HIGH INCIDENCE OF BACTERIA RESISTANT TO WHO RECOMMENDED EMPIRIC ANTIBIOTICS FOR NEONATAL SEPSIS AT A TERTIARY LEVEL NEONATOLOGY UNIT IN RWANDA

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ABSTRACT

Background: In Western countries, one of the leading causes of neonatal sepsis is Group B *Streptococcus* (GBS), which appears to be different from resource-limited countries, where gram negative bacilli (GNB) are reported to be more common. The aim of this study is to describe the bacterial causes of neonatal sepsis in the largest tertiary referral hospital in Rwanda.

Methods: A retrospective review was done of neonates admitted for neonatal sepsis from 1st January 2013-31st December 2013. Data collected included demographics, risk factors for sepsis, microbiologic culture results, and clinical outcomes.

Results: There were 128 neonates with positive bacterial cultures. *Klebsiella* spp. were the most frequent bacteria isolated (37%, 47/128), followed by Coagulase-negative Staphylococcus (29.7%, 38/128). No gram positive cocci were susceptible to ampicillin and only 18% were susceptible to oxacillin. No GNB were susceptible to ampicillin, and only 11% and 13% were susceptible to cefotaxime and gentamicin, respectively. Birth at a district hospital was associated with infection with methicillin-resistant *Staphylococcus aureus* (P=0.02) and multi-drug resistant GNB (P=0.045). Twenty-five percent of neonates died.

Conclusions: Empiric treatment of neonatal sepsis with ampicillin combined with gentamicin or cefotaxime provided poor coverage of bacterial infections in the neonatology unit of this tertiary teaching hospital in East Africa. Revised empirical antibiotic guidelines are needed to minimize the risk of death due to neonatal sepsis in this patient population.

Keywords: neonatal sepsis, antibiotic resistance

RESUME

Contexte : Dans les pays occidentaux, le streptocoque du groupe B représente l'une de principales causes d'infection néonatale, contrairement aux pays en voie de développement où, les bactéries à gram négatifs sont majoritaires. L'objectif principal de cette étude est de décrire les différentes causes d'infections bactériennes chez le nouveau-né dans le plus important hôpital de référence tertiaire au Rwanda.

Méthodes: Nous avons effectué une étude rétrospective des nouveaux-nés hospitalisés pour infection néonatale au cours de l'année 2013. Les informations recueillies, pour chaque nouveau-né, comprenaient les données démographiques, les facteurs de risques de septicémie, les résultats des cultures microbiologiques, et l'issue clinique.

Résultats: Nous avons confirmé 128 cas de culture bactérienne positive. Le germe le plus identifié a été Klebsiella spp (37%, 47/128), suivi par le Staphylocoque à coagulase négative (29,7%, 38/128). Aucun cocci gram positif n'a été sensible à l'ampicilline et seulement 18% étaient sensibles à l'oxacilline. Aucune bacterie à gram négatif n'a été sensible à l'ampicilline, et seulement 11% et 13% étaient sensibles au céfotaxime et à la gentamicine, respectivement. La naissance dans un hôpital de district a été associé à l'infection par le staphylocoque doré résistant à la méthicilline (P = 0,02) et les bactéries à gram négatif multirésistantes (P = 0,045). Vingt-cinq pour cent de nouveaux-nés sont décédés.

Conclusions: Le traitement empirique de la septicémie néonatale avec l'ampicilline combinée à la gentamicine ou céfotaxime n'a pas fourni une couverture adéquate des infections bactériennes dans l'unité de néonatologie de cet hôpital d'enseignement supérieur en Afrique de l'Est. Il est nécessaire de réviser les directives sur le choix d'antibiotiques empiriques pour réduire le taux de décès dû à l'infection néonatale.

Keywords: septicémie néonatale, résistance aux antibiotiques

INTRODUCTION

Neonatal sepsis results in nearly half a million deaths per year, most of which occur in resource-limited settings [1]. Neonatal mortality in Rwanda is 20 per 1000 live births, with neonatal infection being the third leading cause of neonatal mortality, after prematurity and birth asphyxia [2].

Bacterial causes of neonatal sepsis differ significantly between high and low-resource settings. Group B Streptococcus (GBS) is the leading cause of neonatal sepsis in high-resource countries, but it accounts for only 2% of neonatal sepsis cases in developing countries, where most cases of neonatal bacterial sepsis are caused by S. aureus, E. coli, and Klebsiella spp. [3]. Additionally, antibiotic resistance among gram negative bacteria is increasing in Africa [4–6].

