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Characteristics of Healthcare-Associated Infections in a Neonatal Intensive Care Unit

Türkiye'de Bir Yenidoğan Yoğun Bakım Ünitesinde Sağlık Hizmetlerine Bağlı Enfeksiyonların Özellikleri

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ÖZ

Giriş: Sağlık hizmeti ile ilişkili enfeksiyonlar (SHİE), yenidoğan yoğun bakım ünitelerinde (YYBU) neonatal mortalite, morbidite ve sağlık bakım maliyetini artıran risklerden biridir. SHİE'lerin özellikleri farklı bölgelerde ve zaman içinde önemli ölçüde farklılık gösterdiğinden, sürekli SHİE sürveyansı, enfeksiyon kontrolü için SHİE oranlarını ve sağlık bakımıyla ilişkili patojenleri belirlemek açısından önemlidir.

Gereç ve Yöntemler: Türkiye'de üçüncü basamak bir referans merkezindeki SHİE'nin özelliklerini incelemeyi amaçladık. 2011-2013 yılları arasında YYBU'ye kabul edilen tüm yenidoğanlar bu çalışmaya dahil edildi. SHİE ile ilgili bilgiler "Ulusal Hastane Enfeksiyon Gözetim Ağı" ve Hastalık Kontrol ve Önleme Merkezleri (CDC)'nin standartlarına göre toplanmıştır.

Bulgular: Toplam yatan hasta sayısı 1030 idi. Bunların % 29'unda SHİE gelişti. SHİE'nin genel oranı ve yoğunluğu sırasıyla % 29.0 ve % 24.0 idi. Kan dolaşımı enfeksiyonları, SHİE 'lerin % 36.4'ü idi. En sık izole edilen mikroorganizmalar koagülaz negatif Staphylococci ve Klebsiella pneumonia idi. Ortalama metisilin direnci % 87, ESBL oranı % 79 ve VRE oranı %40 idi.

Sonuçlar: Bu çalışma, SHİE 'nin YYBU'de hala ciddi bir sorun teşkil ettiğini belirlemiştir. Sağlık bakımıyla ilişkili patojenler hakkında zamanında ve doğru epidemiyolojik bilgilerin mevcudiyeti, enfeksiyon kontrolü ve uygun ampirik antibiyotik seçimi için gereklidir.

Anahtar kelimeler: Yenidoğan Yoğun Bakım, Sağlık bakımı ile ilişkili enfeksiyon, yenidoğan.

ABSTRACT

Introduction: HCAI is one of the risks which increase neonatal mortality, morbidity, and health care cost in NICUs. As the characteristics of HCAIs vary considerably in different regions and over time, continual HCAI surveillance is important to determine HCAI rates and healthcare-associated pathogens for infection control.

Material and Methods: We aimed to analyze the characteristics of HCAI in a tertiary referring center in Turkey. All newborns admitted to the NICU between 2011-2013 were included in this study. HCAI related information has been collected according to the "National Hospital Infection Surveillance Network" and the definitions of Centers for Disease Control and Prevention.

Results: The total number of inpatients was 1030. Out of them, 29% have developed HCAI. The overall rate and density of HCAI were 29.0% and 24.0%, respectively. Bloodstream infections were 36.4% of HCAIs. The most frequently isolated organisms were coagulase-negative Staphylococci and Klebsiella pneumoniae. Overall methicillin resistance was 87%, ESBL rate was 79%, and VRE rate was 40%.

Conclusions: This study determined that HCAI still presents a serious problem in NICU. The availability of timely and accurate epidemiological information on healthcare-associated pathogens is necessary for infection control and the appropriate selection of empiric antibiotics.

Keywords: Neonatal Intensive Care, Healthcare-associated infection, neonate.

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INTRODUCTION

The medical and technical advances in neonatology have improved the survival of preterm infants with extremely low birth weight (ELBW) along with some possible risks. One of this risks ishealthcare-associated infections (HCAI). These infections cause a significant increase in neonatal mortality, morbidity, hospitalization days, and health care costs in intensive care units (ICUs) (1).

