Original Article

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Retrospective Evaluation of Culture Proven Neonatal Sepsis Cases in Neonatal Intensive Care Unit

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ABSTRACT

Objective: Neonatal sepsis is one of the most frequent and life threatening disorder in the first one month of life. The type of the causative organisms and their resistance may change by the time even in the same hospital. In this study, we aimed to evaluate characteristics of the culture-proven cases in our neonatal intensive care unit.

Methods: Between January 2012-July 2015, 1735 neonates who were hospitalized at neonatal intensive care unit of Bezmialem Vakıf University Hospital. The 56 patients diagnosed as culture proven sepsis were involved in the study.

Results: The mean gestational age of patients was 31.70±4.92 weeks, and the mean birth weight was 1654.07±906.6 grams. The patients were 76.8% premature and 23.2% term newborns. Early onset neonatal sepsis was diagnosed 14.3% of patients, late onset neonatal sepsis was diagnosed 85.7% of patients. KoNS was the most frequently isolated gram positive microorganism in whole cultures. *Klebsiella pneumoniae* was the most frequently isolated gram negative microorganisms. Vancomycin resistance was not determined in any of the gram positive microorganisms. Meropenem resistance was not determined and imipenem had a maximum value of 50% resistance in the evaluated gram negative microorganisms. Mortality rate was 12.5% in both early onset neonatal sepsis and in late onset neonatal sepsis. All of the babies who were died were premature in both sepsis groups.

Conclusion: The type of sepsis and microorganisms and their antibiotic resistance changes amongst neonatal intensive care units and also in the same unit by the time. Active surveillance is recommended to update the treatment protocols.

Keywords: Neonatal sepsis, prematurity, antibiotic resistance

Introduction

Sepsis in newborns presents as an acute condition accompanied by bacteremia and has systemic findings in the first month of life (1-3). It is one of the most common and life-threatening diseases in newborns. It progresses with high morbidity and mortality (2).

It is essential to identify an infected newborn and start the treatment without delay (1-3). It is necessary to reproduce the agent in the blood culture for diagnosis. This requires 48 to 72 hours. Therefore, an empirical antibiotic therapy should be started immediately after taking the blood culture in infants in who neonatal sepsis is suspected. An antibiotic therapy for all newborns with infection-like findings causes the resistant strains of bacteria to emerge (1, 2, 4, 5).

The incidence of bacteria that most commonly cause sepsis in newborns may vary from country to country, one geographical region to another, and hospital to hospital, and it may change over time even in the same hospital (6-12).

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In this study, we aimed to retrospectively investigate the demographic characteristics, laboratory data, microorganisms reproducing in cultures, and antibiotic resistance of these microorganisms in patients followed up and diagnosed with culture-proven sepsis in the Neonatal Intensive Care Unit (NICU) of the Bezmialem Foundation University.

Methods

This retrospective study was conducted by reviewing 1,735 patients who were followed up, diagnosed with culture-proven neonatal sepsis, and treated between January 2012 and July 2015 in the NICU of the Bezmialem Foundation University.

Before the study, an approval was received from the Ethics Committee of Clinical Investigations of the Bezmialem Foundation University (decision no. 20/26 dated November 4, 2015). The data of the patients were obtained from the NICU database and the patient record system of the hospital.

The demographic characteristics, clinical features, types of sepsis, laboratory data, culture results, applied treatments, mechanical ventilation durations, use of umblical vein catheter, and peripherally inserted central catheter were evaluated in the patients.

The Töllner scoring system, in which clinical and laboratory findings are evaluated together, was used for the diagnosis of sepsis (4). The patients in whose blood cultures the breeding occurred were evaluated as culture positive, and the patients in whose blood cultures the breeding did not occur were diagnosed with clinical sepsis. The patients with a positive culture were included in the study. The patients who were younger than 7 days at the time of diagnosis were evaluated as early-onset neonatal sepsis (EONS), and those between 8 and 30 days old were evaluated as late onset neonatal sepsis (LONS). While the patient was followed up and treated in the hospital, infections that occurred after the 3rd day of hospitalization or within 72 hours after discharge from the hospital were evaluated as nosocomial infections and examined within the LONS group.

