

ORIGINAL ARTICLE**BACTERAEamia AMONG SEVERELY MALNOURISHED CHILDREN IN JIMMA UNIVERSITY HOSPITAL, ETHIOPIA****Alem Abrha¹, Alemseged Abdissa^{2*}, Getenet Beyene², Genet Getahun³, Tsinuel Girma³****ABSTRACT**

BACKGROUND: *Sever acute malnutrition severely suppresses every component of the immune system leading to increased susceptibility and severity to infection. However, symptoms and signs of infections are often unapparent making prompt clinical diagnosis and early treatment very difficult. The aim of the study was to determine the magnitude of bacteraemia and antimicrobial sensitivity among severely malnourished children.*

METHODS: *Severely malnourished children admitted in Jimma University Specialized Hospital were enrolled between October, 2009 to May, 2010. Blood samples were collected, processed and bacterial isolates were identified using standard bacteriological procedures. Then, antibiotic susceptibility pattern of the isolates was determined by using Kirby-Bauer technique.*

RESULTS: *Bacteraemia was seen in 35 (20.6%) of the 170 study subjects. There were a total of 35 bacterial isolates, Gram positive bacteria constitute 24(68.6%) of the isolates, where Staphylococcus aureus was the leading Gram positive isolate while Klebsiella species were the dominant Gram negative isolates. Twelve (7.1%) children died and 4 (33.3%) of them had bacteraemia. While susceptibility was more than 80% to Gentamicin, Ciprofloxacin and Ceftriaxone, increased level of resistance was documented to commonly used antibiotics, such as Amoxycillin, Co-trimoxazole and Chloramphenicol.*

CONCLUSION: *High prevalence of bacteraemia with predominating Gram positive isolates and increased level of resistance to commonly used antibiotics was shown among severely malnourished children in Jimma. Further studies are required to revise the current guideline for antibiotic choice.*

KEYWORDS: *Bacteraemia, severe acute malnutrition, Antimicrobial susceptibility, Jimma*

INTRODUCTION

Malnutrition remains one of the most common causes of morbidity and mortality among children throughout the world (1) and more commonly in sub-Saharan Africa and south Asia (1, 2). Acute childhood malnutrition affects about a tenth of the world's children under 5 years of age (2), and contributes to 50–60% of all child deaths (3) particularly those living in circumstances of extreme poverty in the developing world (4,5). In Ethiopia, more than one in two children (52%) under the age of five are stunted (growth

retardation), 11% are wasted (thin for their height) and 47% are underweight (low weight-for-age). Stunting and wasting rates are even higher in rural children (6), where the vast majority of the population is dwelling. Other community based studies in Ethiopia also showed prevalence of wasting from 9-12% (7, 8). Poor infant and young child feeding practice, poor socio-economic background and nutritionally inadequate diet contribute more for severe acute malnutrition (9, 10).

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Severe acute malnutrition (SAM) affects both acquired and innate host defense mechanisms (11-19). This leads to increased susceptibility to infection, more frequent and prolonged episodes, increased severity of disease (20), reactivation of viral infections, and development of opportunistic infections (21). In addition, severe acute malnutrition often masks symptoms and signs of infectious diseases making prompt clinical diagnosis and early treatment very difficult. This in turn, increases the morbidity and mortality from communicable diseases (20). However, the contribution of bacteraemia to the morbidity and mortality among severely malnourished children is poorly investigated.

Bacteraemia can be caused by *Coagulase negative staphylococci* species, *S. aureus* and *Enterobacteriaceae* (22). Different studies in different countries demonstrated prevalence of bacteraemia in severely malnourished children from 11.8%-36% (23-28). The National Treatment Protocol for SAM recommends routine use of antibiotics for all children with SAM(29). Therefore, it is vital to regularly audit antibiotic sensitivity and the magnitude of bacteremia as the pattern could change due to various factors. The objective of this study was to establish the magnitude of bacteraemia in severely malnourished children, and describe the types of bacteria and antimicrobial sensitivity.

