Evaluation of device-associated infections in a neonatal intensive care unit

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Device-associated infections are common in Neonatal Intensive Care Units (NICUs) in accordance with the frequent use of invasive devices, and they must be continuously and closely monitored for infection control. Six hundred newborn infants hospitalized longer than 72 hours in Ege University Children's Hospital NICU between January 2008 and December 2010 were prospectively followed for occurrence of device-associated infections (central venous catheter- and umbilical catheter-associated blood stream infections [CVC/UC BSI] and ventilator-associated pneumonia [VAP]). In a total of 10,052 patient days, the VAP rate was 13.76/1000 ventilator days with a ventilator utilization ratio of 0.29, and the CVC/UC BSI rate was 3.8/1000 catheter days with a catheter utilization ratio of 0.24. The CVC/UC BSI rate was lower than national averages, being close to rates reported from developed countries. The VAP rate was higher than the national and international rates and was associated with prolonged mechanical ventilation and very low birth weight. VAP also appeared to be an important risk factor for mortality. The most frequent agents were gram-negative pathogens for VAP and coagulase-negative staphylococci for CVC/UC BSIs, with resistance patterns similar to the previous years. In conclusion, with device utilization rates similar to those in developed countries, our CVC/UC BSI rate was comparable, but the VAP rate was higher than that of the developed countries. Necessary precautions are urgently needed to decrease VAP rates and VAP-related mortality.

Key words: nosocomial, newborn, device-associated infection, ventilator-associated pneumonia, catheter-associated infection.

Infants in Neonatal Intensive Care Units (NICUs) carry a high risk for hospital infections[1,2]. The mortality rate of hospital infections in this age group is reported as between 10-50%[3,4]. Low birth weight, prematurity, congenital malformations, prolonged hospital stay, frequent invasive procedures, and administration of total parenteral nutrition are important factors that increase the risk of infection[5].

The most common hospital infections in NICUs are blood stream infection (BSI) and pneumonias. BSIs are frequently seen with central venous catheter (CVC) and umbilical catheter (UC) use[6]. Ventilator-associated pneumonias (VAPs) are also seen frequently and even represent the most common type of hospital infections in some NICUs. Premature birth, repeated and prolonged intubation and genetic diseases increase VAP frequency[7].

Active surveillance programs are essential for determination of nosocomial pathogens and antibiotic resistance patterns that vary from unit to unit and also over time. It is also important to know the rates of device-associated infections (DAIs) and device utilization rates to see if the rate of DAIs is compatible with the device utilization rate by comparing the results with national and international data. These steps will provide guidance for measures to be taken to decrease infectious complications.

The purpose of this study was to determine DAI rates with device utilization rates and the distribution and resistance patterns of causative agents in our NICU. We also aimed to compare our results with the national data obtained from the Refik Saydam Hygiene Center (RSHC) regarding DAIs in Turkish NICUs during the period 2008-2009 and also with the current international literature[8].

Material and Methods

Six hundred newborn infants, out of 889 infants admitted to Ege University Children's Hospital NICU between January 2008 and December 2010, were enrolled in this prospective study. Infants who died or were discharged in the first 72 hours of admission were excluded from the study. A trained nurse from the hospital infection control committee recorded DAIs (VAP, CVC/UC BSI and others) prospectively. Only VAP and CVC/UC BSI rates were evaluated in this study because our urinary catheter utilization rates are very low.

Our unit is a Level III NICU with 18 beds and 10 mechanical ventilators. During the study period, our NICU team consisted of 3 neonatologists, 2 neonatology fellows, 1 pediatric resident, and a nurse to patient ratio of 3-4 patients. Every patient area, hosting 5-6 patients, had 2 sinks, and alcohol-based hand antiseptics were available for every patient.

Umbilical arterial and umbilical/central venous catheters were placed in infants who needed intubation and mechanical ventilation and/or had birth weights below 1000 g according to our unit protocols. Patients were evaluated using their clinical status, blood gases and radiological findings for their need of mechanical ventilation.

