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Evaluation of Our Neonatal Sepsis Cases in Terms of Causing Microorganism and Antibiotic Resistance

Yenidoğan Sepsisli Olgularımızın Etken Mikroorganizma ve Antibiyotik Direnci Yönünden Değerlendirilmesi

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Abstract

Objective: The purpose of the study is to evaluate sepsis cases in Neonatal Intensive Care Unit (NICU) in terms of the causative microorganisms and antibiotic resistance.

Material and Methods: We retrospectively reviewed 115 patients who had been diagnosed with clinical sepsis and proven sepsis at the NICU between 01.01.2013 and 30.09.2014. Patients were classified as early (0-3 days), late (3-30 days), and very late (> 30 days) sepsis.

Results: A total of 721 patients were admitted to our hospital during the study period. 11,1% (n= 80) were diagnosed with proven sepsis, and 7.6% (n= 55) were diagnosed with clinical sepsis. Early sepsis (ES), late sepsis (LS), and very late sepsis (VLS) were found to be 37%, 54.8% and 8.15%, respectively. Coagulase-negative *Staphylococcus* (CNS) was the most common etiologic factor in all sepsis groups. The mortality rate of *Klebsiella* spp. (*Klebsiella pneumoniae* 50%, *Klebsiella oxytoca* 40%) were found to be the highest. A decrease in sepsis-related mortality rate from 21.5% to 12.5% and a decrease in rate of *K. pneumoniae* (25% to 8.3%) was found in 2014 compared with 2013. In general, sensitivity of ampicillin and gentamicin was very low (0-18%, 23-50%, respectively). An increase in vancomycin and teicoplanin resistance (3-11%, 3-5.5%) among gram-positive microorganisms and an increase in amikacin resistance (59-83%) among gram negative microorganisms in 2014 compared with 2013 were observed.

Conclusion: Close follow-up of the patient's clinic and culture results and use of microorganism specific narrow spectrum antibiotics and compliance with infection control practices will reduce resistance rates.

Öz

Giriş: Çalışmanın amacı hastanemiz Yenidoğan Yoğun Bakım Ünitesi (YYBÜ)'ndeki sepsis olgularının etken mikroorganizma ve antibiyotik direnci yönünden değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmamız 1 Ocak 2013 ve 30 Eylül 2014 tarihleri arasında YYBÜ'de klinik sepsis ile kanıtlanmış sepsis tanısı almış 115 hasta ile geriye dönük olarak incelendi. Hastalar erken (0-3. gün), geç (3-30. gün) ve çok geç (> 30. gün) sepsis olarak sınıflandırıldı.

Bulgular: Belirtilen çalışma döneminde hastanemiz YYBÜ'de toplam 721 hasta yatmıştır. Hastaların %11.1 (n= 80)'i kanıtlanmış sepsis, %7.6 (n= 55)'sı klinik sepsis tanısı aldı. Sepsis tanısı alan olgularda erken sepsis (ES) %37, geç sepsis (GS) %54.8 ve çok geç sepsis (ÇGS) %8.15 oranında bulundu. Tüm sepsis gruplarında en sık etken olarak koagülaz-negatif stafilokok (KNS) saptandı. Mortalite oranı en yüksek etkenlerin *Klebsiella* türleri (*Klebsiella pneumoniae* %50, *Klebsiella oxytoca* %40) olduğu saptandı. 2014 yılında, 2013 yılına göre sepsis ilişkili mortalite oranının %21.5'ten %12.5'e düştüğü ve gram-negatif etkenlerde, özellikle mortalitesi en yüksek etken olan *K. pneumoniae*'da azalma (%25'ten %8.3'e) olduğu belirlendi. Genel olarak ampisilin ve gentamisin duyarlılığı çok düşük (sırasıyla %0-18; %23-50) bulundu. 2014 yılında 2013 yılına göre gram-pozitif etkenlerde vankomisin ve teikoplanin direncinde artış (sırasıyla %3-11; %3-5.5); gram-negatif etkenlerde ise amikasin direncinde artış (%59-83) saptandı.

