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A Neonatal Unit Experience with Empiric Antibiotics for Late-onset Neonatal Sepsis: A Retrospective Study

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Abstract

Background: Neonatal sepsis remains a major cause of morbidity and mortality and warrants the immediate start of appropriate empiric treatment. Thus, this study compared the effectiveness of the 2 antibiotic regimens (cloxacillin–amikacin or cefotaxime–ampicillin) among neonates with late-onset neonatal sepsis. **Methods:** We conducted a retrospective cohort study comparing mortality between 2 treatment cohorts of very low birth weight neonates with late-onset sepsis, who had received amikacin–cloxacillin or cefotaxime–ampicillin between January 2014 and December 2017. There were 27 neonates in each treatment arm after 1:1 propensity score matching. Univariate analyses (Chi-square and independent *t* tests, where appropriate) were performed to determine the association between variables. We determined the hazard ratio for all-cause mortality using the Cox regression model. **Results:** We identified a total of 132 neonates from the hospital's record. We included 27 neonates each in the amikacin–cloxacillin and cefotaxime–ampicillin groups. Intraventricular hemorrhage, necrotizing enterocolitis, birth weight, and gestational age were significantly associated with mortality ($P < 0.05$). The risk of mortality was significantly higher in neonates receiving empiric cefotaxime and ampicillin than those receiving amikacin and cloxacillin (hazard ratio: 2.91, 95% confidence interval: 1.17–7.30, $P = 0.023$). **Conclusions:** In our center, amikacin–cloxacillin combination therapy was associated with lower mortality in very low birth weight neonates with late-onset sepsis compared with cefotaxime–ampicillin therapy. *(Pediatr Qual Saf 2019;4:e239; doi: 10.1097/pq9.0000000000000239; Published online December 9, 2019.)*

INTRODUCTION

Sepsis is a leading cause of mortality and morbidity in neonates, particularly in developing countries,[1,2] where about 30% of all neonatal deaths are attributed to severe bacterial infections.[3] Approximately 750,000 deaths from neonatal sepsis occur annually worldwide.[4] There is an inverse relationship between the incidence of neonatal sepsis and birth weight.[5,6] The World Health Organization currently recommends ampicillin or cloxacillin (if the staphylococcal infection is suspected) and gentamicin for the empiric treatment of suspected neonatal clinical sepsis.[1] However, third-generation cephalosporins, particularly cefotaxime, are also commonly utilized.

Late-onset neonatal sepsis is usually caused by neonatal intensive care units (NICUs)-acquired pathogens and changes in antimicrobial susceptibility patterns necessitate a regular review of antibiotics regimen. Gram-positive organisms, particularly coagulase-negative *Staphylococcus* and group B streptococci, are major causative agents of late- and early-onset neonatal sepsis, respectively.[7,8] A recent study by Al-Mouqdad et al showed that the incidence of infection with Gram-positive microorganisms was 57% in a Saudi Arabian hospital's NICU and coagulase-negative Staphylococcus was the predominantly isolated pathogen. They also reported that Gram-negative microorganisms, mainly *Escherichia coli*, *Klebsiella* sp., and *Pseudomonas aeruginosa*, accounted for 38% of isolated organisms.[9] The study found that over 90% of the Gram-negative organisms were susceptible to gentamicin and amikacin.[9] The United Kingdom's Health Protection Agency's national bacteremia surveillance also reported that over 95% of organisms causing neonatal sepsis were susceptible to

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gentamicin with either flucloxacillin or amoxicillin and amoxicillin with cefotaxime.[10]

Differentiating between neonatal sepsis and the symptoms of prematurity is challenging, as the symptoms of neonatal sepsis are nonspecific. Therefore, neonatologists prescribe broad-spectrum antibiotics under the assumption that neonatal sepsis exists, even after a negative result on initial blood culture.[11] Evidence for the most suitable empirical antibiotics for late-onset neonatal sepsis is lacking;[12] therefore, there are no consensus guidelines on an antibiotic regimen. Consequently, the empiric treatment of late-onset neonatal sepsis differs between NICUs and among countries. In our center, cloxacillin and amikacin are the commonly used antibiotics for the empiric treatment of late-onset sepsis. However, cefotaxime with ampicillin is also used occasionally.