A whole blood count, C-reactive protein (CRP), peripheral smear, procalcitonin, and blood culture were studied in newborns with sepsis before the antibiotic treatment was started and 48 hours after the treatment was started. Neutropenia was defined as the leukocyte count <5,000/mm^3, leukocytosis >25,000/mm^3, and thrombocytopenia <100,000/mm^3. The CRP serum levels were studied with the immuno-nephelometry method (Dade Behring, Marburg Gmbh, Germany). The CRP>0.5 mg/dL was considered positive. The blood culture was implanted in the pediatric BACTEC culture media. The microorganisms were identified using the VITEC-2 compact (Biomerieux, France) system, which is an automated bacterial identification system. In breeding bacteria, the susceptibility to antibiotics was evaluated in accordance with the Clinical Laboratory Standards Institute criteria.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences Statistics, Version 21 (IBM Corp., Armonk, NY, USA). While evaluating the study data, descriptive statistical analyses (mean, standard deviation, median, frequency, ratio, minimum, maximum), and the T-test and Wilcoxon test, which are the significance tests, were used. The statistical significance level was accepted as $p \leq 0.05$.

Results

Of a total of 1,735 patients followed up in the NICU of the Bezmialem Foundation University Hospital, 56 (3.2%) diagnosed with culture-proven neonatal sepsis were included in the study. The ages of mothers ranged from 15 to 44 years, and the mean age was 28.13±5.42 years. The mean of gestation weeks was 31.70±4.92 (23–40) weeks. The mean birth weight was 1,654.07±906.60 (510–3,950) grams. The distribution of patients according to birth weight is given in Table 1. Among all patients with sepsis, 76.8% (n=43) were premature. Of the patients, 55.4% were male (n=31), and cesarean section was used as the delivery method in 66.1% of cases. The APGAR scores of the patients were 5.56±2.11 (1–8) on average in the 1st minute, and they were 7.47±1.4 (4–10) in the 5th minute. Of the patients, 82.1% (n=46) were from our hospital, and 17.9% (n=10) were from an external center. The most common physical finding on examination was reduction in breast-feeding, abdominal distension, and residue with 33.9% (n=19) of cases. It was followed by respiratory failure findings (rallies, tachypnea, groaning, withdrawal) with 23.2% (n=13) and apnea, bradycardia and tachycardia with 12.5% (n=7). Only 3 (5.4%) patients were found to have fever. The rate of early onset sepsis was found to be 14.3% (n=8), and LONS rate was 85.7% (n=48). The mortality rate was 12.5% (n=7) in the patients who were diagnosed with sepsis.

Coagulase-negative staphylococci (CoNS) were the most frequently detected Gram-positive microorganisms breeding in all cultures at 82.1% (n=32). Penicillin and oxacillin resistance was found at 90%, and teicoplanin resistance was found at 3% in CoNS. Vancomycin resistance was not detected in any of the Gram-positive microorganisms (Table 2). *Klebsiella pneumoniae* (*K. pneumoniae*) was one of the most frequently detected Gram-negative microorgan-

Table 1. Distribution of patients by birth weight

Birth Weight (gr)	n	%
≤1,000	16	28.6
1,001–1,500	15	26.8
1,501–2,000	9	16.1
2,001–2,500	>2,500	5
11	8.9	19.6
Total	56	100

isms with 40% (n=14). In *K. pneumoniae*, the percentage of ceftazidime resistance was 54%, piperacillin–tazobactam resistance was 21.4%, imipenem resistance was 18.2%, meropenem resistance was 9%, and gentamicin resistance was 7.1%. *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Serratia marcescens* (*S. marcescens*) showed no resistance to the carbapenem group of antibiotics (Table 3). In our study, we detected fungal infections at a rate of 10.7% (n=6). One of such cases was a patient that we received from another unit. The other five breedings occurred in 2013, and prophylactic fluconazole treatment was started to be applied routinely as of 2014 in the VLBW newborns under 1,500 grams in our unit, and candida breeding was not observed as of this date. The most commonly applied antifungal agent was fluconazole with 32.2% (n=18).

There was a problem in the prenatal history in 62.5% of patients (n=35). The early membrane rupture (EMR), which is among the risk factors associated with sepsis, occurred in 10.7% (n=6), and urinary tract infections followed with 7.2% (n=4). There was a history of antenatal steroid application in 39.5% (n=17) of the preterm babies, and surfactant was applied in 62.8% (n=27) of preterm babies. Bronchopulmonary dysplasia (BPD) was detected in 18.6% (n=8) of the preterm patients, premature retinopathy in 44.2% (n=19), anemia in 67.4%, intraventricular hemorrhage in 23.2% (n=10), and periventricular leukomalacia in 6.9% (n=3).