Sonuç: Sepsis tedavi yönetiminde asepsi-antisepsi kurallarına uyulması, hastanın kliniğinin ve kültür sonuçlarının yakın takibi, etkene özgü mümkün olduğu kadar dar spektrumlu antibiyotik kullanımı direnç

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Each unit should determine treatment management according to its own culture results.

Keywords: Antibiotic resistance, coagulase-negative *Staphylococcus*, newborn, sepsis

oranlarını azaltacaktır. Her ünite kendi kültür sonuçlarına göre tedavi yönetimlerini belirlemelidir.

Anahtar Terimler: Antibiyotik direnci, koagülaz-negatif stapfilokok, sepsis, yenidoğan

Introduction

Neonatal sepsis is a clinical syndrome caused by the invasion of the organism by the infectious agent in the first 28 days of life and characterized by the isolation of a specific pathogen from the blood cultures, and is the primary cause of infant death (1). However, the cases, in which the agent cannot be demonstrated but sepsis cannot be excluded by clinical and laboratory findings are called clinical sepsis (2). While the average frequency of proven sepsis is 16 in 1000 live births worldwide, the rate of clinical sepsis ranges from 20.7 to 50 in 1000 live births (3). In developed countries, the frequency of culture-positive neonatal sepsis is 1-10 per 1000 live births, whereas in developing countries, the incidence of neonatal sepsis is 49-170 per 1000 live births (4).

Early sepsis (ES) usually occurs within the first 3 days of life and is most caused by mother-related Group B *Streptococcus* (GBS) and *Escherichia coli*. In developing countries, early sepsis is caused by gram-negative bacteria rather than gram-positive bacteria; *Klebsiella types*, *Staphylococcus aureus* and *E. coli* are the most commonly isolated pathogens, followed by GBS (5,6). Late sepsis (LS) is usually associated with low birth weight from day 3 to day 28 of life, and long-term use of a central venous catheter and prolonged hospitalization. It is the sepsis group in which CNS, *S. aureus*, *Klebsiella*, and *Enterococcus* are prominent. Too late sepsis (TLS) is a group of sepsis needed to be defined recently because premature infants and the ones with very low birth weight are hospitalized for a long time and have a chance to survive. After 28th day of TLS, more exposure to invasive procedures is associated with insufficiency of host defense mechanisms. It is thought that active microorganisms in LS are also effective inTLS (7). Considering the importance of early diagnosis and appropriate treatment of neonatal sepsis cases, the risk factors, causative microorganisms, clinical findings and management of ES, LS, TLS cases are different (8).

The aim of this study is to determine the causative microorganisms and to evaluate the antibiotic resistance rates by evaluating sepsis cases in the NICU between January 1, 2013 and September 30, 2014 retrospectively.

Materials and Methods

Patients diagnosed with sepsis proved in the Neonatal Intensive Care Unit of our hospital at 1.1.2013-30.9.2014 and patients who were diagnosed with sepsis and had treatment were included in the study. Patients with possible sepsis (without clinical signs or with clinical signs but not being supported by risk factors and/or laboratory) were not included in the study. Patients were diagnosed in terms of the sepsis beginning time; if it occured in the first 72 hours, the diagnosis was sepsis, if it occurred after 72 hours, the diagnosis was late sepsis andit it occured after the 28th day of hospitalization in premature infants, the diagnosis was too late sepsis. Patients' gender, type of delivery, birth week, birth weight, onset time of sepsis, healing and death conditions were recorded from the patient files.