Healthcare-associated infections is localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not present on admission to the acute care facility. It is known as nosocomial or hospital-acquired infection and is observed after the admittance of the patients with no prior infection (2). Healthcare-associated infections in terms of the key term "ICU-acquired infection" is defined as an infection occurring later than 48 hours after admission to an ICU, whereas CDC/NHSN requires that there is no evidence that the infection was present or incubating at the time of admission to the ICU, without time restriction (3). Although this difference, it has been reported an excellent concordance between US and European definitions of HCAIs as means of pneumonia and bloodstream infection (3).

In neonatal intensive care units (NICUs), HCAI rate varies in the range of 7.5-59 per 100 patients depending on environmental factors and differences in clinical practice (4-7). Since the incidence density is the most convenient way to correct for time (8,9), when reported as incidence density, the HCAI rate per 1000 hospital days in NICUs varies from 7.5 to 44.6, as giving the rates of HCAI from 3.9 to 15.1 per patient (4,10).

The frequency of HCAI depends on the birth weight, gestational age, and health care facilities. Neonatal infections in low- and middle-income countries are higher than that observed in industrialized countries. Turkey is a developing, middle-income country, and a wide range of HCAI rates (4.2-47.2 per 100 patients) and HCAI incidence density (9.4-20.9 per patient-days) have been reported in neonates (11-14). The most common types of HCAIs were reported as bloodstream infections, lower respiratory tract infections, and urinary tract infections respectively (6,15,16). Coagulase-negative Staphylococci (CoNS) is the most prevalent pathogen among the agents that cause HCAI (3) while gram-negative rods are major pathogens in developing countries (16-17).

The characteristics of HCAIs vary considerably in different regions, over time and referring to the hospitals. The availability of timely and accurate epidemiological information on healthcare-associated pathogens is essential for infection control and the appropriate selection of empiric antibiotics (18,19).

In this study, we aimed to analyze the characteristics of HCAIs including the clinical features, pathogen distribution, and antimicrobial susceptibility in a tertiary referral center in Turkey.

MATERIALS AND METHODS

This descriptive study was conducted by active search of infection records among newborns in the NICU of Marmara University Hospital with 568 beds (124 pediatric beds) during the period 1 January 2011- 31 December 2013. The neonatal intensive care unit with 16 beds has an occupancy rate of 100% and offers care to critically ill newborns, extremely low birth weight premature infants, neonates requiring pre-or postoperative management, and those who have congenital anomalies that require close observation or intervention. The nurse/baby ratio has been 1/3 in the study period.

HCAI related information has been collected prospectively according to the "National Hospital Infection Surveillance Network "UHESA" of The Turkish Ministry of Health. HCAI was defined using the criteria of the Centers for Disease Control and Prevention (CDC-2008) for children <1 year of age (2). The HCAIs were analyzed according to the birth weight of the babies. Group 1 included infants with a birth weight of 750 g and below, Group 2 between 751-1000 g, Group 3 1001-1500 g, Group 4 1501-2500g and Group 5 included infants with a birth weight of >2500 g.

Total number of inpatients, number of days in the hospital per patient, number of days on the ventilator, number of catheter days, and device utilization (DU) ratio per type of device were recorded. DU ratios were calculated by dividing the total number of device days by the total number of patient-days (20).

The extra length of stay was the difference between the length of stay of patients with HCAI and the length of stay of patients hospitalized in the NICU during that period who did not acquire a device associated (DA)-HCAI (21). Crude excess mortality in the NICU has defined as the difference between the crude overall case-fatality rate of patients with an HCAI and that of patients admitted without an HCAI and who did not acquire a HCAI in the NICU during the same period (22).

The frequency and causes of HCAIs, antibiotic sensitivities,

and resistance patterns among the NICU patients have been recorded. All information was recorded by a certified infection control nurse after clinical findings and culture results have been discussed with the consultant neonatologist and infectious disease specialist.

The study permission was obtained from Marmara university ethical committee (file number: 09.2021.1005)

Data were analyzed with descriptive statistics. The rates were calculated using overall HCAI rate, incidence density, device-specific infection rates.

