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Research Article

Neonatal Bacteraemia and Antibiotic Resistance at the Angre University Hospital, Abidjan, 2020

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Abstract

Background: Multi-drug resistant bacteria are an increasingly important cause of neonatal sepsis. Nowadays, they are a great concern in neonates because few therapeutic options are available.

Aim: To determine the bacteria responsible of neonatal sepsis and their antibiotic susceptibility pattern in order to improve the quality of antibiotic prescription.

Methods: A retrospective data review on positive blood cultures from the neonatal department at the university hospital of Angre between January to December 2020 was conducted. All neonates with clinical suspicion of sepsis with positive blood cultures were identified. Patient demographics, clinical details, and laboratory data were recorded and analyzed by Epi info software version 7.2.5.0

Results: Out of 221 blood cultures samples, 82 were positive (37%). The predominant age group was that between day 0 and day 7. A preponderance of bacteria of the genus Staphylococcus (48.78%) compared to enterobacteria (43.90%) was observed. The main isolated bacteria were coagulase-negative Staphylococcus (29.27%), *Klebsiella pneumoniae* (26.83%) and *Staphylococcus aureus* (19.51%). *Streptococcus agalactiae* was isolated in 2 cases (2.44%). Among the Enterobacteriaceae strains, 80.56% produced an Extended Spectrum Beta-Lactamase (ESBL). The rate of methicillin-resistant was observed in coagulase-negative Staphylococcus and *Staphylococcus aureus* in 37.50% and 31.25% of cases respectively. Out of ESBL strains, 89.65% were multi-resistant. Of the 14 strains of methicillin-resistant staphylococci, 13 (92.86%) were multidrug resistant.

Conclusion: Coagulase-negative Staphylococcus and *Klebsiella pneumoniae* were the common causes of neonatal sepsis. The high rate of multi-drug resistant bacteria resistant represents a great threat to neonatal survival and warrants modification of existing empirical therapy.

Keywords: Neonatal bacteraemia; Antibiotic resistance; Hospital; Abidjan

Abbreviations: ATCC: American Type Culture Collection; AMC: Amoxicillin-Clavulanic Acid; AMK: Amikacin; BLSE: Extended Spectrum Beta Lactamases; BMR: Multi-drug Resistant Bacteria; CBC: Blood Count; CIP: Ciprofloxacin; CMN: Clindamycin; CN: Gentamycin; CHU: Hospital and University Center; CO2: Carbon Dioxide; CoNS: Coagulase-Negative Staphylococcus; CRO: Ceftriaxone; CRP: C-Reactive Protein; CTZ: Ceftazidime; ESBLs: Extended Spectrum Beta Lactamases; *E. Coli: Escherichia Coli*; ERY: Erythromycin; EUCAST: European Committee on Antimicrobial Susceptibility Testing; FOX: Cefoxitin; *K. Pneumoniae: Klebsiella Pneumonia*; LEV: Levofloxacin; MDR: Multi-Drug Resistant; MRSA: Methicillin-Resistant *Staphylococcus Aureus*; MR-CoNS: Methicillin-Resistant Coagulase-Negative Staphylococcus; NS: Neonatal Sepsis; PTN: Pristinamycine; SA: *Staphylococcus Aureus*; SXT: Sulfamethoxazole-Trimetroprime; TIC: Ticarcillin-Clavulanic Acid; TOB: Tobramycin; VAN: Vancomycin; WHO: World Health Organization

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Introduction

Neonatal Sepsis (NS) is a major cause of morbidity and mortality and is the third leading cause of death worldwide [1]. The rapid evolution of these infections is the source of diagnostic concern for clinicians, which contributes to prescribe a significant and sometimes inappropriate prescription of broad-spectrum antibiotics. This exposition to antibiotics contributes to the emergence of resistant bacteria [2], which complicates the therapeutic treatment. In 2016, the first estimate of neonatal deaths attributable to antimicrobial resistance was published [3]. Multidrug-resistant pathogens accounted for approximately 30% of all neonatal sepsis mortality worldwide [3]. In Africa, the situation is more worrisome [4] due to insufficient access to last-resort antibiotics, a higher burden of infectious diseases, weak health systems, and limited resources. However, in a study conducted in Côte d'Ivoire in 2010, most bacteria causing neonatal sepsis were susceptible [5]. Moreover, in recent years, it is clear that few studies concerning antibiotic resistance in neonatology have been conducted. Therapeutic management may therefore be ineffective. The objective of this study was therefore to determine the bacteria responsible of neonatal sepsis and to describe their antibiotic susceptibility patterns.

