Neonatal sepsis: Bacterial aetiological agents and drug sensitivity pattern in a tertiary hospital in North-Central Nigeria

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Abstract

Background: Neonatal sepsis is an important cause of neonatal morbidity and mortality in developing countries. Its successful treatment requires a foreknowledge of common aetiological agents and their drug sensitivity pattern.

Objective: To determine the prevalence of neonatal sepsis among suspected cases, the pathogens responsible for neonatal sepsis and their drug sensitivity pattern in the neonatal unit of Dalhatu Araf Specialist Hospital, Lafia, Nigeria.

Method: A descriptive cross-sectional study was conducted from 1st January to 31st August 2018. Neonates admitted into the neonatal unit for sepsis had blood taken for culture before commencement of antibiotics. Clinical features of neonates and maternal risk factors for sepsis were documented.

Results: Out of 106 neonates studied, 65 had confirmed bacterial sepsis giving a prevalence of 61%. *Escherichia coli* accounted for 29 (45%), *Klebsiella pneumoniae* for 13 (20%), *Staphylococcus aureus* for 13 (20%), *Coagulase negative Staphylococcus* for 13 (20%) and *Proteus species* for 2 (3%). All four isolates were highly sensitive to ciprofloxacin and gentamycin. *Escherichia coli* and *Klebsiella pneumoniae* showed significant resistance to ceftriaxone.

Conclusions: The commonest cause of neonatal sepsis in the study environment was *Escherichia coli.* Significant resistance against conventional drugs used in the treatment of neonatal sepsis was noted.

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Introduction

Neonatal sepsis (NNS) is a leading cause of neonatal mortality accounting for about 26% of neonatal mortality in developing countries[1-3]. Despite significant progress in the development of antibiotics, sepsis is still a threat to mankind[4]. Ever evolving resistant strains makes the management of sepsis very challenging[5]. The prevalence of NNS among suspected cases as reported in Nigerian literature was 25.3-38.8%[6-9]. A prevalence of 40.7% has been reported in Egypt[10], while 41.6% was reported in South India[11]. The aetiological agents could vary in the same centre with time[12]. *Staphylococcus aureus* was found to be the commonest isolate in most studies done in southwestern and northern Nigeria[6,7,13,14]. However, *Klebsiella pneumoniae* was the commonest isolate in studies done in Benin[8], southern Nigeria and in India[11].

The treatment of NNS is increasingly becoming difficult because of development of resistant strains of bacteria. The Nigerian Standard Treatment Guidelines recommends a combination of cephalosporin and aminoglycoside as first line treatment for NNS[15], while the World Health Organization (WHO) recommends a combination of penicillin and aminoglycoside[16]. However, in the face of increasing development of resistance against antibiotics, it is doubtful if these recommendations are effective in most cases of NNS. Effective treatment of NNS is dependent on a foreknowledge of the possible aetiological agents and their drug sensitivity pattern in a particular locality. There has been no previous study to identify the aetiological agents of NNS and their sensitivity pattern in the present facility. Treatment prior to this study has been based on the Nigerian Standard Treatment Guidelines or the WHO Guidelines.

Objectives

The present study was conducted to determine the bacterial pathogens responsible for NNS and their drug sensitivity pattern, so as to validate either the Nigerian Standard Treatment Guidelines for NNS,

or the WHO recommendations for treatment of NNS at the study centre.

Method

The study was a descriptive cross-sectional study conducted from 1st January 2018 to 31st August 2018 in Dalhatu Araf Specialist Hospital (DASH), Lafia, Nigeria. The hospital is a tertiary health facility situated in north-central Nigeria, and serves as a referral centre for patients in Nasarawa State and parts of neighbouring states of Benue, Plateau and Kaduna. Ethical clearance was obtained from the Ethics Committee in the hospital. Informed consent was also obtained from caregivers of neonates. Neonates admitted with features suggestive of sepsis were recruited provided they had not been commenced on antibiotics before presentation. About 2 ml of venous blood was collected in an aseptic manner from each neonate, and samples were transferred immediately into brain-heart infusion medium. The blood samples were transported to the microbiology laboratory for incubation at a temperature of 37^0C.

Neonatal data, which included birth weight, gender, gestational age at birth and clinical features, were documented. Neonates were commenced on empirical treatment with penicillin and aminoglycoside combination or 3rd generation cephalosporin and aminoglycoside if meningitis was also entertained as a possible diagnosis. Preliminary blood culture result for each neonate was documented on day five of admission, and antibiotics were reviewed based on the preliminary result. Final result of blood culture was made available between days 7 and 10 of admission, when the neonates were reviewed for possible discharge. Treatment of neonates with confirmed bacterial sepsis was for 10-14 days before discharge. Collected data was entered into Microsoft Excel. Analysis of data was by GraphPad InStat 3.0, and Chi square test or Fisher's exact test was used to test for level of significance. A p value of <0.05 was considered significant.

Results

One hundred and six neonates were recruited over the study period. The demographic and clinical characteristics are shown in Table 1.

