HealthCare-associated Infections in a Neonatal Intensive Care Unit in Turkey in 2008: Incidence and Risk Factors, A Prospective Study

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Summary

In this study, we have prospectively recorded healthcare-associated infections (HAIs) in NICU and found incidence density as 18 infections per 1000 patient days. Of the infections, 51.3% was bacteriemia (BSI), and 45.1% was ventilator-associated pneumonia (VAP). Gram-negative microorganisms were predominant in VAP and *Staphylococcus epidermidis* was the leading microorganism (53.0% of BSIs) in BSIs. Multivariate logistic regression analysis showed the importance of hood O_2 use in days (RR: 1.3) and total parenteral nutrition use in days (RR: 1.09) for BSIs. Umbilical arterial catheterization in days (RR: 1.94), ventilator use in days (RR: 1.05), chest tube (RR: 12.55), orogastric feeding (RR: 3.32) and total parenteral nutrition in days (RR: 1.05) were found to be significantly associated with VAP. In conclusion, incidence density in our unit is high and Gram-negative rods are predominant similar to developing countries. These results strongly suggest improving measures of prevention and control of HAIs in the unit.

Key words: Healthcare-associated infections, neonatal intensive care unit, risk factors, Turkey.

Introduction

Neonates are particularly susceptible to infection because of abnormalities of the immune system and extrinsic risk factors, such as the use of central venous catheters (CVC), ventilators and surgical procedures [1]. Healthcare-associated infection (HAI) rates in the Neonatal Intensive Care Units (NICU) range from 15% to 20%, which is significantly higher than in the pediatric ICU patients [2, 3].

The most common HAIs in NICU are blood stream infections (BSIs) (26.2–71.0%), ventilator-associated pneumonia (VAP) (6.8–61.5%) and gastrointestinal diseases (1–20.7%) [4–9]. Active surveillance by Hospital Infections Control Committee (HICC) is very important for control of infections in intensive care units. HICC has been prospectively recording HAIs in our unit since 2001. There are limited numbers of studies in Turkey reporting HAIs mostly from single centers. One recent study held by Turkish Neonatal Society (Turkish NS) reported the epidemiology of HAIs from 16 centers in Turkey in 2005 and found culture proven nosocomial sepsis frequency as 6.4% (ranging from 2.1% to 17%) in all infants admitted to participating centers. Gram-negative microorganisms (especially *Klebsiella* spp.) were dominant in BSIs [10]. We have reported our 6-year (2001–06) infections recently [9]; similarly to Turkish NS study, Gram-negative bacteria were dominant in our unit. However, these studies have not examined the infection density, invasive device-related infections and risk factors for HAI in NICUs. In this study, we aimed to study the infection density, invasive device-related infections, causative agents, resistance pattern of microorganisms and risks of infection in NICU in our institute in 2008.

Subjects and Methods

In this study, we have reported the infection density, invasive device-related infections, causative agents, resistance pattern of microorganisms and risks of infection in NICU, Cukurova University in 2008. Patients admitted to NICU between 1 January and 31 December 2008 were enrolled to the study. A nurse from HICC has prospectively recorded HAIs (pneumonia, VAP, BSI, urinary tract infection, meningitis, necrotizing enterocolitis, conjunctivitis, omphalitis and other infections). The hospital is a

