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Neonatal septicaemia in Ilorin: bacterial pathogens and antibiotic sensitivity pattern

AO Mokuolu, N Jiya and OO Adesiyun
Department of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria.

Summary
All cases of septicemia among neonates admitted to the neonatal intensive care unit of the University of Ilorin Teaching Hospital, Ilorin, Nigeria between Jan 1995 and Dec 1996 were studied. Our aims were (1) to assess the incidence and microbial epidemiology of neonatal sepsis, (2) to generate baseline data and necessary research question for a proposed study on predictors of neonatal sepsis in our centre. Microbiology records of patients with confirmed septicemia was reviewed. Each of these babies had a single venous blood sample from a peripheral vein taken under aseptic conditions and before commencement of antibiotics. The needed data were entered into a *proforma*. Of the 198 neonates screened for sepsis, there were 61 (30.8%) positive blood cultures. Twenty-nine (48%) of these were in-born. The total number of live births in the hospital during the study period was 4118, thus giving a hospital-based incidence of neonatal sepsis of 7.04/1000 for in-born patients. The male: female ratio was 1.2:1. Overall *Staphylococcus aureus* was the commonest pathogen, accounting for 18 (29.5%) of the total isolates. Other pathogens were as follows; coagulase negative *Staphylococcus albus* 15 (24.6%), *Klebsiella spp* 10 (16.4%) and unclassified *Coliforms* 9 (14.8%). The predominant organisms in the first 48 hours were Gram negative bacilli; accounting for (70%) of the 10 isolates. Between 3 and 7 days of life the Gram positive cocci accounted for 12 (60%) of the 20 isolates while the Gram negative bacilli represented 40%. After 7 days, the predominant organism was *Staphylococcus aureus* (38.8%) while coagulase-negative *Staphylococci* were isolated in 7 of 31 isolates (22.6%). The sensitivity pattern showed that 94% of the organisms were sensitive to azythromicin, 77.8% to streptomycin, 73.3 % to gentamicin and 69.2% to ampicillin-sulbactam. For the cephalosporins the isolates showed a sensitivity rate of 69% to ceftriaxone, 66.7% to ceftazidime and 58.3% to cefuroxime. As a group the Gram positive organisms had 100% sensitivity to Azythromcin, 85% to ampicillin-sulbactam, 63% to ceftazidime and 62.5% to gentamicin. In the Gram negative group, the best overall sensitivity was to ceftriaxone (86.4%). Gentamicin had 85.7% while sensitivity to ceftazidime was 60%. The distribution of the organisms causing early and late onset sepsis were different. For early onset sepsis, the Gram negative bacilli as a group were the commonest organisms while *Staphylococcus aureus* was the commonest cause of late onset sepsis. There was a lower incidence of sepsis compared to reports from other parts of the country. This, in addition to differences in antibiotic sensitivity pattern call for more multi-centre studies on predictors of neonatal sepsis. The antibiotic sensitivity profiles suggest that the initial empirical choice of ampicillin-sulbactam and gentamicin appears to be the most rational for our environment.

Keywords: *Neonatal.septicaemia, bacterial pathogens, antibiotic sensitivity.*

Correspondence: Dr. OA Mokuolu, Department of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria. E-mail: mokuolu@ilorin,skannet.com.

