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Original Article

Methicillin resistant staphylococcus aureus infection in neonates- a major concern and a call for action

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Abstract

Background: Methicillin-Resistant *Staphylococcus aureus* (MRSA) is both a human commensal and a pathogen that causes neonatal infection which is associated with significant morbidity and mortality. Its genetic flexibility and versatility have equipped it with the ability to develop resistance to numerous antibiotics. Outbreaks of infections in neonatal intensive care units as well as community infections have been reported mostly in developed countries. However, there is a paucity of data on neonatal MRSA infection in developing countries. The study aims to highlight cases of MRSA infection, describe the clinical presentation, and outline the antibiotic susceptibility pattern among term neonates in our facility.

Methodology: It was a prospective cross-sectional hospital-based study carried out from October 2018 to July 2019. A total of 248 term neonates with suspected sepsis were enrolled in the study and had their blood samples taken for investigations including blood culture. Bacterial identification and antibiotic susceptibility patterns were carried out using Microbact^{TM}24E (Oxiod UK) and Staph ID and modified Kirby-Bauer disk diffusion technique respectively.

Results: Out of the 248 subjects enrolled in the study, 34.2% had proven sepsis, with Staphylococcus species accounting for 56.4% of these cases. Among those with staphylococcal sepsis, 56.3% were found to have MRSA infection. Notably, the majority (94.4%) of cases originated from outside the hospital, presenting as neonatal sepsis with non-specific clinical features. Sensitivity testing revealed that ciprofloxacin and chloramphenicol were the most effective antibiotics against the identified pathogens.

Conclusion: The presence of MRSA infections in neonates poses a critical public health threat. This trend underscores the emergence of antimicrobial resistance, potentially compromising treatment efficacy and jeopardizing neonatal well-being. Urgent and decisive measures are necessary to curb this trajectory.

Keywords: Neonatal sepsis; Methicillin-Resistant *Staphylococcus aureus*; Resistance.

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Quick Response Code:

Introduction

Staphylococcus aureus is one of the most successful, versatile, and well-armed human commensal pathogens that was first described by Ogston in the 1880s.[1] It is a golden yellow gram-positive, non-motile, catalase, and coagulase-positive facultative anaerobe that grows in clusters, hence the name. The success of *Staphylococcus aureus* as a human pathogen arises from the armoury of virulence factors it has evolved to combat host defense mechanisms as well as its ability to develop antibiotic resistance.[2] Resistance to penicillin first appeared in the 1940s just 2 years after initial success[3,4] and to semi-synthetic B-lactams resulting in the birth of Methicillin-Resistant *Staphylococcus aureus* strains (MRSA) in the 1960s.[5] Resistance was achieved through a mobile genetic element called Staphylococcal Chromosome Cassette mec (SCCmec**).**[6] Until the 1990s, MRSA was considered to be a hospital-acquired infection (HA-MRSA) but spread beyond the hospital to become community-associated (CA-MRSA) about 10years later in the 21st century.[2] The difference in the two types of MRSA infection lies in their resistance to non-beta-lactam antibiotics, SCCmec trait, and synthesis of Panton-Valentine leucocidin.[7] The first case of MRSA infection in a neonate was reported in 1981 as a case of osteomyelitis.[8] Since then, several cases have been reported mostly as infection outbreaks in neonatal intensive care units[7], though community-acquired infections have been reported and are on the rise [7,9] in developed countries. There is a paucity of data on the burden of infection in developing countries. Colonisation by the organism precedes infection thus, it predominantly inhabits the anterior nares and less commonly other body parts like the umbilicus, pharynx, axilla, groin, and perineum.[10,11] The routes through which neonates become colonised include the birth canal, breastfeeding, and contact with individuals and the surrounding environment.[10,12,13] The most important risk factor for MRSA colonisation and subsequent infection is prematurity.[7] Other risk factors include prolonged hospitalization, overcrowding and under-staffing in neonatal wards, long-term use of respiratory support, intravascular catheters, antibiotics, total parenteral nutrition, and surgical procedures.[7] The clinical manifestation of MRSA infections is a spectrum from mild focal infection to non-specific or severe invasive disease frequently presenting as late-onset sepsis (LOS).[14,15,16] Varying treatment with antibiotics has been tried with different success, but vancomycin remains the last resort option.[7,17] As MRSA colonisation precedes infection, decolonisation may be the key to preventing infection with its attendant consequences. Varying success has been reported in some nurseries that have adopted active MRSA surveillance cultures and decolonisation using nasal mupirocin with/without an antiseptic bath.[7]