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university hospital in Adana and has 1200 beds. Most of the patients are from low socioeconomic level. The NICU is a tertiary center with 25 beds and cares for patients mostly with medical problems, with 12–14 intensive care (Level III) beds. During this year, healthcare staff to patient ratio was as followings: one staff neonatologist, two neonatology fellows, three residents and one nurse per six to eight intensive care newborns and one nurse per 10 level I–II patients. Residents are changing every 2 months. There are two sinks in each patient room and alcohol-based solutions and chlorhexidine liquid are used for hand disinfection. There are 10 ventilators. During the present study, the neonates have not been cultured at admission if we did not have any suspicion about a risk of early neonatal sepsis. If so, we have got blood culture, and if intubated, a tracheal aspiration culture. We routinely perform urine analysis. Newborns were monitorized for HAIs at all body sites, and blood, tracheal aspirate fluid (TAF), urine and cerebrospinal fluid cultures were taken from the suspected patients. Umbilical/peripheral arterial and umbilical/central venous catheterizations were performed as needed. In NICU, ampicillin and amicasin were used for empirical therapy for early neonatal sepsis in case of prematurely born from a mother with urinary tract infection (UTI), vaginal bleeding, prolonged (>18 h) premature preterm rupture of membranes (PPROM) or clinical chorioamnionitis. In cases of suspected healthcare-associated sepsis, the first-line treatment was a glycopeptid antibiotic combined with a carbanepem in most of the infants. Antibiotics were initiated after cultures were drawn.

Infection was considered to be healthcare associated if a patient had a sign of infection after the first 72 h of admission. For this reason, patients discharged or died in the first 72 h were excluded from the study. HAI site definitions were adopted according to the CDC definition system [11]. Bloodstream infection was defined as a positive blood culture without any significant focus. True infection was defined as a positive sterile body fluid culture accompanied by clinical signs of infection and relief of these signs with appropriate antibiotics. Contamination is defined as a positive culture without any accompanying clinical signs of infection. For skin contaminant species, especially for *Staphylococcus epidermidis,* isolation from a patient with an intravascular device with clinical signs of infection or from two blood culture specimens on separate occasions were accepted as true infection. VAP was defined as a pneumonia developed after 72 h of mechanical ventilation with radiological, and clinical findings: increased sputum production, increased respiratory support on ventilator and progressive pulmonary infiltration not present on admission and with microbiological findings (a positive tracheal aspiration fluid culture with at least 5×10^4 c.f.u. ml^{-1} bacteria in tracheal aspirate fluid). For TAF cultures with mixed pathogens, microorganisms $>5 \times 10^4$ c.f.u. ml^{-1} were assumed to be the principle pathogens. Necrotizing enterocolitis was defined according to Bell staging [12]. Stage I patients were not included in the study. If a patient has >5 leukocytes in urine sediment, suprapubic aspiration was performed. A urinary tract infection was defined as growth of a microorganism with any number of c.f.u. ml^{-1} in urine collected by suprapubic aspiration. HAI incidence was calculated as number of infection per 100 patients admitted and incidence density as number of infections per 1000 days. Invasive device related infections were calculated as BSIs per 1000 central venous catheterization exposure days and VAPs per 1000 ventilator days. To assess the effect of birth weight on infection rate, all newborns were stratified to four categories: ≤1000, 1001–1499, 1500–2499 and ≥2500 g. Mortality was defined as any death during hospitalization in NICU.

Statistical analysis

SPSS 17.0 was used for data analysis. The chi-squared test was used for comparisons of categorical variables and the *t*-test was performed to compare two group means. For non-normally distributed variables, the Mann–Whitney test was performed. Categorical variables were summarized using count and percent whereas continuous variables were summarized in mean ± standard deviation, median, min and max values. Backward multivariate logistic regression results [Relative Risk (RR)] with all univariate significant variables were given for BSI and VAP separately. *p*-value ≤0.05 was accepted as statistically significant.

Results

There were 596 newborns observed in NICU in 2008. Underlying diseases of all admitted patients and patients with HAIs are shown in Table 1. Thirty-two infants died and 151 infants were discharged in the first 72 h. The mean gestational age and mean birth weight of the remaining 413 patients were 35.1 ± 3.84, median 36 (24–42) weeks and 2470 ± 905, median 2500 (570–4950) g, respectively. Of the patients, 235 (56.9%) were boys.

