Rwanda Medical Journal RMJ

ORIGINAL RESEARCH Open access

Neonatal antibiotic use at a district and teaching hospital in Rwanda – a retrospective descriptive study

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ABSTRACT

INTRODUCTION: Infection remains a significant cause of death in the neonatal period. Antibiotics are lifesaving in genuine infection but have been shown to be detrimental if overused in neonates who have no evidence of infection. This study aims to describe baseline length and choice of antibiotic used in a district and referral teaching hospital neonatal unit in Kigali, Rwanda.

METHODS: A retrospective, descriptive chart review was conducted among neonates admitted from January 2015 to December 2017 to Neonatology Units at Muhima District Hospital (MHD) and University Teaching Hospital of Kigali (UTHK).

RESULTS: Convenience sampling was used to identify 178 neonates who were enrolled from MDH (n=112) and UTHK (n=66). 88% of neonates received antibiotics, for a median of 6 days. Neonates spent a mean of 72% of their admission-period on intravenous antibiotics. The most common first-line antibiotics were ampicillin (100%) and gentamicin (97%). Blood cultures were ordered in 70 cases (41.2%) and a positive culture was found in 16 cases, with Klebsiella species and Staphylococcus aureus the only organisms cultured.

CONCLUSION: Infection remains a significant problem for neonates. With increasing challenges from antibiotic resistance, the results of this study demonstrate the need for antibiotic stewardship programs in Rwandan Neonatology Units.

Keywords (MeSH): Anti-Bacterial agents; Neonatal Sepsis; Sepsis; Infant mortality; Neonatal Intensive Care Units; Africa; Rwanda

INTRODUCTION

Each year there are 2.9 million neonatal deaths globally, representing almost half (44%) of all under-five deaths [1], [2]. Ninety-eight percent of these deaths occur in resource-limited countries [2]. The most common causes of neonatal mortality are prematurity, low-birth-weight, infections, asphyxia and birth trauma [3]. Globally, sepsis continues to be a significant cause of neonatal mortality accounting for 13.6% of deaths in 2000 rising modestly to 15% in 2015 [4]. In Rwanda, overall neonatal mortality has fallen dramatically from 38 deaths per 1000 births in 2002 to 17.1 deaths per 1000 in 2015 [4]. Mortality from neonatal sepsis in Rwanda (29% of deaths) remains significantly above the global trend (15%) and is the second most common cause of neonatal death after prematurity [3].

Antibiotic choice should reflect the likely causative organisms. Causative agents of early-onset sepsis (EOS, <72 hours of life) and late-onset sepsis (LOS) in resource-limited countries differ from those in resource-rich countries [2]. The WHO advocates empirical antibiotics in neonates at risk or those with signs of infection. Antibiotics in these situations are potentially life-saving in neonates with infection. A study in Rwanda found that the most common organisms isolated were Klebsiella spp. (37%) and Coagulase Negative Staphylococcus (CoNS) (30%). Only one isolate grew Group B streptococcus (GBS), and no Listeria was identified [5]. This study found no organisms (0%) which were sensitive to ampicillin. Among Klebsiella spp only 14% were susceptible to gentamicin, 33% to cefotaxime, and 41% to ciprofloxacin [5].

Antimicrobial resistance (AMR) is an alarming and rapidly developing global threat highlighted by national governments and public health bodies such as the World Health Organization (WHO) [6]. The development and transmission of multi-drug resistant (MDR) bacteria pose a serious threat to the care of neonates in the future [7].

Corresponding author: Peter Cartledge- peterthomascartledge@gmail.com; **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; **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**: insert here. **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process;

Original submission: 19th December 2017**; Original decision:** 15th February 2018**; Revised submission:** 13th July 2018**; Revised submission accepted:** 22nd October 2018

 Publisher: Rwanda Biomedical Centre (RBC)/Rwanda Health Communication Center, P.O.Box 4586, Kigali.