RESULTS

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Table 1. Distribution of patients with healthcare-associated infection based on birth weight.

Birth weight (g)	Number of in-patients	Number of patient days	Number of infections	No. of HCAI per 1000 patient days
<750	36	1636	59	36.1
751-1000	29	1479	47	31.8
1001-1500	74	2599	76	29.2
1501-2500	224	3089	71	23.0
>2500	729	4580	63	13.7
Total	1092	13383	316	23.6

HCAI: Healthcare-associated infection.

Overall mortality rate (deaths per patient at risk) was 1.3% (14/1092) in this period and the rate of deaths in patients with HCAI (the rate of fatality of HCAI) was 8.0% (14/176). We calculated the crude excess mortality of HCAI as 0.8% (81/916). The total length of stay of 176 patients with HCAI was 9218 days while the total length of stay of 916 patients without HCAI was 4165 days.

The central line-associated bloodstream infection (CLABSI) rate was 0.6 per 1000 catheter days while ventilator-associated

pneumonia (VAP) rate was 13.7 per 1000 ventilator days and catheter-associated urinary tract infection (CAUTI) rate was 7.4 per 1000 catheter days. The patients acquired a total of 39 DA-HCAIs, giving an overall rate of 3.6% or 2.9% DA-HCAIs per 1000 ICU-days or 5.3 DA-HCAIs 1000 device days. The ratios of central line use, ventilator use, and urinary catheter use were 0.18, 0.32, 0.03 respectively.

The distribution of the type of HCAI was shown in Table-2. Of the total number of HCAIs, 115 (36.4%) were bloodstream infections (BSIs) with HCAI rate of 10.5%. Seventy-six (24%) of the bloodstream infections were diagnosed clinically because no growth was detected in the culture.

Table 2. The distribution of healthcare-associated infections.

Type of HCAI	**Number of infections (%)**	**The number of the HCAI per 1000 patient days**
BSI	115 (36.4%)	8.6
-Culture proven sepsis	*36 (11.4%)*	
-CLABSI	*3 (0.9%)*	*0.6 per 1000 catheter days*
-Clinically suspected sepsis	*76(24%)*	*5.7 per 1000 patient days*
Pneumonia	67 (21.2%)	5.0
- VAP	*33 (10.4%)*	*13.7 per 1000 ventilator days*
Eye, Eye, Ear, Nose, Throat or Mouth Infections	39 (12.3%)	2.9
Urinary Tract Infection	35 (11.1%)	2.6
- CAUTI	*3 (0.9%)*	*7.4 per 1000 catheter days*
Gastrointestinal Tract Infection	26 (8.2%)	1.9
- NEC	*14 (4.4%)*	*1.0 per 1000 patient days*
Skin & Soft Tissue Infection	20 (6.3%)	1.5
Central Nervous System Infection	12 (3.8%)	0.9
Surgical Site Infection	1 (0.3%)	0.08
Cardiovascular Infection	1 (0.3%)	0.08
TOTAL	**316**	**23.6**

BSI: Blood Stream Infection, CAUTI: Catheter-associated urinary tract infection, CLABSI: Central line-associated bloodstream infection,

One hundred twenty-seven microorganisms were isolated from 316 infections in 176 patients. The sources of the pathogens were bloodstream infections (33.9%), urinary tract infections (UTIs) (24.4%), conjunctivitis and upper respiratory tract infections (URTIs) (11.8%), pneumonia cases (10.2%), gastrointestinal infections (6.8%), skin and connective tissue infections (6.3%) and central nervous system infections (6.3%). Table-3 shows the distribution of the pathogens isolated from HCAI. The most common microorganisms were CoNS accounting for 23.6% (30/127), Klebsiella pneumoniae 20.5% (26/127), Escherichia coli 6.3% (8/127), influenza virus 5.5% (7/127), and Acinetobacter baumannii 6.3% (8/127).

HCAI: Healthcare-associated infection, NEC: Necrotizing enterocolitis, VAP: Ventilatory Associated Pneumonia.