Table 1

Demographic and clinical characteristics (n=106)

Variable	Frequency (%)
Gender	
Male	54 (51)
Female	52 (49)
Weight	
<2.5kg	31 (29)
≥2.5kg	75 (71)
Mode of delivery	
Vaginal	79 (72.7)
Caesarean section	27 (27.3)
Location of delivery	
Hospital	91 (85.9)
Home	15 (14.1)

The mean maternal age was 27.7±5.2 years, the mean gestational age of neonates was 39.2±2.5 weeks and the mean admitting weight of neonates was 2.8± 0.8 kg as shown in table 2.

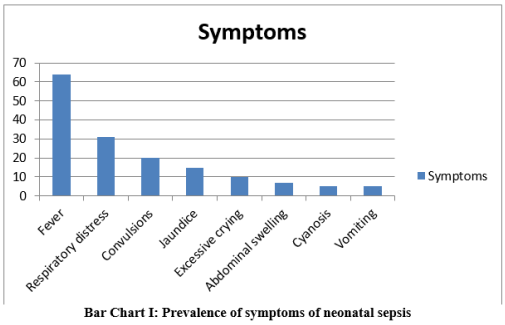
Table 2

Mean maternal age, gestational age, neonatal age and weight

Variable	Mean (SD)	Range
Maternal age (years)	27.7 (5.2)	18.0-45.0
Gestational age (weeks)	39.2 (2.5)	29.0-42.0
Age at presentation (hours)	99.6 (128)	0.5-720.0
Weight (kg)	2.8 (0.8)	1.2-4.4
Weight of neonates with neonatal sepsis	2.7 (0.7)	1.2-4.0
Weight of neonates without neonatal sepsis	2.9 (0.7)	1.3-4.4

SD: standard deviation

Fever was the commonest symptom occurring in 64 (60.4%) neonates. Neonates who presented with fever had a temperature range of 37.7^0C to 40.0^0C, and a mean (SD) temperature of 38.8 $(0.8)^0$C. Other symptoms included respiratory distress which occurred in 31 (29%), convulsions in 20 (18.8%), jaundice in 15 (14.1%), inconsolable cry in 10 (9.4%), abdominal swelling in 7 (6.6%), cyanosis and vomiting each of which occurred in 5 (4.7%) as shown in the bar chart 1.



Bar Chart I: Prevalence of symptoms of neonatal sepsis

Sixty-five (61.5%) neonates had positive blood cultures. The commonest isolate from the present study was *Escherichia coli* accounting for 45% isolates as shown in table 3.

Table 3
Prevalence of bacterial isolates (n=65)

Bacterium	n (%)
Escherichia coli	29 (45)
Klebsiella pneumoniae	13 (20)
Staphylococcus aureus	13 (20)
Coagulase negative Staphylococcus	08 (12)
Proteus species	02 (03)

Early onset NNS was commoner in the present study accounting for 50 (76.9%) of studied neonates, while 15 (23.1%) were due to late onset NNS. *Escherichia coli* was the commonest isolate in early onset NNS, while *Staphylococcus aureus* was the commonest isolate in late onset NNS as shown in table 4.

Table 4
Distribution of bacterial aetiological agents based on time of onset of neonatal sepsis (n=65)

Bacterium	Early onset n (%)	Late onset n (%)
Escherichia coli	25 (86.0)	04 (14.0)
Klebsiella pneumoniae	05 (38.5)	08 (61.5)
Staphylococcus aureus	12 (92.3)	01 (07.7)
Coagulase negative Staphylococcus	08 (100.0)	0 (0)
Proteus species	0 (0)	02 (100.0)
Total	**50 (76.9)**	**15 (23.1)**

Bacterial isolates were most sensitive to ciprofloxacin and gentamycin while significant resistance was demonstrated by gram negative rods against ceftriaxone as shown in table 5.

There was a significant association noted between home delivery and NNS using Fisher's exact test as shown in table 6.

Table 5
Antibiotic sensitivity profile of bacterial isolates

Organism (n)	Amoxicillin	Cloxacillin	Gentamicin	Ceftriaxone	Ciprofloxacin
Escherichia coli (29)	82%	79%	90%	72%	100%
Klebsiella pneumoniae (13)	85%	100%	90%	90%	99%
Staphylococcus aureus (13)	84%	84%	100%	77%	100%
Coagulase negative Staphylococcus (08)	85%	100%	90%	90%	99%
Proteus species (02)	0%	0%	100%	100%	100%

Table 6
Associations between NNS and gender, weight, place and mode of delivery

Variable	Sepsis n (%)	No sepsis n (%)	Total n (%)	p-value
Gender				
Male	32 (30.2)	22 (20.8)	54 (51.0)	
Female	33 (31.2)	19 (17.8)	52 (49.0)	
Total	65 (61.4)	41 (38.6)	106 (100.0)	0.69
Weight				
≥2.5kg	23 (22.0)	08 (07.0)	31 (29.0)	
<2.5kg	42 (40.0)	33 (31.0)	75 (71.0)	
Total	65 (62.0)	41 (38.0)	106 (100.0)	0.12
Place				
Home	13 (12.3)	02 (01.8)	15 (14.1)	
Hospital	52 (49.1)	39 (36.8)	91 (85.9)	
Total	65 (61.4)	41 (38.6)	106 (100.0)	0.04
Mode of delivery				
Caesarean section	15 (14.2)	14 (13.2)	29 (27.4)	
Vaginal delivery	50 (47.2)	27 (25.5)	77 (72.7)	
Total	65 (61.4)	41 (38.6)	106 (100.0)	0.20

There were 6 (6.2%) deaths recorded in the study group during the study period. Two were due to *Escherichia coli* sepsis, two were due to *Coagulase negative staphylococcus* sepsis and the other two

had no bacterial sepsis. Deaths due to bacterial NNS constituted about 11% (4/36) of the overall neonatal mortality over the study period.