A total of 195 HAIs were observed in 96 infants (16%). The HAI incidence density was 18 infections per 1000 patient days. One infectious episode was diagnosed in 54 neonates (56.3%) and multiple episodes were found in 32 neonates (43.7%). Sixty-six infants had 100 BSIs episodes (51.3% of the infections) and 44 patients had 88 VAP infections (45.1% of the infections), four patients had NEC (2% of the infections) and one patient had omphalitis. Fifty-one lumbar punctures (LPs) were performed to 31 of 66 patients with 100 BSIs and 10 patient (32.3%) had meningitis in 18 LPs (more than one neutrophil

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TABLE 1
Underlying diseases of all patients

Diseases[a]	All patients, *n* (596) *n* (%)	Patients with HAIs, *n* (96) *n* (%)
Prematurity (≤37 gestational age)	358 (60.2)	49 (51.0)
Respiratory distress	84 (14.1)	15 (15.6)
Hyperbilirubinemia	136 (22.8)	6 (6.3)
Maternal infections (PPROM, UTI, vaginal discharge etc.)	118 (19.8)	17 (17)
Respiratory distress syndrome treated with surfactant	54 (9.1)	21 (21.9)
Meconium stained baby/meconium aspiration syndrome	88 (14.8)	3 (3.1)
Congenital heart disease	68 (11.4)	14 (14.6)
Intrauterine growth retardation	42 (7.0)	8 (8.3)
Congenital malformation	33 (5.5)	1 (1)
Transient tachypnea of newborn	31 (5.2)	12 (12.5)
Infant of diabetic mother	25 (4.2)	3 (3.1)
Hypoxic ischemic encephalopathy	15 (2.5)	4 (4.2)

[a]Infant may have more than one disease.

on cerebrospinal fluid). A total of 14 LPs (77.7%) revealed a microorganism (five *S. epidermidis*, three *S. epidermidis and Acinetobacter baumannii,* two *A.baumannii,* two *Pseudomonas aeruginosa,* one *Escherichia coli* and *A. baumannii* and one *S. warneri*). Of the 14 positive cultures, nine belonged to two patients who had ventriculitis and hydrocephalus. Ventilator-associated infection rate was 28.1 per 1000 device days and catheter-related blood stream infection (CR-BSI) rate was 14.3 per 1000 device days (Table 2). We have not detected any catheter-related UTI.

Birth weight, gestational age, first minute Apgar score values of the patients with HAIs were lower and prior antibiotic use, duration of hospitalization and mortality rate were higher compared to patients without HAIs, (Table 3). HAI rate was inversely related to birth weight ($p = 0.01$). Mortality rate was higher in HAIs groups weighing >1500 g (Table 4).

In both surviving and non-surviving patients, hospitalization days were longer in infants with HAIs compared to patients without HAIs [39.80 ± 49.47, median 24 (4–208) days vs. 14.20 ± 18.5, median 9 (4–253) days, $p < 0.001$ in survivors] and [37.50 ± 35.57, median 23 (9–194) days vs. 16.23 ± 17.80, median 7.5 (4–70) days, $p = 0.004$ in non-survivors].

Gram-negative microorganisms were predominant in VAP infections: 52.3% of the growing microorganisms in TAF was *A. baumannii*, 30.7% was *P. aeruginosa* and 18.2% was *Klebsiella pneumoniae*. *Staphylococcus epidermidis* was the leading microorganism (53.0% of the growing microorganisms) in BSIs followed by *A. baumannii* (18% of BSIs). There were mixed pathogens in 14 VAPs and seven BSIs. Antimicrobial resistance patterns of microorganisms are shown in Table 5.

TABLE 2
VAP and catheter-related BSI rates and invasive device use rate

Birth weight (g)	Mean infection rate per 1000 invasive device exposure days	Invasive device use rate
VAP		
<1000	23.4	0.51
1000–1499	32.8	0.24
1500–2499	31.4	0.24
>2500	26.2	0.25
CR-BSI		
<1000	5.4	0.20
1000–1499	17.9	0.15
1500–2499	26.8	0.10
>2500	8.3	0.10

As some of the infants (23/66 patients) had more than one BSI episodes, we compared the mortality rate of last BSIs. Mortality rate was higher with Gram-negative organisms when compared to Gram-positive organisms in BSIs (39% vs. 14%, $p = 0.031$).