Materials and Methods

Conception and Study Design

This was a retrospective cross-sectional study that took place at the medical biology department of the CHU of Angre. Data from the neonatal unit from January 1 to December 31, 2020 were examined. On the one hand, clinical data and biological parameters (CBC and CRP) were collected from the patients' medical files. On the other hand, microbiological data that include dates of blood cultures, blood culture positivity, identified organisms, and antibiotic susceptibility were extracted from the laboratory computerized database.

Study Population

Culture-proven NS was defined as one or more blood culture obtained at 0–28 days of life growing a recognized pathogenic bacterium or fungus and a clinical diagnosis of sepsis [6]. After analysis of the medical files, all clinically suspected cases of neonatal sepsis admitted to the neonatal department of the CHU of Angre were listed. Out of them, only neonates with a positive blood culture were included in the study. Neonates were defined as patients whose age ranged from 0 to 28 days of life.

Culture and Identification

Microorganism identification and culture were conducted according to the routine diagnostic standard operation procedure used by the clinical laboratory in the study hospital: For any new-born, 0.5-3 mL of blood sample was inoculated into a commercial culture bottle exclusively for new-borns and analyzed using an automated monitoring system for bacterial detection (BioMérieux Bact/ALERT). Incubation was continued until a positive result was observed or up to a maximum of 7 days. Subcultures are typically made on to blood and chocolate agar. They are incubated aerobically at 37°C with 5 to 10% CO_2 for 24 to 48 hours. The microorganisms were identified to species level by conventional biochemical techniques or automated methods with the VITEK system (BioMérieux). The bacterial isolates were tested for susceptibility to antibiotics using VITEK MD 2 Compact® (BioMérieux) or the manual Kirby–Bauer disc diffusion method, as per interpretive standards established by the CA-SFM/ EUCAST 2019. Quality control strains were used: Escherichia coli ATCC 25922, *Klebsiella pneumoniae* ATCC 700603 and *Staphylococcus aureus* ATCC 29213. Routinely at the laboratory, positive blood cultures are evaluated to determine whether they represent true bacteraemia or contamination. They are each reviewed by the clinical microbiologist for decisions on the significance of the organism and the appropriate antibiotic susceptibility data to report. The clinical microbiologists have access to patients' clinical information. Thus, Coagulase-Negative Staphylococci (CoNS), micrococci, propionibacteria, and corynebacteria grown alone in a single sample were considered contaminants and excluded. CoNS were included only when cultivated in two or more blood samples. Bacteria like *Staphylococcus Aureus* (SA), Enterobacteriaceae, Pseudomonas, and Acinetobacter which grown alone in a single sample without clinical signs were considered contaminants and excluded too. Repeatedly positive samples were considered to represent the same episode of infection.

Statistical Analyses

Data were entered into an Excel spreadsheet (Microsoft excel version 2019). Epi info version 7.2.5.0 was used for data analyses. Mean and standard deviation were used to describe the central tendency of continuous variables based on the distribution of the data. Categorical variables were described using frequency and percentages.

Ethical Approval and Consent to Participate

The study was based entirely on routine clinical and laboratory data. The consent to participate wasn't so obligatory. Ethics approval was obtained from the Biomedical Research Ethics Committee of the University of Felix Houphouet Boigny and the medical and scientific management of the CHU of Angre. All data were de-identified from the routine database used and shared with the investigators in a password-protected file, to which only the principal investigator and the laboratory manager had access.

