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Bacteriological Profile and Antibiotic Susceptibility Pattern of Common Isolates of Neonatal Sepsis in a Tertiary Hospital from Lagos, Nigeria

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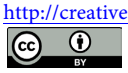

Abstract

Background: Neonatal sepsis is one of the leading causes of mortality in the neonatal intensive care unit (NICU) of most developing countries. Antibiotic resistance is rapidly becoming a challenge in the NICU, particularly in developing countries like Nigeria. Knowledge of the bacteriological agents and their antimicrobial susceptibility pattern is essential to successfully manage sepsis in the NICU. This study was designed to determine the bacteriological etiology and antibiotic susceptibility pattern of isolates obtained from cases of neonatal sepsis in the NICU of our hospital. **Methods**: This was a retrospective analytical study of all blood culture-positive cases of neonatal sepsis in the NICU of Lagos State University Teaching Hospital (LASUTH), Lagos, Nigeria between April 2020 and May 2021. All neonates with a positive blood culture were identified. Patient demographics, clinical details, and laboratory data including bacteriological profiles and antimicrobial susceptibilities were recorded and analyzed using SPSS version 20. **Results**: One hundred and seventy-four neonates with sepsis were investigated. Of these, 56 (32%) were blood culture-positive. A total of 44 (78.6%) out of 56 infected neonates had early-onset sepsis. Of the 56 clinically relevant blood isolates, 47 (84%) were Gram-positive bacteria, 25 (44.6%) of which were *Staphylococcus aureus*. The percentages of the *S. aureus* isolate resistant to commonly used antibiotics were: 36%, 48%, 52%, 0% and 15% against cefotaxime, ciprofloxacin, gentamicin, linezolid and meropenem, respectively. The most common Gram-negative bacterial isolate was *Klebsiella pneumoniae* representing 7.1%. All the *K.*

pneumoniae isolates were resistant to cefotaxime, ceftazidime, ciprofloxacin and gentamicin but fully susceptibility to meropenem (100%) and moderately to amikacin (66%). **Conclusion:** About a third of the neonates in our NICU were septic during the period of investigation. *S. aureus* was the most common cause of neonatal sepsis in our study. A high number of the bacterial isolates were multidrug-resistant, a finding that poses serious treatment challenges in this unit. It is recommended that the choice of antibiotic therapy must be informed by the results of susceptibility testing and the institution of periodic surveillance programs.

Subject Areas

Pediatrics

Keywords

Neonatal Intensive Care Unit (NICU), Early Onset Neonatal Sepsis (EONS), Late Onset Neonatal Sepsis (LONS), Group B Streptococcus (GBS), Coagulase Negative Staphylococci (CoNS)

1. Introduction

Neonatal sepsis is one of the leading causes of neonatal morbidity and mortality worldwide. [1] [2] It accounts for an estimated 30% - 50% of all neonatal deaths in the developing countries [2] [3] [4]. Globally, up to 20% of neonates develop sepsis and 1% die from sepsis-related causes. [1] [4] Important contributing factors in developing countries include delayed identification of causative etiological microorganisms, inappropriate treatment, outdated antibiotic guidelines, and the emergence of resistance strains. [5]

Neonatal sepsis refers to a clinical syndrome that is marked by signs and symptoms of infection in the first 28 days of life, with or without isolation of a pathogen. [4] [6] This can be categorized as early onset sepsis (EONS) and late-onset sepsis (LONS). EONS is defined as onset of signs and symptoms of infection within 72 hours of life and may be associated with isolation of a pathogen or not. In the LONS, signs and symptoms become apparent after 72 hours of life and categorization of EONS and LONS is to show the varying causes and pathophysiology of common isolates related to the time of onset of the condition. It is also crucial in prevention and treatment due to variations in etiological agents.

