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Original Article

Health care-associated infection surveillance: A prospective study of a tertiary neonatal intensive care unit

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Abstract
Introduction: Health care-associated infection (HCAI) is a serious problem of neonatal intensive care units (NICUs) which is related to morbidity, mortality and increased cost of medical care. This study aimed to determine the incidence of HCAI in a tertiary NICU and identify the risk factors.
Methodology: This prospective cohort study was conducted between July 1, 2011 and June 30, 2012. All newborns admitted to the NICU except for those who died or were discharged within 48 hours after admission were included. The definitions of Centers for Disease Control and Prevention (CDC) were used to diagnose specific types of infections. The incidence, causative organisms, risk factors and mortality of HCAIs were evaluated.
Results: Among 352 newborns, a total of 60 HCAI episodes were evaluated in 37 (10.5%) of the patients over 5,212 patient-days. The overall incidence of HCAI was 17%, and the rate was 11.5/1,000 patient-days. Blood stream infection (BSI) was the most common HCAI (n = 42, 70%). In a multivariable logistic regression analysis, the presence of a central venous catheter/umbilical catheter (CVC/UC), the presence of a urinary catheter, and gestational age (< 32 weeks of gestation) were identified as significant independent risk factors. Gram-negative pathogens were the most common isolates. The overall mortality rate was 4%. The HCAI-related mortality rate was 10.8%.
Conclusions: Patient care quality can be improved with surveillance of HCAI. The incidence and rate of HCAI in our NICU were found to be higher than international reports with a direct impact on mortality of preterm infants.

Key words: health care-associated infection; neonatal intensive care unit; surveillance.

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Introduction

Health care-associated infection (HCAI) is a major cause of morbidity, mortality and increased cost of medical care in neonatal intensive care units (NICUs). The incidence of HCAI varies between 3.9% and 57.7% in several reports, accounting for 40% of neonatal deaths in developing countries [1-3]. Prematurity, low birth weight, invasive care including mechanical ventilation, catheterization and parenteral nutrition, and prolonged hospitalization are among the risk factors associated with HCAI at the neonatal period when the immmune system, protective flora and mechanical barriers are insufficient [4-7].

HCAI is defined by the Centers for Disease Control and Prevention (CDC) as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or its toxin without any evidence that the infection was present or incubating at the time of admission to the acute care setting [8]. Studies suggest that HCAIs could be prevented with strategies aiming to limit the susceptibility to infections by improving the compliance with hand hygiene, interrupting transmission of organisms from healthcare givers, avoiding invasive procedures, reducing the indwelling time of catheters and promoting judicious use of antibiotics [6,9-12].

This prospective study aimed to determine the incidence of HCAIs during a period of one year in a tertiary NICU and to identify the related risk factors for nosocomial infection.

Methodology

Patients and setting

The study was conducted in the NICU of the Ankara University School of Medicine which is a 20-bed unit with two wards and two isolation rooms hosting 400-

500 newborns out of 2500 annual inborn deliveries and high-risk referrals. The NICU nurse/patient ratio is 1:3-4. There were three attending neonatologists, three neonatology fellows, a pediatrics resident, and registered nurses in the NICU team during the study period.

Study design

In this prospective cohort stuy, all newborns admitted to the NICU between July 1, 2011, and June 30, 2012 were evaluated. Neonates who died or were discharged within 48 hours of admission were excluded.

The data of patients were recorded on a form including history, clinical course, the presence of catheters, nutrition status, and antibiotic treatments. Patients were followed up on until discharge, referral or death. The infants who were enrolled in the study were grouped into categories of ≤ 1000 g, 1001-1500 g, 1501-2500 g, and > 2500 g according to their birth weights.

