

## **Bacteraemia in severely malnourished children in an HIV-endemic setting**

ESTHER BABIREKERE-IRISO, PHILIPPA MUSOKE\* & ADEODATA KEKITIINWA

*Departments of Paediatrics, Mulago Hospital and \*Makerere University, Kampala, Uganda*

(Accepted June 2006)

### **Abstract**

**Background:** HIV infection predisposes children with malnutrition to recurrent bacterial infections and a high risk of bacteraemia.

**Methods:** A cross-sectional descriptive study to determine the prevalence, causative organisms, antibiotic sensitivity and factors associated with bacteraemia in malnourished children was undertaken at Mulago Hospital, Kampala. The prevalence of HIV infection was also determined. A total of 134 children aged 6–59 months with severe malnutrition were recruited.

**Results:** Sixty-one (45.5%) had oedematous malnutrition and 73 (54.5%) had severe wasting. Fifty-nine (44.0%) were HIV-infected. The prevalence of bacteraemia was 22%. The predominant organisms isolated were gram-negative enteric bacilli (77%) with *Salmonella* species and *E. coli* contributing 67% of the isolates. Hypoglycaemia was significantly associated with bacteraemia ( $p=0.007$ ). Most organisms were resistant to cotrimaxazole (93.3%), ampicillin (76.7%), gentamicin (66.7%) and chloramphenicol (60%). All isolates were sensitive to ceftriaxone. Sensitivity to ciprofloxacin was 97%. There was no strong association between HIV infection and bacteraemia. The relative risk of death in malnourished children with bacteraemia was ten times higher than in those without bacteraemia.

**Conclusions:** Nearly a quarter (22%) of children admitted with severe malnutrition had bacteraemia and gram-negative organisms were the predominant cause. Forty-four per cent were HIV-infected. Most of the bacteria were sensitive to ceftriaxone and ciprofloxacin and resistant to commonly used antibiotics. In the absence of culture and sensitivity, ciprofloxacin or ceftriaxone should be considered as first-line antibiotics for severely malnourished children.

### **Introduction**

The prevalence of malnutrition in developing countries remains unacceptably high.<sup>1,2</sup> It is estimated that there are more than 150 million malnourished children under the age of 5 years in developing countries.<sup>3</sup> More than 20 million children suffer from severe malnutrition.<sup>4</sup>

Malnutrition is a common problem in Uganda. The prevalence of wasting in children <5 years ranges from 0.5% to 7.2%.<sup>5</sup>

The interaction between infection and nutrition is well established and complex. Malnutrition, especially if severe, confers an increased risk of morbidity and mortality, particularly from infectious diseases.<sup>6</sup> On the other hand, infections themselves, particularly if repeated or prolonged, can result in malnutrition.<sup>7</sup>

Many severely malnourished children have bacterial infections when first admitted to hospital.<sup>8</sup> The prevalence of bacteraemia in African children with severe malnutrition ranges from 1.9% to 43%.<sup>2,6,9–11</sup> Gram-negative septicaemia is considered to be the most common and most lethal infection in severely malnourished children, constituting

Reprint requests to: Dr Esther Babirekere-Iriso, Department of Paediatrics, Mulago Hospital, Kampala, Uganda. E-mail: ebabirekere@yahoo.com

about 48.5–55% of bacteraemia.<sup>2,6,9,10</sup> Gram-positive organisms account for 35–45.5% of bacteraemia.<sup>2</sup> Overall, 95.8% of organisms are susceptible to ampicillin, gentamicin, or both.<sup>6</sup> Berkley *et al.* found 76% of isolates to be sensitive to penicillin or chloramphenicol.<sup>12</sup> A 91% coverage of invasive gram-negative bacilli has been reported when a combination of gentamicin and chloramphenicol is used.<sup>13</sup> Chloramphenicol alone covered 62% and gentamicin 73% of isolates.

Acquired immunodeficiency syndrome (AIDS) often presents as malnutrition and repeated opportunistic infections, with a high risk of bacteraemia.<sup>14</sup> Marasmus and marasmic kwashiorkor are predominant forms of severe malnutrition in HIV-infected children.<sup>15</sup> Ticklay *et al.* found a 48.6% prevalence of HIV infection in severely malnourished children in Harare, Zimbabwe.<sup>15</sup> The severity of malnutrition is exacerbated by HIV infection. The high prevalence of HIV infection in malnourished children emphasises the impact of the HIV epidemic on childhood nutritional morbidity and mortality.<sup>16</sup>

Hypoglycaemia is one of the important complications in severely malnourished children and it can be triggered by a serious systemic infection.<sup>1</sup> Severe cases of malnutrition sometimes develop hypothermia and shock, often associated with septicaemia.<sup>1,8</sup> A mortality rate of 22–31% has been reported in malnourished children with bacteraemia compared with a much lower rate of 5–11% in non-bacteraemic children with malnutrition.<sup>2,6,10</sup>

In Uganda, there is little information on factors associated with bacteraemia and the association with HIV infection in severely malnourished children. The aim of this study was to determine the prevalence of bacteraemia, the spectrum of causative organisms and their antibiotic sensitivity pattern and outcome in severely malnourished children. It also describes the prevalence of HIV infection in severely

malnourished children and its association with bacteraemia.

