Central Line-Associated Blood Stream Infections and Non–Central Line-Associated Blood Stream Infections Surveillance in Canadian Tertiary Care Neonatal Intensive Care Units

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Objective To determine if the reported reduction in hospital-acquired infections is due to reduced central line-associated blood stream infections (CLABSI) or non-CLABSIs.

Study design A retrospective cohort study design was used to describe the change in organism pattern and incidence of hospital-acquired infections (CLABSIs and non-CLABSIs) in neonates <33 weeks of gestation admitted to tertiary neonatal intensive care units in the Canadian Neonatal Network between January 1, 2010, and December 31, 2016. Hospital-acquired infection was diagnosed when a pathogenic organism was isolated from blood or cerebrospinal fluid in a neonate with suspected sepsis. CLABSI was diagnosed when a central venous catheter was present at the time or removed in the 2 days before a hospital-acquired infection diagnosis. Cochran-Armitage and Mann-Kendall trend tests and linear regression models were used for statistical analyses.

Results Of 28 144 eligible neonates from 30 Canadian Neonatal Network neonatal intensive care units, 3306 (11.7%) developed hospital-acquired infections. There was a significant decrease in the rate of hospital-acquired infections (14.2% in 2010 and 9.2% in 2016; $P < .01$), and the rate of both CLABSIs and non-CLABSIs ($P < .01$) over the study period concomitant with a significant decrease in the duration of central line use ($P = .01$). The rates of meningitis also decreased during the study period (1.2% in 2010 and 0.9% in 2016; $P < .01$). Infections owing to gram-positive cocci significantly decreased, but infections owing to gram-negative organisms remained unchanged.

Conclusion Although there was a significant decrease in CLABSIs and non-CLABSIs, hospital-acquired infections in preterm neonates remained high. Infections owing to gram-negative organisms remained unchanged and are a target for future preventative efforts. *(J Pediatr 2019;208:176-82)*.

Infection is an important cause of morbidity and mortality in neonates cared for in neonatal intensive care units (NICUs).[1] Infection is associated with a longer length of hospital stay and increased hospital costs.[2,3] Preterm neonates are known to have less responsive immune systems putting them at increased risk of infection.[4] A major source of infections in this population is preventable hospital-acquired infections.[5,6] This finding is particularly true for very low birth weight neonates, very preterm neonates, and those who are exposed to invasive procedures or have indwelling catheters.[7,8] Recognizing the problem with hospital-acquired infections, new practices and protocols are being developed to decrease hospital-acquired infections in NICUs worldwide. Central line-associated blood stream infections (CLABSIs) have been reported as a major cause of hospital-acquired infections[9]; thus, CLABSIs have been a main target of efforts to reduce hospital-acquired infections.

It is not clear whether the preventative efforts have resulted in a decrease in hospital-acquired infections. If so, it is unknown if there has been a decrease in both CLABSIs and non-CLABSIs and whether there has been a change in the type of organisms causing these infections. Understanding the trends in

CLABSI	Central line–associated blood stream infections
CNN	Canadian Neonatal Network
CoNS	Coagulase-negative *Staphylococcus* species
CVL	Central venous line
NICU	Neonatal intensive care unit
SNAP-II	Score for Acute Neonatal Physiology
UVC	Umbilical venous catheter

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hospital-acquired infections with reference to changes in CLABSIs and non-CLABSIs is important for the development of future efforts to reduce infection. We aimed to describe the change in the incidence of hospital-acquired infections, CLABSIs, and non-CLABSIs in Canadian NICUs with reference to trends in rates and organisms.

Methods

The Canadian Neonatal Network (CNN) is a multidisciplinary collaborative research program involving all 30 tertiary-level NICUs in Canada. Our retrospective study includes data from preterm neonates born at <33 weeks of gestation between January 1, 2010, and December 31, 2016, who were admitted to CNN NICUs and had a documented hospital-acquired infection. The median number of funded beds in participating NICUs was 31 (range, 6-87). Neonates were excluded if they had a major congenital anomaly, were moribund on admission, died within 2 days of admission, or had early-onset sepsis. We excluded infants with early-onset sepsis to ensure a clear distinction between early- and late-onset sepsis. Abstractors at each of the tertiary-level NICUs across Canada collected data using a standardized manual[10] and then transmitted them to the CNN Coordinating Center. Data collection at each site was approved by either a research ethics board or quality improvement committee. The database was shown to have high reliability and internal consistency.[11] The current study was approved by the Executive Committee of the CNN and by the Mount Sinai Hospital Research Ethics Board in Toronto, Ontario.