METHODS AND MATERIALS

A hospital based cross-sectional study was conducted in Jimma University hospital from October, 2009 to May, 2010. A total of 170 severely malnourished children who were below 14 years old were enrolled within 24 hrs. Children who took antibiotics within 15 days before admission and those with a length below 49 cm were excluded from the study. Patient's clinical history, physical examination and socio-demographic data of the children and parents/caretakers were recorded.

At enrollment, 2ml of venous blood from two different sites (cubital, dorsum of hand, leg or scalp) of peripheral vein were collected by experienced nurse from each study subject under aseptic condition and inoculated into two sterile

blood culture bottles containing 20 ml of brain-heart infusion broth (Oxoid, Ltd, England) and transported to the laboratory immediately (30,31).

The inoculated brain-heart infusion broth was incubated at 35°C and checked for growth after 24 hrs. Then, Gram staining of isolates was done from bottles with sign of bacterial growth and based on the gram reaction, isolates were subcultured either on to 7% sheep blood and chocolate agar (Oxoid, Ltd, England), MacConkey agar (Oxoid, Ltd, England) and Mannitol Salt Agar (MSA) (Oxoid, Ltd, England). The inoculated Blood, MacConkey and Mannitol Salt Agar media were incubated at 35°C for 24 hours under aerobic condition; however the chocolate media were incubated under 5% carbon dioxide (CO₂) with the same condition. Finally, culture bottles that did not show growth were further incubated for 7 days. If still no turbidity was observed a small portion of the culture broth was inoculated on the media listed above before being reported as negative.

The bacterial isolates were identified based on their Gram reaction, colony morphology and biochemical tests. Gram-positive cocci were identified by using biochemical tests such as catalase test, growth on Mannitol Salt Agar, Coagulase test, Mannitol fermentation, Novobiocin susceptibility, Bacitracin sensitivity, Bile esculin hydrolysis test (Oxoid, Ltd, England). However, Gram-negative bacteria were detected by using Oxidase test, Lysine decarboxylase test, Lactose fermentation, Glucose fermentation, Sucrose fermentation, Citrate test, Motility test, Indole test, Urease test, and Hydrogen sulphide production. Furthermore, *Salmonella* isolates were sero-grouped using polyvalent (O) (Oxoid, Ltd, England) and sero-group specific (O) (Oxoid, Ltd, England) antisera.

Antimicrobial susceptibility testing was performed using the disk diffusion method and results were interpreted based on the criteria of the National Committee for Clinical Laboratory Standards (NCCLS, 2000) (32). The antibiotics used for Gram positive were Ampicillin (AMP, 10 µg), Amoxycillin (AML, 20 µg), Chloramphenicol (C, 30 µg), Trimethoprim-Sulfamethoxazole (SXT, 1.25/23.75 µg),

Tetracycline (TE, 30 µg), Penicillin G (P, 10 IU), Gentamicin (CN, 10 µg), Cefalotin (KF, 30 µg), Ceftriaxone (CRO, 30 µg), Ciprofloxacin (CIP, 5 µg), Vancomycin (VA, 30 µg), Erythromycin (E, 15 µg), Oxacillin (OX, 1 µg) and Methicillin (M, 5 µg), whereas for Gram negative bacteria, Ampicillin (AMP, 10µg), Amoxycillin (AML, 20 µg), Chloramphenicol (C, 30 µg), Co-trimoxazole (SXT, 25 µg), Tetracycline (TE, 30 µg), Gentamicin (CN, 10 µg), Cefalotin (KF, 30 µg), Ceftriaxone (CRO, 30 µg), Ciprofloxacin (CIP, 5 µg) and Nalidixic Acid (NA, 30 µg) were used. All the antimicrobial disks were products of Oxoid, Ltd, England. The quality of the culture media, gram stain and potency of antimicrobial discs were checked using a standardized reference strain of *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923). Finally, data obtained from this study was entered to computer, analyzed using SPSS for windows version 16.0 and interpreted.

The study was approved by Jimma University ethics review board and informed consent was obtained from participants' parents/guardian before enrollment and received appropriate treatment.