Microbiological evaluation: It was achieved culturing the samples taken from peripheral veins and core catheters under proper conditions into (BacT/ALERT 3D (biomerieux) mediums. The microorganisms produced were cultured in blood agar, chocolate agar and EMB media. The mediums were deposited on the stove of the hemoculture device of BacT/ALERT (Becton Dickinson, USA). Definitions using conventional methods have also been verified with API (bioMerieux) kits, if necessary. Antimicrobial susceptibility and resistance were determined by Disk Diffusion method (Vıtek 2 Compact, USA) according to the type of microorganisms produced. The results of the blood culture tests were examined from the records in the Microbiology Laboratory of our hospital. To consider the CNS strains as the primary blood circulation factor, clinical findings (fever, hypothermia, hypotonia, apnea, bradycardia, increased oxygen) and/or laboratory findings (leukocytosis, leukopenia, thrombocytopenia, CRP increase, etc.) related to the infection presence in the patient who has the same morphological type or kind of CNS reproduction in two or more blood cultures taken from different areas and reproduction in blood culture should be observed. CNS reproduction was evaluated as contamination in the peripheral blood culture or the culture of central venous catheter / core catheter of the patients who do not comply with the sepsis according to the clinic or laboratory findings.

Mean and standard deviation were used in descriptive statistics during the study. Chi-square test was used to compare the grouped data. Cases in which p-value was lower than 0.05' were evaluated as statistically significant. The permission was obtained from Sakarya University Medical School Ethics Committee (Date 30.09.2014, number: 71522473 / 050.01.04 / 92).

Results

115 patients who were followed due to sepsis in the NICU of our hospital between 01.01.2013 and 30.09.2014 were included in the study. The total number of the patients who

were hospitalized in the NICU between these dates was 721. Of these, 115 were diagnosed with newborn sepsis. 73% of cases were preterm and 27% were term. The frequency of sepsis in our unit was 18.7%. The mortality rate was 15.7%. While the mortality rate was 21.4% in 2013, it was found to be 12.5% in 2014. The proven LS was found to be 65%, ES was 21.3% and TLS was 13.7%. The mortality rate was higher in LS, but there was no statistical significance (p> 0.05). The percentage of gram-positive microorganisms was higher than gram-negative microorganisms in every two years, but the rate of gram-positive factors was 60.7% in 2013; 75% in 2014; total was 65%. CNS was the highest one in all groups (Table 1). GBS and *Listeria monocytogenes* were only seen in ES, while *Enterobacter aerogenes* was seen only in LS. In gram-negative microorganisms *K. pneumoniae* was the most common cause. In 2014, compared to 2013, while *S. aureus*, GBS, *L. monocytogenes* reduced, and CNS increased in gram-positive factors; *K. pneumoniae* and *Enterobacter cloacea* decreased and the others increased in gram negative factors (p= 0.037) (Table 2). Figure 1 shows the general distribution of all sepsis agents. According to the isolated microorganism, *K. pneumoniae* and *K. oxytoca* infections has the highest mortality rate (n= 8 50%; n= 2 40%) (Table 3). In general, resistance to glycopeptides (3-8%) was low in gram-positive factors, while penicillin and ampicillin resistance (82-88.8%, respectively) was very high. In gram-negative factors, resistance to ampicillin was 100%, while piperacillin resistance was 2.8%. Figure 2 and Figure 3 show the rates of antibiotic resistance of gram-negative and gram-positive agents over the years. Reduction of ampicillin and gentamicin resistance in gram-positive factors (88.8%-82.3%; 61.5%-50%, respectively) and little increase in vancomycin resistance (3%-11%) were detected. In

Table 1. Distribution of isolated microorgaisms by early, late and too late sepsis groups

	ES n (%)	LS n (%)	TLS n (%)
Gram-positive			
Coagulase-positive *Staphylococcus*			
S. aureus	0	6	2
Coagulase negative *Staphylococcus*	10 (55.5)	23 (45.1)	6 (54.5)
S. epidermidis	3	7	1
S. warneri	0	3	0
S. hominis	0	6	3
S. haemolyticus	4	7	2
Other CNS	3	0	0
Group-B *Streptococcus*	2 (11.1)	0	0
L. monocytogenes	1 (5.6)	0	0
E. faecalis	0	1 (2)	1 (9.1)
Gram-negative			
K. pneumoniae	3 (16.6)	12 (23.5)	1 (9.1)
K. oxytoca	1 (5.6)	4 (7.9)	0
E. aerogenes	0	1 (2)	0
E. cloacea	1 (5.6)	4 (7.9)	1 (9.1)
Total	18 (36)	51 (68.9)	11 (100)

CNS: Coagulase-negative *Staphylococcus*.