Results

General Characteristics

Between the study period, the microbiology laboratory received 221 blood cultures of new-borns and a total of 98 (44.34%) organisms were isolated. Out of the isolates, 16 were considered contamination by commensals and were excluded in further analyses: *Staphylococcus aureus* n=7, CoNS n=4, *Klebsiella pneumoniae* n=4, andEscherichia coli n=1. The rate of clinically relevant bacteraemia amongst the neonates was 37.10% (82/221). Of the 82 neonates included, 44 (53.65%) were male with a sex ratio of 1.15. The median age was 3.76 ±7.53 days. According to the time of sepsis, 70/82 (85.36%) cases were in the age range of day 0 to day 7. 24.39% (20/82) were born at term and 13.41% (11/82) were preterm. At birth, 22 (26.83%) were eutrophic, 7 (8.54%) hypotrophic, and 1 (1.22%) had macrosomia. Age and birth weight were not found in 62.20% (51/82) and 63.41% (52/82) of the cases respectively. It should be noted that these clinical data were not recorded by the prescribers in the patients' files.

Isolated Bacteria from Neonatal Sepsis

A total of 82 isolates were identified (Table 1). Sepsis was primarily caused by Gram-positive bacteria (n=45, 54.88%), compared with Gram-negative bacteria (n=37, 45.12%). The most

frequent pathogens were CoNS (n=24, 29.27%), K. pneumoniae (n=22, 26.83%), and S. aureus (n=16, 19.51%). Others pathogens included are shown in the (Table 1).

Table 1: Distribution of isolated bacteria neonatal sepsis.

GRAM	Species	Frequency n (%)
Gram-positive bacteria N=45	*Coagulase negative Staphylococcus*	24 (29,27)
	Staphylococcus aureus	16 (19,51)
	Enterococcus spp	2 (2,44)
	Streptococcus agalactiae	2 (2,44)
	Streptococcus pneumoniae	1 (1,22)
Gram-negative bacteria N=37	*Klebsiella pneumoniae*	22 (26,83)
	Enterobacter cloacae	7 (8,54)
	Escherichia coli	5 (6,10)
	Citrobacter koseri	1 (1,22)
	Citrobacter freundii	1 (1,22)
	Acinetobacter baumannii	1 (1,22)
Total		82 (100)

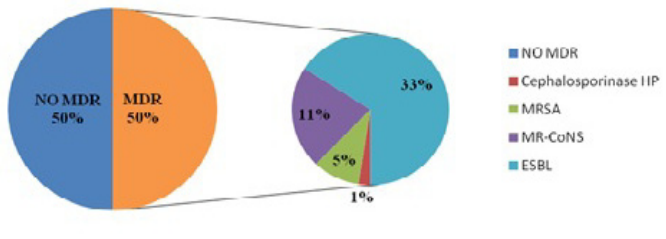

Figure 1: Proportion of multi-drug resistant bacteria.

Antibiotic Susceptibility Pattern

For Gram-positive cocci, the (Table 2) showed the distribution of resistance pattern of CoNS and SA. Out of CoNS, the resistance to methicillin was observed in 37.50% (9/24) of cases. CoNS was resistant to gentamycin (n=5; 20.83%), ciprofloxacin (n=7, 29.16%), levofloxacin (n=7, 29.16%), sulfamethoxazole-trimetroprime (n=9, 37.50%), and erythromycin (n=6, 25%). All strains of CoNS were sensitives to vancomycin.

Methicillin Resistant *Staphylococcus Aureus* (MRSA) was observed in 31.25% (5/16). Among *Staphylococcus Aureus*; 12.50% (n=2) were resistant to gentamycin, 12.50% (n=2) to levofloxacin, and 18.75% (n=3) to ciprofloxacin. Also, SA was resistant to erythromycin (n=5, 31.25%) and vancomycin (n=2, 12.5%). All strains of SA were resistant to sulfamethoxazole-trimetroprime.

Moreover, all strains of *Streptococcus agalactiae* and Streptococcus pneumoniae were sensitives.