Recent reviews of causative agents of neonatal sepsis in the developed world revealed that group B *Streptococcus* (GBS) is a major cause of early-onset neonatal sepsis. [7] This is in contrast with the bacteriological profile of resource-limited settings where GBS rates are lower and *Klebsiella pneumoniae*, *Staphylococcus aureus* and Coagulase-negative staphylococci (CoNS) are the predominant pathogens of EOS. [7] [8] However, the main causative agent of

LONS in neonatal intensive care unit reported globally remains coagulase-negative staphylococci (CoNS). [9]

In Nigeria, a wider spectrum of Gram-negative organisms including *K. pneumoniae*, *Citrobacter* spp., *Escherichia coli*, *Enterobacter* spp., *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Proteus* spp. are prevalent in EONS. This observation was from a report of multicenter studies carried out in the Southwestern part of Nigeria. [10] In the Northwestern part of Nigeria, the frequently isolated organisms from neonatal sepsis were *K. pneumoniae*, *Staphylococcus aureus*, coagulase-negative *Staphylococcus* (CoNS) and *E. coli*. [4] [11]

Bacterial isolates responsible for neonatal sepsis seem to have acquired resistance to a number of antibiotics over the last few decades, and thus making treatment options extremely difficult. [12] [13] Global resistance to first-line empiric treatment regimens is on the increase, adding further complication to antimicrobial choices. [14] Studies from Nigeria have documented the emergence of drug resistance to multiple antibiotics howbeit mostly in an adult population. [4] [15]

Knowledge of prevalent bacterial isolates and their antibiotic susceptibility pattern is crucial when choosing the appropriate empirical therapy in order to decrease morbidity and mortality of neonatal sepsis. There is, however, a paucity of such data in most NICUs of our institutions. The objectives of this study were to: determine the prevalence of culture-positive neonatal sepsis in the NICU of LASUTH, its bacteriological profile and the antibiotic susceptibility pattern of the isolates.

2. Methods

2.1. Study Site

The study site was the NICU of LASUTH located in Ikeja, Nigeria. LASUTH is a 250-bedded tertiary medical center right in the heart of Lagos State, responsible for providing healthcare to a catchment of over 4 million people across all strata of life. Its position makes it the most accessible tertiary and referral medical facility in Lagos. It has a 10-bed NICU caring for about 250 critically ill neonates annually.

2.2. Study Population

The study population comprises newborns younger than 29 days of age admitted to the NICU of LASUTH with suspicion of sepsis, who had a blood culture done as part of the routine septic workup and from whom blood culture results were retrievable and subsequently analyzed.

2.3. Study Design

This was a retrospective analytical cohort study conducted in the NICU from April 2020 to May 2021. The study period was chosen to coincide with when the laboratory unit started using automated blood culture machine for blood culture

processing.

2.4. Ethical Consideration

Approval for the study was obtained from the Ethics and Research Committee of the Lagos State University Teaching Hospital. Reference number: LREC/06/10/1967.

2.5. Inclusion Criteria

All neonates admitted to the NICU who had blood culture result during the study period.

2.6. Specimen Collection and Transportation

1 - 2 mls of blood samples were collected into pediatric BACTEC blood culture bottles (Becton-Dickinson, New Jersey, USA) from neonates with signs and symptoms of sepsis as define by the attending pediatricians following the guideline for culture sample collection for sepsis and transported to the laboratory for processing.

2.7. Sample Processing, Isolation and Identification

BACTEC blood culture bottles (BD) were taken to the Laboratory and processed in the automated BACTEC 9240 Blood Culture System (Becton Dickinson) After 24 hours' incubation period, flagged positive blood culture bottles were removed from the machine and processed manually according to standard laboratory procedure. [16] 0.1 ml aliquot of the growth suspension was inoculated onto a set of selective and non-selective media, which were: Blood agar (Oxoid, Hampshire, Reading, UK), MacConkey agar (Oxoid) and Chocolate agar. The plates were then incubated in ordinary aerobic incubator at 37˚C for 24 hours and extended for 48 hours if indicated.

