Antibiotic Resistance in Children with Bacteremia Admitted in the Largest Tertiary Hospital in Rwanda

E. Ishimwe[1], T. Rogo [2]

1. Ministry of Health, Rwanda
2. Brown University Alpert School of Medicine, 222 Richmond St, Providence, RI 02903, USA

ABSTRACT

Background: Bacteremia is a common cause of morbidity and mortality in children. The causative bacteria and antibiotic sensitivities differ from region to region. Timely administration of effective antibiotics can be life-saving for septic patients, therefore it is important for clinicians to be aware of their local epidemiology when selecting empiric antibiotics for the treatment of bacteremia.

Objectives: The goal of this study was to describe the microbiology and antibiotic resistance patterns of bacteremia in the pediatric department of the University Teaching Hospital of Kigali (UTHK).

Methods: This was a retrospective descriptive study conducted from 1st January 2015 to 31st December 2015. All admitted children with a positive blood culture were included in the study.

Results: Eighty children were identified with positive blood cultures during the period of the study. The most commonly isolated bacteria were Klebsiella species (30%, 24/80), Staphylococcus aureus (27.5%, 22/80), and Escherichia coli (22.5%, 18/80). In terms of resistance patterns, 60.0% of S. aureus was resistant to oxacillin. Among Klebsiella species, 33.3% were resistant to cefotaxime, 77.3% to gentamicin, and 42.8% to ciprofloxacin. There was 100% resistance to ampicillin.

Conclusion: Klebsiella species, S. aureus, and E. coli account for 80% of the cases of bacteremia. Use of ampicillin combined with gentamicin or cefotaxime for empiric treatment of bacterial sepsis provides poor coverage in this pediatric department. Epidemiological surveillance must continue to track changes in antibiotic susceptibility patterns.

Key words (MeSH): Bacteremia, Children, antibacterial drug resistance

INTRODUCTION

The World Health Organization (WHO) reported progress in child survival worldwide as one of the success stories of international development, with child deaths reduced by half in the past two decades since the MDG (Millennium Development Goals) baseline. Despite the obvious achievements, 5.9 million children under 5 years old died in 2015 [1], roughly half of which died of infectious causes. Sepsis mortality has been reduced by antibiotics, but antimicrobial resistance is becoming a huge problem [2]. The changing bacteriological profile of bacteremia in children warrants review of the etiological pathogens and their drug susceptibility patterns [3].

In Sub-Saharan Africa, there is limited data on the microbiology and antibiotic sensitivity patterns of sepsis in children [4]. Sepsis is still a major cause of death, prolonged hospital stays and morbidity among children living in Sub-Saharan Africa. A study done in Kenya showed 25% of hospital deaths in children were due to community acquired bacteremia [4]. In Tanzania it was found that one-third (34.9%) of the children with laboratory confirmed bacteremia died [5]. Little is known about the prevalence of bacteremia in Rwandan children.

Anecdotally, in the pediatrics department at the largest tertiary level hospital in Rwanda (UTHK), there are many drug resistant infections but there have been no formal studies done to show the causes of sepsis in children ages 3 months to 15 years. A study done in the neonatology unit of the same facility as this study reported significant prevalence of drug resistant gram negative infections [6] . Resistance among gram-negative bacteria is now a key global concern. Multi-drug resistance (MDR) is increasing yet there is limited access to the antimicrobial agents needed to treat these infections in low-income countries [7].

The objectives of this study were to describe the causative organisms and antibiotic sensitivity profile of bacteremia in children older than 3 months admitted to the largest tertiary level hospital in Rwanda.

METHODS

This was a one-year retrospective study conducted from 1st January 2015 to 31st December 2015. The study was conducted at the University Teaching Hospital of Kigali (UTHK), the largest tertiary level hospital in Rwanda. The pediatric department has 8 wards, with approximately 2315 children admitted per year from district hospitals and surrounding private clinics.

The target population was all admitted children between 3 months old to 15 years old who had a positive blood culture. The population was enrolled by reviewing the microbiology records to find positive culture in the relevant age-group of patients. Patient records of this children were then reviewed. Admitted children with negative blood cultures and children on antibiotics with no cultures sent for testing were excluded.