All of Gram-negative bacilli, the Extended Spectrum Beta Lactamase (ESBL) producing Enterobacteria represented 80.56% (29/36) of cases. The Acinetobacter baumannii strain also produced an ESBL. All Gram-negative bacilli resistances are listed in (Table 3).

Multi-Drug Resistant Bacteria

Multi-Drug Resistant (MDR) bacteria (resistant to at least 3 families of antibiotics). are showed by (Figure 1). They were mainly represented by ESBL producing Enterobacteria (n=27; 32.93%). The others BMR were represented by MR-CoNS (n=9; 10.98%), MRSA (n=4, 4.87%), and cephalosporinase-hyper producing enterobacteria (n=1; 1.22%).

Table 2: Distribution of antibiotic-resistant Staphylococcus strains.

Species	Resistance to antibiotics tested n (%)										
	FOX	KMN	TOB	CN	CIP	LEV	ERY	CMN	PTN	SXT	VAN
CoNS (N=24)	9 (37.50)			5 (20.83)	7 (29.16)	7 (29.16)	6 (25%)	1 (4.17)	1 (4.17)	9 (37.50%)	0
SA (N=16)	5 (31.25)			2 (12.50)	3 (18.75)	2 (12.50)	5 (31.25)	4 (25%)	2 (12.50)	5 (31.25)	2 (12.50)

CoNS: *Coagulase Negative Staphylococcus; SA: Staphylococcus aureus*; FOX: Cefoxitin; KMN: Kanamycine; TOB: Tobramycin; CN: Gentamycin; CIP: Ciprofloxacin; ERY: Erythromycin; CMN: Clindamycin; SXT: Sulfamethoxazole-trimetroprime; VAN: Vancomycin

Table 3: Distribution of antibiotic-resistant Gram-negative bacilli strains.

Species	Resistance to Antibiotics tested n (%)									
	AMC	TCC	CRO	CTZ	IMP	ETP	CN	AMK	CIP	SXT
K. pneumoniae (N=22)	19 (86.36)	NT	22 (100)	NT	0	5 (22.72)	20 (90.90)	0	9 (40.90%)	21 (95.45)
E. cloacae (N=7)	6 (85.71)	NT	2 (28.57)	NT	1 (14.28)	2 (28.57)	3 (42.85)	0	1 (14.28)	6 (85.71)
E. coli (N=5)	0	NT	3 (60)	NT	0	1 (20)	4 (80)	0	0	5 (100)
A.baumannii (N=1)	NT	1 (100)	NT	1 (100)	0	0	1 (100)	0		1 (100)

K. pneumoniae: Klebsiella pneumonia; E. cloacae: Enterobacter cloacae; E. coli: Escherichia coli; AMC: Amoxicillin-Clavulanic Acid; TCC: Ticarcillin-Clavulanic Acid; CRO: Ceftriaxone; CTZ: Ceftazidime; CN: Gentamycin; AMK: Amikacin; CIP: Ciprofloxacin; SXT: Sulfamethoxazole-Trimetroprime