Definitions

The definitions that were used during the study are listed below [8,13]:

i. HCAI is defined as an infection that occurs after 48 hours of admission and is not present at the time of admission or during the incubation period after admission to the hospital.

ii. Blood stream infection (BSI) is defined as an infection with a cultured pathogen in one or more blood cultures and is not related to an infection at another site.

iii. Devive-associated infection (DAI) is defined as an infection associated with a device occurring after 48 hours of hospital admission.

iv. Central venous catheter (CVC) / umbilical catheter (UC)-related BSI is defined as a laboratory proved BSI with either a positive catheter tip culture or a positive blood culture taken from CVC or UC.

v. Ventilator-associated pneumonia (VAP) is defined as pneumonia which develops later than 48 hours after the patient has been put on mechanical ventilation. The patient has at least two of the following symptoms: new onset of purulent sputum, change in character of sputum, increased respiratory secretions, increased suctioning requirements, new onset or worsening cough, dyspnea, tachypnea, rales or bronchial breath sounds or worsening gas exchange, and at least one of the following signs: new or progressive infiltrates, persistent infiltrate, consolidation, cavitation, pneumatocele in two or more serial chest radiographs.

vi. Urinary tract infection (UTI) is defined as an infection with a positive urine culture, i.e. $\geq 10^5$ colonies/mL microorganisms.

Infection control methods

An infection control nurse visits the unit every day. Our NICU has policies for handwashing and invasive procedures (entubation, catheterization etc.). All catheters were inserted and cared with standard unit protocols. Surveillance cultures are obtained at regular intervals. Infection prevention strategies and surveillance were monitored by the hospital infection control team.

Calculation of the parameters

The following calculated parameters were used to evaluate the HCAIs [13,14]:

i. HCAI incidence: (Number of HCAIs / number of patients) × 100

HCAI rate: number of HCAIs / patient-days × 1000

ii. Device utilization ratio: Device days / patient-days

iii. DAI rate: (number of device use/device use days) × 1000

iv. CVC/UC utilization ratio: (CVC/UC days) / patient-days

v. CVC/UC BSI rate: (number of CVC/UC BSI) / (CVC/UC days) × 1000

vi. Ventilator utilization ratio: Ventilator days / patient-days

vii. VAP rate: number of VAP / ventilator days × 1000

viii. Crude excess mortality was calculated as the difference between the crude overall fatality rate of patients with and without HCAI in the NICU during the same time.

Where patient-days is defined as the total number of days for all patients who were admitted or received a specified management for a period.

Statistical analysis

The data were analyzed with the Statistical Package for the Social Sciences (SPSS) for Windows 20.0 (SPSS Inc. Chicago, USA) package program. Mean ± standard deviation, range and percentages were presented. Chi-square test and Fischer’s exact test were performed to determine differences between the study groups. Differences were considered statistically significant for $p < 0.05$.

Results

Characteristics of study population

During the study period 474 newborns were admitted to the NICU. 122 patients were excluded according to the exclusion criteria. A total of 352 newborns were evaluated. The demographic and clinical characteristics of infants are shown in Table 1.

HCAI incidence and rate

A total of 60 HCAI episodes were evaluated in 37 (10.5%) of the patients over 5,212 patient-days. One or two or more infection episodes were observed in 24 and 13 patients, respectively. The overall incidence of HCAI was 17%, and the rate was 11.5/1,000 patient-days. The most common HCAI was BSI (n = 42, 70%), followed by pneumonia (n = 11, 18.3%), UTI (n = 4, 6.7%), central nervous system infection (n = 2, 3.3%), and surgical site infection (n = 1, 1.7%).

Device associated infections

28 of 60 (47%) HCAI episodes were associated with device utilization. The overall device utilization ratio was 0.31 and DAI rate was 17/1,000 patient-days. 21 of 42 (50%) episodes of BSI were related to CVC/UC use with an overall CVC/UC BSI rate of 18.3/1,000 patient-days. The CVC/UC BSI rates were significantly different in groups that were grouped according to the birth weight ($p = 0.001$), among which infants born ≤ 1000 g showed the highest CVC/UC BSI rate. Five of 11 (45.5%) pneumonias occurred in neonates who were supported with mechanical ventilation with an overall rate of 13.7/1,000 patient-days with no statistical difference according to the birth weight ($p = 0.45$). Two of four (50%) infants with UTI had a urinary catheter. The results of device utilization ratios and DAI rates according to birth weight stratification are shown in Table 2.

Table 1. The demographic and clinical characteristics of infants.

