

Healthcare-associated infections in a Newborn Unit in Nigeria

AE Akindolire¹, OO Tongo¹, II Dada-Adegbola² and OO Akinyinka¹
Departments of Paediatrics and Medical Microbiology and Parasitology,
College of Medicine, University of Ibadan, Nigeria

Abstract

Introduction: Due to immaturity of neonatal immune function, prolonged hospitalisation, invasive procedures and inadequate infection control measures, healthcare-associated infections (HAI) remain a perennial problem in neonatal units globally and impact negatively on outcome. It is essential to quantify the burden and assess the risk factors in order to address this problem.

Objectives: To determine the prevalence, bacterial aetiology of and risk factors for HAI in the neonatal unit of the University College Hospital, Ibadan, Nigeria.

Materials and methods: Fifty-six out of the 435 neonates admitted who developed symptoms or signs of neonatal sepsis after 48 hours of admission or symptom free interval had their clinical history and physical examination recorded. Blood, urine and where indicated, cerebrospinal fluid (CSF) samples were taken for culture and sensitivity before antibiotic therapy.

Results: The incidence of HAI was 4.1% (13 babies) of neonatal admissions, 4.4/1000 patient days (72.2% of infections was septicaemia). There were 7 Gram positive isolates [all Methicillin Resistant *Staphylococcus aureus* (MRSA)] and 11 Gram negative isolates. The blood culture isolates were MRSA (6), *Klebsiella pneumoniae* (3), *Hafnia alvei* (2) and one each of *Stenotrophomas maltophilia* and *Escherichia coli*. The two cerebrospinal fluid isolates were *Chryseobacterium meningosepticum* and *Klebsiella ozaenae*, other isolates were *Escherichia coli* - abscess aspirate, MRSA and *Escherichia coli* urethral catheter tips. MRSA demonstrated 33.3% and 50.0% susceptibility to gentamycin and vancomycin respectively. The Gram negatives demonstrated 81.8%, 45.6% and 90.1% susceptibility to ceftazidime, ciprofloxacin and meropenem respectively. The case fatality rate was 38.9% (7 babies).

Conclusion: MRSA and *Klebsiella pneumoniae* are the common causes of HAI in the neonatal unit and are associated with high mortality.

Keywords: Healthcare Associated Infections; Neonatal Septicaemia; Bacterial pathogens

Correspondence: Dr. Abimbola E. Akindolire, Department of Paediatrics College of Medicine, University of Ibadan, Ibadan, Nigeria. E-mail: abimbola_12@yahoo.com

Résumé

Introduction: En raison de l'immaturation de la fonction immunitaire néonatale, d'une hospitalisation prolongée, de procédures invasives et de mesures inadéquates de contrôle des infections, les infections nosocomiales demeurent un problème chronique dans les unités néonatales et ont un impact négatif sur les résultats. Il est essentiel de quantifier la charge et d'évaluer les facteurs de risque afin de résoudre ce problème.

Objectifs: Déterminer la prévalence, l'étiologie bactérienne et les facteurs de risque d'infection nosocomiale dans l'unité néonatale du Collège Hospitalier l'Universitaire, Ibadan, Nigeria.

Matériel et méthodes : Cinquante-six des 435 nouveau-nés admis qui ont développé des symptômes ou des signes de septicémie néonatale après 48 heures d'admission ou un intervalle sans symptômes ont eu leurs antécédents cliniques et un examen physique enregistré. Du sang, l'urine et dans le cas échéant, des échantillons de liquide céphalo-rachidien (LCR) ont été prélevés pour la culture et la sensibilité avant l'antibiothérapie.

Résultats: L'incidence des infections nosocomiales était de 4,1% (18 bébés) d'admissions néonatales, 4,4 / 1000 jours-patients (72,2% des infections étaient des septicémies). Il y avait 7 isolats Gram positifs [tous *Staphylococcus aureus* résistants à la méthicilline (SARM)] et 11 isolats Gram négatifs. Les isolats de culture de sang étaient SARM (6), *Klebsiella pneumoniae* (3), *Hafnia alvei* (2) et un chacun des *sténotrophomes maltophilie* et *Escherichia coli*. Les deux isolats de liquide céphalorachidien étaient *Chryseobacterium meningosepticum* et *Klebsiella ozaenae*, autres isolats *Escherichia coli* - aspiration d'abcès, SARM et extrémités de cathéter urétrale *Escherichia coli*. SARM a démontré une sensibilité de 33,3% et 50,0% à la gentamycine et à la vancomycine respectivement. Les Gram négatifs ont montré une sensibilité de 81,8% ; 45,6% et 90,1% à la ceftazidime, à la ciprofloxacine et au méropénème respectivement. Le taux de létalité était de 38,9% (7 bébés).

