Early Onset and Late Onset of Neonatal Sepsis in a Tertiary Hospital, South-South, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author AAA conceived the study. Author EOO designed the study protocol. Author AAA collected the data, author CUN analyzed and author EOO interpreted the data. Author AAA wrote the manuscript and author CUN revised the manuscript. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Aims: The study was carried out to determine organisms present during early onset of neonatal sepsis (EONNS), late onset of neonatal sepsis (LONNS) and their antimicrobial susceptibility pattern.
Methodology: This study is a retrospective evaluation of 453 neonatal blood cultures. Two (2) ml of blood from these neonates was cultured in thioglycollate broth and tryptone soya broth. This was carried out in the Department of Microbiology and Parasitology of the University of Port Harcourt Teaching Hospital, Nigeria between January-December 2007.
Results: Out of 453, 272(60.0%) neonates showed negative blood cultures, while 181(40.0%) neonates had positive bacterial cultures and 2 neonates (0.4%) were positive for *Candida albicans.* Overall, *Klebsiella* spp. was the most common pathogen, accounting for (37.8%) of the total isolates. Others were as follows; *Staphylococcus aureus* (28.4%), *Escherichia coli* (11.8%), unclassified coliforms 8.3%, *Pseudomonas* spp. 4.9%, *Enterococcus* spp. (2.9%), coagulase-negative Staphylococcus (CONS) (2.5%) and *Proteus* spp. (3.4%). Early onset neonatal sepsis

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(EONNS) and late onset neonatal sepsis (LONNS) had *Klebsiella* spp and *Staphylococcus aureus* as their common causes of neonatal sepsis respectively. *Klebsiella* spp. was susceptible to spafloxacin (87.0%) followed by ofloxacin (82.0%), amoxycillin-clavulanic acid (79.0%) and ceftazidime (65.0%) among the Gram-negative organisms. In the category of Gram-positive organisms, *Staphylococcus aureus* is highly sensitive to ofloxacin (81.0%) followed by spafloxacin (79.0%) and amoxicillin-clavulanic acid (71.0%).

Conclusion: A viable antibiotic susceptibility surveillance programme coupled with good infection control practices and rational antibiotics use will reduce infection rate, ensure better therapeutic success and prolong the efficacy of available antimicrobials.

1. INTRODUCTION

Neonatal sepsis may be defined clinically [1,2] and/or microbiologically, by positive blood and/or cerebrospinal fluid cultures. In this review, only microbiologically proven cases are included. Neonates represent one of the highest risk groups of hospitalized patients for sepsis, with up to 50% of neonatal intensive care unit (NICU) patients experiencing one or more episodes of sepsis [3]. Septicemia is a common cause of infants' morbidity and mortality in developing countries despite great advances in antimicrobial therapy, life support measures and the early detection of risk factors [4,5,6,7] as well as being associated with an increased risk of long-term neurological sequelae [7] and is also a major contributor to additional healthcare costs [3]. Neonatal sepsis is estimated to cause almost one million deaths and accounts for more than 25% of neonatal deaths worldwide [8]. Premature and ill infants have an increased susceptibility to sepsis and subtle nonspecific initial presentations; therefore, they require much vigilance so that sepsis can be identified and treated effectively [9].

Early-onset neonatal sepsis (EONNS) remains a feared cause of severe illness and death among infants of all birthweights and gestational ages, with particular impact among preterm infants [10]. Several clinical features are associated with the early stages of late-onset neonatal sepsis (LONNS), including primarily feeding intolerance and apnea, along with bradycardia and desaturations [11]. Heart rate variability has also been identified as a potential physiomarker [12], although other studies did not find elevated heart rate characteristics to improve detection of bloodstream infections, [13] and in studies predominantly among premature very low birth weight infants, LONNS hypotension has been noted to be a strong independent predictor [13].

