Burden associated with childhood bloodstream infection in a resource-constrained setting

***Folake Moriliat Afolayan[1], Mohammed Baba Abdulkadir[1,2], Bashirat Ayobola Olanipekun[3], Adedeji Nurudeen Lawal[3], Solomon Olubodunrin Ariyibi[1], Olayinka Rasheed Ibrahim[2], Harifarta Claphton Difirwiti[2], Olugbenga Ayodeji Mokuolu[1,2]**

Sri Lanka Journal of Child Health, 2023; **52**(1): 75-80
DOI: http://dx.doi.org/10.4038/sljch.v52i1.10477

Abstract

Background: In children, bloodstream infection (BSI) causes significant morbidity and mortality. Most studies in Nigeria focused on the aetiology of childhood BSI with little or no appraisal of burden.

Objectives: To determine the direct cost of childhood BSI, length of hospital stay, and deaths in a tertiary health facility in northcentral Nigeria.

Method: This prospective observational study was conducted in a tertiary hospital in Nigeria. We recruited children aged 0-14 years with the diagnosis of sepsis. Blood samples were collected and processed following standard microbiological techniques. The culture was performed using BacT/Alert machine. The direct costs of caregivers were obtained daily using receipts of all rendered services till outcome (discharged/death). This study's length of stay (LOS) was defined as the number of days the children stayed after admission prior to discharge/death.

Results: Of the 179 blood samples obtained, 91 (50.8%) had bacterial BSI. Gram-positive organisms were the commonest isolated pathogens (70.3%). The mean length of hospitalisation was significantly higher among children with BSI than those without BSI (10.24 ± 8.88 vs. 7.640 ± 5.825 days, p=0.034). Similarly, the mean cost was higher among those with BSI than those without BSI ($89.70±4.91 vs. $66.13±3.98, p <0.001). However, the mortality rate was comparable between those with BSI and without BSI (13.2% vs. 7.9% p=0.361).

Conclusions: This study showed that childhood BSI was associated with an increased direct cost, extended hospitalisation, and relatively high mortality.

(Key words: Bloodstream infections, Children, Length of stay, Mortality, Cost).

Introduction

Bloodstream infection (BSI) is the presence of viable infectious bacteria and fungi in the bloodstream that elicit an inflammatory response and is often accompanied by alteration of clinical, laboratory, and haemodynamic parameters[1]. It is a spectrum of inflammatory response that spans from systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multiple organ failure to death if not promptly managed.

BSI is one of the leading causes of morbidity and mortality, with an attendant increase in healthcare expenditure[2,3]. Childhood BSI remains a leading cause of sub-Saharan Africa's neonatal, infant, and under-five deaths[4,5]. Available reports show that BSI in sub-Saharan Africa is about 5-15% higher than in the United States of America (<1.5%), with mortality above 25%[6,7,8,9]. In sub-Saharan Africa, 17 to 29% of neonatal deaths are attributable to BSI, compared to 6% in high-income countries[10]. The BSI mortality rate could be as high as 52% in children admitted to the Paediatric Intensive Care Unit (PICU) compared with 6% for all other children[11]. In a systematic review on the length of hospitalisation (LOS) among children with hospital-acquired BSI, the mean attributable LOS ranged from 4 to 28 days, and a financial burden estimate of $10–$469[11].

In Nigeria, there is a paucity of data on the cost of childhood BSI, with the few available studies focusing on the aetiology and hospitalisation outcomes. Thus, we hypothesized that BSI was associated with increased direct cost, length of hospitalisation, and increased mortality.

[1]*Dept of Paediatrics, Faculty of Clinical Sciences, University of Ilorin, Nigeria*[2], *Dept of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria* [3]*Dept of Medical Microbiology & Parasitology, Faculty of Basic Clinical Sciences, University of Ilorin, Ilorin, Nigeria*
**Correspondence:* folakeafolayan@yahoo.com
https//orcid.org/0000-0003-4041-6564

(Received on 10 October 2022: Accepted after revision on 18 November 2022)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

Objectives

To determine the cost of BSI (direct cost of hospitalisation, the length of stay (LOS), and mortality rate among a cohort of children admitted with sepsis at a tertiary healthcare facility in north-central Nigeria.