ISSN: 2079-097X (print); 2410-8626 (online)

Citation for this article: R. Ndayizeye, E. Sibomana, I. Nyaziyose, et al., Neonatal antibiotic use at a district and teaching hospital in Rwanda – a retrospective descriptive study. *Rwanda Medical Journal, Vol 76, no 2, pp 1-6, 2019*

There are currently insufficient clinical trials being undertaken to address the need for new antibiotics or new antibiotic regimens [8]. Therefore, today's generation of clinicians has a responsibility to use antibiotics responsibly and conserve antibiotics as a finite resource [9]. In Rwanda, resistance to antibiotics is a growing problem in pediatric and neonatal services [5], [10].

The term "antibiotic stewardship" is used to encompass initiatives promoting the responsible use of antibiotics, with the goal of preserving their future effectiveness whilst safeguarding public health [11]. Antibiotics are lifesaving in genuine infection, and therefore premature neonates are almost universally started on empirical antibiotics after birth because of the risk of infection [12]. Starting antibiotics is good practice and can be lifesaving; however, knowing when to stop antibiotics is more of a challenge. When there is no clinical or microbiological evidence of infection, prolonged duration of empirical antibiotics is associated with adverse neonatal outcomes. For example, studies in the USA have explored outcomes amongst very low birth weight (≤1500 g) and very preterm (≤32 weeks' gestational age) neonates who were exposed to prolonged empirical antibiotics (≥5 days) that had no evidence of infection. These studies found that administration of antibiotics for ≥5 days was found to be an independent risk factor for late-onset sepsis (LOS), necrotizing enterocolitis or death [13]–[15]. The odds ratio for NEC or death was 1.30 and 2.66; [9], [11]–[14]. One study showed that the number needed to harm (that is, the number of neonates who would need to be treated with prolonged initial empirical antibiotic treatment before one neonate developed NEC or died who otherwise would not) was 22 neonates [14].

Study objective: This study aims to describe the frequency, length, and choice of antibiotic used in a district and referral teaching hospital neonatal unit in Kigali, Rwanda.

METHODS

Reporting of the current study proposal has been verified in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [16].

Study design: A retrospective, descriptive study (chart review) was conducted at a referral Neonatal Unit (University Teaching Hospital of Kigali (UTHK)) and a district neonatal unit (Muhima District Hospital (MDH)). Both sites are in Kigali, the capital city of Rwanda. UTHK is the largest, tertiary care, referral hospital in Rwanda, where it also serves as a teaching hospital for the University of Rwanda. MDH is a district hospital specializing in obstetrics, gynecology, and neonatology. UTHK and MDH are "twin" sites sharing hospital management structures, but are in different parts of Kigali, and only UTHK is a referral center.

Participants: Neonates born on the site of the study were eligible for inclusion. Only neonates admitted to the neonatal unit were eligible. Neonates who were admitted from home or ER (i.e., Neonates referred or born from other hospitals) to general pediatric wards were not eligible to be included. Convenience sampling was employed between January 2015 and December 2017, with neonates (below 28 days of life) admitted to the NICU at UTHK and MDH enrolled. The sampling was undertaken by reviewing the admission diary of the relevant sites. Short periods of data-collection were performed to aid accessing patient files. Enrollment was undertaken simultaneously whilst collecting data on CPAP use in the same centers [17].

Outcomes: The primary outcome was the frequency of antimicrobial agent use ("antibiotic exposure") which was predefined as the number of neonates who received one or more antimicrobial agents during their hospitalization in the neonatology unit. The secondary outcome was the Antibiotic Use Ratio (AUR) which was pre-defined as the number of days a neonate was exposed to one or more antimicrobial agents divided by the total length of hospital stay. Antimicrobial agents (antibiotics) were pre-defined as medications that were prescribed to actively inhibit (prevent) and/or kill infecting pathogens [18]. The length of stay was pre-defined as the number of days from the day of admission in NICU to the day of discharge or death, with both dates included.

Sample size: Based on a review of the admission diary of the sites there was a predicted population of 1000 annual admissions at the two sites. The primary outcome of the study was the frequency (prevalence) of antimicrobial exposure. Pilot data predicted a frequency of 85% of neonates receiving intravenous antibiotics. Assuming a 95% confidence interval and a power of 80%, we calculated a sample size of 179 neonates was required.

Data Management Patient files of included neonates were reviewed using a non-printed questionnaire, explicitly designed for this study. Data was entered into Microsoft Excel. All data was stored confidentially using a password protected spreadsheet.

