.5\%.\textsuperscript{27} Figure 1 shows that similar ratios of isolated organisms affect populations of HIV infected and non-infected children.\textsuperscript{27} Of gram-negative bacteria, Salmonella enteritidis is mostly commonly seen, followed by E. Coli.\textsuperscript{27}

Fig 1.Organisms isolated from HIV-positive (White) and HIV-negative (Grey) children (Haem., Haemophilus; Salm., Salmonella; Strep, Streptococcus).\textsuperscript{27}
Physiologically speaking, sepsis affects children in a variety of ways:

- **Haemodynamic derangement (leading to shock)**
- **Severe endothelial damage**
- **Hypoglycaemia (due to anorexia, vomiting and hepatocellular damage)**

**Definitions**

**HIV** - Human Immunodeficiency Viruses type 1 and 2 are the cause of Acquired Immunodeficiency Syndrome (AIDS) global pandemic. The WHO clinical staging system (2006) is:

1. **Asymptomatic/Persistent generalized lymphadenopathy**
2. **Mild symptoms**
3. **Advanced**
4. **Severe**

**Malnutrition** - Severe acute malnutrition (SAM)

- **Weight-for-height measurement** of 70% or more below the median/three SD or more below the mean National Centre for Health Statistics reference values, also known as “wasted” (Marasmus)
- **Bilateral pitting oedema of nutritional origin**, also called “oedematous malnutrition” (Kwashiokor)
- **Mid-upper-arm circumference** of less than 110 mm in children age 1–5 years

**HIV status** - is divided into a variety of categories:
• **Reactive** - Tested positive on 2 separate tests and over 18 months old\textsuperscript{25}.
• **Non-reactive** - Tested negative ideally on 2 separate tests\textsuperscript{25}.
• **Exposed** - At risk of infection by vertical transmission, breast feeding, blood to blood contact, sexual exposure\textsuperscript{25}.
• **Untested\textsuperscript{26}**.

*Note* - HIV testing in paediatric patients under 15 months is unreliable due to the vertical transmission of maternal antibodies in HIV seropositive mothers\textsuperscript{28}.

**Bacteraemia** - The presence of bacteria in blood\textsuperscript{25}.

**Sepsis** - Clinical evidence of infection plus evidence of a systemic response manifested by 2 or more of\textsuperscript{25}:
  - **Temperature** >38°C or <36°C\textsuperscript{25}
  - **Heart rate** >90 beats/min\textsuperscript{25}
  - **Respiratory rate** >20 breaths/min\textsuperscript{25}
  - **WBC** >12 or <4 or >10% immature form\textsuperscript{25}

**Millennium development goals:** These global targets agreed by the UN are to be achieved by 2015. 1, 4 and 6 are particularly relevant to my study and this particularly vulnerable group of children will see great benefit if these can be achieved by 2015\textsuperscript{6,25}. Below is an outline of how malnutrition relates to the MDGs.

**Goal 1: Eradicate extreme poverty and hunger\textsuperscript{25}:**
  - Decreased immunity and productivity\textsuperscript{25}.
  - Increased risk of chronic disease\textsuperscript{25}.

**Goal 2: Achieve universal primary education\textsuperscript{25}:**
  - Poor school performance and decreased enrolment rate\textsuperscript{25}.
  - Reduced cognitive development\textsuperscript{25}.
  - Increased risk of visual impairment\textsuperscript{25}.

**Goal 3: Promote gender equality and empower women\textsuperscript{25}:**
  - Increased risk of female malnutrition\textsuperscript{25}.

**Goal 4: Reduce child mortality\textsuperscript{25}:**
  - Increased risk of childhood mortality\textsuperscript{25}.

**Goal 5: Improve maternal health\textsuperscript{25}:**
  - Increased risk of maternal mortality\textsuperscript{25}.
  - Increased risk of pregnancy complications (SPD and obstructed labour)\textsuperscript{25}.

**Goal 6: Combat HIV/AIDS, malaria and other disease\textsuperscript{25}:**
  - Increased risk of malnutrition, disease progression and opportunistic infection in HIV positive individuals\textsuperscript{25}.
  - Decreased survival in TB and HIV patients\textsuperscript{25}.

**Method**

To begin with I brainstormed using, textbooks, Google searching and preliminary browsing through journals along with their references to build up an idea of an appropriate research question. In Liverpool I visited the Harold Cohen Science library along with the Donald Mason Liverpool School of Tropical Medicine for
background reading. Additionally I used Medline (Ovid), Cochrane, Science Direct and Scopus along with direct searches on the WHO website for relevant background information.