	No. of patients (N = 352)
Gestational age, (weeks)*	35.2 ± 3.6
< 37 weeks, n (%)	196 (55.7)
Birth weight (g)*	2419 ± 921
≤ 1000 g, n (%)	27 (7.7)
1001-1500 g, n (%)	43 (12.2)
1501-2500 g, n (%)	118 (33.5)
> 2500 g, n (%)	164 (46.6)
Gender (male), n (%)	184 (52.3)
Type of delivery (CS), n (%)	258 (73.2)
APGAR at 5'**	9 (3-10)
Ventilation support, n (%)	125 (35.5)
MV use, n (%)	26 (7.4)
NIV use, n (%)	53 (15.0)
MV+NIV use, n (%)	46 (13.1)
Catheterization (CVC or UC), n (%)	96 (27.2)
Total patient-days, (d)	5,212
Length of hospitalization, (d)*	14.7 ± 20.7
Mortality, n (%)	14 (3.9)

CS: Cesarean section; CVC: Central venous catheter; MV: mechanical ventilation; NIV: noninvasive ventilation; UC: Umbilical catheter; *Data as mean ± SD, **Data as median.

Analysis of risk factors

Univariate analysis showed that gestational age (< 32 weeks of gestation) and birth weight (< 1500 g) as demographic factors, as well as the presence of CVC/UC, the presence of a urinary catheter, receiving total parenteral nutrition (TPN), use of mechanical ventilator, and initiation of antibiotics on admission as interventional factors were significantly associated with higher incidence of HCAI. The presence CVC/UC showed the highest association (OR 13.41; 95% Cl

Table 2. Device utilization ratio and device-associated nosocomial infection rates.

	Birth weight	No. of patients	Patients-days (d)	Catheter days (d)	CVC/UC BSI, n (%)	CVC/UC utilization ratio	CVC/UC BSI rate	p
BSI	≤ 1000 g	27	1034	246	10 (37)	0.24	40.6	0.001
	1001-1500 g	43	1396	270	6 (14)	0.19	22.2	
	1501-2500 g	118	1365	232	2 (1.7)	0.17	8.6	
	> 2500 g	164	1417	397	3 (1.8)	0.28	7.5	
	Birth weight	**No. of patients**	**Patients-days (d)**	**Ventilator days (d)**	**VAP, n (%)**	**Ventilator utilization ratio**	**VAP rate**	**p**
Pneumonia	≤ 1000 g	27	1034	61	1 (3.7)	0.06	16.4	0.45
	1001-1500 g	43	1396	51	1 (2.3)	0.04	19.6	
	1501-2500 g	118	1365	121	2 (0.8)	0.09	16.5	
	> 2500 g	164	1417	133	1 (0.6)	0.09	7.5	

BSI: blood stream infection; CVC: central venous catheter; UC: umbilical catheter; VAP: ventilator associated pneumonia.

Table 3. Risk factors for HCAIs.

Risk factors	Odds ratio	95% confidence interval (Cl)	p
Demographic factors			
Gender	1.09	0.55-2.17	0.79
Gestational age (< 37 weeks)	2.33	1.09-4.98	0.029
Gestational age (< 32 weeks)	10.02	4.77-21.01	0.001
Birth weight (< 1500 g)	6.23	3.05-12.73	0.001
Interventional factors			
TPN use	6.27	2.38-16.53	0.001
CVC/UC use	13.41	5.86-30.70	0.001
Mechanical ventilator use	6.79	3.32-13.90	0.001
Urinary catheter use	6.11	2.56-14.55	0.001
Start of antibiotic on admission	2.60	1.30-5.20	0.007
Antibiotic use*	1.23	0.62-2.43	0.55

TPN: total parenteral nutrition; CVC: central venous catheter; UC: umbilical catheter; *Antibiotic use: Antibiotic use at any time out of during 72 hours before infection.

5.86-30.70) followed by having gestational age < 32 weeks of gestation (OR 10.02; 95% Cl 4.77-21.01) (Table 3). Multivariable logistic regression of these factors identified the presence of CVC/UC (OR 2.63; 95% Cl 0.94-7.38, p = 0.05), the presence of a urinary catheter (OR 3.32; 95% Cl 1.06-10.37, p = 0.038), and gestational age as being < 32 weeks of gestation (OR 2.98; 95% Cl 1.07-8.26, p = 0.036) as significant independent predictors.