Anecdotally, Klebsiella spp. have been reported to be a frequent cause of bacterial sepsis in the neonatology unit of the University Teaching Hospital of Kigali (UTHK) but there have been no formal studies. Frequently reported multi-drug resistant (MDR) gram negative bacilli (GNB) have prompted pediatricians to use ciprofloxacin empirically, instead of or in addition to ampicillin combined with gentamicin, the empirical antibiotic regimen recommended by WHO and Rwanda national neonatology protocols [7,8]. The aim of this study is to describe the bacterial causes of neonatal sepsis in the largest tertiary referral hospital in Rwanda and their antibiotic susceptibility patterns.

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METHODS

A retrospective chart review was conducted from January 1 2013 to December 31 2013 in the neonatology unit of the University Teaching Hospital of Kigali (UTHK). UTHK is located in the capital city of Kigali and is the largest tertiary referral hospital in Rwanda, where it also serves as a teaching hospital for the University of Rwanda. Eligible records were identified through review of all positive bacterial culture results from urine, blood, and cerebrospinal fluid (CSF) from neonates treated with antibiotics for presumptive sepsis. Neonates without positive cultures were excluded. Data collected included demographics, treatment, microbiology results, and clinical outcomes. Antibacterial susceptibility testing was performed by Kirby-Bauer disk diffusion and interpreted according to the Clinical and Laboratory Standards Institute (CLSI). Bacterial isolates were not consistently tested for the same antibiotics due to intermittent stock-outs of antibiotics disks. Data was analyzed using SPSS version 16 (IBM, Armonk, NY) and SAS version 9.3 (SAS Institute, Cary, NC). This study was approved by the UTHK Research Committee and University of Rwanda College of Medicine and Health Sciences institutional review board.

RESULTS

One hundred and twenty eight neonates with neonatal sepsis had positive cultures. All 128 had blood cultures done, of which 120 were positive; 22 had urine cultures of which 6 were positive; and 3 had CSF cultures of which 2 were positive. Fifty-two percent were male; 40% were premature; 59% had low birth weight; 82% had early-onset sepsis; and only 3% had maternal fever reported (Table 1). Twenty-five percent of these neonates died.

Table 1. Characteristics of neonates with positive cultures

		N=128 (%)
Sex	Male	66 (52)
	Female	62 (48)
Gestational age	<37 weeks	51 (40)
	≥37 weeks	77 (60)
Birth weight	<2.5kg	75 (59)
	≥2.5kg	53 (41)
Place of birth	District hospital	68 (53)
	UTHK[1]	60 (47)
Mode of delivery	SVD[2]	75 (59)
	C/S[3]	53 (41)
Duration of ROM[4]	<18 hours	67 (52)
	≥ 18 hours	61 (48)
Maternal fever	Present	4 (3)
	Not present	95 (74)
	Unknown	28 (22)
Type of sepsis	Early-onset	105 (82)
	Late-onset	23 (18)

Legend: 1. University Teaching Hospital of Kigali; 2. Spontaneous vaginal delivery; 3. Caesarean section; 4. Rupture of membranes

Table 2. Bacteria isolated from neonates with sepsis.

Isolated bacteria	N=128 (%)
Klebsiella spp.	47 (37)
Coagulase negative Staphylococcus	38 (30)
Staphylococcus aureus	30 (23)
Escherichia coli	6 (4.7)
Acinetobacter spp.	3 (2.3)
Pseudomonas spp.	2 (1.6)
Citrobacter spp.	1 (0.8)
Group B Streptococcus	1 (0.8)

The most common bacteria isolated were Klebsiella spp. (37%), followed by coagulase negative *Staphylococcus* (CoNS) (30%) (Table 2). Only one isolate grew GBS. No Listeria was reported.

Among *Klebsiella* spp., only 14% were susceptible to gentamicin, 33% to cefotaxime, and 41% to ciprofloxacin (Table 3). Only half of CoNS and S. aureus isolates were tested for oxacillin sensitivity – 50% of these were resistant to oxacillin. Only 3 GNB isolates were MDR (defined as resistance to gentamicin, cefotaxime, and ciprofloxacin).

Table 3. Antibiotic sensitivities of isolates from neonates with sepsis.

	Percent of isolates sensitive to drug						
Antibiotic	**GBS***	***E. Coli***	***Acinetobacter***	**CoNS**	***S. aureus*******	***Klebsiella***	***Pseudomonas***
Penicillin	100	0	0	50	36	7	0
Ampicillin	0	0	0	n/a	n/a	0	0
Oxacillin	0	0	0	50	50	0	0
Piperacillin	0	33	0	0	33	0	33
Gentamicin	0	0	29	0	43	14	14
Amikacin	0	36	0	0	0	64	0
Cefuroxime	0	0	50	0	0	50	0
Ceftazidime	0	13	13	0	0	63	13
Cefotaxime	0	33	33	0	0	33	0
Ciprofloxacin	0	0	2	30	24	41	2
Erythromycin	0	0	0	50	47	3	0
TMP-SMX#	0	0	0	25	50	25	0
Chloramphenicol	0	0	0	33	0	67	0

Legend: * only 1 isolate; ** only 15 of 30 isolates tested for oxacillin sensitivity; # Trimethoprim-sulfamethexazole.