Univariate risk factors for BSI and VAP were given in Table 6. BSIs and VAP were significantly higher in patients with prior antibiotic use, ventilator use, hood O_2 use, venous–arterial umbilical catheterization and total parenteral nutrition. Multivariate logistic regression results for VAP and BSI were given in Tables 7 and 8. Umbilical arterial catheterization in days, ventilator use in days, chest tube for pneumothorax, orogastric feeding and total parenteral nutrition in days were found to be significantly associated with VAP (Table 7). Ventilator use in days, hood O_2 use in days and total parenteral

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TABLE 3
Characteristics of patients with and without HAIs

	Patients with HAIs ($n=96$) mean ± SD; median (min–max)	Patients without HAIs ($n=317$) mean ± SD; median (min–max)	p
Birth weight (g)	2271 ± 973; 2280 (600–4950)	2530 ± 877; 2580 (570–4830)	0.012
Gestational age (weeks)	34.0 ± 4.4; 35 (25–42)	35.5 ± 3.58; 36 (24–41)	0.008
Apgar score 1 min	5.56 ± 1.83; 6 (2–9)	6.06 ± 2.0; 6 (1–9)	0.029
Apgar score 5 min	7.59 ± 1.51; 8 (4–10)	7.90 ± 1.59; 8 (3–10)	0.062
Hospitalization days	38.08 ± 39.07; 23.5 (4–208)	14.39 ± 18.44; 9 (4–253)	<0.001
	n (%)	*n* (%)	
Gender (male)	48 (50)	187 (60)	0.101
Mode of delivery (C/S)	73 (76)	243 (75)	0.891
Birth place (another unit)	23 (24)	71 (22)	0.782
Prior antibiotic use	96 (100)	201 (63)	<0.001
Mortality rate	23 (24)	30 (9.5)	<0.001

TABLE 4
Relationship between birth weight and HAIs and mortality rates

Birth weight in g (*n*)	Rate of HAIs among birth weight groups* *n* (%)	Mortality rate of patients with HAIs *n* (%)	Mortality rate of patients without HAIs *n* (%)	p**
<1000 (19)	8 (42.1)	3/8 (37.5)	7/11 (63.6)	0.370
1000–1499 (46)	16 (34.8)	3/16 (18.8)	4/30 (13.3)	0.681
1500–2499 (138)	29 (21.0)	7/29 (24.1)	9/109 (8.3)	0.044
>2500 (208)	42 (20.2)	9/42 (21.4)	10/166 (6.0)	0.005

*p-value for HAIs rate among birth weight groups is 0.010.
**p-value for difference between mortality rates of patients with and without HAIs within each birth weight strata.

TABLE 5
Resistance patterns of the microorganisms (%)

	Gram-negative microorganisms			Gram- positive microorganisms	
	A. baumannii	*P. aeruginosa*	*K. pneumoniae*	*S. epidermidis*	
Amikasin	56.5	10.5	13.8	Vancomycin	0
Gentamycin	96.8	47.4	75.9	Teicoplanin	3.7
Netilmicin	50.8	55.3	50	Gentamycin	77.8
Tobramycin	50.7	15.8	88	Tobramycin	78.3
Imipenem/cilastatin	98.4	63.2	34.5	Levofloxacin	80
Meropenem	90.3	84.2	20.7	Ciprofloxacilline	85.2
Piperacillin	98.4	55.3	93.1	Imipenem/cilastatin	96.3
Piperacillin–tazobactam	98.4	28.9	88	Penicillin	96.6
Cefepime	95.1	76.3	74.1	Ampicillin	100
Ceftazidime	98.4	91.9	74.1	Rifampin	100
Ciprofloxacilline	98.4	31.6	24.2	Cefotaxime	100
Ticarcillin	98.4	91.7	84.6	Cefuroxime	100
Ticarcillin–clavulanate	96.8	91.9	84.6		

nutrition use in days were found to be significantly associated with BSIs (Table 8).