The aim of the study is to highlight cases of MRSA (Methicillin-Resistant *Staphylococcus aureus*) infections, examine their clinical presentation, and assess antibiotic susceptibility in neonates in our centre.

Methodology

The cross-sectional study was conducted at the neonatal unit of Ahmadu Bello University Teaching Hospital (ABUTH)- a tertiary hospital located in Zaria, Kaduna state over a 10-month period from October 2018 to July 2019. All term neonates with at least three or more risk factors and/ or clinical features of infection were assessed and consecutive neonates who fulfilled the criteria were recruited and had their samples taken at admission for blood culture, complete blood count (CBC), C-reactive protein (CRP) and procalcitonin (PCT). Neonates with positive blood cultures were recruited for the study and their sociodemographic and clinical parameters were analysed. The study was approved by the Health Research and Ethics Committee of the hospital (ABUTHZ/HREC/Z04/2017).

Bacterial identification and susceptibility testing

Blood specimens (3mls) from neonates with presumptive bloodstream infections were taken under aseptic conditions and immediately transferred into a blood culture bottle containing 15mls of Brain Heart Infusion and incubated aerobically at 37^{o}C for a maximum period of seven days. Broth with signs

of growth was immediately removed and sub-cultured on 5% Sheep blood and MacConkey agar plate and incubated in the same condition as the broth above for 24hours. Growths from both culture plates were examined and gram stained. Isolates were sub-cultured on Nutrient agar (NA) for further identification and biochemical testing with Staph ID was used to identify the organisms according to the manufacturer's instructions.

Antimicrobial susceptibility testing (AST) for every organism isolated using the modified Kirby-Bauer disk diffusion technique, was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines.[18]The following antibiotics were tested; Amoxicillin/clavulanate (20/10ug), Ceftriaxone (30ug), Ceftazidime (30ug), Chloramphenicol (30ug), Ciprofloxacin (5ug), Cefoxitin (30 ug), Gentamicin (10ug), and Meropenem (10ug) according to the Clinical and Laboratory Standards Institute

Methicillin resistance was defined as *Staphylococcus aureus* zone of inhibition of diameter ≤21 mm by cefoxitin (30 µg) antibiotic disk.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22 IBM SPSS Inc, Chicago Illinois, United States of America. Values were expressed as count/percentages, mean/standard deviation, or median and interquartile range (IQR). $P < 0.05$ was considered statistically significant

Results

The study enrolled 248 neonates with suspected sepsis which was confirmed in 94 patients (37.9%). Staphylococcus species were isolated in 32 (34%) of the confirmed cases. Notably, Methicillin-resistant Staphylococcus aureus (MRSA) accounted for 18 (56.3%) of the Staphylococcal isolates, representing 19.1% of the total confirmed cases. There were equal numbers of both males and females. Most of the neonates (66.7%) had late-onset sepsis and a significant portion of which (94.4%) came from outside our hospital. This is depicted in Figure 1 and Table I below.

Table I:General characteristics of the studied subject with MRSA infection

Parameter	Frequency (n)	Percentage (%)
Total number of MRSA infections	**18**	100
Sex		
Male	9	50
Female	9	50
Weight*	2.8±0.6	
Gestational age*	39±1.1	
Age at onset of symptoms		
<72hours	6	33.3
≥72hrs	12	66.7
Mode of ward entry		
In-born	1	5.60
Out-born	17	94.4