Eventually I decided upon my research question as:

**How does HIV infection effect sepsis in children with severe acute malnutrition?**

Following this I began the next two stages of my project: a structured literature search.

**Literature search**

I used a variety of search engines to compare results. Starting simply with single word searches I then gradually built up more complex criteria utilizing Boolean operators and compiled results tables to compare numbers returned. Originally I had planned to compare sepsis in HIV infected and non-infected individuals however the search failed to gain adequate results via this route so I modified the criteria look specifically at sepsis in HIV infected malnourished children. I also checked the quality of my literature findings and finally drew together a broad set of results, removing duplicates. The additional filters I added included:

- **Date of publication in last 20 years, including 'in press' articles.**
- **Language of paper written in English.**
- **Relevant outcomes.**

With the search results collated my next step was to quality appraise the studies using the yes/no section of the Greenhalgh and Taylor assessment tool(33). I removed papers deemed not relevant to my research and with my final selection of articles prepared my results. Two fellow medical students, mentioned in the acknowledgements, carried out the quality assessment.

The important points extracted from my results were:

- **Paper name and year of publication.**
- **Study type.**
- **Number of patients in study (if relevant).**
- **Any confliction of interests stated.**
- **Relevant outcomes.**

**Results**

Step 1 – Preliminary title searches for single terms, using * symbol to increase result return for words with several endings. Cochrane results were dropped as they were not relevant.

Step 2 – Linked searches using collections of terms with the Boolean Operator OR in between.
Step 3 – Combined search using the preceding steps groups of initial terms with Boolean Operators OR in between and then Boolean operator AND used between each of the 4 groups. English language and date of publication in last 20 years, including 'in press' articles were added as filters.

Step 4 – Titles read and studies selected off their relevance. Pubmed results were dropped as they were not specific enough and searching was extremely difficult.

Step 5 – Read abstracts and selected the final 3 studies off their relevance. Duplicate studies removed.

Step 6 – Finally I performed a quality assessment upon the studies to ensure appropriateness using the Greenhalgh and Taylor recommendations.

Date stamp of literature search - 22/07/2011

**Literature search**

Firstly, as expected the literature search revealed that there is a significant deficit in research looking at the effect of HIV upon malnourished children developing sepsis. Despite modifying my search to be as broad as possible I was only able to collect three papers that fitted my criteria.

All of the papers were based in Africa and one was specifically conducted in Lilongwe, Malawi. All of the cases passed my quality assessment and so I was happy to study them and use the relevant results in my project. Sample size used in the studies was adequate to produce significant results. In particular the first and last studies used over 1100 patients respectively and the second paper used 200.

The first and last studies were also retrospective cohorts, which works well for large volume patient numbers in gaining an idea of general trends. Whilst at risk of recall bias the large number of patients helps the reliability of the results.

Conversely the prospective cohort of the second paper provides more reliable results for small patient numbers but was instead at risk of dropouts and loss of patients to follow up. The backing for the studies did not appear to affect the aims of the projects in provided impartial research. The key points that I gleaned from these studies were:

- **Co-infections in severely malnourished children are associated with a much higher death rate**. Infection management in these patients is of paramount importance.
- **There is no difference in the types of intestinal and systemic infections in all HIV reactive and non-reactive patients**.
- **Cryptosporidiosis infection and maramus malnutrition have been associated with a higher rate of mortality compared to other GI tract infections**.
- **Maramus (wasted) malnutrition was more common in HIV seropositive patients, Kwashiorkor (oedematous) malnutrition was more common in HIV seronegative patients**.
• Weight-for-age, weight-for-height, height-for-age scores and mid-upper-arm-circumference are lower in HIV seropositive children\textsuperscript{35}.
• Duration of diarrhoea is longer in HIV seropositive children\textsuperscript{35}.
• Salmonellosis and Cryptosporidiosis are by far the most common intestinal infections in malnourished children irrespective of HIV status\textsuperscript{35}.
• Kwashiorkor can occur in infancy but is more common in the second year of life following abrupt weaning\textsuperscript{35}.
• Maramus results from inadequate protein and calorie intake. This represents the end result of starvation, usually it occurs in the first year of life due to lack of breast-feeding and use of dilute animal milk\textsuperscript{35}.
• Pre-school children in developing countries are often at risk of malnutrition due to reliance on others for food, increased protein/energy requirements and an immature immune system at increased risk of infections\textsuperscript{35}.
• Severe respiratory tract infections (such as PCP) and malnutrition are highly prevalent and associated with an increased rate of mortality in HIV reactive children\textsuperscript{36}.
• The high mortality rates in this group of patients should be a future target in improving child health in the developing world\textsuperscript{36}. 
### Study and year