Organism identification were done using Analytical Profile Index (API-Staph: bioMerieux, Marcy-E'ltiole, France) for Gram-positive and API 20E (bioMerieux) for Gram-negative bacteria. [17]

2.8. Antibiotic Susceptibility Testing (AST)

Antimicrobial susceptibility testing was performed by Modified Kirby-Bauer disk diffusion method and interpreted using the criteria recommended by the Clinical Laboratory Standard Institute (CLSI) guidelines 2019. [18]

Gram-positive bacterial isolates were tested against the following drugs with the appropriate disc concentrations: penicillin (10 IU), cloxacillin (30 µg), cefoxitin (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), gentamicin (10 µg and 120 µg), linezolid (30 µg), erythromycin (30 µg), fusidic acid (30 µg), levofloxacin (5 µg), clindamycin (1 µg) and vancomycin (30 µg). The antibiotics were tested against the Gram-negative bacterial isolates were: gentamicin (10 µg), ciprofloxacin (5 µg), cefotaxime (30 µg), cefepime (30 µg), ceftazidime (30 µg),

amikacin (30 µg), piperacillin-tazobactam (100/10 µg) and meropenem (30 µg). The susceptibility and resistance were interpreted as per CLSI guidelines 2019. *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853), and *Enterococcus faecalis* ATCC 29212) were used in each run as reference strains for culture and susceptibility testing controls.

Drug resistant strains in primary screening were further processed for the detection of extended-spectrum beta-lactamases (ESBL) in Gram-negative bacterial isolates and methicillin resistance in *S. aureus* (MRSA) strains. Detection of MRSA was done by cefoxitin disk diffusion method by placing 30µg cefoxitin disk on the bacterial lawn culture of *S. aureus*. After overnight incubation at 37˚C the zone of inhibition was measured. [19] An inhibition zone of diameter less than or equal to 21 mm indicated the possibility of being a MRSA and were reported as oxacillin-resistant. *S. aureus* ATCC 25923 was used as quality control (QC) for cefoxitin susceptibility. ESBL producers were detected by single disc method using cefotaxime (30 µg) amoxicillin-clavulanic acid (10 µg) at 15 mm apart. After incubation for 18 - 24 hours at 35˚C any enhancement in the zone of inhibition between the cephalosporin and the beta-lactamase inhibitor was taken as indicative of ESBL production.

3. Results

3.1. General Characteristics

Of the 174 neonates suspected of having sepsis, 56 (32%) had blood culture-proven sepsis. Early onset neonatal sepsis (EONS) was 44 (78.6%) while 12 (21.4%) were due to Late onset neonatal sepsis (LONS). Male to female ratio is 3:1. This is further explained in Table 1.

3.2. Etiological Agents

Most of the culture positive isolates were Gram-positive (n = 47) accounting for 84% while Gram-negative were 9 (16%). The most frequent isolate was *S. aureus* 25 (44.6%), closely followed by *S. epidermidis* 21 (37.5%) Further illustration seen in Table 2.

Table 1. Demographic characteristics of the blood culture-positive patients.

Patient characteristics	No (%)
Gender	
Male	42 (75)
Female	14 (25)
Type of sepsis	
Early onset neonatal sepsis (EONS)	44 (88.6)
Late onset neonatal sepsis (LONS)	12 (21.4)

Table 2. Microbial isolates obtained from the infected neonates.

Organism	Frequency (%)
Staphylococcus aureus	25 (44.6)
Staphylococcus epidermidis	21 (37.5)
Enterococcus spp.	4 (7.1)
Klebsiella pneumoniae	3 (5.4)
Pseudomonas aeruginosa	2 (3.6)
Acinetobacter baumannii	1 (1.8)

3.3. Antibiotic Susceptibility Profile

The results of antibiotic susceptibility pattern in this study are shown in **Table 3** and they indicated that 72% of *S. aureus* isolates were resistant to penicillin, 60% to cloxacillin and 52% gentamycin. All the *S. epidermidis* isolates were resistant to cotrimoxazole, 86% to penicillin and 59% gentamycin.