During study period, nose and hand cultures and with intervals cultures for environmental contamination were performed. Of the 16 cultures from staff hand, six revealed methicillin sensitive CONS and nine were negative. Of the 16 nose cultures, 10 showed methicillin sensitive *CONS*,

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TABLE 6
Risk factors for BSIs and VAP

Risk factors	*n*	Patients with BSI *n* (%)	*p*	Patients with VAP *n* (%)	*p*
Prior antibiotic use	(–) 116	0 (0.0)	<0.001	0 (0.0)	<0.001
	(+) 297	66 (22.2)		44 (14.8)	
Ventilator use	(–) 268	26 (9.7)	<0.001	0 (0.0)	<0.001
	(+) 145	40 (27.6)		44 (30.3)	
Hood O_2 use	(–) 265	27 (10.2)	<0.001	12 (4.5)	<0.001
	(+) 148	39 (26.4)		32 (21.6)	
Umbilical arter catheter use	(–) 342	46 (13.5)	0.004	20 (5.8)	<0.001
	(+) 71	20 (28.2)		24 (33.8)	
Umbilical venous catheter use	(–) 325	42 (12.9)	0.003	17 (5.2)	<0.001
	(+) 88	24 (27.3)		27 (30.7)	
Total parenteral nutrition	(–) 216	10 (4.6)	<0.001	1 (0.5)	<0.001
	(+) 197	56 (28.4)		43 (28.1)	
Orogastric feeding	(–) 332	49 (14.8)	0.178	25 (7.5)	<0.001
	(+) 81	17 (21.0)		19 (23.5)	
Chest tube for pneumothorax	(–) 405	64 (15.8)	0.619	39 (9.6)	<0.001
	(+) 8	2 (25.0)		5 (62.5)	
nCPAP use	(–) 337	52 (15.4)	0.313	26 (7.7)	<0.001
	(+) 76	14 (18.4)		18 (23.7)	
Central venous catheterization	(–) 404	62 (15.3)	0.040	41 (10.1)	0.060
	(+) 9	4 (44.4)		3 (33.3)	
Urinary catheterization	(–) 406	64 (15.8)	0.311	40 (9.9)	0.030
	(+) 7	2 (28.6)		4 (57.1)	
Betamethasone use	(–) 398	62 (15.6)	0.275	38 (9.5)	0.003
	(+) 15	4 (26.7)		6 (40.0)	
PPROM	(–) 395	62 (15.7)	0.507	38 (9.6)	0.007
	(+) 18	4 (22.2)		6 (33.3)	
Maternal vaginal discharge	(–) 390	63 (16.2)	0.999	39 (10.0)	0.085
	(+) 23	3 (13.0)		5 (21.7)	
Maternal vaginal bleeding	(–) 408	66 (16.2)	0.999	42 (10.3)	0.090
	(+) 5	0 (0.0)		2 (40.0)	
Maternal urinary tract infection	(–) 355	58 (16.3)	0.703	38 (10.3)	0.999
	(+) 58	8 (13.8)		6 (10.7)	

TABLE 7
Relative Risk (RR) and 95% CI for VAP from multivariate logistic regression analysis

	p	RR (95% CI)
Umbilical arterial catheterization in days	0.011	1.94 (1.16–3.25)
Ventilator use in days	0.014	1.05 (1.01–1.09)
Chest tube for pneumothorax	0.005	12.55 (2.11–74.77)
Orogastric feeding	0.012	3.32 (1.30–8.45)
Umbilical arterial catheterization	0.070	0.03 (0.00–1.31)
Total parenteral nutrition in days	0.010	1.05 (1.01–1.09)
Betamethasone use	0.074	0.30 (0.08–1.12)
Constant	<0.001	0.06

three showed methicillin sensitive *S. aureus*, one showed methicillin resistant *S. aureus* and one methicillin resistant CONS. Only one nose culture was negative. There were 23 environmental cultures from incubators, stethoscopes, infusion pumps, ventilators, desks in patient rooms etc. Eleven revealed methicillin sensitive *CONS* (two in incubators, two on infusion pumps, two on monitors, and five on other places). So *CONS* seems to be an important microorganism in our staff and environment.