Statistical analysis: Analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 22 Fischer's exact and Chi-Squared was used for ordinal tables, ANOVA for normally distributed means and Mann-Whitney for non-normally distributed medians.

Ethics: The study protocol was reviewed and approved by the CHUK/MDH Ethics Committee (Ref: EC/CHUK/301/2017). A case-file review was undertaken with no contact with participants. Therefore, consent was not taken.

RESULTS

A total of 178 neonates were enrolled (Table 1). The majority were male, averaged 33.4 weeks gestation, with a mean birth-weight of 2.0kg. Mean length of admission for all study participants was 28.1 days. Mortality rate was 42% for both sites. Overall, 46% had a diagnosis of septicemia (Table 2). More neonates at MDH received antibiotics and had a diagnosis of septicemia documented than those neonates at UTHK. Mean and medians are presented for data that was non-normally distributed.

88% of the study participants received a period of antibiotics (antibiotic exposure) during the study period (Table 2). The mean length of antibiotic use was 7.7 days in both groups, and the mean Antibiotic Use Ratio (AUR) was 0.72. 79 of 96 (82%) infants without a diagnosis of septicemia received antibiotics.

Table 1: Baseline data

	Muhima (n=112, 62.6%)	UTHK (n=66, 36.9%)	Total (n=178)
Gender (male)	55/104 (52.8%)	37/66 (56.1%)	92/170 (54.1 %)
Mean gestation	33.4 weeks (SD: 5.2)	30.9 weeks (SD: 3.7)	33.4 weeks (SD: 5.3)
Gestational groups			
Term (>37 weeks)	42/79 (53%)	6/62(9.7%)	48/141 (34.0%)
32-37 weeks	14/79 (17.7%)	20/62 (32.2%)	34/141 (24.1%)
28-32 weeks	14/79 (17.7%)	24/62 (38.7%)	38/141 (26.9%)
<28 weeks	9/79 (11.4%)	12/62 (19.3%)	21/141 (14.9%)
Mean weight (Kg)	2.0kg (SD: 1.0)	1.4 kg (SD: 0.8)	2.0kg (SD:1.1)
Antenatal visits	45/54 (%)	59/62 (%)	
Mode of delivery:			
Vaginal	73/91 (80.2%)	35/51 (68.6%)	108/142 (76.0%)
Instrumental	1/91 (1.1%)	0/51 (0%)	1/142 (0.0%)
Caesarian	16/91 (17.6%)	16/51 (31.4%)	32/142 (22.5%)
Mean length of admission			
All neonates	28.0 days (SD: 51.7)	25.0 days (SD: 43.6)	28.1 days (SD:51.8)
Surviving neonates	33.8 days (SD: 60.7)	34.6 days (SD: 43.9)	33.8 days (SD: 57.2)
Neonates who died	21.0 days (SD: 43.4)	20.2 days (SD: 43.4)	20.6 days (SD: 43.0)
Median length of stay			
All neonates	5 days	11 days	6.5 days
Surviving neonates	6 days	21 days	7 days
Neonates who died	3 days	7 days	5 days
Mortality rate	33/112 (29.5%)	42/66 (63.6%)	75/178 (42.0%)

SD = standard deviation; Not all case-files contained the necessary information. Therefore, denominators are given to reflect where data was available for categorical data, (n=) figures are given for means and medians.

The most common first-line antibiotics used by clinicians were ampicillin (100%) and gentamicin (97%) (Table 3). Cefotaxime was used as a first line antibiotic in 10% of neonates. Cefotaxime was also used as a second line antibiotic in 79% of cases where ampicillin and gentamicin had been used as first line.

Blood cultures are generally not performed at MDH due to lack of resources, with only 9% having a blood culture performed. At UTHK , 95% of neonates had a blood culture performed. Klebsiella spp. and Staphylococcus aureus were the only organisms grown (Table 4), and these were all resistant to ampicillin and gentamicin.

DISCUSSION

This study aims to describe the frequency, length and choice of antibiotic used in a district and referral teaching hospital neonatal unit in Kigali, Rwanda. To our knowledge, this is the first study describing antimicrobial choice and duration in neonatal units in Rwanda. The statistics in this study should be interpreted with caution as the study is not powered to find association or causation between antibiotic choice/length and mortality.