Conclusion: SARM et *Klebsiella pneumoniae* sont les causes les plus fréquentes des infections nosocomiales dans l'unité néonatale et sont associées à une mortalité élevée.

Mots-clés: Infections nosocomiales; Septicémie néonatale ; Pathogènes bactériens

Introduction

Nosocomial infections more appropriately referred to as healthcare-associated infections (HAI) are infections acquired in the hospital that were neither present nor incubating at the time of admission [1]. They are common in paediatric and neonatal intensive care units (NICU) due to relative immunodeficiency especially among babies who are preterm and low birth weight, have prolonged hospital stay and undergo invasive procedures. Health-care associated infections may be local or systemic, evidenced by positive culture from a usually sterile site, acquired after 48 hours of admission [2].

The incidence of HAI in neonatal units varies widely depending on the definitions used [3] as well as practices within the unit. The prevalence ranges between 6 and 25% of NICU admission or 8.9 to 62 infections per thousand patient days [4]. It is more prevalent in developing countries where the neonatal units are often overcrowded, understaffed and poorly equipped and lack written infection control policies and antibiotic protocols [5-8].

Healthcare-associated infections are associated with high cost of care, longer hospital stay and higher morbidity and mortality especially in developing countries [5-8]. They also contribute to the incidence and severity of impaired long term outcomes among survivors [9, 10]. Neonatal infection rates are high in developing countries with rates as high as 6.5 to 38 per thousand live hospital born babies and up to 68 per thousand live births among the low birth weight in Nigeria, but the burden due to HAI has not been specifically quantified [4, 7].

The study was carried out to determine the prevalence, bacterial aetiology and risk factors for HAI at the neonatal wards of the University College Hospital (UCH), Ibadan, Nigeria.

Materials and methods

The study was conducted in the neonatal unit of the University College Hospital, Ibadan comprising two neonatal wards, one ward admits babies born within the hospital (inborn) and those born outside the hospital (outborn) but presenting within 48 hours of age. The second ward admits all other neonates. It was a cross sectional study of all 435 neonates admitted into the unit over a four month period out of which 56 developed symptoms or signs of neonatal sepsis after 48 hours of admission or symptom free interval [11].

Maternal demographic data, details of pregnancy, delivery and perinatal history including antibiotic use were documented.

Each neonate that developed symptoms and signs of illness had blood, suprapubic or catheter urine and cerebrospinal fluid (CSF) cultures done as indicated prior to institution of new antibiotics. In cases where there were abscesses, aspirates were also taken for culture. Urethral catheter tips were also sent for cultures in cases of catheterized patients. Between 1.0ml and 1.5ml of blood was taken for cultures, sent to the Microbiology laboratory immediately and incubated in the Bactec 9050 machine at 37° Celsius for four days.

Lumbar puncture for cerebrospinal fluid analysis was performed in 43 neonates who had indications for the procedure.

Descriptive statistics are presented using tables and means (\pm Standard Deviation) as appropriate. Association between socio-demographic characters, perinatal, maternal and dependent variables were analysed using the chi squared test. Statistical significance was set at a p value of <0.05. Binary logistic regression analysis was conducted on variables that had a p value of <0.20 on bivariate analysis in order to determine the clinical predictors of HAI.

Approval for the study was obtained from the Joint University of Ibadan/ University College Hospital, Ibadan Ethics Committee and informed written consent from parent or caregiver was obtained before recruitment

Table 1: Distribution of birth weight and gestational age of neonates screened for HAI

Characteristics	Subjects screened for HAI n (%)	Proportion of total admissions (%)
<i>Birth weight (unit)</i>		
<1.5	24(42.9)	28.5
1.5 - <2.5	12(21.4)	33.8
>2.5	20(35.7)	37.7
<i>Gestational age(weeks)</i>		
< 28	7(12.5)	3
28 - 32	23(41.1)	19.5
33 - 36	18(32.1)	25.4
>37	8(14.3)	52.1

Results

Of the 56 neonates screened, 26(46.4%) were delivered in UCH (inborn) while 30(53.6%) were delivered in facilities other than UCH (out-born). There were 29(51.8%) males and 27 (48.2%) females. The distribution of birth weight and gestational age of the neonates are as shown in Table 1. All episodes occurred within the first 28 days of

admission. The duration of hospital stay prior to episode ranged from 3 to 26 days (mean 7.7±3.8 days). Of the 56 neonates, 44 had prior antibiotic exposure for a mean duration of 4.2±3.3 days prior to episode. Half (28) of the subjects had previous negative blood cultures on admission while one had a previous positive blood culture and had been completely treated with normalized C-reactive protein (CRP) before the episode. The repeat episode was 72 hours after normalization of CRP and completion of initial treatment. The remaining 27 did not have indications for an initial sepsis screening on admission.