Method

Study design and settings: This was a hospital-based prospective cross-sectional study that involved children admitted to the Neonatal Intensive Care Unit (NICU) and Emergency Paediatric Unit (EPU) of the University of Ilorin Teaching Hospital, Ilorin Kwara State from December 1st 2019-June 30th 2020, with a diagnosis of sepsis. The hospital is a tertiary health facility situated in Nigeria's North-Central geopolitical zone with a 650-bed capacity. NICU is a 40-bed capacity nursery with an annual admission of 1300. It provides level II care for a sick baby, while the EPU receives paediatric emergencies from health facilities within the state and surrounding areas.

Sample size estimation: We obtained the minimum sample size (179) for this study from Andrew Fishers' formula based on a previous year's prevalence of 13.5% among children with sepsis (obtained from the EPU register) at a power of 90% and a precision of 5.0%.

Study participants: Children enrolled in the study were aged 0-14 years with clinical and laboratory features of sepsis which included temperature >38^{0}C or <36^{0}C or temperature instability, tachycardia, bradycardia, tachypnoea, refusal to feed, vomiting, malaise, irritability, lethargy, bulging anterior fontanelle, convulsions, unconsciousness, failure to thrive, passage of watery stool, elevated leucocyte count (>20,000/cu mm) or reduced leucocytes (<4000/cu mm) or >25% immature neutrophil, thrombocytopenia (<100,000/cu mm)[14]. Children with complex congenital abnormalities, managed as out-patients, and children who died within 24 hours of admission were excluded from the study.

Data collection: A semi-structured proforma was used to obtain the history and socio-demographic information from the parents or caregivers. The clinical signs and symptoms, such as fever, abnormal jerky movement, poor feeding, loss of consciousness, fast breathing, difficulty breathing, vomiting and diarrhoea, were obtained from parents/ caregivers. The direct costs were measured as a combination of the costs of pharmaceuticals such as intravenous fluid, antibiotics and medical supplies, laboratory tests, hospital charges including medical procedures, utility, bed fees, discharge fees, transportation, and hotel costs incurred by the mother/ caregivers[15]. These were obtained from the caregiver using all purchasing receipts from the services. Verbal accounts of cost of transportation were obtained in cases where there were no receipts. BSI is a recognized bacterial pathogen isolated from a blood culture[1]. LOS was defined as the number of days the children stayed after admission before discharge/ death. We determined the extra length of stay and cost by subtracting the mean LOS and cost between those with and those without BSI. Each child recruited had blood samples collected for blood culture and complete blood counts. Complete blood count was analysed using an automated Sysmex XE 2100 (Sysmex Corporation, Kobe, Japan. The blood culture was analysed using the BacT/Alert 3D60 machine. Positive cultures were identified using standard microbiological methods, and susceptibility testing was performed using the standard Kirby-Bauer disc diffusion method. Susceptibility and resistance results were interpreted using Clinical and Laboratory Standards Institute criteria.

Outcomes measured: The primary outcomes of this study were the assessment of the direct cost, length of hospitalisation and mortality among children with BSI. The secondary outcomes were the comparison of the cost, length of hospitalisation and mortality, between the children with BSI and those without BSI.

Ethical issues: Approval for the study was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital, Nigeria (ERC PAN/2019/111961). All children recruited to the study had informed consent obtained from their respective caregivers after a detailed explanation of the study. This study was conducted in accordance with the declaration of Helsinki.

Statistical analysis: All the data obtained were imputed on a computer and analysed using the statistical package for social sciences (SPSS) version 21.0. Frequency distribution tables of discrete variables were generated. Means, standard deviations and range values (median with interquartile range for skewed data) were provided as appropriate. At the same time, continuous variables were subjected to Student t-test and Mann Whitney U as appropriate. A Chi-square test was used to test the significance of the difference between categorical variables. A p-value less than 0.05 was considered statistically significant.