RESULTS

Of the 170 severely malnourished children, 93 (54.7%) were males with male to female ratio of 1.26. Their age ranged from 1- 14 years where the median age was 2 4/12 years and the majority of the children (77.1%) were below 5 years. Among the study participants, 88 (51.8%) were presented with Marasmus, 69 (40%) with Kwashiorkor and 14 (8.2%) with Marasmic-Kwashiorkor. In addition, 33 (19.4%) were presented with fever, 82 (48.2%) with Bilateral pitting edema and 76 (44.7%) with Diarrhea.

Bacterial isolates: There were a total of 35 bacterial isolates (Table 1), where only single bacterium was isolated from each bacteremic child. Gram positive bacteria constituted 68.6% (24) of the total isolates and *Staphylococcus aureus* was the leading gram positive isolate followed by Coagulase negative staphylococci species (CNS species): *Streptococcus pyogenes*, *Bacillus* species and *Enterococcus* species, respectively. Gram negative bacteria constitute 31.4% (11/35) and of the total isolate *Klebsiella* species were the leading Gram negative isolates followed by *Salmonella* species, *Escherichia coli* and *Citrobacter* species, respectively. The three non-typhoidal *Salmonella* isolates were, *Salmonella enteritica* group D (2) and *Salmonella enteritica* group C₁ (1).

Table 1: Type and frequency of bacterial isolates from 35 severely malnourished children from October, 2009 to May, 2010, Jimma, Ethiopia

Gram reaction	Type of bacteria	Total(%)
Gram +ve n=24(68.6%)	<i>S.aureus</i>	10(28.6)
	CNS species	8(22.9)
	<i>S. pyogenes</i>	3(8.6)
	<i>Bacillus species</i>	2(5.7)
	<i>Enterococcus species</i>	1(2.9)
Gram -ve n=11(31.4%)	<i>Klebsiella species</i>	6(17.1)
	<i>Salmonella species</i>	3(8.6)
	<i>Escherichia coli</i>	1(2.9)
	<i>Citrobacter species</i>	1(2.9)
Total		35(100)

Table 2: Antimicrobial susceptibility result of bacterial isolates from severely malnourished children from October, 2009 to May 2010, Jimma, Ethiopia

Bacterial isolates	AMP	AML	CN	KF	CRO	CIP	SXT	TE	C	E	NA	P	OX	M	VA
<i>S. aureus</i> (n=10)	10 (100)	10 (100)	0 (0)	0 (0)	1 (10)	1 (10)	2 (20)	3 (30)	10 (100)	6 (60)	ND	10 (100)	10 (100)	10 (100)	3 (30)
CNS (n=8)	8 (100)	8 (100)	0 (0)	0 (0)	0 (0)	0 (0)	6 (75)	6 (75)	8 (100)	2 (25)	ND	8 (100)	8 (100)	8 (100)	2 (25)
<i>S. pyogenes</i> (n=3)	0 (0)	0 (0)	ND	ND	0 (0)	ND	ND	3 (100)	0 (0)	3 (100)	ND	0 (0)	ND	ND	ND
Enterococcus spp. (n=1)	1 (100)	0 (0)	1 (100)	ND	ND	ND	ND	1 (100)	1 (100)	0 (0)	ND	0 (0)	ND	ND	0 (0)
Klebsiella (n=6)	6 (100)	6 (100)	3 (50)	4 (66.7)	3 (50)	0 (0)	3 (50)	6 (100)	6 (100)	ND	0 (0)	ND	ND	ND	ND
Salmonella spp. (n=3)	1 (33.3)	1 (33.3)	ND	ND	1 (33.3)	0 (0)	0 (0)	2 (66.7)	1 (33.3)	ND	1 (33.3)	ND	ND	ND	ND
<i>E. coli</i> (n=1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	ND	ND	ND	ND	ND
Citrobactor (n=1)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	ND	0 (0)	ND	ND	ND	ND
Total	27/33 (82%)	26/33 (79%)	5/27 (19%)	5/26 (19%)	6/32 (19%)	1/29 (3%)	13/29 (45%)	22/33 (67%)	27/33 (82%)	11/23 (48%)	1/10 (10%)	18/22 (82%)	18/18 (100%)	18/18 (100%)	5/19 (26%)