The nurse to patient ratio in the unit during the study period was one nurse to 5 – 7 babies.

Table 2: Presenting clinical features necessitating HAI screening

Clinical features	Frequency n (%)
Respiratory distress	41(73.2)
Fever	30(53.6)
Abdominal distension	28(50.0)
Lethargy/reduced activity	22(39.3)
Apnoea	20(35.7)
Poor feeding	20(35.7)
Bleeding diathesis	20(35.7)
Tachypnoea	17(30.4)
Temperature <36°C	17(30.4)
Hepatomegaly	15(26.8)
Mottled skin	13(23.2)
Regurgitation/vomiting	12(21.4)
Jaundice	9(16.1)
Seizures	8(14.3)
Sclerema	6(10.7)
Cyanosis	4(7.1)
Palor	4(7.1)
Significant pre gavage aspirate	1(1.8)
Periumbilical redness	1(1.8)
Prolonged capillary refill	1(1.8)
Coma	1(1.8)

Clinical features

Respiratory distress was the most common presenting feature; fever 30(53.6%), abdominal distension 28 (50.0%), and lethargy 22(39.3%) were the other common features (Table 2).

Culture results

There were 18 culture-proven HAI corresponding to an incidence of 4.1% of all admissions and 4.4 episodes of infection per thousand patient days: 13 (72.2%) of the infections were blood stream infections, 2 (11.1%) were meningitis, 2 (11.1%)

were catheter tip isolates and the last from an abscess. The prevalence rate of meningitis was therefore 3.6% of cases of HAI. The Gram negative organisms predominated, 11(61.1% of all isolates), while the only Gram positive organism was Methicillin Resistant *Staphylococcus aureus* (MRSA) 7(38.9%). The Gram negative organisms were *Klebsiella* spp, 4(22.2%), *Escherichia coli* 3(16.7%) and the other Gram negatives 4(22.2%) [*Hafnia alvei* 2(15.4%), *Chryseobacterium meningosepticum* 1(7.7%) and *Stenotrophomas maltophilia* 1(7.7%)].

Of the 13 blood culture isolates, 6 (46%) were MRSA, 3 (23.1%) *Klebsiella pneumoniae*, 2 (15.4%) *Hafnia alvei* and 1 (7.7%) each were *Stenotrophomas maltophilia* and *Escherichia coli*. One patient who previously had been treated for *Klebsiella Pneumoniae* septicemia but had to be rescreened 72 hours after completion of initial treatment had blood culture positive for *Hafnia alvei*.

The two positive CSF cultures yielded *Chryseobacterium meningosepticum* and *Klebsiella ozaenae*, the two positive urethral catheter tips yielded MRSA and *Escherichia coli*. *Escherichia coli* was isolated from the aspirate of an abscess.

One of the *Hafnia alvei* was isolated from a preterm neonate after an initial culture which yielded *Klebsiella pneumoniae* had been completely treated. Both subjects with positive CSF cultures had negative blood cultures at that time of the positive CSF culture. Both babies were inborn babies with late onset sepsis (LOS) who previously had negative early onset sepsis (EOS) screening.

There were no isolates obtained from the urine of the subjects screened. The neonates with positive urethral catheter tips were previously catheterised for more than three days for urine output monitoring and later developed signs of sepsis.

Antimicrobial susceptibility pattern

The MRSA demonstrated 50%, 0%, 33.3% and 40% susceptibility to Amikacin, cefotaxime, gentamycin and vancomycin respectively. Generally, the Gram negatives demonstrated 81.8%, 45.6% and 90.1% susceptibility to ceftazidime, ciprofloxacin and meropenem respectively. *Escherichia coli* demonstrated 100% susceptibility to Amikacin, Gentamycin, ceftazidime and meropenem while *Klebsiella* demonstrated 80%, 66.7%, 60% and 100%

respectively to Amikacin, Gentamycin, ceftazidime and meropenem. The other Gram negative isolates demonstrated 75%, 50% and 75% susceptibility to ceftazidime, ciprofloxacin and meropenem respectively as shown in Table 3.