Results

There were 1644 paediatric admissions between December 1st, 2019 and June 30th, 2020 and 179 had blood culture samples taken for analysis. The mean age of the children with BSI was 24.95±42.99 months (median 0.92 (IQR 0.06-36.00) months and 54.7% of the children were male. More children in

the lower socio-economic class had BSI (p=0.008), as shown in Table I.

The incidence of BSI was 50.8% (91/179). The BSI incidence was comparable in the neonatal [50.5% (47/93)] and post-neonatal [51.2% (44/86)] age groups. The mean length of hospital stay among children with BSI was 10.24±8.88 days [(median LOS of 9 (IQR-2-79)], which was significantly higher (p=0.034) than those without BSI 7.64±5.83 days [(median LOS 6 (IQR-2 -70)]. In addition, 56% of the children with BSI stayed longer (>seven days) in the hospital than those without BSI (p=0.020). Mortality of 13.2% was recorded among children with BSI, which was comparable to those without BSI (p=0.361) as shown in Table I.

Table I: ***Characteristics of children with or without bloodstream infection (BSI)***

Variable	Total *(n=179)*	BSI *(n= 91)*	No BSI *(n= 88)*	*p-value*
Mean age (months) - Mean ± SD	24.95 ± 42.93	20.12 ± 35.50	28.89 ± 49.22	0.130
Median age (months) – Median (IQR)	0.92 (0.06 -36.00)	0.92 (0.01-156.00)	0.61 (0.01-168.00)	0.975
Neonatal – n (%)	93 (52.0)	47 (51.6)	46 (52.3)	0.933
Post-neonatal – n (%)	86 (48.0)	44 (48.4)	42 (47.7)	
Gender – n (%)				
Male	97 (54.2)	54 (59.3)	43 (48.9)	0.160
Female	82 (45.8)	37 (40.7)	45 (51.3)	
Socio-economic class – n (%)				
Upper	21 (11.8)	04 (04.3)	17 (19.3)	
Middle	69 (38.5)	38 (41.8)	31 (35.2)	**0.008**
Lower	89 (49.7)	49 (53.9)	40 (45.5)	
Length of hospital stay				
Mean ± SD	8.86 ± 7.61	10.24 ± 8.88	7.64 ± 5.83	**0.034**
Median (IQR)	9 (2-79)	8 (2-70)	6 (2-41)	**0.015**
<7 days – *n (%)*	94 (52.5)	40 (44.0)	54 (61.4)	**0.020**
>7 days – *n (%)*	85 (47.5)	51 (56.0)	34 (36.6)	
Outcome – n (%)				
Discharged	154 (86.0)	75 (82.4)	79 (89.8)	
Dead	19 (10.6)	12 (13.2)	07 (07.9)	0.361
Discharged against medical advice	06 (03.4)	04 (04.4)	02 (02.3)	

SD: standard deviation, IQR: Interquartile range

Gram-positive organisms accounted for 70.3% (64/91) of the positive isolates, with *Staphylococcus aureus* responsible for 38.5% of the BSI. Similarly, the frequency analysis of Gram-negative pathogens showed that *Klebsiella* spp. accounted for 12.1% of the total isolates (Table 2)

Table 2: ***Causative microorganisms***

Microorganisms	**Bloodstream infections *(n= 91)*** **n (%)**
Gram positive organisms	**64 (70.3)**
Coagulase negative staphylococcus	18 (19.8)
Enterococcus spp.	06 (06.6)
Staphylococcus aureus	35 (38.5)
Streptococcus pneumoniae	03 (03.3)
Streptococcus viridans	02 (02.2)
Gram-negative organisms	**27 (29.7)**
Acinetobacter spp.	06 (06.6)
Escherichia coli	03 (03.3)
Klebsiella spp.	11 (12.1)
Pseudomonas aeruginosa	01 (01.1)
Salmonella typhi	06 (06.6)

The mean attributable direct cost of BSI was US$89.70±4.91, which was significantly higher (p<0.001**)** than those without BSI, US$66.13 ± 3.98, with a mean extra cost of US$23.57. The overall attributable mean direct cost of hospital charges was ($20.31±17.17), pharmaceutical ($30.03±26.62), laboratories ($23.52±13.23), and hotel/ transport charges ($9.07±14.09), as shown in Table 3. However, the mean attributable direct cost for pharmaceuticals and laboratories was significantly higher among children with BSI than those without BSI (p=<0.0001 and 0.004 respectively). The hospital charges and hotels/transport costs were comparable in those with or without BSI (Table 3)**.**