Early signs of sepsis in the newborn are nonspecific, diagnostic studies are often ordered and treatment initiated in neonates before the presence of sepsis has been proven. Moreover, because the American Academy of Pediatrics (AAP), [14,15] the American College of Obstetricians and Gynecologists (ACOG), [16] and the Centers for Disease Control and Prevention (CDC) [17] all have recommended sepsis screening or treatment for various risk factors related to group B Streptococcus (GBS) infections, many asymptomatic neonates now undergo evaluation and are exposed to antibiotics. Factors predisposing to morbidity or mortality after neonatal sepsis include prolonged use of a central catheter and/or ventilation, recurrent nosocomial infections, and possibly, immunosuppression caused by the use of broad-spectrum antibiotics [18-20]. This study is aimed to determine bacteriological profile of common aetiologic agents present during early onset of neonatal sepsis (EONNS) and late onset of neonatal sepsis (LONNS).

2. MATERIALS AND METHODS

2.1 Study Area

This study was conducted in University of Port Harcourt Teaching Hospital, East West Road, Port Harcourt, Rivers State of the South-South region of Nigeria. Coordinates of study area has latitude 4°53´58" N and longitude 6°55´43" E.

2.2 Study Design

This study was a retrospective evaluation of admitted neonates into the Special Care Baby Unit (SCBU), diagnosed of suspected septicemia. Neonates had blood cultures test carried out in the Department of Microbiology and Parasitology of the University of Port Harcourt Teaching Hospital, Nigeria between the period of January-December 2007.

2.3 Study Population

A total of 453 neonates with septicemia were used for this study. The age and sex distribution of the 453 neonates with suspected septicemia are shown in Table 1. There were 251(55.4%) females and 202(44.6%) males. Bacteriological analysis was done following standard operating protocols in the microbiology laboratory of the hospital to determine aerobic and facultative microbial flora involved in these conditions.

Early-onset neonatal sepsis (EONNS) is most consistently defined as occurring in the first 3 days of life and is caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery [21]. Late-onset neonatal sepsis (LONNS) is sepsis occurring after 72 h in NICU infants and 7 days of life in term infants, has been variably defined as occurring up to the age of _90 or 120 days, and may be caused by vertically or horizontally acquired pathogens [22].

2.4 Inclusion Criteria

The study included neonates with clinical features and risk factors such as respiratory distress syndrome, fever, convulsions, abdominal distension, bronchopneumonia, macrosomia, omphalocoele, upper GIT obstruction, encephalocoele, hypoglycaemia, septic shock, imperforate anus, jaundice, electrolyte imbalance, meningitis, prematurity and prolonged labour.

2.5 Methods

2.5.1 Bacterial isolation and identification

Two (2) mL of blood samples were collected from subjects with suspected septicemia and dispensed into two universal bottles containing 5 mL (in a ratio of 1:5 each) of Thioglycollate and Tryptone soy broth (This was done with great care to avoid contamination of the specimen and culture medium). The blood specimens were incubated overnight. After incubation the samples from the Thioglycollate and Tryptone soy broths were subcultured onto Chocolate and MacConkey agar. The Chocolate agar was incubated at 37°C after being placed in a canister with candle to provide 5-10% CO_2 while the MacConkey agar was incubated aerobically. When there was no growth after the first subculture, cultures were reincubated further up to 7 days for final report, because of possible slow growth of the organisms. Following cultivation, organisms were identified using standard techniques as described by Cheesbrough [23]. Antibiotic sensitivity patterns of bacterial isolates were determined by agar diffusion method using Kirby-Bauer [24]. Control organisms such as *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853) *Enterococcus faecalis* ATTC 2921 and *Streptococcus pneumoniae* ATTC 49619 were included for interpretative standards criteria prescribed by the Clinical and Laboratory Standards Institute (CLSI) [25].

2.5.2 Fungal isolation and identification

Alongside with bacterial cultures, conventional methods (direct microscopic examination, Gram staining and germ tube test) was used to determine yeast cells by plated on Sabouraud Dextrose Agar (SDA) medium, and allowed for 24 hours in an incubator [23].

2.6 Statistical Analysis

Data generated were analyzed statistically using descriptive statistics and Chi square (X^2) using SPSS version 11.0 and EPI info version 6.04. Results of the analysis were expressed in percentages and the chi-square test was used to conclude the significance levels between the parameters, with the significant value set at 0.05 or 5% for 95% confidence interval.

3. RESULTS

A total of 453 samples were collected from neonates and examined over a period of 12 months (January-December 2007) at the University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria, where the female neonates had prevalence of 55.4% (Table 1).