Table 2. Antibiotic resistance in Gram-positive microorganisms (%)

Bacterium	Penicillin	Oxacillin	Teicoplanin	Vancomycin
CoNS	90	90	3	0
E. faecalis	100	100	0	0
GBS	0	-	-	0
S. aureus	66.7	0	-	0
S. parasanguinis	100	-	-	0

CoNS: Coagulase-negative staphylococci; E. faecalis: Enterococcus faecalis; GBS: group B streptococcus; *S. aureus: Staphylococcus aureus; S. parasanguinis: Streptococcus parasanguinis*

Table 3. Antibiotic resistance in Gram-negative microorganisms (%)

Bacterium	GN	CAZ	PIP–TZB	IMP	MEM
K. pneumoniae	7.1	54	21.4	18.2	9
K. oxytoca	0	0	100	100	100
P. aeruginosa	0	0	0	0	0
S. marcescens	33.3	33.3	33.3	0	0
S. liquefaciens	0	0	0	0	0
E. coli	33.3	50	50	0	0
E. aerogenes	0	33.3	33.3	50	0
E. cloacae	0	33.3	33.3	0	0

K. pneumaniae: Klebsiella pneumoniae; K. oxytoca: Klebsiella oxytoca; P. aeruginosa: Pseudomonas aeruginosa; S. marcences: Serratia marcescens; S. liqefaciens: Serratia liquefaciens; E. coli: Escherichia coli; E. aerogenes: Enterobacter aerogenes; E. cloacae: Enterobacter cloacae; GN: gentamicin; CAZ: ceftazidime; PIP–TZB: piperacillin–tazobactam; IMP: imipenem; MEM: meropenem

The mean duration of monitoring with umbilical vein catheter ranged from 12.31±5.67 (1–21) days on average, and the number of monitoring days with PTSK ranged from 5.59±10.38 (1–41) days on average. Erythrocyte suspension was administered in 16.1%, thrombocyte suspension (TS) in 12.5% (n=7), and albumin infusion in 8.9% (n=5) of patients diagnosed with sepsis. There were no patients receiving fresh frozen plasma. As supportive therapy, 16.1% (n=9) of patients received only intravenous immunoglobulin (IVIG), 16.1% (n=9) received only pentoxifylline, and 28.6% (n=16) of them received IVIG and pentoxifylline together. During the sepsis episodes, 19.7% (n=11) of the patients received inotrope treatment, 3.6% (n=2) received granulocyte colony stimulating factor (G-CSF), and 12.5% received insulin.

The number of septic episodes ranged from one to six, and the mean number of episodes was 1.83±1.29 in patients who were followed up with the diagnosis of LONS. The patients who had one sepsis episode constituted 56.3% (n=27), those who had a sepsis episode twice constituted 25% (n=12), and those who had three and more sepsis episodes constituted 18.8% (n=9) of all LONS patients.

The number of white blood cells (WBC) taken before starting the antibiotic therapy ranged from 1,040 to 42,750/mm^3, with a mean of 12,276.61±8,255.36/mm^3. Neutropenia was detected in 11 of the patients (19.6%). The mean WBC values of the neutropenic patients was 3,560.91±1,154.80. Forty-eight hours after the start of antibiotic therapy, the mean WBC values of these patients were calculated as 8,446.36±6,521.32. In neutropenic patients, the difference between the WBC values before the treatment and 48 hours after the treatment was found to be statistically significant (p=0.006).

C-reactive protein (CRP) values taken before the initiation of the antibiotic therapy ranged from 0 to 19.1, and the mean was 3.43±5. The CRP values taken after 48 hours of the antibiotic treatment ranged from 0 to 25.6, and the mean was 3.13±4.6. There was no statistically significant difference between the pre- and post-treatment CRP levels (p=0.521).

The duration of hospitalization was 30.63±21.64 days (10–61) in patients with EONS and 48.56±47.23 days (8–205) in LONS patients. The difference between the two sepsis groups was statistically significant in terms of the duration of hospitalization (p=0.0001).

Discussion

Increases in the frequency of premature infant birth and neonatal sepsis remain an important cause of mortality and morbidity, despite all improvements in the follow-up and treatment of these infants in the NICU (13). In developed countries, the incidence of neonatal sepsis has been reported as 1–10 in 1,000 live births (6, 14). The incidence of culture-proven neonatal sepsis in our country has been reported between 5% and 8.8% (7, 10, 11, 15). In our study, we found that the 3.2% culture-proven neonatal sepsis rate was lower than the one listed in national literature.

Prematurity alone is a risk factor for nosocomial infections. Prematurity rates in this study were similar to other studies conducted in our country, but proven sepsis rate was lower in our study (11, 16). If the mother had an EMR history of premature infants, the EONS risk increased to 5–15% (10, 16, 17). Of our patients, 10.7% had a history of EMR. An increase in premature infections can be observed in infants with neonatal sepsis (18). In the study by Turkmen et al. (16), BPD was found to be 6.7%, and Stage 2 and above PR were found to be 11% in patients with sepsis. In our study, we found that, among the premature complications, BPD increased in 18.6% of the preterm patients, and PR increased in 44.2%.

