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TRENDS IN PROFILES OF BACTERIA CAUSING NEONATAL SEPSIS IN CENTRAL NIGERIA HOSPITAL

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ABSTRACT

Developing countries suffer from a huge burden of neonatal sepsis. Neonatal mortality and long term sequelae or morbidity portends huge costs for the poor Nigerian economy. We identified trends in bacterial agents implicated in neonatal sepsis and their antibiotic susceptibility profiles at the National Hospital Abuja over two periods of three years each a decade apart. A retrospective study of bacterial agents of sepsis from 2013-2015 was carried out and this was compared to an already published study from the same hospital ten years earlier(2002-2004) to determine changing trends using standard statistical methods.

We identified a significant shift to predominance of gram positive organisms especially Staphylococcus aureus (59% vs 40%) as against the predominance of gram negative organisms especially *Klebsiella pneumoniae* (11% vs 44%) in the previous decade. Almost all antibiotics tested (92%) had reduced susceptibility in the later review compared to the former.

Surveillance of bacterial agents of neonatal sepsis is vital for the detection of trends in causative organisms and their susceptibilities. This is important to direct empiric therapy and also to encourage implementation and monitoring of antibiotic stewardship programs.

LES TENDANCES DES PROFILS DE BACTERIES CASANT LA SEPTICEMIE NEONATALE DANS L'HOPITAL AU CENTRE DU NIGERIA

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RESUME

Les pays en développement souffrent d'un énormefardeau de sepsisnéonatal. La mortaliténéonatale et les séquelles à long terme ou la morbidité annonce des coûts pour la pauvre économienigériane. Nous avons identifié les tendances des agents bactériens impliqués dans le sepsisnéonatal et leurs profils de sensibilité aux antibiotiques à l'hôpital national d'Abuja sur deux périodes de trois ans chaque décennie à part. Uneétuderétrospective des agents bactériens de sepsis à partir de 2013 – 2015 a été réalisée et ceci a été comparé à une étude déjà publiée du mêmehôpital dix ans plus tôt (2002 – 2004) pour déterminer les tendances changeantes en utilisant des méthodes statistiques standard.

Nous avons identifié un changement significatif vers la prédominance des organismes gram négative, en particulier le Staphylococcus aureus (59% vs 40%) au contraire de la prédominance des organismes gram – négatifs, en particulier la Klebsiella pneumoniae (11% vs 44%)au cours de la décennieprécédente.

La surveillance des agents bactériens du sepsisnéonatal est vitale pour la direction des tendances des organismes causatif set de leurs susceptibilités. Il est important de diriger la thérapie empirique et d'encourager la mise en œuvre et la surveillance des programmes d'intendance des antibiotiques.

INTRODUCTION

Neonatal sepsis causes significant morbidity and mortality worldwide especially in developing countries where the effects are often devastating for the baby, family and economy. It is estimated that sub-Saharan Africa had 2.6 million cases of serious bacterial infection in 2012, the highest for any WHO region with a case fatality of 14% (1). Mortality rates are high for neonatal sepsis and reports show that 17%- 41% of neonatal deaths in Nigeria are from sepsis (2-5).

Geographical differences in bacterial agents responsible for sepsis occur. Group B Streptococcus for example is not often reported in developing countries including Nigeria but is the most common cause of sepsis in the developed world (6). In Nigeria, the most common bacteria isolated from blood cultures of neonates include; *S. aureus, E.coli, K. pneumoniae, S. aureus* and *P. aeruginosa* (7-12).

Empiric therapy is usually based on international guidelines or local antibiograms that are rarely reviewed in Nigeria. Sometimes pressure from commercial pharmaceutical company representatives may influence the choice of empiric therapy. Because changes do occur over time in the types of bacteria causing sepsis and their susceptibilities to different antibiotics, it is of vital importance that to effectively manage neonatal sepsis, surveillance and tailored strategies to fit the local context are needed.

This study was aimed at assessing possible changes in the profile of organisms causing neonatal sepsis in NHA over a decade and also to detect changes in susceptibilities that have occurred over this time. The result would serve as a guide for modification of current empiric therapy choices and also provide a strong case for institution of efficient and effective infection control/antibiotic stewardship strategies.