For the diagnosis of DAI, a minimum period of 48 hours between the occurrence of infection and utilization of the device was required according to the Centers for Disease Control (CDC) criteria[9]. During the study period, infants with suspected infection were evaluated with complete blood counts, biochemical indicators of inflammation and with appropriate cultures. Only infants with positive blood cultures accompanying the clinical signs were evaluated as culture-proven BSI cases in this study. Transtracheal cultures were obtained from patients on ventilator with suspected pneumonia. Blood and transtracheal lavage materials were transferred to the microbiology laboratory as soon as possible, where they were evaluated in the appropriate culture media.

Ventilator-associated pneumonia (VAP) was diagnosed by clinical (increased secretions and escalation of mechanical ventilation support), radiological (subsequent progressive pulmonary infiltrates) and microbiological (positive tracheal aspiration fluid with growth of $5x10^4$ cfu/ml bacteria) findings that emerged after 48 hours of mechanical ventilation[9].

Patients with clinical signs of infection (apnea, poor feeding, skin color change, temperature instability) that appeared after at least 48 hours of catheter placement and with no other source of infection were diagnosed as CVC/UC BSI if there were at least two positive blood cultures taken at different occasions for skin flora microorganisms (e.g. coagulase-negative staphylococci [CoNS]). One positive blood culture was considered enough for microorganisms other than those of skin flora[9].

Parameters used to evaluate the DAIs were calculated as follows[8,9]:

DAI incidence: number of DAIs/100 device-used patients

DAI incidence density: number of DAIs/1000 device days

CVC/UC BSI rate: number of CVC/UC BSI / CVC/UC days x 1000

CVC/UC utilization ratio: CVC/UC days / patient days

VAP rate: number of VAP / ventilator days x 1000

Ventilator utilization ratio: Ventilator days / patient days

VAP incidence: number of VAP / 100 ventilated patients

All infants with suspicion of infection were closely followed. A combination of glycopeptides, carbapenems and antifungals was started as the first-line treatment in suspected cases of hospital-acquired late sepsis, in accordance with recent antimicrobial susceptibility data from our institution[10]. The continuation of the empirical antibiotic treatment was decided upon culture results in the following days.

All infants enrolled in this study were stratified into four birth weight categories as ≤1000 g, 1001-1500 g, 1501-2500 g, and ≥2500 g in order to evaluate the effects of birth weight on DAIs. Mortality was defined as death during NICU stay.

The Statistical Package for the Social Sciences (SPSS) for Windows 15.0 (SPSS Inc. Chicago, Illinois, USA) was used to evaluate the data. Chi-square test, Fischer exact test, and independent samples t test (with 95% confidence interval) were performed to determine differences between the study groups, as appropriate statistical significance was considered for $p<0.05$.

Results

Patients:

Demographic and clinical characteristics of 600 infants enrolled in this study are summarized in Table I.

DAI, VAP and CVC/UC BSI Rates:

Overall DAI incidence was 8.16/100 device-used patients and incidence density was 9.29/1000 device days. VAP incidence was 6.6/100 ventilated patients and VAP rate was 13.76/1000 ventilator days. CVC/UC BSI incidence and rate were 1.5/1000 catheterized patients and 3.8/1000 CVC/UC days, respectively. During their NICU stay, 9 infants had multiple DAIs and 31 infants had a single episode of DAI.

VAP Rate and Characteristics of Patients with VAP:

Table II summarizes the ventilator utilization rate and VAP frequency of the study group stratified according to birth weight categories compared with the national and international data. Twenty-seven percent of infants in this study (n=162) had received mechanical ventilation support for a mean duration of ventilation of 16.65 ± 19.5 (1- 227) days.