Table 3: ***Mean direct cost in patients with or without bloodstream infection (BSI)***

Variables	Total Mean ± SD	BSI Mean ± SD	No BSI Mean ± SD	*p-value*
Hospital charges ($)	20.31 ± 17.17	20.16 ± 8.42	20.46 ± 23.03	0.908
Pharmaceuticals ($)	30.03 ± 26.62	33.23 ± 28.13	21.70 ± 13.44	**<0.001**
Laboratory ($)	23.52 ± 13.23	26.29 ± 14.45	20.66 ± 11.22	**0.040**
Hotel /Transport ($)	9.07 ± 14.09	9.86 ± 12.53	8.24 ± 15.56	0.447
Total direct cost ($)	78.11 ± 43.96	89.70 ± 4.91	66.13 ± 3.98	**<0.001**

$-United State Dollar, Exchange rate at the study was 407 naira to 1$. SD-Standard deviation,

Discussion

Despite advances in diagnosing and treating bacterial infection, it remains a significant cause of paediatric morbidity and mortality, especially among neonates in low-middle income countries. Incidence of BSI varies globally. Our study shows an incidence of 50.8%. This is comparable to that reported in studies in the United States (46%)[16] and Central Asia (39%)[17] but higher than that from Cameroon (28.3%)[18], Nigeria (22%)[19] and Indonesia (20.2%)[20]. The relatively high incidence of BSI compared with some African studies may be attributable to the methodology and type of patients enrolled in this study. In this study, all positive blood cultures were considered true pathogens, unlike the Tanzania study[3], where children with *coagulase-negative staphylococcus* and children with prior antibiotics were excluded.

Though there is limited study on cost of analysis of BSI among children in sub-Saharan Africa, the mean direct cost of BSI in this study was $89.7, less than the $103.2 reported in Enugu, south-eastern Nigeria[21]. Also, cost of BSI was higher among those with BSI, with an average extra cost of $24.2. Further analysis in this study showed that increased cost was driven by cost of laboratory investigation and pharmaceutical costs. In contrast, the Enugu study showed that hospital and utility costs were responsible for the increased cost associated with BSI. In support of our findings is a study in the United States among children with BSI that showed both pharmaceutical and laboratory costs were significantly higher among children with BSI[15]. The relatively high laboratory and pharmacy expenditure cost observed in this study may be related to the need to purchase more antibiotics and supportive therapy like intravenous fluids from prolonged hospitalisation. In addition, presence of BSI may warrant further investigations that may increase laboratory expenditure during hospitalisation.

The burden of childhood BSI in most African countries is under-researched. Mean LOS among children with BSI in current study was comparable to that reported in Nigeria, Ghana, and a systematic review study on BSI among children and neonates[21-23]. In addition, LOS in children's BSI was an average of an extra 2.5 days. This finding is consistent with many previously reviewed studies from high- and low-middle-income countries[23,24]. This finding further buttresses a previous observation that morbidity associated with BSI results in long hospital stay. The prolonged hospitalisation will further result in an enormous economic burden.

In this study, mortality associated with BSI was 13.2%, comparable to that reported in South Africa (14.4%)[25] and Tanzania (14.2%)[14] but higher than that reported in Uganda (5.4%)[26] and lower than the Tanzania (37%)[3] study. The relatively high mortality among children with BSI in this study could be because the hospital is the referral centre for critically ill children in the state. Besides, most sick children present late to the hospital with advanced sepsis and a corresponding poor outcome.

Strengths of our study included it being a prospective one and analysis of the direct cost of BSI in resource-constrained settings. Our study has some limitations, which include being a single hospital-based study and findings may not reflect the whole country. Furthermore, the cost analysis was limited to periods from admission to outcome and we did not assess the indirect cost.

Conclusions

This study showed a high burden of childhood BSI, with an increased direct cost and length of hospitalisation. The presence of BSI was associated with an extra $24 in direct healthcare spending per child and an extra two and a half days of hospitalisation. In addition, BSI was associated with a relatively high mortality rate.