Résumé
Tous les cas de la septicémie parmi les nouveau-nés admis entre la période de janvier 1995 à décembre 1996 au service de réanimation des nouveau-nés au centre hospitalier universitaire d'Ilorin ont été étudiés. Nos buts étaient (1) d'évaluer la fréquence et l'épidemologie microbien de la septicité néonatale (2) de générer des bases de données et des questions de recherche pour une étude proposé sur l'indice de septicité néonatal dans notre centre. Les dossiers microbiologie des malades de septicémie ont été réexaminés. Chacun de ces bébés avait un prélèvement de sang veineux prise d'une veine périphérique sous des conditions aseptiques et avant le commencement des antibiotiques. Les données réquises ont été inscrites dans un proforma. Parmi les 198 des nouveau-nés, qui ont subit un essai de dépistage de septicité, il y avait 61 (30,8%) de culture de sang positif. Vingt-neuf (48%) d'eux étaient congénitales. Le total des naissances dans l'hôpital pendant cette période d'étude était 4118 ainsi la fréquence de septicité néonatal basé sur les cas à l'hôpital était 7,04/1000 pour les malades congénitaux. La proportion de sexe masculin et de sexe féminin était 1 :2 :1. En totale, *staphylococcus aureus* était la pathogène causatif le plus commune dans 18 (29,5%) de la totalités des isolées. Les autres pathogènes étaient les suivants : *Staphylococcus albus* de coagulasse négatif 15(24,6%), *Klebsiella spp.* 10(16,4%) et les coliforms 9 nonclassifiés (14,8%). Les organismes prédominants dans les premiers 48 heures étaient *bacilli* de Gram négatif causatif de 7 (70%) des 10 isolées. Entre 3-7 jours de vie de cocci de Gram positif était causatif pour 12 (60%) des 20 isolées tandis que le bacilli de Gram négatif a représenté 40%. Après 7 jours l'organisme prédominant était *staphylococcus* aureus (38,8%). Alors que le staphylococci de coagulase négatif était identifiés dans 7 de 31 cas isolés (22,6%). Le type de sensibilité a montré que 94% d'organisme étaient sensible à l'Azythromicine, 77,8% à la Streptomicine, 73,3% à la Gentamicine et 69,2% à l'Ampicilline-sulbactam. Pour les cephalosporines, les isolées ont montré une propotion de sensibilité de 69% à ceftriaxone, 66,7% à ceftazidime et 58,3% à la cefuroxime. En temps que groupe, les organismes du Gram positive avaient 100% de sensibilité à l'Azythromicine, 85% à l'Ampicilline-sulbactam, 63% au ceftazidime et 62,5% au gentamycine. Dans le groupe de Gram négatif, la meilleure sensibilité était pour ceftriaxone (86,4%). Gentamycine avait 85% tandis que la sensibilité à ceftazydime était 60%. La distribution des organismes qui sont responsable de la septicité précoce et tardif étaient différents. Il y avait une fréquence inférieur de la septicité par comparaison aux rapports en provenance des autres parties du pays. En plus des différences dans le type de sensibilité antibiotique, ceci nécessite plus d' études de multicentre sur les indices de la septicité néonatale. L'esquisse de la sensibilité antibiotiques suggère que le choix empirique initial d'ampicilline-sulbactam et gentamicin est le plus rationnel pour notre milieu

Introduction

Neonatal septicaemia (NNS) remains an important cause of morbidity and mortality in Nigeria [1-4]. Hospital based incidence of NNS is high, ranging from 5 to 25/1000 live births and accounting for 20-25% of neonatal mortality [2,4-6]. This high

incidence is related to the prevalence of predisposing factors, and lack of basic amenities for optimal hygiene, especially potable water [5,6]. Management of the newborn with sepsis consists essentially of appropriate antibiotic therapy and supportive care. The choice of antibiotic therapy is best guided by the knowledge of aetiologic agent. This however, is usually not immediately possible. Thus, it is customary to initiate treatment with an empiric choice of antibiotic(s) that is informed by the epidemiology of causative agents and sensitivity patterns in a given locality [7].

In Nigeria, various neonatal units have reported different bacterial pathogens as leading causes of NNS. The most important causes were *Staphylococcus aureus*, *Klebsiella species* and *Escherichia coli*. Expectedly there has been a varied and changing antibiotic sensitivity pattern [8-10]. Recommendations for initial empirical choice of antibiotics include combinations of cloxacillin/gentamicin [7,11], or third generation cephalosporins/ gentamicin [12]. However, a recent study from Lagos raised the concern about possible inadequacies of these combinations. This was predicated on the observation of poor sensitivity of *Staphylococcus aureus* and *Klebsiella pneumoniae* to ceftazidime, 16.67% and 17.65%, respectively, while the sensitivity to gentamicin was 54.17% and 11.76% for the two organisms, respectively [13]. Recognizing the variation in the epidemiology of septicaemia from one newborn unit to the other, this study was undertaken to determine the antibiotic sensitivity pattern of bacterial isolates at the University of Ilorin Teaching Hospital, Ilorin. It was our intention that the findings would guide our initial empiric choice of antibiotics as well as the development of a protocol on a prospective study of neonatal sepsis in the unit.