## Subjects and Methods

The study was conducted in the Acute Care Unit and the *mwanamugimu* (malnutrition) wards of Mulago Hospital, Kampala. Mulago Hospital is a tertiary care facility and teaching hospital. It serves a community of several suburbs within the city of Kampala and referrals from throughout the country. The Acute Care Unit is an overnight holding ward attached to the paediatric outpatient department and admits severely ill children. The *mwanamugimu* ward is for the specific management of children with severe malnutrition.

### Study design and patients

All children aged 6–59 months with severe malnutrition attending Mulago Hospital were eligible for enrolment on admission. Severe malnutrition was defined according to the 1999 WHO classification, which includes children whose weight-for-height is  $< -3SD$  or  $< 70\%$  of the median NCHS/WHO reference values, termed severely wasted, or who have symmetrical oedema involving at least the feet, termed oedematous malnutrition.<sup>17</sup> Severe stunting was defined as a height-for-age SD score  $< -3$  ( $< 85\%$  of median). Children whose age was not known, whose blood cultures were not done on admission and with proteinuria significant enough to suggest renal disease were excluded.

This was a cross-sectional analytical and descriptive study. Using the Kish formula,<sup>18</sup> the sample size was calculated to be 130:

$$n = \frac{Z^2 \cdot P \cdot (1 - P)}{d^2}$$

Z = the standard normal variate corresponding to the 95% confidence interval (1.96),

$P$ =the expected prevalence of bacteraemia in severely malnourished children (9.3%),<sup>10</sup> and  $d$ =the required precision of the estimate (5%).

Children who fulfilled the entry criteria were enrolled consecutively until the required sample size was achieved. Their weight, height or length and mid-upper arm circumference were measured (MUAC). They then had a general examination for anaemia, skin changes, oedema and hydration status and the axillary temperature was taken. Shock was diagnosed if there was hypothermia, a weak or absent radial pulse, rapid pulse rate, cold hands and feet with no history of diarrhoea, with or without decreased level of consciousness and with or without hypoglycaemia.

#### *Blood culture methods*

The dorsum of the hand or anterior cubital fossa was disinfected with 2% povidone-iodine solution and 70% isopropyl alcohol before drawing 6 ml of blood while wearing sterile gloves. The stoppers of the blood culture bottles were also disinfected. A new needle was used to inoculate 2 ml of blood under negative pressure into two sterile blood culture bottles containing 10 ml of brain-heart infusion broth which were taken to the laboratory immediately. The bottles were incubated at 35°C for 24 hours following which a gram stain was done followed by subculture on chocolate and blood agar for the growth of gram-positive and -negative organisms and MacConkey agar for selective gram-negative organisms. The agar plates were incubated at 35°C under aerobic conditions. The chocolate agar was incubated in a candle jar to facilitate growth of *Haemophilus influenzae* and *Neisseria meningitidis*. After 24 hours, visible colonies were examined by gram stain and biochemical and serological tests. All blood culture bottles showing no growth after 24–48 hours were further incubated for 7 days before being discarded as negative. All isolates were tested for antimicrobial

susceptibility using the Kirby-Bauer disc diffusion method.

On admission, venous blood glucose level was estimated using a glucometer (ACCU-CHEK products, Roche Diagnostics GmbH, D-68298 Mannheim, Germany). Hypoglycaemia was defined as a blood glucose level  $\leq 3.0$  mmol/l. All children were screened for HIV infection using both ELISA and RNA PCR qualitative tests. Urinalysis was undertaken on oedematous children to determine gross proteinuria using Uristix (Roche Diagnostics).

All children were managed according to WHO guidelines for empirical case management of children with severe malnutrition.<sup>17</sup> All were given intravenous ampicillin 50 mg/kg/6 h and intravenous gentamicin 7.5 mg/kg/24 h. Where necessary, the antibiotics were changed according to sensitivity results and treatment was given for 7 days. Those with hypoglycaemia were treated according to WHO guidelines.<sup>17</sup> The children were fed every 2 hours using high energy milk prepared to a local recipe. Outcome was determined at discharge or death. The main outcome measures were survival or death.