Discussion

Diagnosis of neonatal sepsis is a challenge. Signs and symptoms of neonatal sepsis are non specific especially in the first days of life and difficult to differentiate from other neonatal pathologies [7,8]. Blood cultures are the « gold standard » for the detection of bacteraemia. The objective of this study was therefore to determine the bacteria responsible of neonatal sepsis and to describe their antibiotic susceptibility patterns. In our study, the prevalence of neonatal bacteraemia was 37.10% (82/221). This result is comparable to those of some studies from West African countries: 37.6% in Nigeria [9], 38.95% in Benin [10], and 34.7% in Cameroon [11]. However; lower prevalences were found in 2016 in Cocody, Ivory coast (22.7%) [5], Ghana (17.3%) [12], and Johannesburg, South Africa (8.5%) [13]. In developed countries, the prevalence of neonatal sepsis range at 0.5% to 1% [14]. Generally, these high rates of neonatal bacteraemia observed in our countries contrast with those in developed countries. This could be explained by real differences in the qualification of maternal and neonatal care, and neonatal units' types [15]. and the lack of hygiene in ours hospitals. Furthermore, not all negative blood cultures exclude sepsis [16]. Indeed, a low rate of blood culture positive could be due to the administration of an antibiotic before blood collection or to the possibility of infection with other microorganisms. Adenovirus, enterovirus, coxsackievirus, rubella virus, and toxoplasma species have been implicated in neonatal sepsis [17]. Also, about 26% of all neonatal sepsis cases could be attributed to anaerobes [18]. Unfortunately, there is no uniform consensus definition for neonatal sepsis [19-21]. Many neonates are therefore diagnosed with "probable or possible" sepsis or "presumed symptomatic infection but without an identified bacterial cause" [22]; conditions often referred to as "culture-negative sepsis" [23]. Therefore, there is an urgent need to unify guidelines for the identification and management of neonatal sepsis.The main isolated bacteria were Gram-positive cocci (n=44, 53.65%). This is in accordance with findings from Saudi Arabia (27/40; 67.5%) [24], and China (57,49%) [25]. However, Gram-negative bacilli were the predominant bacteria isolatedin anothers countries like Congo [15], Nigeria [9], Cameroun [26], and Nepal [27]. CoNS (28.04%) was the predominant bacteria identified in our study followed by *Klebsiella pneumoniae* (26,83%).

Andrianarivelo in Madagascar [28], Li and Guo in China [25,29], and Tessema in Germany [30] also reported a predominance of coagulase-negative Staphylococcus in their respective studies. However, in anothers studies in Africa, *Klebsiella pneumoniae* and Escherichia coli were the main species. These are the cases of Nigeria [9], Congo [15], Cameroon [26], and India [31]. This disparity in the isolated bacteria is in accordance with the fact that the epidemiology of neonatal sepsis is extremely variable throughout the world [32], making it difficult to establish differences between countries.

Antibiotic resistance is a global problem. In our study, the rates of MRSA and methicillin-resistant CoNS were 31.25% and 39.13% respectively. This finding is similar to a study performed in Morocco [33] which observed a MRSA rate of 31.08%. Lower MRSA rates have been observed. This is the case of a study carried out by the Pasteur Institute of Madagascar in 2007, which reported an MRSA rate of 9% out of 54 isolated strains of *Staphylococcus aureus* [34]. These differences may be justified by the fact that our study is much more recent and that reports of multidrug-resistant bacteria causing neonatal sepsis in developing countries are increasing [35]. Elsewhere, the prevalence of MRSA is much higher. This is the case in Nepal, where Chaudhary et al. found a prevalence of MRSA of 60% [27]. In a study in Ethiopia, MRSA was found in 66.7% of cases [36]. Also, we estimated the proportion of ESBL producing Enterobacteriaceae at 80.56%. This is contrary in Madagascar where the proportion of ESBL producing Enterobacteriaceae was estimated at 100% [28]. Lower rates were observed in South Africa (60.9%) [37] and China (62%) [29]. In our study, the overall rate of MDR bacteria was 50% and was mainly represented by ESBL producing Enterobacteriaceae, MR CoNS, and MRSA. This rate is comparable to a study performed in Dessie (Ethiopia) [36]. Higher rates were found by Chaudhary [27], Agarwal [38], and Pokhrel [39].

Our study has several limitations. It was a retrospective study that did not allow for an exhaustive collection of all data. Some clinical files were missing data. It was therefore impossible to analyze the risk factors associated with neonatal bacteraemia, the acquisition of multidrug-resistant bacteria, and sepsis-related mortality. Also, the high rate of MDR bacteria makes us suspect a nosocomial character, which was not investigated in our study. Finally, the small size of the population studied, due to the fact that the CHU of Angré is a new hospital, does not allow us to generalize the results.

Conclusion

In our study, the prevalence of neonatal bacteraemia is high. The main bacteria were *Coagulase negative Staphylococcus* and *Klebsiella pneumoniae*. The increasing rate of multi-drug resistance bacteria makes the treatment of neonatal bacteraemia difficult. It is very important to respect the rules of antibiotic prescription and the need to establish new guidelines for the management of neonatal bacteraemia.

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