On account of the increased survival of preterm neonates and their more extended hospitalization, late-onset sepsis will continue to be a challenge. In this study, we compared the difference in mortality between cloxacillin–amikacin and cefotaxime–ampicillin regimens in neonates with neonatal sepsis. We hypothesize that on account of better bacterial susceptibility to amikacin, empirical treatment of very low birth weight (VLBW) neonates with an amikacin-based regimen would result in lower mortality.

METHODS
Study Population and Setting
This study was carried out at a 70-bed NICU of a tertiary hospital in Saudi Arabia. We retrieved the electronic medical records of consecutively admitted VLBW neonates with first episodes of late-onset sepsis between January 2014 and December 2017. Only VLBW neonates (<1,500 g) with suspected late-onset neonatal infection were eligible for inclusion. We defined late-onset sepsis as sepsis occurring after 72 hours of birth. Demographic data including birth weight, gestational age, and sex were extracted, in addition to data regarding comorbid conditions such as intraventricular hemorrhage, necrotizing enterocolitis, hypoxic-ischemic encephalopathy, patent ductus arteriosus, and periventricular leukomalacia. We also extracted data regarding sedative and inotropic drug treatment during hospitalization; invasive respiratory support (ie, intubation) during hospitalization; the types of antibiotics received; the number of courses and the duration of antibiotics; and the number of days of hospitalization and the outcome of treatment. This study was approved (Reference number: H1RI-02-Jun16-01) by the institutional review board of the King Saud Medical City.

Study Design
We performed a retrospective cohort study and identified 2 treatment cohorts. The primary cohort was neonates receiving empiric amikacin and cloxacillin for suspected late-onset sepsis. The comparison cohorts were neonates receiving empiric cefotaxime and ampicillin for suspected late-onset sepsis. A 1:1 propensity score matching of the 2 treatment groups to the nearest neighbor using the birth weights, gestational ages, need for respiratory support (received ventilatory support during hospitalization), and or central line support as the matching variables was carried out. We included respiratory and central line requirements in the matching variables because the choice of empiric antibiotics may be influenced by the clinical picture. The primary outcome of this study was the all-cause mortality during the first 120 days of life or discharge.

Definitions
Clinical (suspected) sepsis: The exact definition of suspected neonatal sepsis remains vague. As the clinical features of sepsis may be influenced by strong pro-inflammatory cytokines, clinicians rely on clinical features in their decision to suspect sepsis and start antimicrobial agents.[13,14,15]

Confirmed (proven) sepsis: Detection of a pathogen (positive culture) in otherwise sterile body fluid, in addition to clinical and laboratory signs of sepsis.[13,14,15]

Early-onset sepsis: Sepsis caused by pathogens transmitted vertically from mother to infant occurring in the first 3 days of life.[13,14,15]

Late-onset sepsis: Sepsis caused by horizontally acquired pathogens that occurs after 3 days of an infant's life.[14,16]

Blood sample for culture: We use standardized culture techniques to reduce false-negative results by taking 1-mL blood sample via venipuncture before starting antibiotics.

Narrow-spectrum antibiotics: These antibiotics include ampicillin, gentamicin, cloxacillin, and amikacin.

Broad-spectrum antibiotics: These antibiotics include any antibiotic not listed under narrow-spectrum antibiotics; we frequently use vancomycin, meropenem, and cefotaxime.

Statistical Analysis
The baseline characteristics of both treatment groups were compared using Chi-square and independent t tests where appropriate. We used Cox regression to calculate adjusted hazard ratio. Statistical analyses were carried out using R version 3.4.3.