Table I. Characteristics of the Study Population (n=600)

Clinical characteristics	Value (mean ± SD, min-max or n, %)
Birth weight (g)	2165 ± 953 (540-4640)
Birth weight category	
≤1000 g	60, 10%
1001-1500 g	119, 20%
1501-2500 g	217, 36%
≥ 2500 g	204, 34%
Gestational age (wk)	33.88 ± 4.68 (22-41)
Premature birth (<37 weeks)	426, 71%
Duration of hospitalization (d)	22.4 ± 35.24 (1-360)
Male gender	368, 61%
C/S	499, 83%
Referred infants	6, 10%
Mortality	73, 12%
Duration of TPN (d)	9.39 ± 15.6 (0-109)
Total enteral feeding (d)	5.27 ± 12.1 (0-137)
Invasive procedures	
CVC/UC*	24% (n=144)
Ventilation support	32% (n=194)
MV	83.5% (n=162)
CPAP**	16.5% (n=32)

SD: Standard deviation. C/S: Cesarian section. TPN: Total parenteral nutrition. CVC: Central venous catheter.

UC: Umbilical catheter. MV: Mechanical ventilation. CPAP: Continuous positive airway pressure.

* Central venous and umbilical catheters were placed consecutively in some patients.

** Some patients received both invasive and noninvasive ventilation support.

Ventilator utilization ratio was 0.29 and VAP rate was 13.76‰ for the whole group. Ventilator utilization ratio was highest for the subgroup of patients with birth weights ≤1000 g; however, the highest VAP rate of 17.24‰ was found in the 1001-1500 g birth weight category (Table II). Ninety-five percent of VAP cases were seen in preterm infants, showing significantly higher VAP frequency in preterm infants ($p=0.007$). Mean duration of ventilation was significantly longer in VAP patients (50.95 ± 63.03 days) than patients without VAP (2.77 ± 7.84 days) ($p<0.001$). VAP was diagnosed on day 29.04 ± 24.10 (3–90) of mechanical ventilation.

CVC/UC BSI Rate and Characteristics of Patients with CVC/UC BSI:

Table III summarizes the CVC/UC utilization ratio and CVC/UC BSI rate of our study group classified according to the birth weight categories together with the national and international data. The CVC/UC utilization ratio was 0.24 in the entire study group and the CVC/UC BSI rate was 3.8‰. CVC/UC catheters were most commonly used in the infants with birth weights <1000 g. However, the highest CVC/UC BSI rate of 6.6‰ was seen in the 1501-2500 g birth weight category. All CVC/UC BSI cases were born prematurely. Infection was diagnosed 20.25 ± 12.84 (11–39) days after catheter insertion. Patients with CVC/UC BSI had received longer total parenteral nutrition and had tolerated enteral nutrition much later than infants without CVC/UC ($p=0.005$ and $p=0.011$, respectively).

Mortality:

The mortality rate in patients enrolled in this study was 12.1% (73/600). The mortality rate was 44.9% (22/49) for patients with DAI; 52.5% (21/40) for VAP cases and 11.1% (1/9) for CVC/UC BSI cases. Five hundred and fifty-one patients out of 600 study patients who did not have any kind of DAI had a mortality rate of 9.25% (51/551).

Distribution and Resistance Patterns of DAI Causative Agents:

Overall, most of the DAIs (77.5%) were caused by gram-negative microorganisms, followed by gram-positive pathogens (20.5%) and fungi

Table II. Comparison of Our Ventilator Utilization Ratios and VAP Rates with National and International Data

Birth weight groups	Number of patients (n)	Patient days	Ventilator days	VAP (n)	Ventilator utilization ratio*				VAP rate** (‰)			
					Study group	RSHC α data	INICC β data	NHSN γ data	Study group	RSHC α data	INICC β data	NHSN γ data
Total	600	10052	2907	40	0.29	0.16	0.13	0.20	13.76	7.17	9.5	1.64
≤ 1000 g	60	3113	1558	22	0.50	0.34	0.34	0.38	14.12	6.87	7.42	2.07
1001-1500 g	119	2423	348	6	0.14	0.16	0.15	0.14	17.24	7.53	8.19	1.4
1501-2500 g	218	2920	734	9	0.25	0.11	0.11	0.09	12.26	7.11	9.64	0.9
> 2500 g	203	1596	267	3	0.17	0.12	0.10	0.14	11.24	7.21	11.82	0.7

VAP: Ventilator-associated pneumonia.