It is standard practice at UTHK for blood cultures to be sent to the microbiology laboratory in culture medium bottles. Growth time is 7 days at 35 degrees Celsius. Blood culture bottles are manually examined daily for macroscopic evidence of microbial growth (e.g., hemolysis, turbidity of the media, gas production, or formation of discrete colonies). An aliquot of the contents of the aerobic bottle are gram stained and sub-cultured after the first overnight incubation. A terminal subculture was usually done at the end of the incubation period. The facility did not have an automated system during the period of data collection. Antibiotic susceptibility testing was performed

by disk diffusion (Kirby-Bauer testing) and interpreted per the Clinical and Laboratory Standards Institute (CLSI) standards.

Patient records were reviewed for demographic data, clinical presentation, comorbidities (such as surgery, burn, trauma, congenital heart disease, etc.), and clinical outcome (death or discharge home). The microbiologic data collected was species of bacterium and antibiotic susceptibility. The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23.0 (Armonk, NY: IBM Corp). Ethical clearance for this study was obtained from the UTHK research department prior to data collection.

RESULTS

There were 80 children with a positive blood culture during the study period (Table 1). Nineteen children (23.8%) died. Thirty-one children (38.8%) were treated empirically. Twenty (24%) received ampicillin combined with gentamicin, and 11 (13.75%) received cefotaxime as a monotherapy.

The most common isolated bacteria found were Klebsiella spp. (30%), S. aureus (27.5%), and E. coli (22.5%) (Table 2). There was only 1 isolate of Group B Streptococcus. Sixty percent of S. aureus isolates were resistant to oxacillin, and therefore classified as MRSA (Methicillin-resistant Staphylococcus aureus) (Table 3). 19% of S. aureus also had resistance to vancomycin, 7% had resistance to clindamycin, and no resistance to TMP-SMX was reported. All Klebsiella isolates had resistance to ampicillin, ceftazidime and cefuroxime; 77% to gentamicin; 43% to ciprofloxacin; and 33% to cefotaxime (Table 2). All E. coli isolates had resistance to ampicillin, 47% to cefotaxime, and 40% to gentamicin. There was no E. coli resistance to ciprofloxacin.

Overall, there were no gram-positive cocci (GPC) or gram-negative bacilli (GNB) sensitive to ampicillin (Table 4). When grouped together, GPC were 100% resistant to cefotaxime and gentamicin., while 69% of GNB had resistance to cefotaxime and 65% to gentamicin. Among all GNB, only 1 isolate was multi-drug resistant (MDR), defined as resistance to gentamicin, cefotaxime and ciprofloxacin.

DISCUSSION

Among children with bacteremia admitted at UTHK, 80% of the causative bacteria were Klebsiella spp., S. aureus, and E. coli. Sixty percent of tested S. aureus isolates were classified as MRSA. Gram negative bacilli constituted 65.1% of infections, and 69% were resistant to cefotaxime, and 65% were resistant to gentamicin, both of which are the most common gram-negative antibiotics used locally in septic children.

The high frequency of Klebsiella spp. and S. aureus correlates with other studies [6] [8]. Specifically in eastern African countries, a review found high levels of antimicrobial resistance (AMR) to commonly used antibiotics, including 50%-100% resistance to ampicillin, emerging resistance to gentamicin (20-47%), and relatively high levels of resistance to third generation cephalosporins (46-69%) among gram-negative infections [9]. Moreover, most of the resistance was reported to be among Klebsiella spp. and E. coli. Among Gram-positive infections, 100% resistance was reported to ampicillin which is similar to this study; however we report a much higher level of MRSA (60%) compared to 2.6%-4% reported in a review of articles from the East African regions [9].

The Rwanda national pediatric guidelines recommend cefotaxime or ceftriaxone as the first line treatment for septicemia [10] but our results show that only 41% of all gram-negative bacilli were sensitive to these drugs. For pneumonia, the national guidelines recommend the use of ampicillin and gentamicin, but our study results show that gram-positive cocci are 100% resistant to ampicillin and gentamicin. Granted, we are reporting on hospitalized patients with bacteremia so our antibiogram may not necessarily reflect the epidemiology of community-acquired pneumonia in Rwanda. Furthermore, not all children with pneumonia have bacteremia, so further studies need to be done on the antibiotic sensitivity of respiratory pathogens in admitted children in this setting. Overall, these results suggest that current empiric antibiotic guidelines provide inadequate coverage for bacteremia in our setting, and this is likely the key contributor to the mortality rate of 23.8% in this study. Based on the high rate of MRSA and the significant gram-negative resistance rates to cephalosporins and aminoglycoside, the best empiric antibiotic regimen for a child older than 3 months admitted with suspected sepsis at would be vancomycin combined with a carbapenem.