Microbiological analysis

The bacteriological profile causing HCAI in the study shows predominance of Gram-negative pathogens with *Enterobacter spp.* being the most common isolates. *Enterococcus spp*. was the major Gram-positive genus (Table 4). BSI was predominantly caused by *Enterobacter spp.*, whereas pneumonia was mainly caused by *Acinetobacter baumannii*. The rate of methicillin resistance was 75% for coagulase-negative staphylocci (coNS). Resistance to glycopeptide antibiotics was not observed. Extended spectrum ß-lactamase (ESBL) was detected in 75% and 17% of *Escherichia coli* and *Enterobacter* spp., respectively. ESBL was not detected in *Klebsiella pneumoniae* isolates. Respiratory syncytial virus (RSV) was the causative agent in two cases of pneumonia.

Table 4. Distribution of isolated pathogens.

Pathogens	Number, (%)
Gram-negative bacteria	36 (60)
Enterobacter spp.	12 (33.3)
Acinetobacter baumannii	9 (25)
Klebsiella pneumonia	5 (13.9)
Escherichia coli	4 (11.1)
Serratia spp.	4 (11.1)
Pseudomanas aeruginosa	2 (5.5)
Gram-positive	17 (28.3)
Enterococcus spp.	8 (47.1)
Staphylococcus aureus	4 (23.5)
CoNS	4 (23.5)
Group B Streptococcus	1 (5.9)
Yeasts	5 (8.3)
Candida spp.	5 (8.3)
Viruses	2 (3.3)
RSV	2 (3.3)

CoNS: coagulase-negative staphylococci; RSV: respiratory syncytial virus.

Length of hospitalization and mortality

The mean length of hospital stay for all neonates in the study was 14.7 ± 20.7 days. The mean length of hospital stay for neonates with nosocomial infection was four times longer than for neonates without infection (45.6 ± 40.5 days vs. 11.1 ± 12.9 days, p = 0.001).

The overall mortality rate was 4%. The HCAI-related mortality rate was 10.8%. This study showed a mortality rate of 13%, 19%, 12.5% and 20% for patients with BSI, CVC/UC BSI, pneumonia and VAP, respectively. The crude rates for excess mortality associated with HCAIs, CVC/UC BSI and VAP were determined to be 7.7%, 9.8% and 9.4%, respectively.

Discussion

HCAI is still one of the most important cause of morbidity and mortality in hospitalized neonates with increased health care cost, despite the advances in neonatal care and intensive efforts to improve the survival of newborns over the last decades [6,15,16]. The initiation of a surveillance program to determine the rate of HCAI, identify the risks and problems and evaluate the measures taken are the first step to help reduceing the frequency of HCAI [17]. To help lowering the number of nosocomial infections in our NICU, we evaluated the infection surveillance of our

NICU, and compared it with national and international data in this study.

The incidence of HCAI (17%) in this study was higher whereas the HCAI rate (11.5/1,000 patient-days) was slightly lower compared with a previous International Nosocomial Infection Control Consortium (INICC) study in which we were a site between 2011-2014 [18]. The overall incidence of HCAI was consistent with results of previous studies conducted in Turkey and other countries [19-21]. The incidence of HCAI varies in the literature [1,22-25]. Low rates such as 3.9% were reported from developed countries whereas HCAI rates as high as 57% were reported from developing countries [1,2]. All these variations were explained by differences in clinical practices and resource utilization in NICUs [9,26].

In our study, the most common cause of HCAIs was BSIs (70%) followed by pneumonia (18.3%), and UTI (6.7%). BSI and pneumonia are the most frequent HCAI reported in the literature withrates ranging from 16%-78% for BSI and 10%-40% for pneumonia [27,28].