* Ventilator utilization ratio: Ventilator days / Patient days

** VAP rate: VAP / Ventilator days x 1000

α The Refik Saydam Hygiene Center[8]

γ NHSN (National Healthcare Safety Network) report[23]

β INICC (International Nosocomial Infection Control Consortium) report[24]

(2%). The most common causative agents for VAP were gram-negative microorganisms (92.5%), but for CVC/UC BSI cases were gram-positive microorganisms (77.7%).

The distribution of causative agents for VAP was as follows: *Stenotrophomonas maltophilia* (30%), *Klebsiella pneumoniae* (27.5%), *Pseudomonas aeruginosa* (17.5%), and *Enterobacter cloacae* (12.5%).

The distribution of CVC/UC BSI causative agents was as follows: CoNS (55.5%), *Klebsiella pneumoniae* (11.1%), *Enterobacter cloacae* (11.1%), *Streptococcus viridans* (11.1%), Enterococcus spp. (11.1%), and *Candida albicans* (11.1%).

Discussion

Newborn infants, particularly very low birth weight infants, are at increased risk for hospital infections, mainly DAIs, due to their immature immune systems and also because of the increased need of mechanical ventilation and invasive procedures necessary for their underlying diseases[11,12]. Differences in DAI incidence among different NICUs are related not only to the success of infection control precautions but also to the ratio of low birth weight infants followed, device utilization ratio, number of patients/health care providers, and presence of active surveillance[13].

Although DAIs may not be completely preventable with the high frequency of device utilization in NICUs, clinicians should aim to decrease these infectious complications by taking the necessary precautions. Therefore, every NICU should evaluate its own DAI trends regularly and compare with the national and international data available to determine problems and resolve them.

Device-associated infection (DAI) incidence density is reported to be 7-8.9/1000 patient days in multicenter studies from the European Union and United States (US)[14,15]. From a Turkish NICU, Yapıcıoğlu et al.[16] reported their DAI incidence as 14.1-29.7/100 patients and DAI incidence density as 10.9-17.3/1000 patient days between 2001-2006. The same group reported a DAI incidence of 18% for 2008[17]. In our NICU, DAI incidence was 8.16/100 patients and incidence density was 9.29/1000 device days during the study period. Data from RSHC is not available by means of incidence and incidence density; however, our results seem to be comparable with data from developed countries.

Studies from developed countries show that CVC/UC BSIs are the most common (32-53%) DAIs in NICUs followed by VAPs (12-18%)[18,19]. A recent metaanalysis of Allegranzi et al.[20] showed that a great percentage of all DAIs (more than 50%) in developing countries is VAP. A multicenter study from Brazil reported a very high VAP frequency of 80%[21]. National data from RSHC show that in Turkey, VAP is the most common DAI, constituting 75.9% (n=1095) of all DAIs in the NICU[8]. Other studies from Turkey have reported that VAP constitutes nearly 70.15% of all ventilator- and catheter-associated infections in the NICU[16,17]. Our VAP/DAI ratio of 81.6% also confirms that DAI is an important problem in our unit as in other Turkish NICUs.