#### *Statistical methods*

Data were entered into a computerised database and analysed using the Statistical Package for Social Sciences (SPSS version 10.0). Proportions were compared using the  $\chi^2$  test, and relative risks with 95% confidence intervals (CI) were calculated. A logistic regression model was performed to examine the relative risk of the different types of malnutrition and bacteraemia in relation to outcome. The Cox regression model was employed to analyse the prognostic significance of bacteraemia in predicting survival. A survival curve for bacteraemia was determined by the Kaplan-Meier method.

#### *Ethical considerations*

The study was approved by the Department of Paediatrics and Child Health, Makerere

University and Makerere University Faculty of Medicine Research Committee. Written informed consent for the study and HIV testing was obtained from parents or caretakers. Parents/caretakers were given pre- and post-test HIV counselling. All caretakers consented to HIV testing. However, two mothers accepted testing but preferred not to know the results. HIV-positive children were referred to the infectious disease clinic of Mulago Hospital for follow-up.

## Results

Between September and November 2001, 226 severely malnourished children were admitted and 134 were enrolled in the study. Mean age was 17.7 months, range 6–48 and median 14.8 months. The male to female ratio was 1.2:1.

Thirty children (22.4%) had bacteraemia. Most with bacteraemia were <24 months of age with a mean of 18.6 months. On comparison of the nutritional status of children with and without bacteraemia, there was no significant difference in mean weight, height and MUAC.

The mean weight-for-height Z-score for oedematous children was -3.00 and for severely wasted children -4.05 ( $p < 0.0001$ ). There was no strong association between bacteraemia and the different Z-scores.

There were 30 bacterial isolates, as follows: *Salmonella* spp (15), *Escherichia coli* (5), *Haemophilus influenzae* (4), *Streptococcus pneumoniae* (3), and one each *Klebsiella pneumoniae*, *Morganella morganii* and *Proteus mirabilis*. Coagulase-negative Staphylococcus was isolated in three children. However, it was regarded as a contaminant because the organisms were isolated from only one of the two blood culture bottles and repeat cultures were not done. Furthermore, there was no deterioration in the patients' condition in the face of inappropriate antimicrobial therapy and the clinical features were not compatible with serious infection. Considering the above, these children were excluded. Five children had blood cultures with growth of mixed organisms in both culture bottles and further analysis to identify the organisms was not done. The blood samples were considered contaminated and these children were also excluded from the study.

Sixty-one children (45.5%) had oedematous malnutrition and 73 (54.5%) had severe wasting. Eighteen children had severe stunting and three (16.7%) had bacteraemia. Table 1 shows the association with bacteraemia of type of malnutrition, previous antibiotic use and HIV. Previous antibiotic use was strongly associated with bacteraemia ( $p = 0.019$ ). Four of the children with bacteraemia had received chloramphenicol, three cotrimaxazole and two

TABLE 1. Association of type of malnutrition, previous antibiotic use and HIV status with bacteraemia.

Variable	Bacteraemia, n (%)	No bacteraemia, n (%)	OR	95% CI	p-value
<i>Malnutrition</i>					
Oedematous	14 (23.0)	47 (77.0)	0.942	0.417–2.128	0.886
Severe wasting	16 (21.9)	57 (78.1)			
<i>Previous antibiotic use</i>					
Yes	12 (37.5)	20 (62.5)	2.800	1.163–6.739	0.019*
No	18 (17.6)	84 (82.4)			
<i>HIV infection</i>					
Positive	11 (18.6)	48 (81.4)	0.675	0.293–1.559	0.358
Negative	19 (25.3)	56 (74.7)			

OR, odds ratio; CI, confidence interval; \* statistically significant.

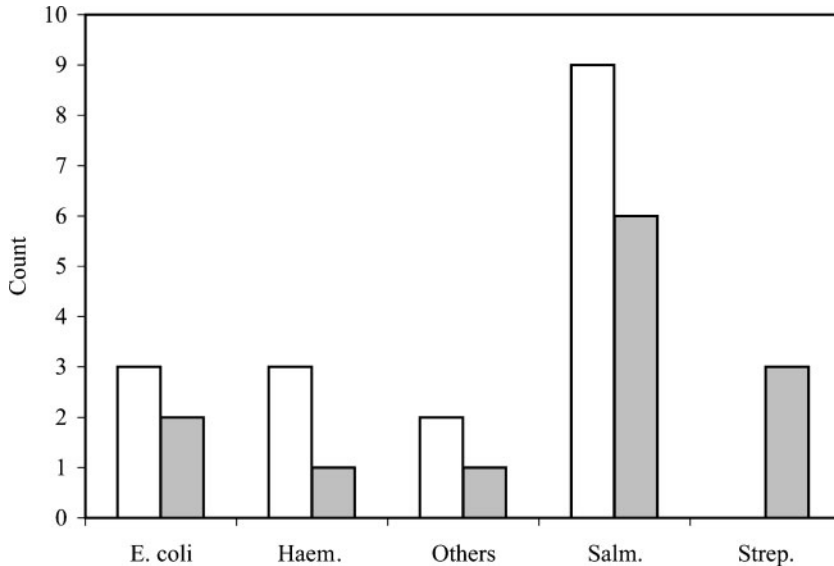


FIG. 1. Organisms isolated from HIV-positive (■) and HIV-negative (□) children (Haem., Haemophilus; Salm., Salmonella; Strep., Streptococcus).