The age group of the neonates in this study ranges from 0-28 days. The age group 0-3 days had positivity rate of 43.2% of bacterial cultures (Table 2).

The clinical features at admission were respiratory distress syndrome, jaundice, electrolyte imbalance, meningitis etc. Most babies had many clinical features in combination as seen in Table 3.

Out of 453 cases studied, growth of bacteria was obtained in 181(39.9%) blood samples and 2 neonates (0.4%) were positive for *Candida albicans.* Of the bacterial isolates the most frequent offender was *Klebsiella* spp. (37.7%)

followed by *Staphylococcus aureus* (28.4%), spp. *Escherichia coli* and unclassified coliforms (10.4%) respectively and other less frequent isolates (Table 4). In early onset disease (age 0-3 days), the most common isolate was *Klebsiella* (40.3%) and *S. aureus* (26.7%) followed by *E. coli* and unclassified coliforms (10.6%). In late onset illness (age 4-28 days) however, *S. aureus* (41.0%) was the major pathogen followed by *Klebsiella* spp (18.1%) as shown in Table 4.

The pattern of sensitivity of these organisms was analysed for two groups of antibiotics: tetracycline and resistance was common with cotrimoxazole (82.6%), gentamicin (97.1%),

chloramphenicol (58.0%), erythromycin (100%) and cloxacillin (85.5%) respectively (Table 5), which are used as first line antibiotics; amoxicillin-clavulanic acid, cephalosporins and quinolones were used as a second line antibiotics.

Among the Gram-positive organisms, *Staphylococcus aureus* is highly sensitive to ofloxacin (86.5%) followed by spafloxacin (84.6%) and amoxicillin-clavulanic acid (67.3%), ceftadizime (59.6%) while cotrimoxazole (82.7%), cloxacillin (65.3%) and erythromycin (78.8%) were found to be less effective. Other Gram-positive organisms had less isolates (Table 5).

Table 1. Sex-related distribution of subjects

Number of subjects (neonates) examined						
Status	Male	Female	Total	No (%) of positive isolate	Chi square	P-value
EONNS	173	219	392 (86.5)	161(88.9)	11.07	0.050
LONNS	29	32	61(13.5)	20(11.1)		
Total(%)	202(44.6)	251(55.4)	453(100)	181(100)		

Legend: EONNS: - Early Onset of Neonatal Sepsis; LONNS: - Late Onset of Neonatal Sepsis; Sex-related distribution: - p > 0.05

Table 2. Age group distribution of subjects

Age Group (Day)	Number (%) with positive bacterial cultures	Number of neonates examined				
		Male (%)	Female (%)	Total(%)	Chi square (X^2)	P-value
0-3	161(43.2)	170(84.2)	202(80.5)	372(82.1)	3.84	0.059
4-28	20(24.7)	32(15.8)	49(19.5)	81(17.9)		
Total(%)	181(39.9)	202(100)	251(100)	453(100)		

Age group distribution - (p > 0.05)

Table 3. Clinical manifestations of subjects (n=453)

Clinical features	Number (%)
Respiratory distress syndrome	105(37.5)
Meningitis	22(7.9)
Jaundice	59(21.1)
Fever	20(7.1)
Electrolyte imbalance	6(2.1)
Abdominal distension	3(1.1)
Bronchopneumonia	13(4.6)
Macrosomia	10(3.6)
Omphalocoele	10(3.6)
Upper GIT obstruction	6(2.1)
Encephalocoele	9(3.2)
Hypoglycaemia	7(2.5)
Septic shock	7(2.5)
Imperforate anus	3(1.1)
Total	280(100)

Table 4. Bacterial and fungal isolates from blood cultures of 183 neonates with neonatal sepsis

Organisms	EONNS (%)	Chi square	P-value	LONNS (%)	Chi square	P-value	Total
Gram-positive							
Staph. aureus	43(26.7)	4.37	0.037	9(41.0)	11.70	0.110	52(28.4)
CONS	3(1.9)			0(0.0)			3(1.6)
Enterococcus spp	3(1.8)			2(9.1)			5(2.7)
Gram-negative							
Klebsiella spp	65(40.3)			4(18.1)			69(37.7)
Escherichia coli	17(10.6)			2(9.1)			19(10.4)
Unclassified coliforms	17(10.6)			2(9.1)			19(10.4)
Pseudomonas spp	7(4.4)			2(9.1)			9(5.0)
Proteus spp	5(3.1)			0(0.0)			5(2.7)
Fungi							
Candida albicans	1(0.6)			1(4.5)			2(1.1)
Total	161(100)			22(100)			183(100)