The device-associated infection (DAI) rate has been reported as 7-8.9/1,000 patient-days in multicenter studies from the European Union and United States [29,30]. There is limited data from developing countries. Yalaz *et al*. reported DAI rate as 9.2/1,000 patient-days from their NICU during a 5-year period [31]. In this study, the DAI rate (17/1,000 patient-days) was found to be higher than reported rates. Although studies from developed countries reported that CVC/UC-related BSIs are the most common (32%-53%) DAIs in NICUs [22,23], VAPs have been shown to predominate more than half of the DAIs in developing countries [32]. In our study, the CVC/UC-related BSI is the most frequent (75%) DAI followed by VAP (17.9%). According to the HCAI distribution, CVC/UC-related BSI has the highest incidence (35%) followed by VAP (8.3%), which is in contrast to INICC data reporting BSI and VAP rates of 30% and 41%, respectively [25]. The results of our study may be explained by a high utilization ratio of devices, a shortage of nursing staff, a high patient load, and the presence of severely ill neonates in the patient population. Identifying a higher CVC/UC utilization ratio and CVC/UC-related BSI rate as compared to other studies led us to evaluate our catheterization policies and take urgent measures [33,34].

Many factors such as length of hospitalization, gestational age, birth weight, mechanical ventilation, use of central catheter, parenteral nutrition, male sex, surgical operation, fifth-minute APGAR score and use of intravenous antibiotics have been reported as risk factors for HCAIs in various studies [22,24,35-37]. In the multivariate analysis, we identified the use of CVC/UC, being born before < 32 weeks of gestation and the use of urinary catheter as independent risk factors for HCAI. Similarly, Aurit *et al*. and Djordjevic *et al*. reported the same determinants as independent risk factors [36,37]. Administration of TPN, the use of devices such as catheters and ventilators was found to be a risk factor by Yapicioglu *et al*. [20].

The variety of pathogens isolated from nosocomial infections may vary from unit to unit even from region to region [2]. Gram-positve organisms especially *CoNS* are the most common pathogens in developed countries, whereas the predominant pathogens reported from developing countries are Gram-negative organisms [22,23,39]. In the present study, the most common pathogens isolated from HCAIs were Gram-negative organisms.

In our study, the mean length of hospital stay for neonates with a nosocomial infection was four times longer than for neonates without an infection (45.6 ± 40.5 days vs. 11.1 ± 12.9 days, p = 0.001). Other studies also showed longer hospital stays with HCAI [35,40]. However, it is difficult to conclude whether the increased length of stay is a cause or a result of the HCAIs.

HCAI is known to be a significant cause of morbidity and mortality in NICUs. HCAI-related mortality rate was 10.8% of which BSI and CVC/UC BSI have the highest rates (13% and 19%) in the present study. These rates are lower when compared with those reported in the literature [41-43]. On the other hand, since patients without HCAI have a lower mortality rate (3.1%) than those with nosocomial infection, it seems like we should continue to focus on preventive strategies to reduce BSI such as limiting the use of devices in our NICU.

This study is important due to its prospective nature and providing the data of a tertiary referral center from our country. There are some limitations which can be attributed to the present study, considering that data are from a single center and that we performed surveillance for a one-year period only.

Conclusion

Advances in neonatal care increase the number of technology-dependent infants, which is a primary determinant in the increase of HCAIs that account for longer hospital stay and more health care costs. Therefore, surveillance of HCAIs is an essential part of patient care quality. It is important to know the rates of

HCAI, determine the pathogen profile over the years, identify the risk factors and compare the results with national and international data to provide guidance for measures that can be taken to decrease nosocomial infections and related complications.

Authors' contributions

Design of the study: Atila Kılıc, Begum Atasay; *Collection of the data:* Atila Kilic, Emel Okulu, Bilge Aldemir Kocabas, Ufuk Cakir, Duran Yildiz, Dilek Kahvecioglu; *Analysis and interpretation of the data:* Atila Kilic, Begum Atasay, Ilke Mungan Akin, Omer Erdeve; *Literature review:* Atila Kilic, Serdar Alan, Ufuk Cakir, Duran Yildiz; *Writing the article*: Emel Okulu, Atila Kilic; *Control/supervision:* Saadet Arsan, Erdal Ince, Begum Atasay; *Approval of the manuscript:* Atila Kilic, Emel Okulu, Bilge Aldemir Kocabas, Serdar Alan, Ufuk Cakir, Duran Yildiz, Dilek Kahvecioglu, Ilke Mungan Akin, Omer Erdeve, Saadet Arsan, Erdal Ince, Begum Atasay.

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