amoxicillin before presentation at hospital. Twenty-five (41.0%) of the 61 oedematous children and 34 (46.6%) of the 73 severely wasted children were HIV-infected. There was no significant difference in the rate of HIV infection in the different types of malnutrition.

Similar organisms were isolated from children infected with HIV and those without HIV infection (Fig. 1). There was no significant difference in the organisms isolated between the two groups.

On admission, 73 (54.5%) of the 134 children had diarrhoea and 56 (41.8%) had pneumonia. Sixteen (11.9%) had skin ulceration and 39 (29.1%) had had measles within the past month. Nine (6.7%) had hypothermia, 19 (14.2%) had hypoglycaemia, 30 (22.4%) presented in shock and 9 (6.7%) had severe anaemia. Some children presented with more than one diagnosis. Twenty-six (19.4%) had diarrhoea and pneumonia. Nineteen (14.2%) had diarrhoea and were in shock. Nine (6.7%) children had hypothermia and shock. The relationship between hypothermia and

shock was statistically significant ( $\chi^2 = 24.381$ ,  $p < 0.0001$ ). Four (3.0%) of the children had hypoglycaemia and hypothermia and the association was significant ( $p = 0.035$ ). The major presenting diagnoses and bacteria isolated are shown in Table 2. There was a strong association between hypothermia and bacteraemia ( $p = 0.018$ ) and the association between hypoglycaemia and bacteraemia was significant ( $p = 0.003$ ).

On logistic regression analysis of hypoglycaemia and hypothermia for bacteraemia, hypoglycaemia was strongly associated with bacteraemia ( $p < 0.0001$ , 95% CI 1.457–11.140, OR 4.028).

All isolates were tested for antibiotic sensitivity. Overall, only 6.7% of the organisms were sensitive to cotrimoxazole, 23.3% to ampicillin, 40.0% to chloramphenicol and 33.3% to gentamicin (Table 3). Thus, 76.7% of isolates were resistant to ampicillin, 66.7% were resistant to gentamicin and 72% resistant to both. A combination of gentamicin and chloramphenicol was effective against only 36.7% of organisms (63.3% resistant). All isolates were sensitive

TABLE 2. Association between major presenting diagnoses in severely malnourished children with positive blood cultures.

Diagnosis	No. (%*)	Organisms isolated (n)
Diarrhoea	14 (46.7)	<i>E. coli</i> 3, <i>H. influenzae</i> 1, <i>H. parainfluenzae</i> 2, <i>Klebsiella pneumoniae</i> 1, <i>S. enteritidis</i> 4, <i>S. typhimurium</i> 2, <i>Strep. pneumoniae</i> 1
Pneumonia	16 (53.3)	<i>E. coli</i> 2, <i>H. influenzae</i> 2, <i>H. parainfluenzae</i> 2, <i>Morganella morganii</i> 1, <i>S. enteritidis</i> 4, <i>S. typhimurium</i> 3, <i>Strep. pneumoniae</i> 2
Skin ulceration	7 (23.3)	<i>Klebsiella pneumoniae</i> 1, <i>Proteus mirabilis</i> 1, <i>S. enteritidis</i> 3, <i>S. typhimurium</i> 2
Measles	9 (30.0)	<i>E. coli</i> 1, <i>H. influenzae</i> 1, <i>H. parainfluenzae</i> 2, <i>Proteus mirabilis</i> 1, <i>S. enteritidis</i> 2, <i>S. typhimurium</i> 2
Hypothermia	4 (13.3)	<i>Morganella morganii</i> 1, <i>Proteus mirabilis</i> 1, <i>S. enteritidis</i> 2
Hypoglycaemia	9 (30.0)	<i>E. coli</i> 1, <i>Klebsiella pneumoniae</i> 1, <i>Morganella morganii</i> 1, <i>S. enteritidis</i> 5, <i>S. typhimurium</i> 1
Shock	9 (30.0)	<i>E. coli</i> 2, <i>Klebsiella pneumoniae</i> 1, <i>Morganella morganii</i> 1, <i>Proteus mirabilis</i> 1, <i>S. enteritidis</i> 4
Severe anaemia	2 (6.7)	<i>S. enteritidis</i> 2
Occult	2 (6.7)	<i>S. dublin</i> 1, <i>Strep. pneumoniae</i> 1

Some children had more than one diagnosis and so the percentage of diagnoses is >100%; \* relates to the children with bacteraemia.

to ceftriaxone. All organisms except one *E. coli* were sensitive to ciprofloxacin.