Table 3. Isolated microorganisms in healthcare-associated infections.

Microorganism	No.	Rate (%)
CoNS	**30**	**23.62**
Klebsiella pneumonia	**26**	**20.47**
Escherichia coli	**8**	**6.3**
Acinetobacter baumannii	**8**	**6.3**
İnfluenza virus	**7**	**5.51**
Stenotrophomonas maltophilia	**5**	**3.94**
Pseudomonas aeruginosa	**5**	**3.94**
Clostridium difficile	**4**	**3.15**
Viridans group streptococcus	**4**	**3.15**
Rotavirus	**4**	**3.15**
Staphylococcus aureus	**3**	**2.36**
Klebsiella oxytoca	**3**	**2.36**
Serratia marcescens	**3**	**2.36**
Enterococcus faecalis	**3**	**2.36**
Enterobacter cloacae	**3**	**2.36**
Enterobacteriaceae	**2**	**1.57**
Enterococcus faecium	**2**	**1.57**
Citrobacter spp.	**2**	**1.57**
Candida glabrata	**1**	**0.79**
Candida lusitaniae	**1**	**0.79**
Other klebsiella strains	**1**	**0.79**
Other streptococci	**1**	**0.79**
Morganella morgagnii	**1**	**0.79**
TOTAL	**127**	**100%**

When the antibiotic resistance of the microorganisms in this study is analyzed, methicillin resistance was detected in 33.33% of Staphylococcus aureus strains (MRSA) (1/3), and 89% of coagulase-negative Staphylococci (24/27). Overall methicillin resistance was 83%. Of 88% of Klebsiella pneumoniae isolates were extended-spectrum β-lactamase (ESBL) producers (23/26), whereas 66.67% of Klebsiella oxytoca isolates produced ESBL(2/3). Of Escherichia coli, 63% were ESBL producers (5/8). All Enterococ-

cus faecium strains were vancomycin-resistant (100%) (2/2) whereas Enterococcus faecalis showed no resistance to glycopeptides (0/3). Overall vancomycin-resistant Enterococci rate was 40%. Of Acinetobacter spp. isolates, 75% were resistant to carbapenems. Overall carbapenem resistance was 23.5%. All Acinetobacter baumannii isolates in our unit were sensitive to colistin.

DISCUSSION

Neonatal infection is an important cause of mortality and morbidity worldwide. Monitoring infection rates is increasingly regarded as an important contributor to high-quality health care. HCAIs usually appear due to multidrug-resistant microorganisms, thus blood culture results and surveillance studies have significant contributions in planning proper antibiotic treatment (9).

HCAI rate in NICUs varies between 17.4-157.7 per 100 patients in the literature (10,16,23). The characteristics of HCAIs vary considerably in different regions, over time and referring to the hospital thus the availability of timely and accurate epidemiological information on healthcare-associated pathogens is crucial. In this study, the HCAI rate and density in our neonatal intensive care unit were determined as 28.9 per patient and 23.6 per 1000 patient days, respectively. Turkey is a middle–income country and HCAI rates and antimicrobial resistance is serious problem in the intensive care units overall. However, there are a limited number of studies reporting HCAIs in NICUs. Among them, only a few studies are following CDC criteria (24-27). In the surveillance study done by our group in 2001, HCAI rates of 11.3 per 100 patients and 16.1 per 1000 patient days were recorded (28). The reasons for the recent increase in HCAI rates in our unit could be due to the relocation of the hospital in a low income-suburban area with inadequate antenatal care, the admittance of high-risk pregnancies, increase in the hospitalization of surgical cases, and survival of premature infants due to the advances in the technology that results in prolonged hospitalization. A similar study on 314 patients in 2007 at the Uludag University School of Medicine in Turkey showed HCAI rates of 42.3 per 100 inpatients and 17.9 per 1000 patient days (13).