Discussion

The overall of HAI incidence density in our unit was 18.1 infections per 1000 patient days. Sixteen percent of patients had at least one HAI. These results are very high compared to results from developed world [4, 5, 13]. The main reasons of the high rate in our clinic may be overcrowding, and especially, low nurse staff to patient ratio. As even in Level III patients, one nurse cared about six to eight infants in our clinic in 2008. However, this ratio is 1:1–1:2.7 in other studies [5, 6].

According to the reports from NICUs, BSIs represent the most frequent HAI among neonates, often associated with the use of CVC [5, 7, 8, 14]. In our unit, we also found that BSI was the main infection.

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TABLE 8
Relative Risk (RR) and 95% CI for BSIs from multivariate logistic regression analysis

	p	RR (95% CI)
Ventilator use in days	0.003	0.96 (0.94–0.99)
Hood O_2 use in days	<0.001	1.13 (1.06–1.20)
Total parenteral nutrition in days	<0.001	1.09 (1.06–1.14)
Constant	<0.001	0.08

However, between 2001 and 2006 years, the most frequent infection was VAP (61.5%), followed by BSI (26.2%) in the same unit [9]. Surveillance studies of HAIs in NICU patients indicate that pneumonia comprises 6.8–32.3% of HAIs in NICUs [15]. Multivariate and univariate analysis confirm invasive devices such as umbilical catheterization and ventilators as important risk factors for infections in neonates [14, 16–18]. NNIS data from 2002 to 2004 showed VAP rates ranged from 1.4 to 3.5 per 1000 ventilator days in USA [19]. A prospective surveillance study of nosocomial infections in seven Brazilian NICUs reports that the rate of VAP varied between 3.45 and 5.96 per 1000 ventilator days among birth weight groups [6]. In a NICU in Italy, Orsi *et al*. [8] reported VAP rate as 13.1 per 1000 ventilator days and CR-BSIs as 12.5 per 1000 catheterization days. Unfortunately, rate of VAP in our clinic in 2008 was 28.14 per 1000 ventilator days. The ratio is really high compared to these studies. Also CR-BSI rate is high compared to other studies [6, 19, 20]. The NNIS System has reported rates of 9.1 umbilical and CVC related BSIs per 1000 device days for infants ≤1000 g and 5.4 infections per 1000 catheter days for infants 1001–1500 g [19]. In the present study, CR-BSIs rate is 14.3 per 1000 catheter days. These results emphasize that highly sophisticated and aseptic procedures are required in newborn patients in our unit. We have not detected any catheter-related UTI, probably, as we seldomly use urinary catheters. In the present study, multivariate logistic analysis revealed that umbilical arterial catheterization in days, ventilator use in days, chest tube for pneumothorax, orogastric feeding and total parenteral nutrition use in days were found to be significantly associated with VAP; and ventilator use in days, hood O_2 use in days and total parenteral nutrition use in days were found to be significantly associated with BSIs. We had prepared guidelines to reduce VAP and CR-BSIs rate in our clinic in June 2009 and shared with the staff.

Birth weight, gestational age and first minute Apgar scores were lower and mortality rate, duration of hospitalization and prior antibiotic use were higher in patients with HAIs in our study. Birth weight has been an identified risk factor for HAIs in NICUs [5, 8, 10, 14, 18, 19]. Also in our study, HAIs rate has increased as birth weight decreased. Similarly, in Turkish Nosocomial Infections Study Group's report, sepsis frequency increased as birth weight decreased (22% in infants <1500 g, 6% in 1500–2500 g and 3% in ≥2500 g) [10]. In our study, mortality rate did not differ in birth weight groups <1500 g, but mortality rate was higher in ≥1500 g group with HAIs. Also Aziz *et al*. [21] reported that mortality was more strongly associated with HAIs for infants ≥1500 g, but not for infants <1500 g. We assume that this result may be due to other factors increasing mortality in <1500 g group such as severe respiratory distress syndrome or intraventricular hemorrhage. However it may be due to low numbers of patients in our study, because we have shown that HAI increases mortality rate in all weight groups in our previous study [9]. When we compared hospitalization days of infants who died or survived in HAI group, hospitalization days were significantly longer when compared with patients without infection. We may conclude that these patients had higher risk of HAIs as they survived longer.