Overall, 27 (20.1%) of the 134 severely malnourished children died. The association between outcome and bacteraemia, hypoglycaemia, HIV and type of malnutrition is summarised in Table 4. The odds ratio of death in bacteraemic malnourished children was 9.7 times that in non-bacteraemic ones ( $p < 0.0001$ ). Hypoglycaemia was strongly associated with death ( $p = 0.01$ ). The association between HIV infection and outcome was not statistically significant. There was no significant association between outcome

and different types of malnutrition. Of the bacteraemic children who died, 87.5% had ampicillin-resistant organisms. However, the relationship between ampicillin resistance and death was not significant. Of the bacteraemic children who died, 75% had gentamicin-resistant organisms, although there was no strong association between death and gentamicin resistance. The relationship between the pattern of chloramphenicol sensitivity and outcome approached significance ( $p = 0.063$ ).

Multivariate analysis of outcome for bacteraemia and hypoglycaemia showed

TABLE 3. Isolates and the number sensitive to the antibiotics tested.

Organism (n)	COT	AMP	PEN	AMX	CHL	GM	CTX	CF	CZ	CTM	CIP
<i>E. coli</i> (5)	0	0	0	0	1	1	5	5	5	5	4
<i>H. influenzae</i> (2)	0	0	0	0	0	1	2	0	1	0	2
<i>H. parainfluenzae</i> (2)	0	0	0	0	1	1	2	1	2	1	2
<i>Klebsiella pneumoniae</i> (1)	0	0	0	0	1	0	1	1	1	1	1
<i>Morganella morganii</i> (1)	0	0	0	0	0	0	1	1	1	1	1
<i>Proteus mirabilis</i> (1)	0	0	0	0	0	0	1	1	1	1	1
<i>S. dublin</i> (1)	0	0	0	0	0	IM	1	1	1	1	1
<i>S. enteritidis</i> (10)	2	2	2	2	3	3	10	10	9	10	10
<i>S. typhimurium</i> (4)	0	2	2	2	3	3	4	4	4	4	4
<i>Strep. pneumoniae</i> (3)	0	3	2	2	3	Not tested	3	2	3	3	3

COT, cotrimoxazole; AMP, ampicillin; PEN, penicillin G; AMX, amoxicillin; CHL, chloramphenicol; GM, gentamicin; CTX, ceftriaxone; CF, cefuroxime; CZ, cefotazime; CTM, ceftazidime; CIP, ciprofloxacin; IM, intermediate response.

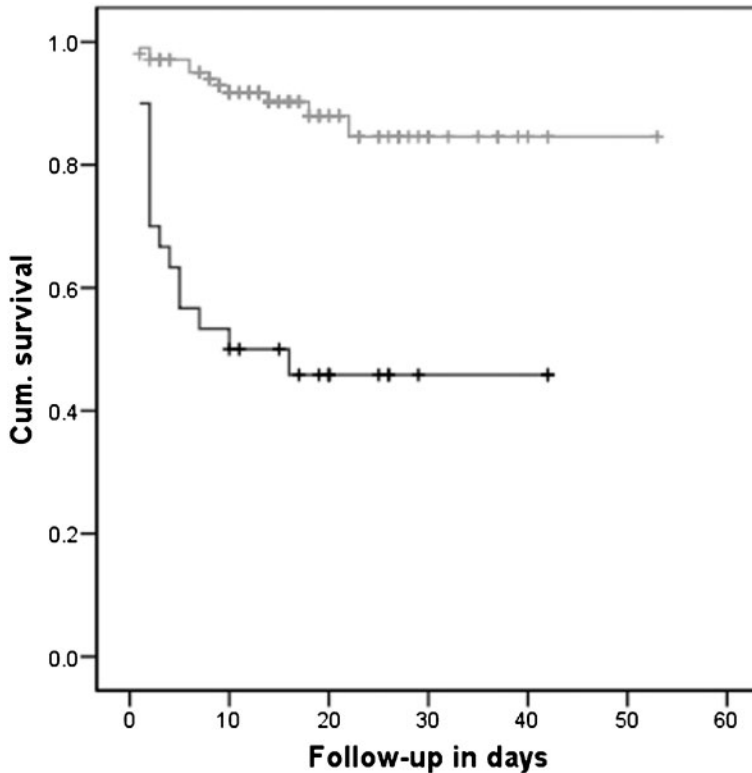


FIG. 2. Kaplan-Meier survival curve for bacteraemia (upper, no bacteraemia, lower, bacteraemia).

bacteraemia to be an independent prognostic indicator of death ( $p=0.0001$ , 95% CI 3.20–22.34, OR 8.45).