Although many previous studies worldwide have been done to identify the epidemiology of the HCAIs among neonates in NICUs, the incidence or prevalence of HCAI differs within different regions in the world because it varies based on birth weight, underlying diseases, medical facilities, and level of care in different centers. Centers for Disease Control and Prevention reported HCAI data of USA as device-related infection rates based on birth weight and but not overall HCAI rates in NICUs during recent years. Spain and Brasil reported their HCAI rate as 74.3 and 157.7 HCAIs per 100 patients respectively (16,29). Taiwan has a much lower HCAI rate (13.6 per 100 patients) (30). Similarly, it has been reported that European countries have an HCAI rate of 7-17.4 per 100 patients (23,31). The rates obtained in our study are significantly higher than the rates in industrialized countries. It has been reported that the rates of neonatal nosocomial infections in low-income and middle-income countries are 3 to 20 times higher than observed in industrialized countries (17). This is mainly because of the lack of proper infection control measures and infrastructure to provide appropriate care to vulnerable infants.

Some investigators believe that reporting overall incidence rates may be misleading, because of the wide variations in practice and patient characteristics in different centers; therefore the NHSN system monitors DA-HCAI rates by using an approach that accounts for variability in device use and length of hospital stay (32). For this reason, it is difficult to compare the data on HCAI rates between different centers in different regions of the world and every hospital should implement its own strategy to prevent HCAIs and compare the results with its previous data. It is necessary that common HCAI monitoring methods, terminologies, and statistics should be implemented worldwide.

In NICUs, the most frequently reported HCAIs are bloodstream infections (25-60%) followed by pneumonia (6.8-32.3%) and urinary tract infections (1,32,33). In our study, bloodstream infection rate was 36.4% followed by pneumonia (21.2%), conjunctivitis, and URTI and UTI, respectively. Contrary to the literature, conjunctivitis, and URTI had the third-highest rates, possibly referring to the 2012 influenza virus epidemics.

Critically ill premature infants are especially vulnerable to HCAIs due to their immature immune systems, poor skin integrity, contact with invasive devices, and contact with multiple careers (15). Birth weight and gestational age are inversely proportional to HCAI (32). It has been reported that in Japan between 2002 and 2003, the HCAI rate was 25.2 per 100 patients among the babies with birth weights less than 1000 g, yet 8.4 per 100 patients among the babies with birth weights between 1000 and 1500 g, and 3.7 per 100 patients with birth weights more than 1500 g (34). According to a study in Italy in 2002, the HCAI rate has been reported as 48 per 100 patients among babies less than 1500 g (31). Similar to the numbers in the lite-

rature, our studyrevealed a HCAI rate of 34.1 per 100 patients among the babies with birth weights less than 1000 g, 25.4 per 100 patients between 1001 and 1500 g. 20.7 per 100 patients between 1501 and 2500 and 19.8 per 100 patients among the babies with birth weights more than 2500 g. Even though our high HCAI rate among ELBW infants showed similarity to other reports, the rate among bigger babies is considerably higher than those reported in the literature for these cases. We believe that the main reason for the high rates in this group is the high rate of surgical cases, each of isolation facilities, staffing numbers. Cases that require surgery, prolonged hospitalization such as babies with a congenital heart defect (CHD), congenital anomalies and congenital diaphragmatic hernia (CDH) increase the rate of infection in these babies. A new detailed program of infection control has been implemented after this study. As a result, the HCAI rate was reduced from 36.2 to 24.9 per 100 patients compared with the rate in the previous year.

Device associated-HCAI has been a primary and serious cause of patient morbidity and attributable mortality in developing countries, and it has shown to be a critical factor, predisposing hospitals to increased healthcare costs. For the year 2012, NHSN facilities reported more than 3957 VAPs and the incidence for various types of hospital units ranged from 0.0-4.4 per 1000 ventilator days (35). This data is quite lower than those presented by other Turkish centers (15.4-28.1 per ventilator days) (12,14). In this study, the VAP rate was 13.7 per ventilator days which is higher than those of developed countries. In our unit, the patient: nurse ratio (3:1) can negatively affect adherence to infection control measures and may have played a role in the higher VAP rate.