Table 2. Evaluation of isolated microorganisms by years

	2013 n (%)	2014 n (%)	p
Gram-positive			
Coagulase-positive *Staphylococcus*	6 (10.7)	2 (8.3)	
S. aureus	0	6	
Coagulase-positive *Staphylococcus*	23 (41)	16 (52.2)	
S. epidermidis	5	6	
S. warneri	1	2	
S. hominis	4	5	
S. haemolyticus	11	2	
Other CNS	2	1	
Group-B *Streptococcus*	2 (3.6)	0	**0.037**
L. monocytogenes	1 (1.8)	0	
Enterococcus faecalis	2 (3.6)	0	
Gram-negative			
K. pneumoniae	14 (25)	2 (8.3)	
K. oxytoca	2 (3.6)	3 (12.5)	
E. aerogenes	0	1 (4.1)	
E. cloacea	6 (10.7)	0	
Total	56	24	

CNS: Coagulase-negative *Staphylococcus*, Chi-square test was used.

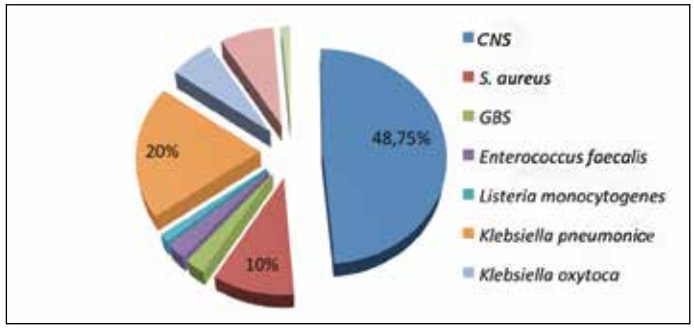

Figure 1. Distribution of active microorganisms.

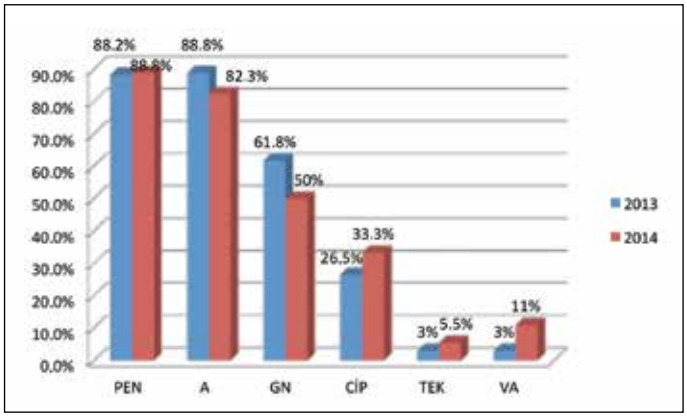

Figure 2. Antibiotic resistance of gram-positive bacteria over years.
PEN: Penicillin, A: Ampicillin, GN: Gentamicin, CİP: Ciprofloxacin, TEK: Teicoplanin, VA: Vancomycin.

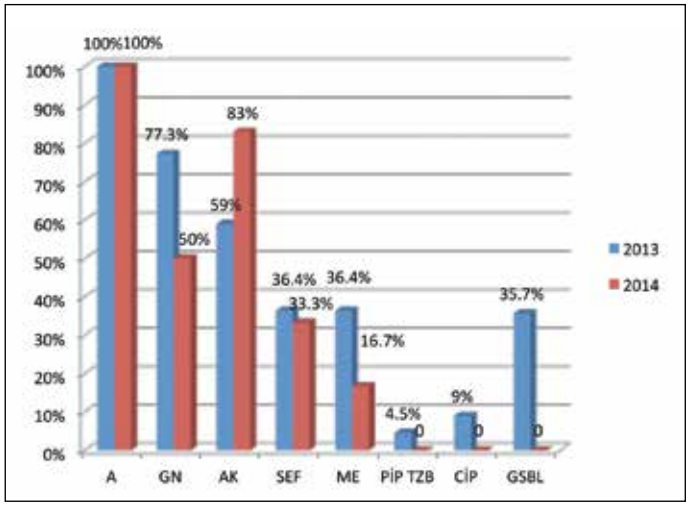

Figure 3. Antibiotic resistance of gram-negative bacteria over the years.
A: Ampicillin, GN: Gentamicin, AK: Amikacin, SEF: Cefotaxime, ME: Meropenem, PİP TZB: Piperacillin tazobactam, CİP: Ciprofloxacin, GSBL: Extended spectrum beta-lactamase.