References

1. Viscoli C. Bloodstream infections: The peak of the iceberg. *Virulence* 2016; **7**(3): 248–51. https://doi.org/10.1080/21505594.2016.1152440 PMid: 26890622 PMCid: PMC4871637

2. Bhabhor H, Bhabhor U, Shingala H, Sinha M. Bacteriological study of bloodstream infection (BSI) in ICU patients. *Indian Journal of Microbiology Research* 2018; **5**(3): 368–73. https://doi.org/10.18231/23945478.2018.0077

3. Manyahi J, Kibwana U, Mgimba E, Majigo M. Multi-drug resistant bacteria predict mortality in bloodstream infection in a tertiary setting in Tanzania. *PLoS One* 2020; **15**(3): e0220424. https://doi.org/10.1371/journal.pone.0220424 PMid: 32130227 PMCid: PMC7055912

4. WHO. WHO | Child mortality and causes of death.

5. WHO. Newborns: improving survival and well-being. World Health Organisation, https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality (2020).

6. Moyo S, Aboud S, Kasubi M, Maselle SY. Bacteria isolated from bloodstream infections at a tertiary hospital in Dar es Salaam, Tanzania - antimicrobial resistance of isolates. *South African Medical Journal* 2010; **100**(12): 835-8. https://doi.org/10.7196/SAMJ.4186 PMid: 21414278

7. Seni J, Mwakyoma AA, Mashuda F, Marando R, Ahmed M, DeVinney R, *et al*. Deciphering risk factors for bloodstream infections, bacteria species and antimicrobial resistance profiles among children under five years of age in North-Western Tanzania: A multicentre study in a cascade of referral health care system. *BMC Pediatrics* 2019; **19**(1): 32. https://doi.org/10.1186/s12887-019-1411-0 PMid: 30684964 PMCid: PMC6347777

8. Blomberg B, Manji KP, Urassa WK, Tamim BS, Mwakagile DSM, Jureen R *et al.* Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infectious Diseases* 2007; **7**: 43. https://doi.org/10.1186/1471-2334-7-43 PMid: 17519011 PMCid: PMC1891109

9. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates the causes of death in children. *Lance*t 2005; **365**: 1147–52. https://doi.org/10.1016/S01406736(05)71877-8

10. Ranjeva S, Warf B, Schiff S. Economics burden of neonatal sepsis in sub-Saharan Africa. *BMC Global Health* 2018; **3**(1): e000347. https://doi.org/10.1136/bmjgh-2017-000347 PMid: 29564153 PMCid: PMC5859806

11. Grisaru-Soen G, Sweed Y, Lerner-Geva L, Hirsh-Yechezkel G, Boyko V, Vardi A, *et al.* Nosocomial bloodstream infections in a paediatric intensive care unit: a 3-year survey. *Medical Science Monitor* 2007; **13**: 251-7.

12. Primo MGB, Guilarde AO, Martelli CMT, Batista LJD, Turchi MD. Healthcare-associated *staphylococcus aureus* bloodstream infection: Length of stay, attributable mortality, and additional direct costs. *Brazilian Journal of Infectious Diseases* 2012; **16**(6): 503–9. https://doi.org/10.1016/j.bjid.2012.10.001 PMid: 23158266

13. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The Impact of methicillin resistance in *Staphylococcus aureus* bacteraemia on patient outcomes: Mortality, length of stay and hospital charges. *Infection Control and Hospital Epidemiology* 2005; **26**(2): 166–74. https://doi.org/10.1086/502522 PMid: 15756888

14. Kortz TB, Sawe HR, Murray B, Enanoria W, Matthay MA, Reynolds T. Clinical presentation and outcomes among children with sepsis presenting to a public tertiary hospital in Tanzania. *Frontiers in Pediatrics* 2017; **5**: 1. https://doi.org/10.3389/fped.2017.00278 PMid: 29312910 PMCid: PMC5743673

15. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in paediatric intensive care unit patients. *Pediatrics* 2005; **115**(4): 868–72. https://doi.org/10.1542/peds.2004-0256 PMid: 15805357