This study had 2 major limitations. First, there was intermittent stock-out of some antibiotic disks, leading to inconsistent reporting of antibiograms. Second, the isolates per species of organism were not enough for every bacteria, as CLSI recommends a minimum of 10 isolates per species of organism for an antibiogram to be very effective [11].

CONCLUSION

We report a high level of antibiotic resistance in children with bacteremia at the largest tertiary hospital in Rwanda. Based on the study antibiogram, empiric use of ampicillin with gentamicin or cefotaxime/ceftriaxone as recommended by the national guidelines provides poor coverage. There is universal resistance to ampicillin, therefore it should not be used for empiric treatment of bacterial sepsis in Rwandan children. Epidemiological surveillance must continue to track changes in antibiotic susceptibility patterns.

Table 1: Characteristics of children with bacteremia admitted at the University Teaching Hospital of Kigali. (N=80)

Sex	Male	37 (46%)
	Female	43 (54%)
Patient's origin	Kigali	34 (42.3%)
	East Province	23 (28.7%)
	North province	9 (11.3%)
	South province	8 (10%)
	West province	6 (7.5%)
Referred from	District hospital	59 (74%)
	Private clinic	12 (15%)
	Others	9 (11%)
Age (months)	3-12 months	50 (63%)
	>12 months	30 (37%)
Comorbidities	Malnutrition	30 (37.5%)
	Infection other than bacteremia	35(43.8%)
	Hematologic diagnosis*	24 (30%)

Legend: * Most common was anemia

Table 2: Organisms isolated from children with bacteremia admitted at the University Teaching Hospital of Kigali.

Organism	Frequency
Klebsiella spp.	24 (30%)
Staphylococcus aureus	22 (27.5%)
Escherichia coli	18 (22.5%)
Acinobacter spp.	5 (6.3%)
Proteus spp.	3 (3.8%)
Salmonella typhi	3 (3.8%)
Pseudomonas aeroginosa	2 (2.5%)
Streptococcus spp.	2 (2.5%)
Group B *streptococcus*	1 (1.3%)
Total	**80 (100%)**

Table 3: Antibiotic resistance of organisms isolated from children with bacteremia admitted at the University Teaching Hospital of Kigali.

Antibiotic	Streptococcus sp. **	S. aureus *	GBS***	Klebsiella sp.	Proteus sp.	Pseudomonas aerugino sa	Acinetobacter	E. coli	Salmonella typhi
Penicillin	100	89	100	50	0	n/a	100	0	0
Ampicillin	100	100	0	100	100	n/a	100	100	0
Oxacillin	0	60	0	0	0	n/a	0	0	0
amoxicillin	0	100	0	100	0	n/a	0	3	0
Piperacillin	0	0	0	1	0	25	12	0	0
Amoxicillin-clavulanate	0	0	0	18	67	n/a	0	17	10
ceftazidime	0	0	0	100	11	50	67	15	0
Cefotaxime	0	0	0	33	0	n/a	0	47	50
Cefuroxime	0	7	0	100	67	n/a	0	2	100
Vancomycin	50	19	100	n/a	n/a	n/a	n/a	n/a	n/a
Clindamycin	0	7	100	n/a	n/a	n/a	n/a	n/a	n/a
Gentamicin	0	100	0	77	0	0	40	40	100
Amikacin	0	0	0	23	0	0	0	44	0
Ciprofloxacin	0	0	0	43	0	0	0	0	0
Pefloxacin	0	7	0	27	0	0	12	2	0
Tetracycline	0	10	0	0	0	0	0	2	0
Erythromycin	50	62	100	0	0	n/a	n/a	0	0
TMP-SMX	100	0	0	100	50	n/a	0	4	10
Chloramphenicol	0	0	0	1	11	0	0	9	67

Note that the percentage reported is the resistance of the tested bacteria of each species.

