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Original Research Paper

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COMPARISON BETWEEN TWO COMMONLY USED EMPERIC ANTIBIOTOC REGIMENS IN NEONATAL SEPSIS

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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 march 2014 and april 2016. 32 neonates were selected in each group after proper matching.
Results: We identified a total of 150 neonates from the hospital's record. We included 32 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 .
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.

KEYWORDS :

INTRODUCTION

Sepsis is a leading cause of mortality and morbidity in neonates, particularly in developing countries like india where neonatal deaths contribute 70% to the total under five mortality rate, and about 30% of all neonatal deaths are attributed to severe bacterial infections (1,2). Approximately 750,000 deaths from neonatal sepsis occur annually worldwide and 99% of these take place in developing countries settings.(3). There is an inverse relationship between the incidence of neonatal sepsis and birth weight(4,5). 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 (6). 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 neo-natal sepsis, respectively.(7,8) . various studies done in different NICUs showed that the incidence of infection was predominantly with Gram-positive microorganisms around 60% 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) and 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 gentamicin with either fucloxacillin or amoxicillin and amoxicillin with cefotaxime(10).

Due to the difficulties in a prompt diagnosis of LOS, LOS-associated high risk of mortality and long-term neurodevelopmental sequelae, the symptoms of neonatal sepsis being nonspecific, differentiating between neonatal sepsis and the symptoms of prematurity is often difficult, empirical antibiotic treatment is initiated on suspicion of LOS. Neonatologists prescribe broad-spectrum antibiotics under the assumption that neonatal sepsis exists, even after a negative result on initial blood culture. As the evidence for the most suitable empirical antibiotics for late-onset neonatal sepsis is lacking; 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 unit, 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 :

This study was carried out in the NICU of GB Pant hospital, a tertiary hospital in kashmir. We retrieved the medical records of consecutively admitted VLBW neonates with first episodes of late-onset sepsis between march 2014 and april 2016. 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 periven-tricular 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 out-come of treatment.

Study Design

It is 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 neighbour using the birth weights, gestational ages, need for respiratory support (received ventilatory support during hospitalization), was carried out. The primary outcome of this study was the all-cause mortality during the first 120 days of life or discharge.

Defnitions

Clinical (suspected) sepsis: The exact definition of suspected neonatal sepsis remains vague. As the clinical features of sepsis may be infuenced by strong pro-infam-matory cytokines, clinicians rely on clinical features in their decision to suspect sepsis and start antimicrobial agents(11,12,13).

Confirmed (proven) sepsis: Detection of a pathogen (positive culture) in otherwise sterile body fluid, in addition to clinical and laboratory signs of sepsis(11,12,13)

Early-onset sepsis: Sepsis caused by pathogens transmitted vertically from mother to infant occurring in the first 3 days of life(11,12,13).

Late-onset sepsis: Sepsis caused by horizontally acquired pathogens that occurs after 3 days of an infant's life.(11,12,13)
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.

Statistical Analysis

The baseline characteristics of both treatment groups were compared using Chi-square and independent t tests where appropriate.

RESULTS:

TABLE 1

	Amikacin+ cloxacillin (32)	Cefotaxime+ ampicillin (32)	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 (%)	17 (53.1)	12(37.5)	0.054
PDA (%)	15 (46.8)	20 (62.5)	0.268
IVH (%)	16 (51.9)	19 (59.3)	0.409
PVL (%)	3 (11.1)	0(0)	0.299
NEC (%)	20 (62.5)	15 (46.8)	0.273
HIE (%)	0 (0)	2 (6.2)	0.552
Positive blood culture (%)	13 (40.6)	5(15.6%)	0.02*
No. deaths (%)	9(28.1)	16 (50%)	0.097
Invasive respiratory support	22 (68.75)	26 (81.25)	0.715
Median hospital stay (d)	42 (IQR: 18–79)	23 (IQR: 5–74)	
Median days on antibiotics	17 (IQR: 9–30)	13 IQR: 3–25)	

TABLE 2 Microrganisms recovered from culture

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

We identified a total of 150 VLBW neonates who had received empiric amikacin–cloxacillin or cefotaxime–ampicillin for late-onset sepsis. 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 2), E. coli (2 cases), Candida sp. (1 case). One hundred and eighteen neonates received amikacin–cloxacillin, whereas 32 received cefotaxime–ampicillin. The median duration of hospitalization among the patients was 42 (31–71) days, and the duration of antibiotics during hospitalization was 23 (IQR: 9–26) days. The neonates received an average of 3 courses of antibiotics during hospitalization. After 1:1 matching of neonates in both treatment groups, we included 32 neonates each in the amikacin–cloxacillin and cefotaxime–ampicillin groups. Of those included in the study, 54.7% (35/64) were females. The mean gestational age of all the neonates in the study was 27.4 weeks, and the mean birth weight was 918g.

The risk of mortality was signifcantly 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)

DISCUSSION

In this study, we found 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.14 Several studies have reported an increased risk of fungal infection, death, and neurodevelopmental delay with starting cefotaxime in the first few days of life.15,16 Clark et al reported a higher mortality rate among infants who had received cefotaxime in the first week of life, compared with gentamicin.16 Resistance to cefotaxime is increasing on account of extended-spectrum beta-lactamase infections, commonly by A. baumannii, K. pneumonia, and E. coli.17 Coagulase-negative staphylococci (CoNS) are the most frequent bacteria isolates in late-onset neonatal sepsis.. 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. 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.. 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 among the first to compare empiric amikacin–cloxacillin with cefotaxime–ampicillin for late-onset neonatal sepsis.. 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.. To control the misuse of antibiotics, institutions need to develop clearer guidelines based on antibiotics prevalence and susceptibility patterns.

CONFLICT OF INTEREST : None

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