Hospital-acquired infection was defined as the presence of a pathogenic organism in the blood or cerebrospinal fluid culture obtained from a neonate suspected of having sepsis after 2 days of age. For this study, we only included viruses when culture from blood or cerebrospinal was positive; we did not include viral polymerase chain reaction test results. Also, we did not include urinary tract infections or pneumonia in the calculation of hospital-acquired infections because diagnosis of urinary tract infection is variable depending on sampling technique, and there are not well-defined criteria for diagnosing ventilator-associated pneumonia in preterm neonates. CLABSI was diagnosed when a central venous catheter (ie, umbilical venous catheter [UVC], peripherally inserted central catheter, or central venous line [CVL]) was present at the time of a hospital-acquired infection diagnosis or removed in the 48 hours before an hospital-acquired infection diagnosis.[12] Neonates with >1 hospital-acquired infection had each infection counted as a separate entry; however, for baseline patient characteristics, data from neonates were used only once. A neonate was considered to have a second episode of hospital-acquired infection if the same organism was identified >9 days after the first episode (giving a window of 10 days total). There was no mandatory requirement for obtaining 2 cultures from 2 different sterile locations to identify a hospital-acquired infection, and the majority of neonates had only 1 blood culture drawn. There is mandatory reporting of hospital-acquired infections by hospitals in Canada; however, the reported rates are by hospital and not individual units within the hospital.

The total duration of UVC, peripherally inserted central catheter, and CVL use, as well as probiotic and prophylactic fluconazole use and day of initiation of enteral feeding (for the years when data were available), were collected from the CNN database to assess changes in patterns of use over the years. Gestational age was calculated using in vitro fertilization date, last menstrual period, antenatal ultrasound dating, obstetrical estimate, or neonatal estimate (in that order). A neonate was classified as small for gestational age if the birth weight was <10th percentile for age and sex. Admission severity of illness was characterized by the Score for Neonatal Acute Physiology, version II (SNAP-II).[13] The SNAP-II score was calculated from mean blood pressure, lowest temperature, serum pH, partial pressure arterial oxygen/fractional inspired oxygen ratio, seizures, and urine output. Choriomanionitis was defined based on clinical and/or histologic criteria.

Statistical Analyses

Neonatal characteristics were compared using Cochran-Armitage trend tests for categorical variables and Mann-Kendall trend tests for continuous variables. Rates of infection and duration of catheter use over time were compared using Mann-Kendall trend tests. Infection per 1000 patient-days was examined using linear regression model analysis. The analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina). All P values were 2 tailed, and a P value of <.05 was considered statistically significant.

Results

The study included 28 144 (93%) of the 30 241 neonates born at <33 weeks of gestation and admitted to a CNN NICU. We excluded 1030 neonates who had a major congenital anomaly, 367 who died within 2 days of birth, 324 who had early-onset sepsis, 283 who were moribund on admission, and 84 who had a missing birthdate. Of the 324 patients with early-onset sepsis, 257 survived and 39 went on to develop late-onset sepsis; these cases were excluded.

Neonatal characteristics for each study year are shown in Table I. There was a significant decrease in the number of multiple pregnancies ($P < .01$) and mean gestational age ($P = .03$) across the study period among neonates who developed hospital-acquired infection. Both the percent of neonates born following chorioamnionitis and rupture of membranes >24 hours increased significantly over the study period ($P < .01$ for both) among neonates with hospital-acquired infection. Of note, there was no change in the percent of neonates with SNAP-II scores of >20 across the study period among neonates with

Table I. Demographic characteristics of neonates who developed any hospital-acquired infection

Characteristics	Admission year 2010 (n = 4037)	2011 (n = 3819)	2012 (n = 4144)	2013 (n = 4140)	2014 (n = 4110)	2015 (n = 3887)	2016 (n = 4007)	*P* value*
Multiples, n (%)								
Hospital-acquired infection	174 (30)	167 (31)	135 (28)	147 (30)	123 (28)	91 (23)†	88 (24)†	<.01
No hospital-acquired infection	1123 (32)	1032 (32)	1160 (32)	1201 (33)	1166 (32)	1000 (29)†	1073 (30)†	<.01
Chorioamnionitis, n (%)								
Hospital-acquired infection	102 (23)†	88 (21)†	64 (21)	78 (20)	80 (24)	109 (36)†	89 (30)†	<.01
No hospital-acquired infection	463 (18)†	420 (17)†	423 (17)	470 (19)	526 (20)	497 (20)†	516 (19)†	<.01
ROM >24 hours, n (%)								
Hospital-acquired infection	91 (17)†	95 (18)	94 (21)	86 (18)	76 (18)	105 (27)	85 (23)	<.01
No hospital-acquired infection	677 (21)†	637 (20)	714 (21)	744 (21)	693 (20)	768 (23)	785 (22)	.01
Caesarean birth, n (%)								
Hospital-acquired infection	339 (59)	306 (56)	288 (61)	295 (59)	263 (60)	240 (60)	203 (55)†	.67
No hospital-acquired infection	2039 (59)	1896 (58)	2153 (59)	2171 (60)	2131 (58)	2099 (60)	2335 (64)†	<.01
Gestational age (weeks), mean (SD)								
Hospital-acquired infection	26.9 (2.4)†	26.9 (2.4)†	27.0 (2.6)†	26.9 (2.5)†	26.8 (2.4)†	26.4 (2.4)†	26.1 (2.3)†	.03
No hospital-acquired infection	29.3 (2.4)†	29.4 (2.3)†	29.4 (2.4)†	29.3 (2.4)†	29.3 (2.4)†	29.3 (2.4)†	29.3 (2.4)†	.25
BW (grams), mean (SD)								
Hospital-acquired infection	981 (345)†	1000 (341)†	1006 (399)†	1000 (361)†	977 (381)†	945 (328)†	888 (321)†	.07
No hospital-acquired infection	1366 (439)†	1393 (447)†	1392 (450)†	1378 (441)†	1373 (445)†	1375 (445)†	1372 (450)†	.29
Male, n (%)								
Hospital-acquired infection	325 (57)	329 (60)†	278 (58)	262 (53)	235 (54)	231 (57)	208 (56)	.27
No hospital-acquired infection	1885 (54)	1745 (53)†	2030 (55)	1995 (55)	2016 (55)	1863 (54)	2027 (56)	.40
SGA, n (%)								
Hospital-acquired infection	80 (14)†	65 (12)†	76 (16)†	54 (11)	65 (15)†	51 (13)	49 (13)†	.83
No hospital-acquired infection	337 (10)†	298 (9)†	323 (9)†	338 (9)	347 (9)†	355 (10)	351 (10)†	.33
SNAP-II >20, n (%)								
Hospital-acquired infection	166 (29)†	152 (28)†	148 (31)†	143 (29)†	133 (30)†	119 (30)†	115 (31)†	.44
No hospital-acquired infection	450 (12)†	402 (12)†	477 (13)†	463 (13)†	455 (13)†	400 (12)†	439 (12)†	.07