Table 3. Mortality rates according to isolated microorganisms

	Exitus n (%)
S. aureus	1 (12.5)
CNS	3 (7.7)
GBS	0
E. feacalis	0
L. monocytogenes	0
K. pneumoniae	8 (50)
K. oxytoca	2 (40)
E. aerogenes	0
E. cloacea	1 (16.6)
Total	15 (18.7)

CNS: Coagulase-negative *Staphylococcus*, GBS: Group B *Streptococcus*.

gram-negative factors, amikacin resistance (59%-83%) was increased, but meropenem, piperacillin and Extended Spectrum Beta-Lactamase (ESBL) resistance (36.4%-16.7%, 4.5%-0.2%, 35.7%-0%) decreased.

Discussion

Neonatal sepsis is an important matter because it is one of the leading causes of neonatal death in our country and all over the world and is preventable (8-10). Timing and initiation of appropriate antibiotherapy significantly reduce mortality.

The frequency of neonatal sepsis varies between 1.8% and 39.8% and between units in our country (11). In our study, the frequency of sepsis was found to be 18.7% as in other studies conducted in our country. However, when we look at the frequency of neonatal sepsis in developed countries, it can be thought that this high rate may be related with the adaptation process of the personnel and that our unit is in foundation phase.

Sepsis in term male infants is two times more than term female babies, but this is not apparent in premature and low birth weight infants (12). In our study, 60 (52.2%) of the cases were male and 55 (47.8%) were female. 73% of our cases were preterm and 27% were term infants. In our study, we found the LS ratio to be high similar to many other studies conducted in our country. 54% of our cases and 65% of proven sepsis were LS.

The microorganisms that cause sepsis differ depending on countries, and units. In developed countries, the most frequent one is GBS, and the second one is *E. coli* in ES. In developing countries, gram-negative factors (*Klebsiella*, *Enterobacter*, *E. coli*, etc.) are seen in the foreground. In LS, CNS, *S. aureus*, *E. coli* and *Klebsiella* are more common (13). In our study, CNS was found to be the most common factor with a rate of 48.75%. *K. pneumoniae* was the second one with the rate of 20% and at the same time, it had the highest mortality rate. In all sepsis groups, CNS was detected too much.

Infections caused by CNS have been an important problem for Europe and America recently. In studies conducted, CNS is generally caused by that especially very low birth weight infants have change to survive, and by the invasive interventions such as especially the central venous catheters applied to them (14-16). That 73% of our cases were preterm and that they have more invasive intervention risk may be related to CNS rates. The most common factor in the studies conducted in our country as in the developed countries was reported to be CNS while in ES, *Klebsiella* types, and *S. epidermidis* (CNS subtype) were reported as the most common cause; GBS is a rare factor (17). In the study by the Turkish Neonatology Association, which investigated hospital-acquired infections in 2010; it has been stated that *Klebsiella* types are the most common factor in seven of 16 centers, CNS in three, *Serratia* in three, *E. coli* in one center and CNS has been reported to have a high overall rate. The study of Özkan et al. in 2014, which includes 7 years

of experience, has showed that in all sepsis groups, similar to our study, CNS has been found to be the most common factor. Similarly, in the study of Kara et al. CNS rate was 46.1%. In recent years in our country, there are similar studies stating that CNS is a serious problem (18-20). In our study, while in 2014, there was an increase in CNS compared to 2013, other gram-positive factors, *Klebsiella* types and other gram-negative factors were decreased. Although CNS was the most common factor; CNS-induced death was seen in 3 cases (7.7%). *K. pneumoniae* and *K. oxytoca*-induced mortality rates were found to be high; 50% and 40%, respectively. Consistent with literature, mortality rates due to gram-negatives were high (21,22).