Table 3: Percentage sensitivity of HAI isolates to antibiotics

Organisms Antibiotics	MRSA	Kleb.	E.Coli	Other Gram negatives
Ampicillin	0	0	50	0
Ampicillin sulbactam	0	66.7	-	0
Amoxicillin	0	25	0	0
Ampiclox	0	0	-	-
Amikacin	50.0	80	100	100
Gentamicin	33.3	66.7	100	75
Vancomycin	40.0	0	-	-
Ciprofloxacin	66.7	66.7	0	50
Ceftazidime	0	60	100	75
Cefotaxime	0	60	0	-
Cefuroxime	0	60	0	100
Cefepime	0	100	50	0
Meropenem	14.2	100	100	75
Chloramphenicol	50	66.7	0	0

Risk factors for HAI

Very low birth weight and gestational age less than 32 weeks were associated with four and threefold increased risk respectively of HAI as shown in Table 4.

Table 4: Risk factors for HAI

Postnatal risk factor	OR	CI	p value
Male sex	1.250	0.405-3.856	0.698
Birth weight <1.5kg	4.710	1.424-15.576	0.006
GA<32weeks	3.034	1.141-8.065	0.020
Exchange blood transfusion	1.486	1.236-1.787	0.546
Umbilical venous catheterization	2.675	0.949-7.542	0.054
Endo tracheal Intubation	2.431	0.277-21.365	0.408
Urethral catheterization	1.998	0.676-5.909	0.203
Prior antibiotic use	1.238	0.180-8.504	0.828

Outcome

More than a third, 7 (38.9%), of neonates with culture proven HAI died compared to 70 (16.9%) of those who were culture negative (OR = 3.123, CI: 1.146-8.512, $p = 0.020$).

The mean length of hospital stay was 20.8 ± 9.4 among neonates with culture proven HAI and 9.3 ± 7.00 among those without ($p = 0.000$).

Discussion

Healthcare-associated infections in neonates continue to be a major challenge to improved outcomes despite the technological advances in the area of respiratory and nutritional support particularly for the extreme preterms. The rate of culture proven HAI in this study was 4.4 per 1000 patient days and 4.1% of total neonatal admissions. This figure includes all babies who had either a septicaemia or positive culture in sites like the CSF and urine which should normally be sterile. These rates are much lower than 13.8 per 1000 patient days reported from Australia and 19.2% and 21.4% of total admissions reported in Saudi-Arabia, and Egypt respectively [6, 12].

This might be due to the fact that the unit does not use or indeed, have facilities for invasive neonatal intensive care such as mechanical ventilation, total parenteral nutrition or even central lines which are known to predispose to HAI [13, 14].

The HAI rate in this study was also slightly lower than the 8.9% reported by Osinupebi *et al* [15], the reason for this lower figure is not clear as the special care baby unit at Sagamu is in the same geopolitical zone of the country, with similar facilities.

Majority of the positive cultures were from the blood. The blood stream is known to be the most common site for isolation of hospital acquired organisms [16]. This is not surprising in neonates who are known to have limited ability to localise

infections hence infections from any site readily disseminate into the blood stream.

The 3.6% prevalence of positive CSF culture in this study was similar to the 5% documented in a review of HAI in neonatal intensive care units by Carey [17] though this 5% included non-bacterial causes.

There were isolates from the urethral catheter tips of two babies who developed features of illness after urethral catheterisation. Though the

Centre for Disease Control (CDC) definition of HAI does not include cultures from catheter tips, the positive cultures from the catheter tips in this study were regarded as significant because the babies developed signs of illness necessitating the screening.

As shown in this study, all the infections occurred within 26 days of admission with a mean of 7.7 ± 3.8 days, which is consistent with previous reports that HAIs occur in the early days in 85% of cases [18]. It is therefore necessary to intensify efforts at prevention of HAI during this critical period when they are likely to be undergoing the most intensive care for their primary conditions.

The most prevalent organisms found in this study were methicillin resistant *Staphylococcus aureus* (MRSA), *Klebsiella* spp and other Enterobacteriaceae which are known to thrive in solutions, containers and other hospital equipment if not adequately sterilised. This is consistent with what is reported in developing countries [5] though *Klebsiella* predominated in this review. *Staphylococcus aureus* continues to be an important HAI pathogen in neonatal units in developing countries as seen in this study and its spread is mainly attributed to the hands of healthcare workers [5]. On the contrary coagulase negative staphylococcus (CONS) and *Staphylococcus aureus* are more commonly reported in developed countries [14].