The National Nosocomial Infections Surveillance System (NNIS) in the US reported the VAP rate to range between 1.4-3.5 ‰ in NICUs[22]. In the National Health Safety Network (NHSN), the VAP rate is reported as 1.64‰ with a ventilator utilization ratio of 0.20[23]. The VAP rate was reported as 9.5‰ with a ventilator utilization ratio of 0.13 in a multicenter study of the INICC (International Nosocomial Infection Control Consortium) involving 173 centers from 25 countries, most of which were developing countries[24]. The VAP rate was reported as 13.8-28.14‰ from two different Turkish NICUs[16,25]. Turkish National Registry data from RSHC for the years 2008–2009 show a VAP rate of 7.17‰ at a ventilator utilization ratio of 0.16[8]. In our NICU, our VAP rate was 13.76‰ at a ventilator utilization ratio of 0.29, both being higher than the national data. The highest ventilator utilization ratio was observed in infants ≤1000 g, and the highest VAP rate was seen in infants with birth weights between 1001-1500 g (Table II). VAP seems as an important problem nationwide that needs to be evaluated, and for which urgent precautions should be taken.

In previous epidemiological studies, premature birth, a weak immune system, increased permeability of the mucous membranes, prolonged intubation, prolonged mechanical ventilation, empirical antibiotic usage, use of H_2 blockers and antacids, prior BSI, low birth

weight, opiate treatment, and re-intubation were reported as the factors related to VAP[7,13,26]. Noninvasive ventilation, such as nasal continuous positive pressure ventilation (NCPAP) or nasal synchronized intermittent mandatory ventilation (NSIMV), decreases VAP frequency significantly when compared to invasive methods[27]. In our study, VAP frequency was closely related to prolonged ventilation.

During the study period, noninvasive ventilation was used for only 16.5% of all mechanically ventilated infants (Table I). Our ventilator utilization ratio, being higher than both national and INICC data from developing countries, together with only rare use of noninvasive ventilation, may have caused our high VAP rate.

We performed an extensive literature search and conducted educational sessions for all NICU personnel in order to reduce VAP frequency. Written information regarding the VAP prevention strategy is presented on the most easily viewed walls of the NICU. We give particular attention to minimizing days on ventilation and more frequent use of noninvasive ventilation. Meticulous oral care, decreased use of H_2 receptor blockers, prevention of gastric distension, prone or side and head-elevated positioning, and parallel positioning of circuits to the patient bed to avoid the aspiration of infected material are executed. A decrease in aspiration frequency together with increased compliance in general infection control measures and a more strict hand hygiene control, limitation of changes and manipulations of disposable ventilator circuits to only when visibly soiled or malfunctioning, and frequent drainage of the condensed ventilator circuits have also been started in order to decrease the high VAP rate. Closed aspiration systems are not used in our center since their efficiency in reducing VAP has not been proven[13]. Planned extubation after cessation of sedation, careful assessment of the readiness of the patient, and administration of NCPAP or NSIMV in the postextubation period to avoid reintubation are the other important measures that have been taken.

The CVC/UC BSI rate is reported as 2.64‰ in the US, 8.84‰ in the INICC and 4.37‰ in the RSHC for Turkish NICUs. The CVC/UC utilization ratio is reported as 0.17 in the US, as 0.21 in the INICC and as 0.12 RSHC for Turkish NICUs[23,24,28]. In our NICU, the CVC/UC BSI rate was 3.8‰ at a CVC/UC utilization ratio of 0.24. Our CVC/UC utilization rate seems similar to those of developed countries, and our CVC/UC BSI rate is lower than national Turkish data and the data of developing countries and closer to the rates from developed countries (Table III).

Most of the catheter-associated BSIs were observed in very low birth weight infants. This may be the result of the high percentage (70.9%) of very low birth infants in our patient population and our better manipulation of infants with birth weights over 2500 g.

Mortality related to hospital infections inversely correlates with birth weight and is reported as 24-40% in different studies[16,21]. BSI-related mortality was reported as 24.3% in the multicenter study of the Turkish Neonatal Society[28] and as 16% in our previous study for the period 2000-2002[10]. In the INICC study of developing countries, CVC/UC BSI mortality was 34.5% and VAP mortality was 27.1%[24]. This study showed a mortality rate of 44.9% for all DAI cases, 52.5% for VAP cases and 11.1% for CVC/UC BSI cases. VAP was responsible for 95.45% of DAI-related mortality. Patients who did not acquire any DAI had a lower mortality of 9.25%. Therefore, decreasing our VAP rates seems to be extremely important to decrease our overall mortality.