The mortality rates related to sepsis in the NICUs are between 15-50% in the ES while 10-20% in the LS (23). Mortality rate in neonatal sepsis was 15% in our study. It was 21.4% in 2013; 12.5% in 2014. In 2014, a significant decrease in mortality was observed in proven sepsis. This situation was evaluated as a positive result of infection control measures in 2014. Our findings are similar to other studies in our country (24,25). However, contrary to the literature, mortality in LS was not found to be significant but higher. It was thought to be related to that most of our cases were preterm and had low birth weight.

With the widespread use of antibiotics, neonatal sepsis mortality decreases from 60-80% to 10% but antibiotic resistance resulting from the use of broad-spectrum antibiotics is an important problem. Recent studies have shown increased incidence of sepsis caused by multiple resistant bacteria, especially in developing countries (26). In our study, while CNS was sensitive to glycopeptides in 2013, penicillin was resistant in the rate of 100%, ampicillin 91%, gentamicin 73.9%; in 2014, penicillin and ampicillin were resistant in the rate of 87.5%, gentamicin 56.3%, teicoplanin 6.3% and vancomycin 12.5%. In compliance with the literature; penicillin, ampicillin sensitivity was low, glycopeptide sensitivity was high (27,28).

High ampicillin resistance detected in CNS reproduced in cases of sepsis increased the use of vancomycin especially in LS. Vancomycin resistance was not found in the literature until 2010. However, after 2010, low levels of vancomycin resistance have been reported. In a study conducted in China in 2013, vancomycin resistance was found to be 7% in ES and 10% in LS (29). According to the study of Kavuncuoğlu et al. in 2011, CNS and GBS had no resistance to vancomycin while there was 1% resistance against *S. aureus* (30). In the same study, penicillin resistance was 94% and ampicillin resistance was %72 in *S. aureus*. The study of Özdemir et al. stated that for *S. aureus*, these rates were 94.2% and 82%, whereas teicoplanin resistance was 3.3%; and vancomycin resistance was 0% (31). In our study, for CNS, penicillin and ampicillin resistance decreased while resistance to glycopeptides increased in 2014. In our clinic, it was thought that broad spectrum antibiotic use should be directed to rational antibiotic use. In our study, GBS and *Enterococcus* strains were sensitive to all antibiotics. For *K. pneumoniae*, in the study of Ozdemir et al., the resistances of ampicillin, gentamicin and amikacin were 92%, 92%, 0%, respectively (31). In the study of Özkan et al., these rates were 80%, 20% and 20%, respectively. In our study, the resistance rates in *K. pneumoniae* strains in 2013 and 2014 were respectively 100%, 100% for ampicillin, 87.5%, 50% for gentamicin; 57.5%, 50% for amikacin. In many studies in our country such as Sağlam et al., carbapenem resistance was not observed in gram-negative factors while this rate was found to be 23.8% in a study in Egypt in 2015 (32,33). In our study, meropenem resistance was 35.7% in 2013, but no resistance was found in 2014. In our study, the resistance of gentamycin, meropenem, piperacillin and ciprofloxacin was decreased in all gram-negatives in 2014 while amikacin resistance increased. The increase in amikacin resistance was thought to be related to virulence change.

In conclusion, close follow-up of the patient's clinic and culture results as well as compliance with asepsis-antisepsis rules in sepsis treatment management will reduce the resistance rates to the factor-specific antibiotics with narrow-spectrum as much as possible. Each NICU should periodically review the dominant factors and antibiotic resistance status in sepsis and develop appropriate treatment modalities with the outcomes to be obtained.

Ethics Committe Approval: The permission was obtained from Sakarya University Medical School Ethics Committee (Date 30.09.2014, number: 71522473 / 050.01.04 / 92).

Informed Consent: Written informed consent was not obtained due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have not reported a conflict of interest.

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