EONNS p-value- < 0.05; LONNS p-value- >0.05

Table 5. Antimicrobial susceptibility pattern of gram-positive isolates

Drugs		*Staphylococcus aureus (n=52)*	CONS (n=3)	*Enterococcus* spp. (n=5)
		First line antibiotics		
TET	S	29(55.8)	2(66.7)	2(40.0)
	R	23(44.2)	1(33.3)	3(60.0)
COT	S	9(17.3)	0(0.00)	0(0.00)
	R	43(82.7)		
GEN	S	27(52.0)	0(0.00)	1(20.0)
	R	25(48.0)		4(80.0)
CXC	S	18(34.6)	0(0.00)	1(20.0)
	R	34(65.4)		4(80.0)
ERY	S	8(15.4)	0(0.00)	1(20.0)
	R	44(84.6)		4(80.0)
CHL	S	20(38.5)	1(33.3)	1(20.0)
	R	32(61.5)	2(66.7)	4(80.0)
		Second line antibiotics		
OFL	S	45(86.5)	1(33.3)	3(60.0)
	R	7(13.5)	2(66.7)	2(40.0)
CAZ	S	31(59.6)	2(66.7)	4(80.0)
	R	21(40.4)	1(33.3)	1(20.0)
SPA	S	44(84.6)	1(33.3)	3(60.0)
	R	8(15.4)	2(66.7)	2(40.0)
AUG	S	35(67.3)	1(33.3)	3(60.0)
	R	17(32.7)	2(66.7)	2(40.0)

Legend: S- Sensitivity, R- Resistant, CONS- coagulase negative Staphylococcus, n- Number of isolates, Parenthesis - Percentage of susceptibility.
Legend: TET: Tetracycline, ERY: Erythromycin, CHL: Chloramphenicol, CAZ: CeftazidimeCXC: Cloxacillin, COT: Cotrimoxazole, SPA: Spafloxacin OFL: Ofloxacin, GEN: Gentamicin.

For the Gram-negative organisms, the antimicrobial sensitivity pattern showed that *Klebsiella* spp. was susceptible to spafloxacin (79.7%) followed by ofloxacin (59.9%), amoxycillin-clavulanic acid (72.5%) and ceftazidime (68.1%) among all the Gram-negative organisms. Resistance was common with cotrimoxazole (82.6%), gentamicin (97.1%), chloramphenicol (58.0%), erythromycin (100%) and cloxacillin (85.5%) respectively. Other Gram-positive organisms had less isolates (Table 6).

Table 6. Antimicrobial susceptibility of gram-negative organisms

Drugs		*Klebsiella* spp. (n=69)	*E. coli* (n=18)	*Proteus* spp. (n=5)	*Pseudo*. spp (n=3)	Coliforms (n=19)
First line antibiotics						
TET	S	40(58.0)	6(33.3)	2(40.0)	1(33.3)	6(31.6)
	R	29(42.0)	12(66.7)	3(60.0)	2(66.7)	13(68.4)
COT	S	18(26.0)	4(22.2)	0(0.00)	0(0.00)	4(21.0)
	R	51(74.0)	14(77.8)			15(78.9)
GEN	S	2(2.9)	0(0.00)	0(0.00)	2(66.7)	5(26.3)
	R	67(97.1)			1(33.3)	14(73.6)
CXC	S	13(18.8)	0(0.00)	1(20.0)	0(0.00)	5(26.3)
	R	56(81.2)		4(80.0)		14(73.6)
ERY	S	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	R					
CHL	S	29(42.0)	3(16.7)	0(0.00)	2(66.7)	4(21.0)
	R	40(58.0)	15(83.3)		1(33.3)	15(78.9)
Second line antibiotics						
OFL	S	40(58.0)	6(33.3)	4(80.0)	2(66.7)	10(52.3)
	R	29(42.0)	12(66.9)	1(20.0)	1(33.3)	9(47.4)
CAZ	S	47(68.1)	8(44.4)	0(0.00)	1(33.3)	0(0.00)
	R	22(31.9)	10(55.6)		2(66.7)	
SPA	S	55(79.7)	16(18.9)	4(80.0)	2(66.7)	12(63.2)
	R	14(20.3)	2(81.1)	1(20.0)	1(33.3)	7(36.8)
AUG	S	50(72.5)	3(16.7)	3(60.0)	2(66.7)	10(52.3)
	R	19(27.5)	15(83.3)	2(40.0)	1(33.3)	9(47.4)