*=mean

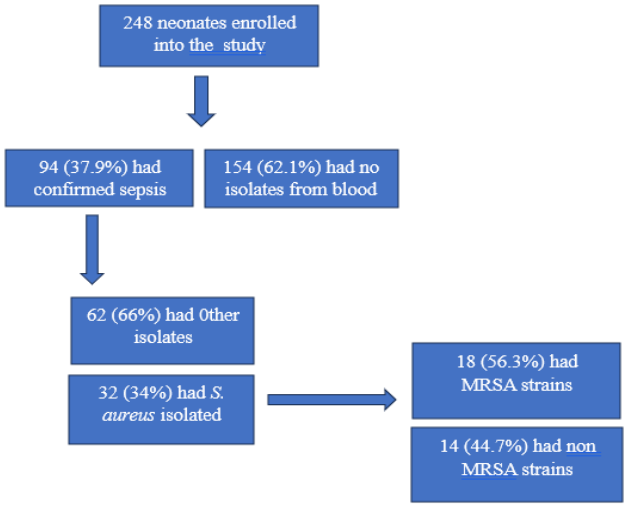

Figure 1: Flowchart showing the pattern of blood culture isolates in studied neonates

Table II showed the common symptoms of MRSA infection to be fever, poor suck, and convulsion while the signs were pyrexia, depressed primitive reflexes, and lethargy.

Table II: Common presenting symptoms and signs of neonatal MRSA infection

Symptoms	Frequency(n)	Percentage (%)
Fever	13	72.2
Poor suck	12	66.7
Convulsion	11	61.1
Yellowish discoloration of the body	9	50.0
Poor activity	4	22.2
Abnormal cry	3	16.7
Signs		
Pyrexia	10	55.6
Depressed primitive reflexes	10	55.6
Lethargy	7	38.9
Hypotonia	6	33.3
Hypoxaemia	5	27.8
Pallor	4	22.2

Table III below shows Ciprofloxacin, and chloramphenicol had the highest sensitivity (61.1%) while penicillin and cefoxitin had the highest resistance (100%). Resistance to ciprofloxacin was also high.

Table III: Antibiotic susceptibility pattern of MRSA isolates

Antibiotic tested	Sensitive, n (%)	Resistant, n (%)
Amoxycillin-clavulanate	2(11.1)	1(5.6)
Ceftriaxone	-	1(5.6)
Cefoxitin	-	18(100)
Ceftazidime	1(5.6)	-
Ciprofloxacin	11(61.1)	6(33.0)
Chloramphenicol	11(61.1)	3(16.7)

Clindamycin	6(33.3)	7(38.9)
Gentamicin	8(44.4)	1(5.6)
Penicillin	-	18(100)

Table IV below shows that most (77.8%) of our studied neonates were discharged with an average duration of hospital stay of nine days.

Table IV: Outcome of admission of neonates with MRSA infection

Outcome of admission	Frequency (n)	Percentage (%)
Discharged	14	77.8
Died	1	5.6
Missing	3	16.6
Duration of hospital stay	9±4.4*	