Patients and methods

Study site: The University of Ilorin Teaching Hospital is a tertiary institution, which also functions as a secondary health facility due to inadequacy of manpower in the neighbouring government health facilities. It is located in the middle belt region of the country and receives referrals from six adjourning states. The labour and delivery unit is responsible for about 2,000 deliveries annually. The neonatal unit, which provides level II care, admits 600-700 babies annually.

Neonatal care practices: To keep nosocomial and other cross infections to the barest minimum, in-born and out-born patients are admitted to different sections of the ward. Strict asepsis is observed for all procedures, with meticulous hand washing in between patient contacts. Intravenous lines are sparingly used and when clearly indicated we prefer to insert an umbilical vein catheter (UVC) that is left in-situ until intravenous access is no more required. Thereafter the UVC is changed to a peripheral line for a brief transitional period preceding the commencement of oral feeds. To further reduce our need for intravenous access, most drugs are given intramuscularly except this is contraindicated (e.g., poor tissue perfusion and bleeding diathesis) or an intravenous administration is mandatory, either on account of the drug formulation or the index clinical condition. For all cases of suspected sepsis, the initial management usually consists of blood sampling for bacteriological and haematoglogical studies and initiation of an empiric antibiotic therapy. The outcome of the laboratory studies and the pattern of clinical progression guides subsequent treatment.

Data collection: A two-year review of the microbiology records of cases of confirmed septicemia was carried out. Each of these babies had a single venous blood sample from a peripheral vein taken under aseptic conditions and before commencement of antibiotics. Blood was cultured in glucose broth for aerobic organisms and in thioglycolate broth for anaerobic organisms. Processing of blood and identification of organisms was carried out in the microbiology laboratory using standard procedure[15]. Inoculated blood culture media were usually discarded as negative if there was no growth after 7 days of continuous incubation. Sensitivity was performed on Mueller-Hitton agar by the diffusion method of Baver and Kirby[16]. Data collected for each subject were date of admission, age, sex, indication for culture, bacteria isolates and antibiotic sensitivity pattern.

Data Analysis: Data was analyzed using the Epi-info version 6 statistical package on an IBM compatible microcomputer. Frequency tables were generated and the proportion of the desired variables were determined.

Results

Of the 198 neonates screened for sepsis, there were 61 (30.8%) positive blood cultures. Twenty-nine (48%) of these were in-born. The total number of live births in the hospital during the study period was 4118, thus giving a hospital-based incidence of neonatal sepsis of 7.04/1000 for in-born patients.

There were 33 males to 28 females thus giving a male: female ratio of 1.2:1. Ten (16.4%) of the babies presented within the first 48 hours, 20 (32.8%) presented between 3 and7 days and 31 (50.8) presented after the first week of life. Table 1 shows the distribution of causative organism isolated. Overall *Staphylococcus aureus* was the commonest pathogen, being responsible for 18 (29.5%) of the total isolates. Other pathogens were as follows; coagulase negative *Staphylococcus albus* 15 (24.6%), *Klebsiella* spp 10 (16.4%) and unclassified coliforms 9 (14.8%). The ratio of Gram positives to Gram negatives was 1.3:1.

Table 1: Distribution of organisms isolated by age at presentation

Organisms	Age at time of blood culture			Total isolates
	0-2days	3-7days	8-28days	
Staphylococcus aureus	1(10)*	5(25)	12(38.7)	18(29.5)
Coagulase negative Staphylococcus	2(20)	6(30)	7(22.6)	15(24.6)
Klebsiella pneumoniae	4(40)	1(5)	5(16.1)	10(16.4)
Coliforms	3(30)	5(25)	1(3.2)	9(14.8)
E-Coli	0(0)	2(10)	1(3.2)	3(4.9)
Acinectobacterspp	0(0)	0(0)	3(9.7)	3(4.9)
Enterococcus s faecalis	0(0)	1(5)	1(3.2)	2(3.3)
Pseudomonas aeroginosa	0(0)	0(0)	1(3.2)	1(1.6)
Total	10(16.4)	20(32.8)	31(50.8)	61(100)

Regarding the occurrence of organisms by the age at presentation, the predominant organisms in the first 48 hours were the Gram negative bacilli; accounting for 7(70%) of the 10 isolates. Between 3 and7 days of life the Gram positive cocci accounted for 12 (60%) of the 20 isolates while the Gram negative bacilli represented 40%. After 7 days the predominant organism was *Staphylococcus aureus* (38.8%) while coagulase-negative cocci were isolated in 7 of 31 isolates (22.6%).