16. Larru B, Gong W, Vendetti N, Sullivan KV, Localio R, Zaoutis TE, *et al.* Bloodstream infections in hospitalized children: Epidemiology and antimicrobial susceptibilities. *Pediatric Infectious Disease Journal* 2016; **35**(5): 507–10.

https://doi.org/10.1097/INF.0000000000001057
PMid: 26766146

17. Kolesnichenko SI, Lavrinenko AV, Akhmaltdinova LL. Bloodstream infection aetiology among children and adults. *International Journal of Microbiology* 2021; **2021**: 6657134. https://doi.org/10.1155/2021/6657134 PMid: 33727928 PMCid: PMC7939735

18. Kamga HL, Njunda A, Nde P, Assob JCN, Nsagha DS, Waledji P. Prevalence of septicaemia and antibiotic sensitivity pattern of bacterial isolates at the University Teaching Hospital, Yaoundé, Cameroon. *African Journal of Clinical and Experimental Microbiology* 2011; **12**: 1. https://doi.org/10.4314/ajcem.v12i1.61037

19. Omoregie R, Egbe CA, Ogefere HO, Omijie R. Effects of gender and seasonal variation on the prevalence of bacterial septicaemia among young children in Benin City, Nigeria. *Libyan Journal of Medicine* 2009; **4**(3): 107-9. https://doi.org/10.4176/090206 PMid: 21483524 PMCid: PMC3066726

20. Rusmawatiningtyas D, Rahmawati A, Makrufardi F, Markrufardi N, Murni ID, Uiterwaal CSPM, *et al*. Factors associated with mortality of paediatric sepsis patients at the paediatric intensive care unit in a low-resource setting. *BMC Pediatrics* 2021; **21**: 471. https://doi.org/10.1186/s12887-021-02945-0 PMid: 34696763 PMCid: PMC8543407

21. Ekwochi U, Osuorah DC, Ndu IK, Ezenwosu OU, Amadi OF, Nwokoye IC, *et al*. Out-of-pocket cost of managing sick newborns in Enugu, Southeast Nigeria. *Clinico-Economics and Outcomes Research* 2014; **6**: 29–35. https://doi.org/10.2147/CEOR.S54674 PMid: 24470764 PMCid: PMC3896288

22. Karagiannidou S, Triantafyllou C, Zaoutis TE, Papaevangelou V, Maniadakis N, Kourlaba G. Length of stay, cost, and mortality of healthcare-acquired bloodstream infections in children and neonates: A systematic review and meta-analysis. *Infection Control and Hospital Epidemiology* 2020; **41**(3): 342-54. https://doi.org/10.1017/ice.2019.353 PMid: 31898557

23. Fenny AP, Otieku E, Labi KAK, Asante FA, Enemark U. Costs and extra length of stay because of neonatal bloodstream infection at a Teaching Hospital in Ghana. *Pharmaco-Economics Open* 2021; **5**(1): 111-20. https://doi.org/10.1007/s41669-020-00230-x PMid: 32940852 PMCid: PMC7895877

24. Mireya UA, Martí PO, Xavier KV, Cristina LO, Miguel MM, Magda CM. Nosocomial infections in paediatric and neonatal intensive care units. *Journal of Infection* 2007; **54**(3): 212-20. https://doi.org/10.1016/j.jinf.2006.03.023 PMid: 16678905

25. Lochan H, Pillay V, Bamford C, Nuttall J, Eley B. Bloodstream infections at a tertiary level paediatric hospital in South Africa. *BMC Infectious Diseases* 2017; **17**(1):750. https://doi.org/10.1186/s12879-017-2862-2 PMid: 29207958 PMCid: PMC5718141

26. Wiens MO, Larson CP, Kumbakumba E, Kissoon N, Ansermino JM, Singer J, *et al.* Application of sepsis definitions to paediatric patients admitted with suspected infections in Uganda. *Pediatric Critical Care Medicine* 2016; **17**(5): 400-5. https://doi.org/10.1097/PCC.0000000000000708 PMid: 27043996 PMCid: PMC5237844