Other pathogens like *Candida* and viruses have also been implicated in the aetiology of HAI in the neonatal intensive care units in developed countries [19]. No case of *Candida* was found in the present study probably because there was a policy of prophylactic fluconazole for high risk babies in place at the time of the study [6, 14, 18, 20]. Other organisms known to be associated with HAI in neonates include respiratory syncytial virus and rotavirus in cases of respiratory and gastrointestinal infections but none of those were sought in this study.

The organisms found in this study are known to be more virulent than coagulase negative staphylococcus reported in developed countries, which is associated with less morbidity and mortality [21]. The challenge of HAI in this set up is therefore of a higher magnitude in terms of illness severity and risk of death. These organisms especially the MRSA are often associated with outbreaks in NICUs and with prompt institution of necessary infection control strategies and specific measures like isolation, cohorting, use of antiseptic agents such as chlorhexidine and mupirocin and microbiological surveillance, they are brought under control [22].

MRSA infections are largely preceded by colonization. Colonized babies then serve as a reservoir for the cross-transmission among babies through the hands of handlers who may themselves be carriers. MRSA outbreaks are known to be difficult to contain and may go on to become endemic if not promptly controlled [23, 24]. It is not known if the finding of 46% of the HAI in this study being due to MRSA was actually endemic in the unit or an outbreak because no previous data was available.

In some other developing countries, *Staphylococcus aureus* is also the most commonly isolated organism in LOS in the hospital setting, with a few studies from Nigeria also reporting CONS [25, 26]. The finding of *Klebsiella pneumoniae* as a common cause of HAI in our study is also consistent with previous reports from our centre and other parts of Nigeria [27-30]. This was a common cause of HAI in the developed world in the 1960s but remains a major burden in Nigeria till date [19]. *Klebsiella* and the other Enterobacteriaceae isolated in this study are known to be prevalent where there is unrestricted use of broad spectrum antibiotics such as third generation cephalosporins [21]. Unrestricted antibiotic use is prevalent in centres in resource limited settings such as ours where financial and logistic challenges with laboratory support for routine patient care exist. Many of these Gram-negative Enterobacteriaceae are able to express extended spectrum beta lactamases and even transfer resistance across other organisms.

Chryseobacterium meningosepticum was found as a cause of neonatal meningitis in one of the neonates who had no septicaemia at that time. This organism is a recognised cause of nosocomial meningitis especially in immunosuppressed patients and it has been cultured from swabs of incubators in the neonatal intensive care unit [31].

Healthcare-associated infections are frequently due to resistant organisms be they Gram positive or negative hence the difficulty in treating them and the associated poor outcomes. The MRSA found in this study demonstrated significant resistance to vancomycin as is now being increasingly reported from other parts of the world [32]. This particularly portends danger in developing country settings with limited availability of antibiotics. This is of special significance in developing countries in view of the other challenges with staffing, overcrowding, laboratory support and antibiotic availability and cost in the area of hospital care of newborn babies. The Gram negative organisms demonstrated reasonable susceptibility to ceftazidime and meropenem expectedly. It is

therefore crucial that these drugs be protected from overuse at this time to prevent development of resistance. Having written evidence-based antibiotic guidelines and regular microbial surveillance is essential to achieve this.

Very low birth weight and gestational age below 32 weeks were associated with the highest risk of HAI. This observation conforms to what obtains globally as this group of babies have compromised immunity and often require the most invasive procedures.

Prolonged use of empiric antibiotics in the face of negative cultures will alter the normal flora of the neonate and predispose to colonisation and ultimately infection especially by resistant organisms [33]. Prior use of empiric antibiotic, was not significantly associated with an increased risk of HAI in this study as reported in previous studies [21].

The mortality rate among babies with culture proven HAI in this study was higher than those who were negative as previously documented. The mean length of hospital stay was also significantly longer among those with proven HAI as documented in the literature. This adds to the challenge of health care costs in this group of babies. Apart from costs to parents, it also adds to the burden of care on the already overstretched human and material resources.

The high HAI rate, virulent type of organisms, low susceptibility to "reserve" antibiotics and poor outcomes of the babies underscore the need emphasize appropriate prevention and control measures like scrupulous hand hygiene and proper antibiotic stewardship.

Conclusion

The prevalence of HAI at the UCH is high and the most common organisms responsible for HAI are MRSA and *Klebsiella pneumoniae*. Very low birth weight neonates and neonates with gestational age below 32 weeks were found to be at a higher risk of HAI. The high mortality rate among neonates with culture proven HAI underscores the need for intensifying infection control measures in order to improve neonatal outcomes especially in developing countries.

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