The sensitivity pattern of the organisms is shown in Table 2. Ninety-four percent of all the organisms were sensitive

to azythromicin, 77.8% to streptomycin, 73.3 % to gentamicin and 69.2% to ampicillin-sulbactam. For the cephalosporins the isolates showed a sensitivity rate of 69% to ceftriaxone, 66.7% to ceftazidime and 58.3% to cefuroxime. As a group the Gram positive organisms had 100% sensitivity to azythromcin, 85% to ampicillin-sulbactam, 63% to ceftazidime and 62.5% to gentamicin. In the Gram negative group, the best overall sensitivity was to ceftriaxone (86.4%). Gentamicin had 85.7% while sensitivity to ceftazidime was 60%.

Sensitivity of the four leading organisms to the various antibiotics was as follows: *Staphylococcus aureus*, had 100% sensitivity to azithromycin, 88.9% to ampicillin-sulbactam and 71.4% to ceftazidime and 58.3% to gentamicin while sensitivity to cloxacillin was 25%. *Staphylococcus albus* had 100% sensitivity to Azithromycin, 83.3% to ampicillin, 75% to cefuroxime and 60% to gentamicin. For the *Klebsiella* species the sensitivity profile was 83.3% to ceftazidime, 75% to cefuroxime and cloxacillin and 66.7% to gentamicin. Regarding the unclassified coliforms there was 100% sensitivity to gentamicin, 88.9% to streptomycin and 80% to ceftriaxone and ceftazidime.

Table 2: Antibiotic sensitivity pattern for the various bacterial isolates

Organism	Erythro mycin	Penici llin	Ampici llin	Gentam icin	Ceftria xone	Ceftazi dime	Cloxa cillin	Strepto mycine	Cefuro xime	Ampicillin Sulbactam	Azythro omicin
Gram positives											
Staphylococcus	11(14)*	1(14)	1(6)	7(12)	6(11)	5(7)	3(12)	6(12)	1(5)	8(9)	8(8)
aureus	78.6%	7.1%	16.7%	58.3%	54.5%	71.4%	25%	60%	20%	88.9%	100%
Coagulase	5(11)	1(10)	5(6)	6(10)	1(3)	1(3)	2(7)	5(7)	3(4)	3(4)	2(2)
negative	45.5%	10.0%	83.3%	60.0%	33.3%	33.3%	28.6%	71.4%	75%	75%	100%
Staphylococcus											
Enterococcus	2(2)	0(2)	2(2)	2(2)	2(2)	1(2)	0(1)	2(2)	2(2)	1(1)	---
faecalis	100%	0%	100%	100%	100%	50%	0%	100%	100%	100%	---
Gram negatives											
klebsiella	---	---	1(4)	6(9)	5(6)	2(4)	3(4)	5(6)	5(6)	2(5)	2(2)
			25%	66.7%	83.3%	50%	75%	83.3%	83.3%	40%	100%
Coliforms	---	---	0(5)	9(9)	4(5)	4(5)	---	8(9)	1(5)	3(6)	4(5)
			0%	100%	80%	80%	---	88.9%	20%	50%	80%
Escherichia coli			0(2)	3(3)	2(2)	0(1)	---	2(2)	2(2)	1(1)	----
			0%	100%	100%	0%	---	!00%	100%	100%	----
Total	18(27)	2(26)	9(25)	33(45)	20(29)	14(21)	8(24)	28(36)	14(24)	18(26)	16(17)
	66.7%	7.7%	36.0%	73.3%	69.0%	66.7%	33.3%	77.8%	58.3%	69.2%	94.1%

*Figures in parenthesis represent total no of the isolates tested. † = Percentage sensitivity