Survival rate was significantly lower in bacteraemic children than in non-bacteraemic ones (Fig. 2).

Using Cox's regression model for survival, bacteraemia was a significant prognostic indicator for death in children with severe malnutrition. Eighty per cent of deaths of children with bacteraemia occurred within 2 days of admission. Mean (SD) duration of

TABLE 4. Impact of bacteraemia, hypoglycaemia, HIV and type of malnutrition on outcome.

Variable	Survived, <i>n</i> (%)	Died, <i>n</i> (%)	OR	95% CI	<i>p</i> -value
<i>Bacteraemia</i>					
Positive	14 (46.7)	16 (53.3)	9.662	3.732–25.017	<0.0001*
Negative	93 (89.4)	11 (10.6)			
<i>Hypoglycaemia</i>					
Present	11 (57.9)	8 (42.1)	3.675	1.305–10.346	0.01*
Absent	96 (83.5)	19 (16.5)			
<i>HIV status</i>					
Infected	48 (81.4)	11 (18.6)	0.836	0.387–1.807	0.650
Not infected	59 (78.7)	16 (21.3)			
<i>Type of malnutrition</i>					
Oedematous	50 (82.0)	11 (18.0)	0.783	0.542–3.005	0.732
Severe wasting	57 (78.1)	16 (21.9)			

\* Statistically significant.

hospital stay of the total group was 16 (10.8) days with a range of 1–53.

## Discussion

A total of 45.5% of the children had oedematous malnutrition and 54.5% had severe wasting. In contrast, Friedland<sup>2</sup> and Reed<sup>6</sup> in South Africa found a higher prevalence of oedematous malnutrition than of severe wasting. In this study, the higher proportion of severely wasted children might be owing to the current HIV epidemic which commonly presents as severe wasting.<sup>14</sup> The prevalence of bacteraemia was 22.4% which is similar to other African studies in which the prevalence ranged from 1.9% to 43%.<sup>2,6,9–11,19</sup> An earlier study in Uganda found a 9.3% prevalence of bloodstream infections.<sup>10</sup> The higher prevalence of bacteraemia in the current study was not strongly associated with HIV infection, although it is known to predispose children to frequent bacterial infections.<sup>14,15,20</sup> The lack of association of bacteraemia with HIV infection might be owing to the small sample size.

Children with oedematous malnutrition had a prevalence of bacteraemia (23%) similar to those with severe wasting (22%), which contrasts with other reports.<sup>2,6</sup> However, this was a hospital-based study and so the risk of bacteraemia in non-hospitalised children is not known.

Gram-negative enteric bacilli were the predominant organisms isolated (76.6%) with *Salmonella enteritidis* being the single most common isolate, followed by *E. coli*. This observation supports other reports.<sup>2,6,9–11,21</sup> *Streptococcus pneumoniae* was the only gram-positive isolate. Surprisingly, *Staphylococcus aureus* and *Staphylococcus epidermidis* were not isolated as pathogens, contrary to what has been reported.<sup>2,6,9,10,19,22</sup>

The causative organism could not be predicted from the major presenting features. Gram-negative enteric bacilli were isolated from 93% of the bacteraemic children presenting with diarrhoea. It is

postulated that in malnourished children there is disturbance of the normal immune mechanism and intestinal lining, leading to intestinal bacteria gaining entrance to the bloodstream.<sup>23</sup> Although the association of diarrhoea with bacteraemia was not statistically significant, a high proportion of children with bacteraemia presented with diarrhoea.

*Salmonella* species were isolated from 44% of the bacteraemic children presenting with pneumonia, whereas *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *E. coli* were isolated less frequently. This is contrary to Friedland who reported a higher isolation of *Streptococcus pneumoniae* and *Haemophilus influenzae*.<sup>2</sup> Gram-negative enterobacilli were found in children with skin ulceration, contrary to previous studies which reported that Staphylococci and Streptococci were the common pathogens.<sup>24</sup> Patients' use of antibiotics, especially penicillins and chloramphenicol, before presentation at hospital might have reduced the chances of isolating *Streptococcus*.