Analysis of the susceptibility profiles of the Gram-negative isolates showed that the majority of the commonly prescribed antibiotics demonstrated poor activities *K. pneumoniae*: all isolates were resistant to gentamycin, the 3rd and 4th generation cephalosporin and piperacillin-tazobactam. Against *P. aeruginosa*, all isolates were resistant to gentamycin and 50% were resistant to cefotaxime.

4. Discussion

Neonatal sepsis is considered as the leading cause of mortality and morbidity in the NICU. Several studies conducted in Nigeria with the same study population put the culture-positive rate between 28.1% and 35.6%. [3] [12] [20] This study which is first to be conducted in the NICU of LASUTH gives a culture-positive rate of 32.3%. This is also similar to studies conducted in Ghana and Nepal which gave the culture-positive rate of 28% [21] and 32.4% [22] respectively. Some studies, however, gave a much higher culture-positive rate. [4] This variation may be due to the volume of blood collected, the timing of blood collection and the laboratory technique employed.

The majority of the culture-positive sepsis were early onset neonatal sepsis (EONS) accounting for 78.6%. This finding is consistent with other studies which gave between 65% and 78% culture-positive rate in EONS. [3] [12]

In this study, the frequency of isolation of gram-positive bacteria 47 (84%) is much higher than gram negative bacteria 9 (16%). This is in sharp contract from other authors from Nigeria, where the preponderance of gram positive bacteria is not as high as reported in this study. [12] [20] [23] Studies from Ghana, Nepal and Germany also gave gram positive preponderance with 71% [22], 72% [21] and 74% [24] respectively. However, some studies gave gram negative preponderance. [25] These differences may be due to the spectrum of causative organisms across geographical locations and the level of compliance with IPC measures in various hospital settings.

Table 3. Antimicrobial susceptibility patterns of the clinical isolates.

Antibiotic Breakpoints	Number of isolates and % resistant											
	Staphylococcus aureus		*Staphylococcus epidermidis*		*Enterococcus*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Acinetobacter baumannii*	
	N	%R	N	%R	N	%R	N	%R	N	%R	N	%R
Penicillin	18	72	18	86	NT		NT		NT		NT	
Amoxicillin	NT		NT		0	0	NT		NT		NT	
Cloxacillin	15	60	14	70	NT		NT		NT		NT	
Erythromycin	12	48	17	80	NT		NT		NT		NT	
Cotrimoxazole	13	81	8	100	NT		NT		NT		NT	
Gentamycin	13	52	10	59	0	0	3	100	2	100	1	100
Amikacin	NT		NT		NT		1	33	0	0	0	0
Ciprofloxacin	12	48	8	38	NT		3	100	0	0	1	100
Levofloxacin	NT		NT		NT		NT		0	0	0	0
Clindamycin	8	32	10	50	NT		NT		NT		NT	
Vancomycin	NT		5	83	0	0	NT		NT		NT	
Linezolid	0	0	14	74	0	0	NT		NT		NT	
Cefotaxime	9	36	7	33	NT		3	100	1	50	NT	
Ceftazidime	NT		NT		NT		3	100	0	0	0	0
Cefepime	NT		NT		NT		0	0	2	100	1	100
Meropenem	NT		NT		NT		0	0	0	0	0	0
Piperacillin-Tazobactam	NT		NT		NT		3	100	0	0	1	100

Staphylococcus aureus was the highest organism isolated from this study 25(44.6%) followed closely by *Staphylococcus epidermidis* 21 (37.5%). This finding combined the predominant pathogens from developing and developed countries together. *S. aureus* remains the dominant pathogen causing neonatal sepsis in developing countries accounting for 18% - 25% [12] [21] of all isolates from neonate with neonatal sepsis whereas in developed countries group B *Streptococcus* and CONS are the predominant pathogen isolated. [26] The reason for this may not be far from the cosmopolitan nature of Lagos and LASUTH itself that receives patient from all strata of the cosmopolitan society.