Discussion

The hospital based incidence rate of neonatal septicaemia of 7.04/1,000 live births is comparable with that of 1-8/1000 live births reported from developed countries [18,19]. It is possible that this figure may be a slight under estimation of the burden of sepsis, because some of the in-born babies might have been taken else where for treatment when they fell ill. Nevertheless, it is much lower than the rates of between 17 and 35/1000 live births reported from several centres in the country in recent times [20,21,22]. This is in spite of similar blood culture positivity rate of about 30% in all the studies. While this study did not address the predisposing factors for NNS, the lower incidence may not be unconnected with the adoption of a number of locally pragmatic measures to curtail infection in our newborn unit. In addition to routine aseptic practices, we personalize the use of suctioning catheters, restrict the use of intravenous access to mandatory situations and administer most drugs intramuscularly except where there is poor tissue perfusion or when mandatory on the basis of the index condition/drug property. We adopted these measures because a previous in-house audit of sepsis in the unit revealed that of the 73% Gram negative organisms isolated among neonates with meningitis, 69% were nosocomially acquired [14]. The major culprit being practices related to securing intravenous access, especially by the house staff [14]. Such association between establishing venous lines and nosocomial sepsis has been reported elsewhere [15].

Of the 61 patients with positive blood cultures, 10 (16.4%) had early onset sepsis (<48hours) while 51 (73.6%) had late onset sepsis. Iroha *et al.* [21] also reported a higher preponderance of late onset sepsis in Lagos. This may be due to the prevalence of unhygienic practices in the community that promote sepsis. Regarding the distribution of the aetiologic agents, there was a sharp difference in the pattern of organisms responsible for early onset sepsis as compared to those causing late onset sepsis. About $^{2}/_{3}$ of the early onset infections were due to Gram negative organisms with *Klebsiella* accounting for 57% of these (Table 2), while Gram positive organisms constitute the remaining fraction. However, in late onset category the Gram positive organisms were predominant with *Staphylococcus aureus* accounting for 38.8% of the cases after the 1st week of life. The distribution of organisms in this study was different from those reported from other regions of the country [17,21]. In these studies, *Klebsiella pneumoniae* accounted for $^{2}/_{3}$ of the cases of NNS across all ages among inborn babies. When the distribution was stratified by the place of birth in one of the studies from Lagos, the predominant organism was *Staphylococcus aureus* among out-born babies [13], suggesting that late onset sepsis must have been mostly community acquired infections. The implication is that future studies from this region

need to stratify bacterial aetiology by place of birth and postnatal age. This would enhance identification of factors that may be related to hospital based neonatal care practices.

A major difference between our study and that from Lagos is in the sensitivity pattern. Most of the Gram negative organisms still retained their in vitro sensitivity to 3rd generation cephalosporins and gentamicin (Table 2). The Gram positive organisms on the other hand had high sensitivity to sulbactam-ampicillin and the macrolides. However, *in vitro* sensitivity of *Staphylococcus aureus* to cloxacillin was very low (28.6%), suggesting a high prevalence of methicillin resistant staphyococcus in the unit. This calls for the review of the empiric use of this antibiotic in suspected staphylococcal infections. We have since adopted the combination of sulbactacm-ampicillin and gentamicin as our initial empiric choice of antibiotics in cases of presumed or probable sepsis. An important question raised by the observed differences in distribution of organisms and their sensitivity to antibiotics between this study and a number of previously cited ones from the country is that of the burden of nosocomially acquired infection. Unfortunately many of the studies (including ours) did not set out to determine nosocomial acquisition rates. However, multi-drug resistant strains of organisms are some of the characteristics of nosocomially acquired infection. In our unit, we evaluated the impact of nosocomial acquisition in 22 patients with meningitis between 1989 and 1992. We found 16 (73%) of the 22 isolates that were Gram negative of which 11(69%) were nosocomially acquired [14]. This led us to adopt specific measures to reduce the incidence of nosocomial infections.

Thus, the challenge is not to merely monitor the epidemiology of septicaemia but to determine the agents *viz* a *viz* the onset of illness. It is also important to maintain surveillance for nosocomially acquired organisms and the factors/practices that predispose to such nosocomial acquisition. A better understanding of these issues would facilitate necessary behavioural changes in the care of the newborn and rational antibiotic therapy in management of neonatal septicaemia. More studies are also needed from this region that address maternal risk factors for neonatal sepsis in order to provide a better anticipatory care of the newborn at risk for sepsis.

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