* Mean

Discussion

This study identified a concerningly high prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) at 36% among patients with sepsis. This percentage is significantly higher than those reported in previous studies by Idris et al[19]. in Kano (27.2%), Sa'adu et al[20]. in Ilorin (37%), and Uwe et al[21].in Lagos (47%). While lower than the prevalence observed by Obadare et al. in Ile-Ife (87%), it nonetheless represents a cause for concern. This study contributes to a growing body of evidence suggesting a concerning shift in the predominant aetiology of neonatal sepsis (NS) within our institution. Prior investigations by Onalo et al[22]. identified Staphylococcus aureus as the primary causative pathogen, followed by a subsequent period where Escherichia coli emerged as the most prevalent organism, as documented by Olorokooba et al[23]. Our current data demonstrates a seemingly cyclical shift, with Staphylococcus aureus re-emerging as the leading cause of NS. Furthermore, this phenomenon is compounded by a particularly troubling trend: the emergence of MRSA strains within this species. Notably, neither of the aforementioned studies reported the presence of MRSA in their investigations. This observation aligns with recent findings documented by Uwe and Medugu et al[21,24]. in their respective centres in Lagos and Abuja, respectively, suggesting a broader geographical trend of a shift from predominantly Enterobacteriaceae to MRSA as the primary culprit in neonatal sepsis. A review of prior investigations conducted in Kano, Ilorin, and Ile-Ife by Nwanko, Mokoulu, and Ako-nai et al.[25,26,27] revealed a notable shift in the epidemiology of neonatal sepsis (NS) caused by Staphylococcus aureus. While these earlier studies (conducted over a decade ago) documented Staphylococcus aureus as the most prevalent causative agent of NS, with a prevalence ranging from 25% to 33.8%, they did not report any MRSA strains. Conversely, more recent studies conducted in these same regions have documented the presence of MRSA in neonates with *Staphylococcus aureus* sepsis. The prevalence of MRSA in this context has been reported to range from 27.2% to 87%.[19,20,28] The reasons for this observed shift remain unclear, warranting further investigation. Potential contributing factors could include changes in the microbial organism colonizing the maternal genital tract or the environment, a rise in antimicrobial resistance, the influence of climate change, or a combination of these. Regardless of the specific cause, this trend necessitates further exploration to understand its implications and develop appropriate interventions. We also found MRSA Infection in our study to be sporadic presenting as either EOS or LOS and therefore, likely to be community-acquired. This observation was similarly reported by Idris, Saadu, Uwe, and Obadare et al in Kano, Ilorin, Ile-Ife, and Lagos respectively.,[20,21,28] and also in contrast

to reports in developed countries where MRSA infection in neonates was mostly as a result of outbreaks in NICUs and therefore, hospital-associated.[7] Despite the lack of extensive data on the actual prevalence of neonatal MRSA colonization and infection in developing countries, including Nigeria, the number of neonatal MRSA cases presenting at hospitals, as we've pointed out, suggests a potentially high burden of colonization or infection within the community. It may be safe to extrapolate that, while MRSA infection in neonates in developed countries is likely a result of advances in neonatal care, in developing countries it is a problem of poverty with its attendant consequences. In our study, we discovered that early-onset MRSA (EOS) infection occurred in 33.3% of cases. This is likely attributed to acquisition through the maternal genital tract as the baby traverses the birth canal during delivery. This assumption is supported by previous studies in Nigeria, which have reported high MRSA carriage rates in urine samples from healthy women and high rates of MRSA detection in vaginal swabs of pregnant women, reaching up to37%.[29,30] Additionally, there is a possibility of contamination of delivery items with MRSA from the environment, especially in home deliveries. We found that almost all the deliveries occurred outside the hospital and usually home deliveries attended by either a relative or a traditional birth attendant are the norm in our environment. We believe that the potential source of early colonization and subsequent infection may be linked to either the maternal birth canal or the hands of the birth attendant. The question arises: which is a safer option in terms of minimizing the risk of transmission? Conversely, we suspect that the source of LOS MRSA infection could potentially be through breastfeeding, as reported by Schaumburg et al.[13] Additionally, contact with the mother and other individuals may play a role, especially considering our cultural practices where newborns are often passed around to well-wishers in the first few days of life potentially increasing the risk of exposure to MRSA. Moreover, the lack of data on MRSA colonization in the general population in our country, coupled with poor environmental sanitation, further complicates the situation. Clinical features of MRSA are a spectrum with non-specific features at one end and invasive disease leading to death at the other end. We found non-specific features similar to the report by Vergnano et al [14] and in contrast to reports by other authors.[16,31,32] We speculated the reasons for such differences to arise from; the level of maturity and immune system development, type of MRSA strain, source of infection, initial infecting dose, and time of presentation to the hospital. Community-acquired MRSA is known to be more sensitive to antibiotics, unlike hospital-acquired infections.[7] Antibiotics with the most sensitivity in this study were ciprofloxacin and chloramphenicol and at best this can be said to be fair, a similar finding was reported by Medugu et al[24] and in contrast to the report by Uwe et al[19] and Obadare et al[28] who reported poor sensitivity to levofloxacin and ciprofloxacin respectively. Again, this shows an increasing trend in antimicrobial resistance and there is virtually non-existent data on the genotype of the MRSA strain causing neonatal infection and what role it plays on antimicrobial resistance in Nigeria. We speculated on several plausible reasons for the observed trend, including the emergence of HA-MRSA strains in the community, loss of phenotypic and genotypic distinctions between HA-MRSA and CA-MRSA, as reported in literature.[7]Additionally, we considered the possibility of new mutations giving rise to hybrid or novel strains, particularly since strains with un-typeable genotypes have been reported in adults in our country in previous years.[33] We also think that indiscriminate and rampant use of antibiotics in our environment is widespread and this is as a result of easy access to most if not all antibiotics over the counter for both humans and animals, fake and substandard drugs and lack of antibiotic stewardship even in formal setting may be contributory.