RESULTS
We identified a total of 132 VLBW neonates who had received empiric amikacin–cloxacillin or cefotaxime–ampicillin for late-onset sepsis between January 2014 and December 2017. Thirty-six cases had reports of isolated microorganisms. The commonly isolated organisms include *Staphylococcus epidermidis* (21 cases), *Acinetobacter baumannii* (3 cases), and *Enterobacter cloacae* (3 cases) (Table 1), *E. coli* (2 cases), *Candida*

Table 1. List of Cultured Organisms

Amikacin + Cloxacillin	Cefotaxime + Ampicillin
Staphylococcus epidermidis (13 cases), *Staphylococcus haemolyticus* (1 case), *Staphylococcus lugdunensis* (1 case), *Staphylococcus capitis* (1 case), *Acinetobacter baumannii* (1 case), *Enterobacter cloacae* (2 cases), *E. coli* (1 case)	*Staphylococcus epidermidis* (8 cases) *Pseudomonas aeruginosa* (2 cases) *Klebsiella* (1 case) *Acinetobacter baumannii* (2 cases) *Enterobacter cloacae* (1 case) *E. coli* (1 case) *Candida* sp. (1 case)

sp. (1 case). One hundred and five neonates received amikacin–cloxacillin, whereas 27 received cefotaxime–ampicillin. The median duration of hospitalization among the patients was 45 (Interquartile range [IQR]: 31–71) days, and the duration of antibiotics during hospitalization was 16 (IQR: 9–26) days. The neonates received an average of 4 courses of antibiotics during hospitalization. After 1:1 matching of neonates in both treatment groups, we included 27 neonates each in the amikacin–cloxacillin and cefotaxime–ampicillin groups. Of those included in the study, 53.7% (29/54) were females. The mean gestational age of all the neonates in the study was 27.2 weeks, and the mean birth weight was 918 g. Table 2 describes the general characteristics of neonates in each of the treatment groups. Univariate analyses indicated a significant association of intraventricular hemorrhage, necrotizing enterocolitis, birth weight, and gestational age with mortality ($P < 0.05$). Hence, we used a Cox regression model that included all significant variables. The risk of mortality was significantly higher among neonates who received empiric cefotaxime and ampicillin compared with those who received amikacin and cloxacillin (hazard ratio: 2.91, 95% confidence interval: 1.17–7.30, $P = 0.023$) (Table 3).

Table 2. General Characteristics of Neonates in Both Treatment Groups

	Amikacin + Cloxacillin (n = 27)	Cefotaxime + Ampicillin (n = 27)	*P*
Mean GA, wk (SD)	27.4 (2.7)	27.0 (3.3)	0.585
Mean birth weight, g (SD)	937.6 (323.8)	898.3 (388.1)	0.639
Male (%)	15 (55.6)	8 (33.3)	0.054
PDA (%)	14 (51.9)	18 (66.7)	0.268
IVH (%)	14 (51.9)	17 (62.9)	0.409
PVL (%)	3 (11.1)	0 (0)	0.299
NEC (%)	17 (62.9)	13 (48.2)	0.273
HIE (%)	0 (0)	2 (7.4)	0.552
Positive blood culture (%)	13 (48.2)	5 (18.5%)	0.02*
No. deaths (%)	8 (29.6)	14 (51.9%)	0.097
Invasive respiratory support	22 (81.5)	23 (85.2)	0.715
Median hospital stay (d)	45 (IQR: 18–79)	22 (IQR: 5–74)	
Median days on antibiotics	18 (IQR: 9–30)	13 IQR: 3–25)	

*Statistically significant.
GA, gestational age; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia.