Legend: *15 of 22 isolates were the only ones tested for Oxacillin sensitivity; ** 2 isolates found;
*** Only one isolate found; n/a – not applicable

Table 4: Overall antibiotic RESISTANCE of gram-positive cocci and gram-negative bacilli isolated from children with bacteremia at the University Teaching Hospital of Kigali.

Antibiotics	Gram positive cocci	Gram negative bacilli
Ampicillin	100%	100%
Oxacillin	60%*	-
Cefotaxime	100%**	69%
Ciprofloxacin	0%	27%
Gentamycin	100%	65%
Amikacin	-	23%

Legend: * only S. aureus was tested for Oxacillin ** for Streptococcus species and GBS

Correspondence. *ielicien@gmail.com ; Ministry of Health, Kigali, Rwanda*
Potential Conflicts of Interest (CoI). All authors: *no potential conflicts of interest disclosed.*
Funding. *All authors: no funding was disclosed.*
Academic Integrity. *All authors: confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE.*
Acknowledgments: *We would like to thank lab technicians in University Teaching Hospital of Kigali who helped us in collection of data.*
Ethics of human subject participation: *The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable.*
Originality: All authors: *this manuscript is original has not been published elsewhere*
Type-editor: *Sean Batenhorst (USA)*
Review: *This manuscript was peer-reviewed by 3 reviewers in a double-blind review process.*

REFERENCES

1. World Health Organization. Children: reducing mortality [Internet]. 2017 [cited 1 June 2017]. Available from: http://www.who.int/mediacentre/factsheets/fs178/en/

2. Vlieghe E, Phoba M, Tamfun J, Jacobs J. Antibiotic resistance among bacterial pathogens in Central Africa: a review of the published literature between 1955 and 2008. Int J Antimicrob Agents. 2009;34(4):295-303.

3. Tariq T. Bacteriologic profile and antibiogram of blood culture isolates from a children's hospital in Kabul. J Coll Physicians Surg Pak. 2014;24(6):396-399.

4. Berkley J, Lowe B, Mwangi I, Williams T, Bauni E, Mwarumba S et al. Bacteremia among Children Admitted to a Rural Hospital in Kenya. New England Journal of Medicine. 2005;352(1):39-47.

5. Bloomberg B. Antimicrobial resistance in bacterial infections in urban and rural Tanzania [PhD]. University of Bergen; 2007.

6. Rogo T, Habimana R, Chow B, McCulloh R. Bacteria resistant for neonatal sepsis in Rwanda High incidence of bacteria resistant to WHO recommended empiric antibiotics for neonatal sepsis at a tertiary level neonatology unit in Rwanda. Rwanda Medical Journal. 2016;73(2):10-14.

7. Le Doare K, Bielicki J, Heath P, Sharland M. Systematic Review of Antibiotic Resistance Rates Among Gram-Negative Bacteria in Children With Sepsis in Resource-Limited Countries. J Pediatric Infect Dis Soc. 2014;4(1):11-20.

8. Perez G, Martiren S, Reijtman V, Romero R, Mastroianni A, Casimir L et al. Community-acquired Staphylococcus aureus bacteremia in children: a cohort study for 2010-2014. Arch Argent Pediatr. 2016;114(6):508-513.

9. Ampaire L, Muhindo A, Orikiriza P, Mwanga-Amumpaire J, Bebell L, Boum Y. A review of antimicrobial resistance in East Africa. African Journal of Laboratory Medicine. 2016;5(1):432.

10. Rwanda Ministry of Health. Pediatric clinical treatment guidelines [Internet]. 2012 [cited 1 June 2017]. Available from: http://www.moh.gov.rw/fileadmin/templates/Clinical/Pediatrics-National-Clinical-Treatment-Guideline-ok-version-after-corrections.pdf

11. Wyoming Department of Health. Burke K. Section 12: Antibiotic Stewardship - Wyoming Department of Health [Internet]. 2014 [cited 1 June 2017]. Available from: https://health.wyo.gov/publichealth/infectious-disease-epidemiology-unit/healthcare-associated-infections/infection-prevention-orientation-manual/antibiotic-stewardship/