Our unit policy for the treatment of neonatal sepsis is ampicillin-cloxacillin and gentamicin as is also obtained in the WHO and national guidelines and ciprofloxacin is used as 2nd line drug. Looking at our findings, while ciprofloxacin and chloramphenicol have the highest sensitivity, ciprofloxacin is cheap, readily available with fewer side effects than chloramphenicol, and therefore, maybe the better option as a first-line drug. The dilemma is, ciprofloxacin is one of the 2nd line drugs used in the treatment of multi-drug resistance (MDR) tuberculosis (TB). If it is made antibiotic of first choice in the treatment of NS, it could potentially impact the future treatment of MDR TB, especially considering the high burden of TB in our environment. This is exacerbated by issues such as poor antibiotic stewardship, the adaptability of the causative organism with genetic flexibility, and the likely escalation of resistance to antimicrobials

inclusive of fluoroquinolones[17]on one hand. Conversely, it offers the advantage of reduced hospital stay, cost of care, and improved short and long-term clinical outcomes. This scenario highlights the delicate balance between addressing immediate healthcare needs and safeguarding the efficacy of antibiotics for future challenges. Vancomycin sensitivity was not assessed in our study. Being the antibiotic of last resort, it could serve as a beacon of hope for the treatment of MRSA infection in the future if the current trend persists unabated. The unavailability and high cost of vancomycin in our environment might serve as a barrier against the development of resistance to the organism thereby providing a vital treatment option in cases where other antibiotics fail. However, this unaffordability may again hinder its use in our environment as most of the population lives in extreme poverty.

The prognosis from our study was excellent; however, the hospital stay was extended. We suspect that the reported higher virulence of CA-MRSA leading to a more pronounced inflammatory response is contributory. Also, the choice of the first-line antibiotic may be another factor, particularly since the traditional method of organism isolation, which is cumbersome and takes an average of 5-6 days was employed. This may have likely increased the overall cost of care and long-term morbidity.

Conclusion

This study revealed a high prevalence of (MRSA) infection in neonates with Staphylococcus sepsis, potentially signifying an emerging trend. The non-specific nature of the clinical features and the predominance of cases coming from the community may add another layer of complexity. While ciprofloxacin and chloramphenicol exhibit moderate in vitro sensitivity to some MRSA strains, their deployment as first-line therapy for suspected neonatal MRSA sepsis may not be the best option painting a concerning picture. This trend, compounded by the dearth of novel antibiotic development, presents a significant public health challenge, akin to a ticking time bomb. While reversing this trend entirely may prove challenging, decisive action is necessary to curb its progression and alter the current narrative I

Recommendation

Understanding our starting point is crucial for charting a successful course forward. In alignment with this principle, we highly recommend conducting a multi-site study to accurately determine the true burden of MRSA colonization and infection in both neonates and the general population. This study should aim to identify the common types of MRSA strains present, their genotypes, and how these strains impact the clinical course of infection and antimicrobial resistance. By obtaining comprehensive data through such a study, we can better inform our strategies for the prevention, treatment, and control of MRSA infections in our population. These interventions should encompass public health enlightenment efforts, comprehensive MRSA surveillance both in hospitals and communities, enhanced hygiene practices (both personal and environmental, with a focus on hand hygiene), prudent antibiotic stewardship, and periodic decolonization measures. As the saying goes, "A stitch in time saves nine!"

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