The rate of CLABSI is reported as 3.8 -12.8 per 1000 catheter days in the literature (36). However, the rate of CLABSI in this study is 0.6 per 1000 catheter days, which is quite low compared to those reported in the literature. This result however is thought to be deceptive. The main reason is probably the low frequency of obtaining both catheter and peripheral culture from small preterm infants and small amounts of blood culture samples.

The agents that cause HCAI in NICUs vary over the years. While the most isolated agent is CoNS in most developed countries today, it is Klebsiella pneumoniae in developing countries (17). In a study that included 16 centers, Turkish Neonatology Society reported that most of nosocomial sepsis were due to gram-negative bacteria, mainly Klebsiella (37). Our study revealed that the most frequently isolated agent in our unit is CoNS, followed by Klebsiella pneumoniae, which is the most frequently isolated agent overall in neonatal intensive care units in Turkey. Coagulase-negative Staphylococci still remains the most common microorganism associated with catheter-related BSIs including peripheral intravenous (PIV) catheter-related BSIs and CLABSIs (1,32,38). PIVs are the most commonly used device for vascular access in newborns. As the lack of evidence to recommend elective removal of PIVs after 72 hours, these catheters are used until they are occluded or there is any extravasation. Although PIVs might be the main source of CoNS infections as well, a conclusive correlation has not been shown between the higher colonization noted after 72 hours and an increased rate of catheter-related BSI (32).

In the developed world, the increase in CoNS related infections is tied to the increased survival rate of ELBW infants, the common use of intravascular catheters, parenteral nutrition, and the use of intravenous lipid emulsions. On the contrary, inappropriate use of broad-spectrum antibiotics and lack of appropriate infection prevention measures can be shown as the main reasons for Klebsiella pneumoniae or other negative gram-negative bacteria.

Although fungi is one of the common causes for blood-stream infections in NICU (36), we found that the rate of Candida isolates was 1.57% in our group. Furthermore, these fungi isolates were only non-albicans species. We interpret this finding that we have implemented fluconazole prophylaxis in preterm infants (< 1000 g) for last 8 years.

There is a direct association between antibiotic overuse and antibiotic resistance, which is becoming increasingly common in NICUs. It is shown that the microorganisms causing HCAI in developed countries are 70% multi-drug-resistant (36,39). Among these, 28.5% of the enterococci are resistant to vancomycin, 59% of Staphylococcus aureus and 89% of CoNS are resistant to methicillin (36). In the study presented here, it is observed that CoNS is 90% methicillin-resistant, and that Klebsiella pneumoniae produced 82.6% ESBL.

Enterococcus faecalis and Enterococcus faecium are common and important healthcare-associated pathogens worldwide today (40). Most enterococcal infections are due to E. faecalis (80%), although epidemiology is changing, and E. faecium isolates now account for up to 20% concomitantly with the rise of vancomycin-resistant isolates (40) E. faecium isolates are ten-times more likely to be vancomycin-resistant than E. faecalis. In Europe, surveillance data shows a large variability between the various countries and the HCAI rate due to vancomycin-resis-

tant enterococci (VRE) ranges from <2% (Finland, Holland) to >20% (Ireland, Greece, Portugal) (40). According to the culture results in this study, the rate of isolated Enterococci was 4% (5 cases), which consisted of vancomycin-resistant E. faceium (2 cases) and E. faecalis with no resistance to vancomycin. The reason for the minimal VRE infections seen in our NICU is tied to the proper use and control of antibiotics. The education of the hospital staff, cohorting of VRE-exposed babies, active surveillance, hand hygiene, an inspection of infection prevention measures, and proper antibiotic strategies are the most important components in preventing VRE infections (39).

CONCLUSIONS

This study determined that the most frequently seen HCAI bacteria are gram-positive bacteria followed by Klebsiella strains. It is also shown that Klebsiella and ESBL rates are higher than the rates observed in developed countries. HCAI still presents a serious issue in Turkey. It is believed that determining the HCAI rates and agents through widely spread prevalence studies along with the information obtained from these studies will help to reduce the mortality and morbidity rates of HCAI.

Strength and limitations: The tests were performed in an advanced microbiology laboratory, and the study was conducted in a referral center. But the limitation of the study was its retrospective nature.

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