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. Of patients</th>
<th>Any conflict of interests?</th>
<th>Relevant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Infections associated with severe malnutrition among hospitalised children in East Africa41</td>
<td>Retrospective cohort</td>
<td>1121</td>
<td>No</td>
<td>Co-infections complicate the management of severe malnutrition and are associated with higher death rate. Management of such infections is of paramount importance to reduce case fatality rates.</td>
</tr>
<tr>
<td>2. Intestinal and Systemic Infection, HIV, and Mortality in Zambian Children With Persistent Diarrhea and Malnutrition11</td>
<td>Prospective cohort</td>
<td>200</td>
<td>No</td>
<td>Although intestinal and systemic infections did not differ for HIV-seropositive and HIV-seronegative children, HIV influenced nutritional states of all children. Cryptosporidiosis and marasmus were associated with higher mortality.</td>
</tr>
<tr>
<td>3. Pneumonia and Malnutrition are Highly Predictive of Death among African Children Hospitalized with Human Immunodeficiency Virus Infection or Exposure Early in the Era of Antiretroviral Therapy12</td>
<td>Retrospective cohort</td>
<td>1185</td>
<td>No</td>
<td>Severe respiratory tract infections and malnutrition are both highly prevalent and strongly associated with death among hospitalized children who are HIV infected or exposed. Novel programmatic and therapeutic strategies are needed urgently needed to reduce the high mortality rate among inpatients with HIV infection and HIV exposure in African pediatric hospitals.</td>
</tr>
</tbody>
</table>
Discussion

As I discovered during my background research, there is a great deal of work left to improve the management of this vulnerable group of patients. It’s interesting to note that there is no difference in the types of intestinal and systemic infections children contract whether they are HIV seropositive or negative regardless of malnutrition. However HIV increases the chance of contracting gastrointestinal infection and raises the length of time infection may persist. The most common gastrointestinal infections regardless of HIV status in malnourished children are Salmonellosis and Cryptosporidiosis, the later associated with a greatly increased mortality rate.

Serious infections such as PCP are highly predictive of mortality along with severe malnutrition suggesting HIV patients, in particular those that are malnourished are much less resilient to infection than their non-reactive counterparts. This agrees with existing literature suggesting malnutrition disrupts T and B cell function along with thymus development in children. Literature also suggests severely malnourished children are at increased risk of mortality.

With this in mind, if children are HIV reactive and severely malnourished there are two mechanisms by which their immune system is being compromised rendering them more vulnerable than children with HIV or malnutrition in isolation. Another interesting point highlighted by the literature is that pre school children are at increased risk of malnutrition due to their dependence on others for food, an increased protein/energy requirement and an immature immune system at risk of infection. Therefore family food provision is a clear target for intervention to reduce levels of malnutrition.

Two of the papers from my literature search highlighted diagnostic resource problems at hospitals in Africa. Whilst at QECH I saw first hand these problems with blood cultures and HIV testing often never returning results from the lab.

Taken, as a whole HIV appears to increase the severity of malnutrition, increase the rates of infection in malnourished children and increase the mortality rate in malnourished children with infection.

Recommendations

Future studies could look specifically at patients admitted and comprehensively ascertain diagnosis and organisms responsible for sepsis. Larger population sizes for comparison between sepsis in malnourished HIV reactive and non-reactive would give a clear idea of the differences in presentation and outcome.

Conclusion

A large proportion of child deaths worldwide are due to preventable causes. Malnutrition is one of these and when coupled with HIV is seriously debilitating causing immunodeficiency and exacerbation of malnutrition. HIV appears to increase:

- The severity of malnutrition
The rate of infection

The rate of mortality

Future studies could take large cohorts of patients and compare sepsis in malnourished children with or without HIV.

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Key

AIDS - Acquired Immunodeficiency Syndrome
ART - Anti-Retroviral Therapy
HIV - Human Immunodeficiency Virus
MDGs - Millennium Development Goals
PCP - Pneumocystis carinii pneumonia
PCR - Polymerase Chain Reaction
PMTCT - Prevention of Mother to Child Transmission
QECH - Queen Elizabeth Central Hospital
SAM - Severe Acute Malnutrition
SD - Standard deviation
SPD - Symphysis pubis dysfunction
TB - Tuberculosis
UN - United Nations
WBC - White blood cell count
WHO - World Health Organization

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