The most common hospital infection pathogens of NICUs are gram-negative pathogens in developing countries and CoNS in the developed countries[18,19,26]. Klebsiella spp. were the most common pathogens for nosocomial sepsis in seven centers as reported in the study of the Turkish Neonatal Society[28]. However, in our hospital, CoNS (32.2%) and *Staphylococcus aureus* were the most frequent agents for BSI between 2000-2002[10]. The present study shows that CoNS (56%) were still the most common catheter-related BSI agents for the period 2008-2010. No VAP but one CVC/UC BSI was caused by fungi (*C. albicans*) in this period compared to 19.2% of BSIs in our previous study, probably due to the more rational use of antibiotics and protocol change for oral nystatin prophylaxis.

Comparing the resistance patterns of microorganisms in this study to our previous

Table III. Comparison of our CVC/UC Utilization Ratios and CVC/UC BSI Rates with National and International Data

Birth weight groups	Number of patients (n)	Patient days	CVC/UC days	CVC/UC BSI (n)	CVC/UC utilization ratio*				CVC/UC BSI rate** (‰)			
					Study group	RSHC α data	INICC β data	NHSN γ data	Study group	RSHCα data	INICC β data	NHSN γ data
Total	600	10052	2363	9	0.24	0.12	0.21	0.17	3.8	4.37	8.84	2.64
≤ 1000 g	60	3113	1087	6	0.35	0.23	0.39	0.23	5.5	3.75	11.41	3.57
1001-1500 g	119	2423	368	0	0.15	0.14	0.25	0.16	0	4.50	10.32	2.27
1501-2500 g	218	2920	304	2	0.10	0.09	0.20	0.12	6.6	4.56	8.74	1.98
> 2500 g	203	1596	232	1	0.15	0.08	0.17	0.15	4.3	4.90	6.51	1.53

CVC/UC: Central venous catheter/umbilical catheter. BSI: Bloodstream infection.
* CVC/UC utilization ratio: CVC/UC days/ patient days
** CVC/UC BSI rate: CVC/UC BSI / CVC/UC days x 1000
α The Refik Saydam Hygiene Center[8]
γ NHSN (National Healthcare Safety Network) report[23]
β INICC (International Nosocomial Infection Control Consortium) report[24]

report, gram-negative pathogens such as *Pseudomonas aeruginosa, Serratia marcescens* and *Klebsiella pneumoniae* are still highly susceptible to the carbapenem group of antibiotics, but are less susceptible to cephalosporins and piperacillin-tazobactam. The high resistance of CoNS to penicillin (96.1%) and methicillin (92.3%) in the period 2000-2002 reached 100% for both antibiotics in this study period. Susceptibility of CoNS for glycopeptides and linezolid still exists.

There are very few reports on DAIs in NICUs from Turkey. The active surveillance method used in this study and the comparison of our NICU's birth weight-classified device utilization and DAI data with the national and international registries are the important aspects of this study. To our knowledge, this is the first report from Turkey that not only analyzes the device utilization rates and the DAI rates, but also compares these results to national registry and international data, together with analyses of the causative agents.

In conclusion, for the period 2008-2010, although central catheters are placed regularly, catheter-related infection rates of our NICU are lower than the rates reported from developing countries and our national averages and are comparable with the data of developed countries. However, a high ventilator utilization ratio causing higher VAP rates than the reported rates from national and international studies have warned us to take urgent precautions on ventilation protocols. Similarly, every NICU should closely monitor the DAI rates and pathogens over the years and compare with national and international data in order to evaluate and resolve the problems.

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