Legend: S- Sensitivity; R- Resistant, n- Number of isolates; Parenthesis () - Percentage of susceptibility; TET: Tetracycline; ERY: Erythromycin; CHL: Chloramphenicol; CAZ: Ceftazidime; CXC: Cloxacillin; COT: Cotrimoxazole; SPA: Spafloxacin; OFL: Ofloxacin; GEN: Gentamicin

4. DISCUSSION

This study has demonstrated the continued role of septicemia in pediatric morbidity and mortality in this environment. In this study, it was observed that early-onset neonatal septicemia was more common than late-onset neonatal septicemia, this is similar to reports of Chako and Sohi in [26], Rasul et al. [27], West and Tabansi in [28], Peterside et al. [29], and Kurma, et al. [30] in which early-onset septicemia generally was more common.

In the blood stream infection, aetiological agents were isolated in 39.9% per 1000 neonates amongst 453 neonates. Other studies locally reported 29.7% and 44.9% of incidence in Ilorin and Calabar, Nigeria [31,32].

Recent studies carried out has authenticated the findings discovered in our study with slight increase in the incidence rate of 41.6%, 43.5%, 40.5%, 41.2% in Port Harcourt, Bayelsa, Jos and Enugu [28,29,33,34].

The reported incidence of neonatal sepsis varies from place to place; 7.1% to 38% by per 1000 live births in Asia [35,36] and 35.2% in India [30].

Respiratory distress syndrome was the major clinical features amongst other features with 36.0% in this study which is similar to recent studies by Kurma et al. [30] with 31.2%, Khante et al. [37] with 34.15% and 56% for study by Sathyamurthi et al. [38]. This indicates that, this clinical feature has been one of the greatest problems to neonates till date.

In this study early onset of neonatal sepsis (EONNS) (0-3 days of birth) was observed in 88.9% and late onset of neonatal sepsis (LONNS) (4-28 days) in 11.1% of neonates (Table 1). Other studies had reported 83.4% and 16.5%, 82.4% and 17.5%, 77.8% and 22.2%, 65% and 35% and 58.1% and 41.9% for early and late onset of neonatal sepsis respectively [36,39,40,30,41].

The females (251/453; 55.4%) are more susceptible to septicemia than males (202/453; 44.6%) in all age groups. This variation had no statistical significance (*p >0.05*). Suggesting that septicemia affect boys and girls equally. This observation was also reported in work carried out in Ile-Ife [42] and in Calabar [32], Nigeria. On the contrary, similar studies carried out in Bayelsa [29] had males 63.9% and females 36.1%, India

had males 70% and females 30% and Male 64.5% and Female 35.5% [39,41].

Gram-negative bacteria accounted for 66.2% of all isolates and were more recorded in early-onset of neonatal septicemia while Gram-positive bacteria had 33.8%. Elsewhere with similar studies, had the same report in Abeokuta and Enugu, Nigeria and India [43,34,30]. This recent studies have re-affirmed the role played by Gram-negative bacteria in this study. In contrast, Gram-positive organisms were reported in studies conducted in Ilorin, Bauchi and Bayelsa in Nigeria [30,44,28] and in India [39,41].

Klebsiella spp. was found to be the predominant organisms in the early onset of neonatal septicemia (EONNS). The bacterial isolated among the EONNS were statistically significant (*p* <0.05). Similar reports were observed in Abeokuta [43] and in India [30]. In contrast, reports in Ethiopia [45], in Nepal [46] and in India [39] found coagulase-negative Staphylococcus (CONS) as the predominant organism in EONNS.