Table 3. Multivariate Cox Regression Model

	Exp (coef)	Lower 0.95	Upper 0.95	*P*
Ampicillin+ cefotaxime	2.9163	1.1646	7.3025	0.022*
Birth weight	0.9968	0.9941	0.9996	0.025*
Gestational age	0.9102	0.7118	1.1639	0.453
NEC	0.2662	0.1025	0.6912	0.006*
IVH	1.6400	0.6175	4.3559	0.321

*Statistically significant.
IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

DISCUSSION

In this study, we report a lower risk of mortality among neonates receiving empiric amikacin–cloxacillin for late-onset neonatal sepsis, compared with cefotaxime–ampicillin treatment. Cloxacillin, cefotaxime, and ampicillin are generally protective for Gram-positive bacteria and amikacin and cefotaxime for Gram-negative organisms. However, cefotaxime may not always provide sufficient Gram-negative antibacterial coverage, with only about 75% of the *Enterobacteriaceae* other than *E. coli* and 46% of the *Pseudomonas* spp. susceptible in the United Kingdom.[10] Several studies have reported an increased risk of fungal infection, death, and neurodevelopmental delay with starting cefotaxime in the first few days of life.[17–22] Clark et al reported a higher mortality rate among infants who had received cefotaxime in the first week of life, compared with gentamicin.[18] Resistance to cefotaxime is increasing on account of extended-spectrum beta-lactamase infections, commonly by *A. baumannii*, *K. pneumonia*, and *E. coli*.[23] Extended beta-lactamase infection account for approximately 15% of all neonatal infections in Saudi Arabia.[24–26]

Coagulase-negative *staphylococci* (CoNS) are the most frequent bacteria isolates in late-onset neonatal sepsis.[8] In some countries, gentamicin–flucloxacillin or gentamicin–amoxicillin/penicillin is often adequate.[10,27] However, in Saudi Arabia, the causative organisms and their antibiotic susceptibility patterns are different,[9,28,29] thereby justifying the selection of other first-line empiric antibiotics. Although CoNs are often susceptible to vancomycin, targeted empiric therapy with vancomycin is usually reserved for neonates with the highest risk of severe infections.[11] An ideal antibiotic combination regimen should cover the most frequently isolated organisms, without causing selection pressure for antibiotic resistance. The strategies adopted by various NICUs to prevent and treat late-onset neonatal sepsis may influence the pattern of bacteria, causing sepsis in the respective units. For example, the use of cefotaxime–amoxicillin in an NICU may increase the risk of cefotaxime resistance to Gram-negative organisms.[29] Thus, with ampicillin–cefotaxime, Gram-negative bacteria like *Enterobacter* spp. may flourish following the elimination of normal intestinal flora. These organisms may degrade cefotaxime and cause cefotaxime-resistant invasive infections.[17] In a previous study carried out at our center, enterobacter sepsis accounted for about 19% of neonatal sepsis.[9] Therefore, it is prudent to consider

these organisms when empiric therapy is prescribed for sick patients, those with previous positive blood culture, or following a prolonged course of antibiotics.

It is noteworthy that the selection of antibiotics in this study was not informed by a change in practice over time; rather, it was based on the hospital guidelines premised on the factors mentioned earlier. The first-line empiric treatment for late-onset sepsis in our center is a combination of amikacin and cloxacillin. Consequently, more neonates received this regimen compared with ampicillin–cefotaxime. This study, to our knowledge, is the first to compare empiric amikacin–cloxacillin with cefotaxime–ampicillin for late-onset neonatal sepsis. The propensity matching ensures an adequate comparison of both treatment groups. However, the study is limited by the small sample size, which limits the generalizability of the findings. Hence, the result should be interpreted with caution. Furthermore, we do not maintain a central line-associated bloodstream infection database at our center. Thus, we are unable to account for the effect of these infections on mortality.

In conclusion, amikacin–cloxacillin combination therapy was associated with lower mortality in neonates with late-onset sepsis at our NICU, compared with cefotaxime–ampicillin. Other important influences that can impact mortality need to be investigated in future studies. Therefore, a randomized controlled trial, which is likely to have better internal validity, is essential to determine the true effects of the treatment regimens. To control the misuse of antibiotics, institutions need to develop clearer guidelines based on antibiotics prevalence and susceptibility patterns.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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