A third of the children with bacteraemia had had measles during the month before presentation with severe malnutrition. Measles infection depresses the immune system and interferes with host defences, which facilitates the development of bacteraemia.<sup>25</sup>

Hypothermia was associated with bacteraemia.<sup>8,10</sup> Septic shock could have contributed to hypothermia. Sepsis and septic shock comprise a cascade of metabolic, immunological and clinical changes, initiated by a focus of infection and ending with severe endothelial damage and profound haemodynamic derangement.<sup>25</sup> Severely malnourished children are at risk of developing hypoglycaemia.<sup>8</sup> Constitutional symptoms such as anorexia and vomiting during infection result in reduced food intake, which predisposes to hypoglycaemia. Septicaemic processes are reported to cause a breakdown of the hepatic gluconeogenic mechanisms by damaging

liver cells which results in hypoglycaemia.<sup>26</sup> About half of the hypoglycaemic children had bacteraemia. The relative risk of hypoglycaemic children having bacteraemia was four times higher than in those without hypoglycaemia.<sup>1,8</sup>

Previous antibiotic use was strongly associated with bacteraemia. Perhaps very sick children compelled their parents to seek medical treatment and hence received antibiotics. Such children might have had resistant strains of organisms, resulting in positive cultures despite previous antibiotic use.

The prevalence of HIV infection was 44%. Severe wasting was more common among the HIV-infected group, which is in keeping with other African studies.<sup>16,27</sup> HIV infection causes frequent opportunistic infections and infection-induced cachexia.<sup>28</sup> Nutrient absorption is reduced owing to HIV-related enteropathy which leads to persistent diarrhoea and malabsorption.<sup>29</sup> There is failure of the adaptive fall in the basal metabolic rate which renders HIV-infected children catabolic.

The organisms isolated from HIV-infected children were similar to those from the uninfected ones.

It is advised that all severely malnourished children receive routine antibiotics when admitted.<sup>8,17</sup> Pending culture results, a combination of ampicillin and gentamicin has been recommended as initial treatment.<sup>8,17</sup> Of the gram-negative organisms, 76.7% were resistant to ampicillin and 66.7% to gentamicin. A combination of ampicillin and gentamicin would therefore not be effective in 72% of the gram-negative organisms. This contrasts with studies in South Africa where 86–95.8% of the organisms were sensitive to ampicillin or gentamicin or both.<sup>2,6</sup> This might be owing to varying resistance patterns in different geographical regions and the times when the studies were conducted. Similar to Friedland's and Reed's findings, two-thirds of the gram-negative organisms were resistant to chloramphenicol.<sup>2,6</sup> There was no

resistance to ceftriaxone. Sensitivity to ciprofloxacin was 96.7%.

Ciprofloxacin is now being used increasingly to treat infectious conditions in children.<sup>19,30</sup> However, its use is limited by concern about adverse reactions, especially in growing cartilage, tendon ruptures and arthralgia.<sup>31,32</sup> Despite its reported safety, it is not widely recommended in paediatric practice.

There was a higher overall mortality rate (20%) than in similar studies.<sup>2,6,10</sup> Although the difference in mortality rate between the types of malnutrition was not significant, more deaths were registered in severely wasted children than in oedematous ones. The lack of association between oedematous malnutrition and death might be partly attributable to the higher numbers of wasted children in this study as opposed to previous reports in which more deaths occurred in oedematous ones. The high mortality rate might be attributed in part to the very high resistance of the organisms to gentamicin and ampicillin, which are routinely administered to malnourished children. The mortality rate was five times higher in the bacteraemic patients than in those without bacteraemia. Mortality rates of 13–78% have been reported elsewhere.<sup>2,6,9,20</sup> Although HIV infection predisposes to death,<sup>33</sup> there was no significant difference in mortality between the HIV-infected and uninfected groups.

When preparing guidelines for management of patients with severe malnutrition, the high rate of mortality in bacteraemic children and the possibility of antibiotic resistance should be addressed.

### Acknowledgment

The authors wish to thank the WHO in Uganda, the Uganda Virus Research Institute, the Nuffield Foundation and the Ministry of Health, Uganda for financial support, Dr Najjuka and Mr Philip Ombasa for the microbiology work, Dr Carol Nakisige for statistical assistance,

Dr Robert Iriso for encouragement and support, and all the children and their caretakers who participated in this study.