METHODS

Neonatal blood cultures received at the medical microbiology laboratory of the National Hospital Abuja were reviewed for the periods 2002-2004 and 2013-2015. While in the 2002-2004 period the Oxoid signal system (Oxoid USA, Inc., Columbia, Md.) was used to process blood cultures, in the later period, the BACTEC system (Becton Dickinson, Ireland) was used. Otherwise, all protocols were the same for the two periods under review. The 2013-2015 data were compared with an already analysed and published data from 2002-2004 from the same laboratory. Paediatricians made the initial impression of sepsis based on clinical features in the neonate following which they collected 1-2mls of blood aseptically into culture bottles; Oxoid signal in 2002-2004 as previously described[9] and BACTEC Paeds-Plus in 2013-2015. Briefly, at the laboratory, culture bottles were incubated in aerobic conventional incubator for the oxoid signal system or in the BACTEC 9040 instrument following all manufacturer's instructions and incubated until growth was signaled or for a maximum of five days. Bottles that signal growth were removed and sub-cultured unto Blood agar, Chocolate agar and MacConkey agar. Isolates were identified according to standard methods and criteria. Isolates such as *K. pneumoniae, E. coli, S. aureus and P. aeruginosa* were regarded as pathogens while most coagulase negative Staphylococci and aerobic spore bearers were regarded as contaminants. Where there were doubts, the clinical features of the patients were factored into the decision making process as to whether an isolate was a pathogen or a contaminant. Antibiotic susceptibility test was performed using modified Kirby-Buer disc diffusion method and interpreted for all according to CLSI guidelines. *Escherichia coli* ATTC 25922, *Staphylococcus aureus* ATTC 25923, and *Pseudomonas aeruginosa* ATTC 27853 were used as controls.

RESULTS

A total of 1209 blood cultures were processed at the NHA medical microbiology laboratory during the 2013-2015 period. There were 260 blood cultures processed from neonates; 21.5% of the total. Bacteria were isolated in 85 of the 260 (32.7%) neonatal cultures while in the 2002 - 2004 report

, isolation rate was 22% (Table 1). Contamination rate in the present review was 1.5%. The study done 10 years ago did not evaluate for contamination.

Gram positive cocci accounted for 56 of 81 (69%) of isolates while it was 49.5% ten years ago. Gram negative bacteria were 31% and 51% in the two time periods respectively (Table 1).

TABLE 1: BACTERIAL ISOLATES IN NEONATAL SEPSIS

	2013-2015	2002-2004	p value
Total Blood cultures processed	1209	1555	
Neonatal blood cultures processed	290 (21.5%)	390 (25.0%)	0.6
Isolation rate	81 (32.7%)	85 (22%)	0.2
Contamination rate	4 (1.5%)	-	-
Bacterial Isolates during the two study periods			
S. aureus	48 (59.3)	34 (40.0)	0.01
K. pneumonia	9 (11.1)	37 (43.5)	0.001
P. aeruginosa	7 (8.6)	4 (4.7)	0.3
CoNS	5 (6.2)	2 (2.4)	0.3
E. coli	3 (3.7)	1 (1.2)	0.5
Enterobacter spp	3 (3.7)	-	-
Enterococcus spp	3 (3.7)	4 (4.7)	1.0
Alkaligenes spp	1 (1.2)	-	-
Salmonella spp	1 (1.2)	-	-
N. lactamica	1 (1.2)	-	-
Acinetobacter spp	-	1 (1.2)	-
S. pneumonia	-	2 (2.4)	-
Gram positive bacteria	56 (69.1)	42 (49.5)	0.01
Gram negative bacteria	25 (30.9)	43 (50.5)	0.3

Staphylococcus aureus accounted of 59% for isolates from newborn in this review but accounted for 40% in the prior review while Klebsiella pneumoniae constituted 11.1% as against the previous review where it accounted for 43.5% of neonatal isolates (table 1 below).

Decrease in susceptibility of *S.aureus* to various antibiotics was observed from 2002-2004 period to 2013-2015 period as follows; Amoxicillin-clavulanate from 85% to 76%, Cefuroxime from 45% to 0%, Ciprofloxacin from 71% to 67%; Erythromycin from 64% to 30%; Gentamicin from 40% to 29% and Ceftriaxone from 36% to 27%. See Figure 1.

For *K. pneumonia* isolates susceptibility decreased from 100% to 75% for Imipenem, from 15% to 0% for Ceftazidime, 100% to 63% for the fluoroquinolones for 2002-2004 and 2013-2015 respectively. An increase in susceptibility was observed for ceftriaxone from 12.5% to 66%.