In the late onset of neonatal septicemia (LONNS), *Staphylococcus aureus* was the most common organisms among all the organisms found. The bacterial isolated among the LONNS were not statistically significant (*p* >0.05). The result is similar to that in Ilorin [31] and in Iran [47]. This is because the association between late onset disease and neonatal septicemia could partly be related to passive acquisition of pathogenic *Staphylococcus aureus* from adult carriers like health workers and relatives at home. Mugalu et al. [48] suggested that since neonates more than 8 days old had been staying at home with the caretakers, the majority (70.9%) had *Staphylococcus aureus* isolated in their blood cultures. *Klebsiella pneumoniae* and CONS were the most common microorganisms. These data were comparable with other developing countries [49,50,51] in LONNS.

Klebsiella spp., coagulase-negative Staphylococcus (CONS) and *Staphylococcus aureus* were found to be the predominant organisms in both EONNS and LONNS in some studies in Osogbo and Saudi Arabia [52,53].

Two (2) patients were reported to have *Candida albicans* (0.4%) in this study. *Candida* spp. was also reported in studies carried out in Ile-Ife [42], Nigeria, India [54,55] and the China [56].

Candida is the third most common aetiologic agent in late-onset neonatal sepsis (>72 hrs of age) and is responsible for 8 to 15% of hospital-acquired infections [57]. According to Schrag et al. [58], *Candida* spp. are increasingly important causes of late-onset of neonatal septicemia (LONNS), occurring in 12 to 13% of very low birth weight (VLBW) infants. Candida colonization may also be acquired horizontally, primarily from the hands of health care workers. Candida infections are responsible for an 'attributable mortality' of 18-25%, significant morbidity and healthcare costs [59,60]. In a multicentre trial examining fungal colonization in six NICUs, *Candida* species were isolated on the hands of 29% of health care workers (859 of 2,989) [61]. From 1994 to 1998 at a single centre, 30% of infants with Candida sepsis (32 of 107) had growth of bacteria from the same blood culture or during the period of candidemia [62]. In another study in two NICUs, among 58 infants with Candida sepsis, 19% had concurrent bacteremia and fungemia [63].

Preterm infants have high Candida colonization rates compared to term infants and it is well established that colonization with Candida is inversely proportional to gestational age [64,65]. Premature infants with low birth weights have underdeveloped immune response and are hence predisposed to neonatal sepsis by Candida. This is because Candida colonization of the gut starts soon after birth and the administration of antibiotics and other predisposing factors such as prematurity may cause the spill-over of the organism into the blood and cause neonatal sepsis. This might have happened in the present case, as the mother was neither suffering from Candidal vaginitis nor was she a carrier [55].

Standard bacteriological and biochemical procedures were done to identify the organisms [23].

Klebsiella spp., the most common organism of neonatal sepsis, had Spafloxacin as the most effective antibiotic in the *in vitro* susceptibility testing. There was low degree of resistance to quinolones, particularly Spafloxacin a third generation quinolone.

In this study, first line antibiotics were less effective to the Gram-negative organisms.

Staphylococcus aureus was susceptible to Ofloxacin a second generation quinolone. This sensitivity of Ofloxacin was also confirmed in the

study carried out by Adejuyigbe et al. [66] on all the organisms isolated.

The quinolones have also been the drug of choice to similar and recent studies [67,34].

Spafloxacin and Ofloxacin were the most sensitive antibiotics to the predominant isolates seen in our study which indicated more concern. This is due to the side effects associated with the use of quinolones. However, more data from controlled trials are needed to further elucidate the safety profile of these drugs in neonates.

5. CONCLUSION

This research study identified *Klebsiella* spp and *Staphylococcus aureus* as the predominant aetiological agents of neonatal septicemia among neonates. Quinolones were found to be the drug of choice. Effective prophylactic measures, prompt and accurate diagnoses, and subsequent administration of targeted therapy are vital to curb the excessive burden of the disease.

This study had shown relevance to recent findings by researchers in septicemia in neonates, owing to the questions raised during the course of work, where quinolones was predominantly sensitive and replaced cephalosporins in their treatment regimens for septicemia.

CONSENT AND ETHICAL APPROVAL

Ethical clearance was obtained from the Research and Ethics Committee of the University of Port Harcourt Teaching Hospital. Informed consent was obtained from parents and guardian of in and out-patients subjects used for this study at the University of Port Harcourt Teaching Hospital, Nigeria prior sample collection.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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