Table 4. Antibiotic sensitivities of gram positive cocci and gram negative bacilli.

Antibiotic	Gram positive cocci	Gram negative bacilli
Oxacillin	18%	-
Ampicillin	0	0
Erythromycin	48%	-
Ciprofloxacin	69%	78%
TMP-SMX[1]	26%	20%
Gentamicin	-	13%
Amikacin	-	79%
Cefotaxime	-	11%

Legend: 1. Trimethoprim-sulfamethoxazole.

When grouped together, no gram positive cocci (GPC) were susceptible to ampicillin and only 18% to oxacillin when susceptibilities were performed (Table 4). No GNB were sensitive to ampicillin, and only 11% and 13% were sensitive to cefotaxime and gentamicin respectively.

We analyzed if the following factors had an association with having MRSA (methicillin-resistant S. aureus) or MDR GNB infection: gestational age <34 weeks, male sex, birth weight category, born in district hospital (DH), cesarean delivery, maternal fever/infection, infant surgery, and intravascular catheter > 7 days. Only DH birth had a significant association for both MRSA (p=0.02) and MDR GNB (p=0.045).

DISCUSSION

In this study we report on the epidemiology of bacterial sepsis in neonates in the largest tertiary referral hospital in Rwanda. One-quarter of neonates with invasive bacterial infections died. Forty-six percent of bacterial isolates were GNB, of which Klebsiella spp. were the most common. Only 14% of Klebsiella spp. were susceptible to gentamicin, and 33% to cefotaxime. GPC caused 54% of infections, the most common of which was CoNS. No isolates were susceptible to ampicillin. Half of tested CoNS and S. aureus isolates were resistant to oxacillin.

The predominance of Klebsiella spp., CoNS, and S. aureus is similarly reported in other studies performed in East Africa [5,6]. Looking broadly at antibiotic susceptibilities of GPC and GNB (Table 4), it is very apparent that ampicillin, gentamicin, and cefotaxime do not provide adequate empirical coverage for neonatal bacterial sepsis in our setting. This significant mismatch between the recommended empirical antibiotics and the local antibiotic susceptibilities is likely the main contributor to the 25% mortality in neonates in our cohort. The antibiogram we report suggests that vancomycin should be combined with ciprofloxacin and/or amikacin for improved empirical coverage [9]. However, there are limited published data on the pharmacokinetics of ciprofloxacin in neonates [10]. Carbapenems are not readily available in this setting, and are prohibitively expensive when they are available.

Majority of the neonates had early-onset sepsis (EOS), defined as occurring before day 7 of life. EOS is supposed to be largely due to maternal vaginal colonization which raises the question of whether the mothers may have had vaginal colonization with drug resistant organisms (majority of the neonates were born via vaginal delivery) [11,12]. There was also only one isolate reported with GBS, further suggesting that maternal vaginal colonization may be different in this setting. However the only factor found to be associated with MRSA and MDR GNB infection was delivery at the district hospital, which may represent a bias towards sicker infants referred to UTHK. More research is needed to examine if some of these infections are hospital-acquired prior to referral [13]. There have been outbreaks of MDR Klebsiella in several tertiary neonatology units in Rwanda [14].

Our results have significant limitations. In the microbiology laboratory, antibiotic discs are frequently out of stock, resulting in only partial susceptibility testing for many isolates. Antibiograms do not consistently report the same drugs for susceptibilities (for example, half the S. aureus isolates were not tested for oxacillin susceptibility). In addition, there was a period when vancomycin resistance was reported for Staphylococcus isolates but it was subsequently discovered that the vancomycin discs were expired. Therefore we excluded vancomycin from the antibiograms reported in Tables 3 and 4. There is also no testing for extended-spectrum beta-lactamase (ESBL).

However these results give an idea of an alarming picture of antibiotic resistance among neonates, particularly in a setting where access to microbiology is limited.

This study adds to emerging reports of drug resistance in neonatology units in resource-limited countries. More research is needed to ascertain the etiology and mechanisms of drug resistance in these settings. Neonatology units in developing countries should attempt to investigate their local epidemiology and tailor empiric antibiotic recommendations accordingly.

CONCLUSION

In this tertiary level neonatology unit in Rwanda, no isolated bacteria were susceptible to ampicillin, and only 11% and 13% were susceptible to cefotaxime and gentamicin respectively. Therefore neonatology units should take steps to ascertain their local epidemiology and adjust empiric antibiotic choices accordingly.

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