FIGURE 1: SENSITIVITY PROFILE OF *STAPHYLOCOCCUS AUREUS* TO VARIOUS ANTIBIOTICS AT TWO TIME PERIODS

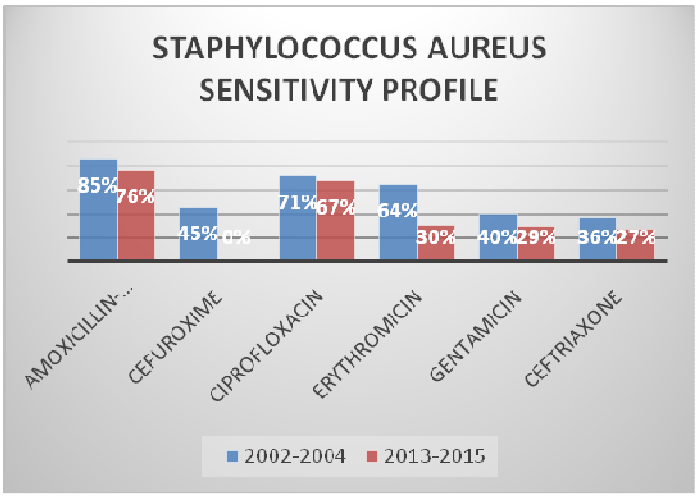
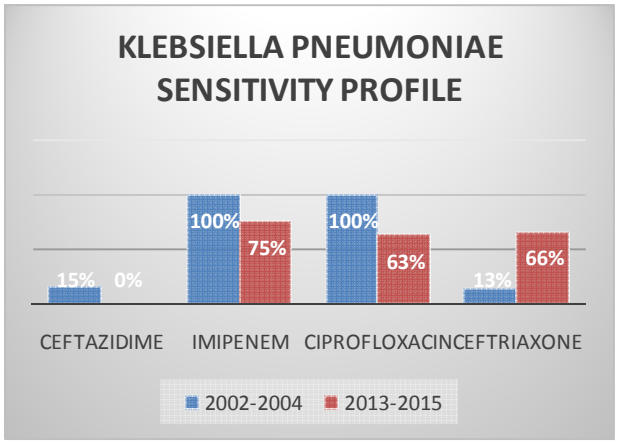


FIGURE 2: SENSITIVITY PROFILE OF KLEBSIELLA PNEUMONIAE TO VARIOUS ANTIBIOTICS AT TWO TIME PERIODS



DISCUSSION

The study showed that *S. aureus* and *K. pneumoniae* were the two dominant aetiologic agents of sepsis in the two periods evaluated. However, whereas the gram negative *K. pneumoniae* was the predominant agent in the 2002-2004 period, the gram positive, *S. aureus* was the predominant organism in the 2013-2015 period. Thus, over one decade the organisms causing neonatal sepsis had shifted from a predominance of gram negatives to gram positives. Previous studies have also established the predominance of gram positives in this decade (13-17). While bacteria are known to vary temporally, we postulate other reasons for this shift to more *S. aureus* in particular and consequently gram positive bacteria as a group; one postulate is that this may have resulted from a change in the type of bacteria colonizing the ano-genital region of the mother to mainly staphylococci and consequent newborn colonization with these organism; a future study assessing the maternal ano-genital colonization and newborn colonization with *S aureus* could answer this question. Another postulate is a changing antibiotic exposure of the population to groups active mainly against gram negative bacteria.

Similarly, the antibiotic susceptibility pattern changed remarkably. There was an alarming increase in resistance of major pathogens to most antibiotics commonly used in the management of neonatal sepsis. This will inadvertently lead to negative impact on the pattern of morbidity and mortality in the hospital, including resulting in longer hospital stay and increased cost of care. If the current trend continues, with the looming dryness of antibiotic pipeline, Nigeria will be faced with a situation similar to the pre-antibiotic era where even minor bacterial infections will be untreatable.

The NICU/SCBU at the National Hospital Abuja is a vital place to initiate antibiotic stewardship and infection control programs to mitigate this adverse antibiotic resistance trend. Intensive care units have been described as the factories where antibiotic resistance genes are created and spread to other parts of the hospital and community (18). This probably arises from the relatively large amounts of antibiotics consumed which in many instances are unnecessary or inappropriate. Regular antibiotic susceptibility surveillance is necessary to ensure evidence-based empiric treatment, while definitive treatment must be based on individualized testing. Notably, the antibiotics Cefuroxime and Gentamicin will be ineffective in the current decade as empiric choices for management of neonatal sepsis at National Hospital Abuja.

The isolation of coagulase negative staphylococci in pure culture warrants further investigation as to their role as agents of neonatal sepsis. They have hitherto been considered contaminants in developing countries. Perhaps there is a need to report susceptibilities for this group of isolates until it is proved that they are not a cause of sepsis in developing countries.

Conclusion

Continuous local surveillance of bacteria causing invasive disease in newborn units and their antibiotic susceptibilities is vital in ensuring improved outcomes for neonates. The implementation of standard infection control practices could also result in reduced incidence of neonatal sepsis at the National Hospital Abuja. Antibiotic stewardship as a vital part of infection control also needs implementation, and could result in decreased acceleration towards resistance or even reverse to susceptibility of particular drug classes.

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