Invasive procedures during the follow-up in the hospital were the main factors that increased the LONS risk (1). In the study by Meral et al. (7), surfactant was administered in 50% of premature babies in whom sepsis developed, umbilical catheter was placed in 30.4%, and respiratory support (invasive–noninvasive) was given to 56.5% of them. In our study, we found that the rate of invasive procedures was higher, and we think that it increased the infection rates.

Clinical findings in neonatal sepsis are characteristically subtle and widespread. In our patients, gastrointestinal findings such as the reduction in breast-feeding, abdominal distension, and residue were detected at the forefront. While the respiratory system findings were in the first place, gastrointestinal findings were in the second place in the study by Kara et al. (15) in which they investigated culture-positive patients.

Although the sensitivity of the low WBC count in the laboratory is 29% for the sepsis diagnosis, the specificity can reach up to 91% (5). Different rates (11.5–31%) of neutropenic incidence were given in the studies conducted (10, 15, 19). In our study, neutropenia was found in 11 (19.6%) patients, and this finding was consistent with the literature. We also observed in our study that neutropenia in the patients recovered rapidly in the 48th hour of the antibiotic treatment. This suggests that when the patients are diagnosed and treated early, especially neutropenic patients, the treatment response will also be faster.

The causes of neonatal sepsis differ in developed countries and in developing or undeveloped countries (6, 20, 21). While the group B streptococci were more causative in EONS in developed countries, Gram-negative bacteria were mostly found in developing countries. In our study, we found in all culture breedings that CoNS was the most frequent among the Gram-positive microorganisms, and *K. pneumoniae* was the most frequent in the Gram-negative ones. Our results were consistent with the development level of our country.

Multiple antibiotic resistance is a major problem in microorganisms that cause sepsis (22). While the CoNS were found to be susceptible to glycopeptides (teicoplanin and vancomycin) in the study by Yalaz et al. (11), penicillin and methicillin resistance was 100%; while methicillin resistance in CoNS strains was detected as 96% in the study by Kavuncuoğlu et al. (10), no resistance was found against vancomycin and teicoplanin. In our study, the resistance to penicillin, oxacillin, and teicoplanin in CoNS was 90%, 90%, and 3%, respectively. Vancomycin resistance was not detected in any Gram-positive microorganisms. The resistance pattern in Gram-positive microorganisms was similar to the one found in the literature. While there was no amikacin–gentamicin resistance in *K. pneumoniae* in the study by Meral et al. (7), gentamicin resistance was found at a rate of 7% in our study. Turkmen et al. (16) found in their study that carbapenem, quinolone, aminoglycoside, and ceftazidime were susceptible in *P. aeruginosa*. In our study, neither gentamicin, ceftazidime, piperacillin–tazobactam resistance, nor carbapenem resistance was detected in *P. aeruginosa*. While gentamicin, ceftazidime, and piperacillin–tazobactam resistance was 33.3% in *S. marcescens*, carbapenem resistance was not detected.

It was reported that the FFP was administered in 19%, TS in 14.2%, and G-CSF in 4% of the patients by Meral et al. (7); blood transfusion was performed in 62.5% of the patients by Ünal et al. (9). In our study, transfusion of blood products was found to be lower than that in the literature. It was observed that supportive treatments were applied in similar proportions to the literature. Because IVIG is not recommended for use according to the reviews published in Cochrane, it has been removed from our treatment protocol of neonatal sepsis since 2015 (23).

The rates of hospitalization increase with the development of sepsis in patients. Yalaz et al. (11) found the mean hospitalization duration as 30.7±18.5 days, and Ünal et al. (9) found it as 29.0±17.8 days. In our study, the duration of hospitalization was found to be significantly longer in patients with LONS, which was attributed to the fact that the patients in this group were often small preterm infants and had a more severe sepsis table.

In the study by Turhan et al. (24), the mortality rate was 10% in EONS, 5% in LONS, and the total mortality rate was 10.6%; in the study by Rabie Shehab El-Din et al. (25), the mortality rate was 51% in EONS and 42.9% in LONS. In our study, the mortality rates in EONS and LONS were found to be 12.5%, consistent with the data from our country.

Study limitations

Because our study was planned as a retrospective study, and the number of patients diagnosed with culture-positive sepsis was low, the efficacy of supportive treatments such as IVIG and pentoxifylline could not be compared.

Conclusion

It is essential to start the treatment of neonatal sepsis without delay. For this reason, it is necessary to determine an empirical treatment protocol by specifying the sepsis factors and antibiotic resistance with regular surveillance studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Bezmialem Vakıf University.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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