## References

- World Health Organization. *Management of Severe Malnutrition: a Manual for UNICEF. The State of the World's Children 1998*. Oxford University Press 1998; 98–101.
- Friedland IR. Bacteraemia in severely malnourished children. *Ann Trop Paediatr* 1992; **12**:433–40.
- World Health Organization. *Global Database on Child Growth and Malnutrition*. Geneva: WHO, 1999; 6–9.
- UNICEF Policy Review. Strategy for improved nutrition of children and women in developing countries. *Int Child Health* 1991; **2**:1–12.
- Kikafunda JK, Walker AF, Collett D, Tumwine JK. Risk factors for early childhood malnutrition in Uganda. *Pediatrics* 1998; **104**:e45.
- Reed RP, Wegerhoff FO, Rothberg AD. Bacteraemia in malnourished rural African children. *Ann Trop Paediatr* 1996; **16**:61–8.
- Curran JS, Berness LA. Malnutrition: In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 16th edn. Philadelphia, PA: Saunders, 2000; 169–72.
- World Health Organization. *Management of Severe Malnutrition: A Manual for Physicians and Other Senior Health Workers*. Geneva: WHO, 1999; 4–19.
- Berkowitz FE. Infections in children with severe protein-energy malnutrition. *Ann Trop Paediatr* 1983; **3**:79–83.
- Phillips I, Wharton B. Acute bacterial infection in kwashiorkor and marasmus. *Br Med J* 1968; **1**:407–9.
- Cotton MF, Burger PJ, Boderstein WJ. Bacteraemia in children in the south-western Cape. A hospital-based survey. *S Afr J* 1992; **18**:87–90.
- Berkley JA, Maitland K, Mwangi I, et al. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. *Br Med J* 2005; **330**:995.
- Bejon P, Mwangi I, Ngetsa C, et al. Invasive Gram-negative bacilli are frequently resistant to standard antibiotics for children admitted to hospital in Kilifi, Kenya. *J Antimicrob Chemother* 2005; **56**:232–5.
- Blokzijl ML. Human immunodeficiency virus infection in childhood. *Ann Trop Paediatr* 1988; **8**:1–17.
- Ticklay IM, Nathoo KJ, Siziya S, Brady JP. HIV infection in malnourished children in Harare, Zimbabwe. *East Afr Med J* 1997; **74**:217–20.
- Prazuck T, Tall F, Nacro B, et al. HIV infection and severe malnutrition; a clinical and epidemiological study in Burkina Faso. *AIDS* 1993; **7**:103–8.
- Ashworth A, Sultan K, Jackson A, et al. *Guidelines for the Inpatient Treatment of Severely Malnourished Children*. The WHO/UNICEF strategy of integrated Management of Childhood illness (IMCI), 2003; 10–16.
- Kish L. *Survey Sampling*. New York: Wiley, 1965.
- Noorani N, Macharia WM, Oyatsi D, Revathi G. Bacterial isolates in severely malnourished children at Kenyatta National Hospital, Nairobi. *East Afr Med J* 2005; **82**:343–8.
- Norton EB, Archibald LK, Nwanyanwu OC, et al. Clinical predictors of bloodstream infections and mortality in hospitalized Malawian children. *Pediatr Infect Dis J* 2004; **23**:145–55.
- Morehead CD, Morehead M, Allen DM, Olsen RE. Bacterial infections in malnourished children. *J Trop Pediatr Environ Child Health* 1974; **20**:141–7.
- Berkowitz FE. Bacteremia in hospitalized black South African children. A study emphasizing nosocomial bacteremia and bacteremia in severely malnourished children. *Am J Dis Child* 1984; **138**:551–6.
- Smythe PM. Changes in intestinal bacterial flora and role of infection in kwashiorkor. *Lancet* 1958; **4**:724–7.
- Purtilo DT, Connor HD. Fatal infections in protein-calorie malnourished children with thymolymphatic atrophy. *Arch Dis Child* 1975; **50**:149–52.
- Hussey G, Simpson J. Nosocomial bacteremias in measles. *Pediatr Infect Dis J* 1990; **9**:715–17.
- Beisel WR. Metabolic response of the host to infections. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*, 3rd edn. Philadelphia: WB Saunders, 1997; 1–6.
- Kurawige JB, Gatiyizi T, Kleinfeldt V, et al. HIV-1 infection among malnourished children in Butale, Rwanda. *J Trop Pediatr* 1993; **39**:93–6.
- Nicholae SW, Leung J, Fenoy I. Guidelines for nutritional support of HIV-infected children. *J Pediatr* 1991; **119**:559–62.
- Grunfield C, Pang M, Shimizu L, Shigenaga JK. Resting energy expenditure, caloric intake and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Am J Clin Nutr* 1992; **55**:455–60.
- Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use—safety report. *Pediatr Infect Dis J* 1997; **16**:127–9; discussion 160–2.
- Karande SC, Kshirsagar NA. Adverse drug reaction monitoring of ciprofloxacin in pediatric practice. *Indian Pediatr* 1992; **29**:181–8.
- Harrell RM. Fluoroquinolone-induced tendinopathy: what do we know? *South Med J* 1999; **92**:622–5.
- Yogev R, Chadwick EG. Acquired immunodeficiency syndrome (human immunodeficiency virus): In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 16th edn. Philadelphia, PA: WB Saunders, 2000; 1022–33.

Copyright of *Annals of Tropical Paediatrics* is the property of Maney Publishing and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.