In the present study, Gram-negative rods were dominant; however *S. epidermidis* was the predominant microorganism in BSIs. The distribution of microorganisms in our study is mostly similar to reports from developing countries [6, 22–25]. However Orsi *et al*. [8] from Italy also reported Gram-negative bacteria predominance (54.1%), followed by Gram-positive (42.8%) microorganisms. Indeed, the predominant organisms isolated from invasive neonatal infections in advanced countries are mostly Gram-positive cocci, probably due to low VAP ratio and sophisticated tertiary neonatal care units using invasive devices such as CVCs [4, 5, 19, 26]. *Staphylococcus epidermidis* has been the leading microorganism in BSIs in our unit since 2002 [9]. As shown in staff nose, hand cultures and environmental cultures, CONS is the main microorganism colonized. So hand and environmental disinfection is very important as well as adequate staffing. HICC has evaluated hand hygiene compliance rate in NICU in 2010 and reported that compliance rate is 60% before a procedure and 80% after the procedure for nurses and 40% and 60% for residents. So staff, especially residents, should be regularly educated about hand disinfection. We have not detected any Candida species in any infection although we do not start prophylactic fluconazole to premature babies, however it is not a striking observation as Candida species accounted for only 3.0% of the infections as shown in the other prospective surveillance in our unit [9]. In 2008, Turkish Neonatology Society has asked the etiologic agents of BSIs in NICUs and 22 centers (19 university hospitals) responded [27]. There were 503 nosocomial BSIs in all patients. There were 229 (45.5%) Gram-positive

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microorganisms (mainly *S. epidermidis*, CONS and *S. aureus*), 216 (42.9%) Gram-negative microorganisms (mainly *Klebsiella spp., Enterobacter spp., Pseudomonas spp.* and *Acinetobacter spp.*), 25 (4.97%) Candida species and 33 mixed pathogens.

About 15–30% of babies with early-onset septicemia and 10% of babies with late-onset septicemia have concurrent meningitis [28]. We have seen that incidence of meningitis concurrent with BSIs is very high in our study although we have performed LP approximately on half of the patients. However omitting LP as a part of sepsis evaluation may cause the diagnosis of meningitis to be delayed or missed completely in some infants. So, it is vital that if sepsis is suspected a LP should be in mind.

In our study, we have found that mortality rate due to Gram-negative microorganisms in BSIs was higher. Similarly Gordon *et al.* [29] showed mortality rate was significantly higher in Gram-negative late onset neonatal sepsis, particularly in *P. aeruginosa* infections.

Antibiotic resistance is a major problem in HAIs. In the present study, we see multi-drug resistant microorganisms. Prior antibiotic use was 100% in patients with HAIs and 63% in patients without infection. Broad spectrum antibiotic use may increase antibiotic resistance and incidence of late onset sepsis [9, 30]. Studies have reported that administration of prophylactic antibiotics to neonates can increase the incidence of HAIs with drug-resistant pathogenic microorganisms. About 64.8–100% of neonates presenting with HAI had received prior broad-spectrum antibiotics [9, 22, 31, 32] and use of cephalosporins increases HAIs caused by extended-spectrum β-lactamase-producing bacteria [33]. Also in this study prior antibiotic use was more in HAIs group and we detect multi-drug resistant microorganisms. So we suggest empirical antibiotic treatment should be carefully discussed and stopped as soon as possible.

In conclusion, in our unit, HAIs rate, especially VAP and BSIs are higher when compared with data from developed countries and Gram-negative bacteria are predominant, similar to results from Turkey and developing world. These results strongly suggest improving measures of prevention and control of HAIs, increase staff to patient ratio and hand hygiene compliance in our neonatal intensive care unit.

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