Among the gram-negative bacilli, the *Klebsiella pneumoniae* demonstrated maximum susceptibility to Meropenem and Cefepime (100% respectively) and fair susceptibility to Levofloxacin (67%) while showing maximum resistance to 3rd generation cephalosporin, ciprofloxacin and gentamycin. This is in agreement with several studies from India, Egypt and Ghana where MDR Klebsiella pneumoniae were isolated and only sensitive to Meropenem and levofloxacin. [27] [28]

The pseudomonas demonstrated high susceptibility to Aminoglycosides, Le-

vofloxacin, Cefepime and Piperacillin/tazobactam but high resistance to cefotaxime and ciprofloxacin. This finding is in concurrent with studies from Ghana [26].

The Acinetobacter isolated from this study is generally susceptible except to ciprofloxacin, gentamycin and piperacillin/tazobactam. This is quite uncommon as most isolate of *Acinetobacter baumanii* in clinical settings are MDR strains.

The findings from this study revealed very encouraging results in that gram-positive bacteria isolate are susceptible to linezolid and vancomycin, which is also supported by the findings of other studies. [24] Whereas it showed high resistance to penicillin, cloxacillin, ciprofloxacin and cotrimoxazole. Vancomycin and linezolid could be considered as safe antibiotics of choice for the successful empiric treatment of suspected neonatal sepsis cases caused by gram positive bacterial infections.

The overall resistance of gram-positive isolates to cefotaxime is 34.5% while that of gram negative is 50%. This is a big threat to the unit as cefotaxime and amikacin are currently used as the first line empirical antibiotic. This will account for about 40% failure in first line antibiotic therapy.

The overall resistance to ciprofloxacin among gram positive and gram-negative isolate is 48% and 100% respectively. This is quite alarming as neonates with gram negative sepsis on 2nd line antibiotic is likely to die thereafter.

In general, the high antibiotic resistance rates among bacterial isolates might be due to the emergence of antimicrobial resistance which is a normal evolutionary process for microorganisms that is accelerated by the selective pressure exerted by widespread antibiotic use and misuse; poor infection prevention and control measures in neonatal unit and lack of adherence to the unit protocol on Infection prevention and control.

5. Conclusions

The culture-positive rate in this study was 32.5%. Gram positive organisms were predominant accounting for 84.0%. *Staphylococcus aureus* was the predominant isolate accounting for 44.6%. Both gram positive and gran negative organisms showed high resistant to commonly used antibiotic.

This study will recommend the combination of vancomycin and meropenem as the 2nd line antibiotic. However, continuous surveillance and periodic evaluation is necessary.

6. Limitations

This study had some limitations. Firstly, is the retrospective nature of the study that is based on the data collected form laboratory records which lack information about the neonates' hospitalization date, clinical information, and treatment outcome. Second, this study was conducted only at the inborn session of the neonatal unit of the hospital; therefore, the antibiotic resistance patterns observed in our study might not generalize the entire state and country at large even though other reports in the country supported our findings.

7. What Is Already Known

It is already known that bacterial are the commonest cause of neonatal sepsis and also that this bacterial are becoming resistance to commonly used antibiotic.

8. What This Study Adds

This study is able to identify the common bacterial isolate of neonatal sepsis in our facility and it also reveals the resistance profile of such bacterial isolates.

Authors Contribution

Author 1 (Oluwadamilare Afolabi Obe): Conceptualization, design, data collection, data analysis, funding, literature review, and writing.

Author 2 (Wasiu Bamidele Mutiu): Conceptualization, design, data collection, data analysis, funding, critical review.

Author 3 (Peter Odion Ubuane): Conceptualization, design, sample collection, literature review.

Author 4 (Ibrahim Oladipupo Odulate): Data collection, laboratory work, data analysis, literature review.

Conflicts of Interest

The authors declare no conflicts of interest.

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