Key: AMP=Ampicillin, AML=Amoxycillin, C=chloramphenicol, SXT=Trimethoprim-Salfamethoprim (Co-trimoxazole), TE=Tetracycline, P=Penicillin G, CN=Gentamicin, KF=Cephalothin, CRO=Ceftriaxone, CIP=Ciprofloxacin, VA=Vancomycin, E=Erythromycin, OX=Oxacillin, NT=Non tested, N=Number of isolates tested, T=Total number of isolates tested

Antimicrobial susceptibility Testing: The bacterial isolates were tested for 15 commonly prescribed antimicrobial agents. All the ten *Staphylococcus* species were resistant to Methicillin, Penicillin G and Chloramphenicol, while they were sensitive to Cephalothin and Gentamicin. In addition, 90% (9/10) of them were sensitive to Ceftriaxone and Ciprofloxacin, 70% to tetracycline and Vancomycin and 40% to Erythromycin. Whereas all the eight CNS species

were sensitive to Cephalothin, Ceftriaxone, Gentamicin and Ciprofloxacin and 75% (6/8) of them showed sensitivity for Vancomycin and Erythromycin and 25% (2/8) of them were sensitive to Tetracycline (Table 2). All the three *Streptococcus pyogenes* isolates were sensitive to Penicillin, Ampicillin, Ceftriaxone, Chloramphenicol and Vancomycin and they were resistant to Tetracycline and Erythromycin.

Table 3: Antibiogram showing resistance of isolates to one or more antibiotics from October, 2009 to May 2010, Jimma, Ethiopia.

Bacterial isolates (total No.)	Antimicrobial agents	No. of resistant species
<i>S. aureus</i> (10)	P,OX,C,AMP	10
	P,OX,C,AMP, E	2
	P,OX,C,AMP,CIP	3
	P,OX,C,AMP, TE	3
	P,OX,C,AMP, TE, SXT	2
	P, OX, C,AMP, TE, SXT,CIP,CRO	1
	<i>CNS species</i> (8)	P,OX,AMP
P,OX, AMP,C		6
P,OX,AMP,SXT		6
P,OX,AMP,TE		5
P,OX, AMP,C,SXT		5
P,OX, AMP,C,TE		5
P,OX, AMP,C,SXT,TE		2
P,OX, AMP,C,SXT,TE,E		1
<i>S. pyogenes</i> (3)	TE, E	3
<i>Enterococcus spp.</i> (1)	CN, C, TE	1
<i>Klebsiella spp.</i> (6)	AMP	6
	AMP, TE	5
	AMP, TE, C, KF	4
	AMP, TE, C, KF, CN, SXT	3
	AMP, TE, C, T E, CN, SXT, CRO	2
<i>Salmonella spp.</i> (3)	TE	2
	AMP, CRO, SXT, TE,C	1
<i>E. coli</i> (1)	SXT	1
<i>Citrobacter spp.</i> (1)	AMP, KF, CN, CRO, SXT, TE, C	1

Abbreviations are the same as described for the Table 2

All the six *Klebsiella* species were susceptible to Ciprofloxacin and Nalidixic acid, 50 % (3/6) to Conversely, all were resistant to Ampicillin, Chloramphenicol and tetracycline. Furthermore, all the three *Salmonella* isolates were sensitive to Ciprofloxacin and two of them were susceptible to Ampicillin, Ceftriaxone, Chloramphenicol, Trimethoprim-Sulfamethoxazole and Nalidixic acid, and one of them was only sensitive to Tetracycline.

Of all the isolates 86.7% were sensitive to Ciprofloxacin, 81.5% to Gentamicin, 81.2% to Ceftriaxone, 76.9% to Cephalothin, 51.7% to Trimethoprim-Sulfamethoxazole (Co-trimoxazole), 33.3% to Tetracycline, 21.2% to Ampicillin and 15.2% to Chloramphenicol (Table 2). From the total of 33 isolates tested for antimicrobial susceptibility, 30 (90.9%) were resistant for two or more antimicrobials (multi drug resistant) (Table 3).