A large proportion of enrolled neonates (88%) received one or more courses of antibiotic which is consistent with the 85% prevalence in a Cohort study of more than 13,000 neonates in Canada [19]. Neonates at the two sites received a median of 6 days of antibiotics. In addition, the high antibiotic use rate (AUR) described in this study (0.72 at both sites) reveals that neonates spend most of their admission on antibiotics. This rate is 3 times higher than that of Canada's NICU (0.25) though this could reflect that the Canadian study only recruited VLBW infants (<1500g) [19]. This study found that a 10% increase in AUR was associated with increased mortality (aOR=2.04; 95% CI=1.87-2.21). Antibiotics in genuine neonatal infection are life-saving, and this is reflected in the longer courses of antibiotics in neonates who were found to be blood culture positive (median 17 days).

The most important result to note from our study is the median length of antibiotic in neonates who were found to be blood culture negative (6 days). Most neonates admitted in any neonatal unit will be blood culture negative and not have microbiological evidence of infection. Previous research has shown that prolonged antibiotics (≥5 days) are associated with worse outcomes with a Number Needed to Harm (NNH) of 22 [14]. Rather than protecting these neonates in neonatology wards in Rwanda with prolonged courses of antibiotics, we are potentially placing them at risk of poor outcomes. This needs to be addressed at a policy level.

We speculate that the implementation of antibiotic monitoring systems would not put additional strain on our resource-limited environment, but could, in fact, be cost and time efficient while minimizing the risk of infection. First, having diagnostic tools such as blood cultures and C-reactive protein available in a well-equipped hospital laboratory to all patients would help clinicians decide to stop antibiotics and to limit their duration. In addition, stopping antibiotics at 48 hours when there is no evidence of infection would reduce the cost to the family, reduce the nursing time for administering medication and reduce the need for painful cannulation which also breaks the skin barrier posing the neonate at further infection risk.

Table 2: Antibiotic stewardship

	Muhima	UTHK	Both	P-value
Received antibiotics (antibiotic exposure)	103/112 (92.0%)	53/65 (81.5%)	156/177 (88.1%)	*0.053
Received antibiotics by gestational group				
Term (>37 weeks)	41/42 (92.3%)	4/6 (66.7%)	45/48 (93.7%)	*0.38
32-37 weeks	13/14 (92.9%)	17/19 (89.5%)	30/33 (90.1%)	*1.0
28-32 weeks	14/14 (100%)	21/24 (87.5%)	35/38 (92.1%)	*0.283
<28 weeks	5/9 (55.6%)	8/21 (38.1%)	13/30 (43.3%)	*0.38
Diagnosis of septicemia documented	53/112 (47.3%)	28/66 (42.4%)	81/178 (45.5%)	0.526
***Received antibiotic WITHOUT diagnosis of septicemia**	50/59 (84.7%)	29/37 (78.3%)	79/96 (82.3%)	0.426
In neonates receiving antibiotics				
Mean length of antibiotic use (in neonates receiving antibiotics)				
All neonates	7.4 days (SD 7.0, n=103)	8.2 days (SD 7.70, n=52)	7.7 days (SD 7.2, n=155)	
Surviving neonates	7.9 days (SD: 6.20, n=76)	11.4 days (SD: 9.97, n=19)	8.6 days (SD: 7.2, n=95)	
Neonates who died	6.0 days (SD: 8.77, n=27)	5.4 days (SD: 5.4, n=33)	6.3 days (SD: 7.0, n=60)	$0.887
Median length of antibiotic use				
All neonates	5 days	6 days	6 days	
Surviving neonates	6 days	7 days	6 days	
Neonates who died	3 days	4 days	4 days	@0.302
Mean Antibiotic Use Ratio (AUR)				
All neonates	0.75 (SD: 0.38, n=83)	0.69 (SD: 0.36, n=51)	0.72 (SD: 0.57, n=137)	
Surviving neonates	0.73 (SD: 0.37, n=62)	0.49 (SD: 0.33, n=17)	0.68 (SD: 0.38, n=81)	
Neonates who died	0.79 (SD: 0.38, n=21)	0.77 (SD: 0.34, n=51)	0.78 (SD: 0.36, n=56)	*<0.001
Mean length of antibiotics				
Blood culture positive	ND	17.0 days (SD: 8.1, n=14)	NA	
Blood culture negative		7.8 days (SD: 6.4, n=47)		$<0.001
Median length of antibiotics				
Blood culture positive	ND	17.0 days	NA	
Blood culture negative		6.0 days		@<0.001
Mean antibiotic to day ratio				
Blood culture positive	ND	0.49 (SD: 0.40, n=0.60, n=11)	NA	
Blood culture negative		0.62 (SD: 0.39, n=38)		$<0.001
Median antibiotic to day ratio				
Blood culture positive	ND	0.50	NA	
Blood culture negative		0.80		@0.005