Discussion

The study has shown that the prevalence of bacterial NNS is high among suspected cases. The prevalence obtained in the present study is higher than studies done in other parts of the country. The highest reported prevalence in Nigeria was 55%, in Ile-Ife, south-western Nigeria[13]. A prevalence of 40.7% has been reported in Egypt[9], while 41.6% has been reported in South India[10]. The prevalence of bacterial sepsis among suspected cases is dependent on the selection criteria of cases. Most patients presenting to tertiary health facilities for treatment of sepsis usually would have sought treatment in a primary or secondary health facility before presenting[17,18]. These exposures to antibiotics before presenting to a referral centre can give a false negative culture result in about 50% of culture positive cases[19]. The deliberate exclusion of subjects who have had antibiotics prior to presentation in the present study, could have accounted for the higher prevalence of bacterial sepsis among suspected cases when compared to other studies which did not adopt the same exclusion criterion.

The present study has shown that home delivery is a risk factor for NNS and similar findings have been reported by other authors[20,21]. Home deliveries in Nigeria are usually characterized by unhygienic environment, use of unsterilized sharps and poor cord care[20,21.] It is sad to note that despite attendance for antenatal care in health facilities, many women for a number of reasons still choose to deliver at home. The prevalence of home deliveries among women who attend antenatal clinic is in the range of 15-74%, with the higher prevalence in northern Nigeria[22-24]. There are several factors that contribute to this unfortunate incidence and they include inaccessibility to health facilities, labour occurring at night, attitude of health workers to pregnant women and high cost of delivery in some health facilities. Most of these home deliveries have no skilled birth attendants[25].

Escherichia coli was the commonest isolate from the present study. *Escherichia coli* was also the commonest isolate from another study done in Jos, north-central Nigeria[26]. However, studies done in south-western Nigeria found *Staphylococcus aureus* to be the commonest isolate[7,13]. A study carried out in a rural district of eastern Uganda also found *Staphylococcus aureus* as the commonest isolate,[27] while a study done in rural part of India found *Klebsiella pneumonia* as the commonest isolate[11]. These findings are a reflection of the biological environment of the study centres. The implication of these different bacterial isolates responsible for NNS in different locations is that antibiotics useful in the management of sepsis in one region may not be effective in another region.

The Gram negative bacteria predominated in the early-onset NNS in the present study, and this has been reported by other authors[8.26]. Organisms causing early-onset neonatal sepsis are colonizers of the maternal genitourinary tract with vertical transmission through the amniotic fluid or placenta to the neonates. The pathogen may ascend when the amniotic membranes rupture or prior to the onset of labour, causing an intra-amniotic infection. Thus, the infant may acquire the pathogen either *in utero* or during labour and delivery[28,29]. The Gram positive bacteria predominated in late onset NNS as reported by other authors[8,26,30].

Bacterial agents were most susceptible to gentamicin and ciprofloxacin in the present study and a similar finding has been reported by other authors[7,8]. Despite the remarkable susceptibility profile of ciprofloxacin against bacterial isolates in the present study, there are concerns about its safety in children. Clinicians have used ciprofloxacin in special circumstances to treat children as reported in the literatures, but their findings are inconclusive[31,32]. Significant resistance against ceftriaxone was noted especially with the Gram negative bacteria. In recent times, ceftriaxone has been shown to be one of the most used and misused parenteral antibiotics and resistance has been widely reported across the globe[33,34]. This development is of serious concern to stakeholders in the health sector.

Cloxacillin in the present study was shown to be effective against all *Staphylococcus aureus* isolates. Cloxacillin has been shown to be effective against methicillin-susceptible *Staphylococcus aureus* in other studies[35,36]. Therefore, the combination of cloxacillin and gentamycin appears to present the best prospect for the treatment of neonatal sepsis from the present study. This combination will be effective against the isolates from this study that included Gram negative rods, *Staphylococcus aureus, Coagulase negative staphylococcus* and *Proteus spp.*

The overall mortality from the study was lower than the reported mortality in other studies[7,13]. However, this mortality may not be a true reflection of neonatal mortality from NNS because of the exclusion of neonates who were already commenced on antibiotics before presentation.

Conclusions

The predominant organism involved in early onset NNS was *Escherichia coli* while *Staphylococcus*

aureus predominated in late onset NNS. Significant resistance to ceftriaxone was observed in the present study.

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