DISCUSSION

Bacteraemia among severely malnourished children was poorly investigated and this study provides information about the common etiologic agents and their antimicrobial susceptibility pattern.

Bacteraemia can be caused by both Gram positive and Gram negative bacteria. Among the Gram positive bacteria *Coagulase negative staphylococci* species and *S. aureus* were common whereas *Enterobacteriaceae* were the most common among Gram negative isolates (22). Among the current study population 48.2% of the severely malnourished children had edematous malnutrition and 51.8% severe wasting, which is a with similar finding with the previous study done in Ethiopia (23) in 1992 and in Uganda in 2001 (25). In this study 21% of the participants had bacteraemia, which is lower than the previous report (36%) in Addis Ababa (23).

This study also revealed that Gram positive organisms, especially *Staphylococcus* species, were the predominant cause of bacteraemia (68.6%) in severely malnourished children, consistent to other reports (33) where they found 71% of their total isolates were Gram-positive

Gentamicin, Ceftriaxone and Trimethoprim-Sulfamethoxazole and 33.3% (2/6) to Cephalothin. bacteria. However, our current finding is different from previous findings in Ethiopia (23), Uganda (25, 28), Kenya (34) and South Africa (24). In our finding, the 68.6% prevalence of Gram-positive organisms suggests a change in the epidemiology from the predominant Gram-negative etiologies (up to 77%) described in previous reports. However, the reason for the predominance of *Staphylococcus aureus* in this study is not clear and warrants further study.

In the current study, CNS species were the second leading Gram positive bacteria following *Staphylococcus aureus*. Our finding shows CNS species are becoming great health problems and this agrees with von Eiff *et al* (35) statement “the proportion of all bloodstream infections caused by CNS and the overall incidence of true CNS bacteraemia is increasing”. These bacteria are normal inhabitants of human skin and mucous membranes and patients with CNS infections are usually immuno-compromised (36). The high bacteremia prevalence by CNS species in our study might be largely due to the suppressed immunological response of the severely malnourished children (11).

In our study, from the overall tested isolates, 86.7% were sensitive to Ciprofloxacin, 81.5% to Gentamicin, 81.2% to Ceftriaxone, 76.9% to Cephalothin, 51.7% to Trimethoprim-Sulfamethoxazole, 33.3% to Tetracycline, 21.2% to Ampicillin and 15.2% to Chloramphenicol. In support of our finding, Bachou *et al* (28) demonstrated high bacterial resistance to commonly used antibiotics such as Co-trimoxazole, Ampicillin and Chloramphenicol but more than 80% susceptibility to Ciprofloxacin, Ceftriaxone, and Gentamicin among the severely malnourished children. Increased resistance to Ampicillin, Trimethoprim-Sulfamethoxazole and Chloramphenicol was also demonstrated by Babirekere-iriso *et al* (25) in Uganda. The increased antimicrobial resistance documented in our finding might be related to the higher prevalence of self medication here in Jimma town and its surroundings (37, 38). The high rate of resistance to the routinely prescribed antimicrobials such as Amoxicillin raise great

concern as Amoxicillin, in combination with Gentamicin, is routinely given to children admitted with severe malnutrition to Jimma University specialized hospital (23). The best combination of antimicrobials in our finding was Gentamicin and Ciprofloxacin, although safety of quinolones is of concern. Some studies however, reported that the safety profile of ciprofloxacin in children is not substantially different from that of adults (39, 40).

In conclusion, bacteremia constitutes about 21% of the overall severely malnourished children visiting our hospital. Gram positive bacteria were the predominating organisms, with *Staphylococcus species* contributing for the high proportion followed by *Streptococcus pyogenes* which suggests a change in the epidemiology from the predominant Gram-negative etiologies. Moreover, there was high level of antimicrobial resistance to commonly used antibiotics, such as Amoxicillin, Trimethoprim-Sulfamethoxazole and Chloramphenicol but more than 80% susceptibility was documented to Gentamicin, Ciprofloxacin and Ceftriaxone. This calls for further studies to determine the most feasible combination of antibiotics for the management of bacteraemia in severely malnourished children in Ethiopia.

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