**Fischer's exact test; @Mann-Whitney U test. $ANOVA. Not all case-files contained the necessary information. Therefore, denominators are given to reflect where data was available for categorical data, (n=) figures are given for means and medians. ND=no data as no blood cultures undertaken at Muhima; *neonates who received antibiotics WITHOUT diagnosis of septicemia: all neonates who received antibiotics.*

Table 3: Antibiotic choice in those neonates receiving antibiotics

	Muhima	UTHK	P-value
First line antibiotics			
Ampicillin	99/99 (100%)	52/52 (100%)	0.010
Gentamicin	99/99 (100%)	47/52 (90.4%)	
Cefotaxime		5/52 (9.6%)	
Second line antibiotics			
Cefotaxime	16/25 (64.0%)	15/19 (78.9%)	0.112
Ciprofloxacin	1/25 (4.0%)	3/19 (15.8%)	
Imipenem/Meropenem	8/25 (32.0%)	0	
Metronidazole	0	1/19 (5.3%)	
Third line antibiotics			
Cefotaxime	2/12 (16.7%)	1/10 (10%)	0.312
Ciprofloxacin	3/12 (25%)	5/10 (5%)	
Cloxacillin	2/12 (16.7%)	0	
Imipenem/Meropenem	4/12 (33.3%)	0	
Metronidazole	1/12 (8.3%)	4/10 (4%)	

[£]*Pearson Chi-Squared; Not all case-files contained the necessary information. Therefore denominators are given to reflect where data was available for categorical data, (n=) figures are given for means and medians. The line of therapy was determined by the sequence of antibiotic choice per neonate in the chart record.*

Table 4: Blood cultures and organisms identified

	Muhima	UTHK
Blood culture performed	9/106 (8.5%)	61/64 (95%)
Organism identified	8/9 (88.9%)	8/61 (13.1%)
Growth of organism		
Klebsiella spp.	7/8 (87.5%)	6/8 (75.0%)
Staphylococcus Aureus	1/8 (12.5%)	2/8 (25.0%)

Antibiotic choice in our study reflected WHO guidelines with ampicillin and gentamicin being the most common antibiotics prescribed. A Rwandan study at the same study site (UTHK) found that no organisms were sensitive to ampicillin and that most organisms were resistant to gentamicin [5]. This needs to be addressed with wider studies looking at local antibiograms and local prescribing policy being adapted accordingly.

The results of blood cultures once again support that Gram Negative (Klebsiella spp.) and Gram Positive bacteria (Staphylococcus aureus) are more common in this setting [5], [20]. This once again supports the implementation of antibiotic stewardship programs to minimize the risks of MDR organisms, which lead to the use of newer antibiotics. These are not only a precious resource for future generations but also more expensive for families. Further studies are needed in Rwanda to explore causes and factors behind antibiotic misuse by clinicians.

Limitations of the study: A significant limitation of this study was the availability of required data in the case-files at both sites, but in particular at MDH. For example, limitations in the information available in the patient-files made assigning cases as EOS or LOS nearly impossible. Neonatal mortality was found higher in UTHK (64%) than MHD (30%). This again should be interpreted with caution. The Neonatal Database at CHUK reveals an overall mortality rate of 16.3% between 2011-17. These mortality statistics represents the opportunistic sampling of patients rather than a true reflection of overall mortality at these units which are known to be lower.

CONCLUSION

Infection remains a significant problem for neonates. With increasing challenges of antibiotic resistance, the results of this study demonstrate the need for antibiotic stewardship programs in Rwandan Neonatology Units.

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