BW, birth weight; *N*, number of neonates with hospital-acquired infections; *n*, number of neonates in characteristic category; *ROM*, rupture of membranes; *SGA*, small for gestational age.
**P* values were calculated using the Cochran-Armitage trend test for categorical variables (% of neonates) and Mann-Kendall trend test for continuous variables (gestational age, BW).
†There is a statistically significant difference ($P < .05$) between the hospital-acquired infection group and the no hospital-acquired infection group for the same year.

hospital-acquired infection. No other significant differences in neonate characteristics were identified.

Of the 28 144 eligible neonates, 3306 (11.7%) developed a hospital-acquired infection. The mean age at diagnosis of the first infection was 21.2 ± 21.5 days and the median age was 14 days (IQR, 9-24 days). The distribution of age at diagnosis of first infection owing to coagulase-negative *Staphylococcus* species (CoNS), group B *Streptococcus*, *Escherichia coli*, or *Staphylococcus aureus* is displayed in **Figure 1** (available at www.jpeds.com). There was a significant decrease in the incidence of hospital-acquired infections ($P < .0001$) over the study period (14.2% to 9.2%; **Figure 2** and **Table II**). This was true of both CLABSIs and non-CLABSIs (both $P < .01$). In 2010, 10.2% of neonates developed a CLABSI compared with 6.8% in 2016. Similarly, in 2010, 5.0% of neonates developed a non-CLABSI compared with 2.9% in 2016 (**Table II**). Rates of meningitis also decreased during the study period, especially in those cases associated with presence of central line (**Table II**).

There was a significant decrease in hospital-acquired infections per 1000 patient-days over the study period (**Table II**). The number of CLABSIs per thousand catheter days reduced significantly from 8.25 per 1000 catheter-days in 2010 to 6.44 per 1000 catheter-days in 2016 (**Table III**; available at www.jpeds.com). When examined by NICU, the hospital-acquired infection rate decreased >5% over the study period in 21 NICUs, changed <5% in 6 NICUs, and increased >5% in 3 NICUs (**Figure 3**; available at www.jpeds.com). When the number of hospital-acquired infections per 1000 patient-days was examined by NICU, there was variation noted among the NICUs for both CLABSIs and non-CLABSIs (**Figure 4**; available at

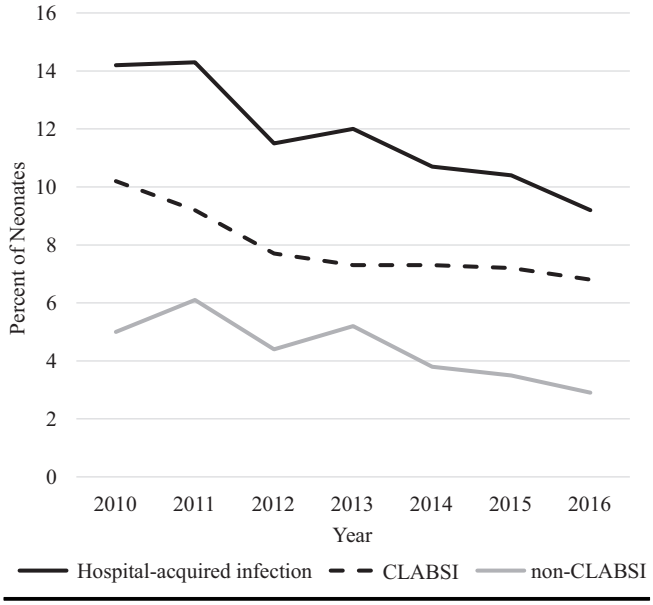

Figure 2. Rate of hospital-acquired infection, CLABSI, and non-CLABSI.

Table II. Types of infections and etiologic agents in neonates with hospital-acquired infections

Infection characteristics	Admission year 2010 (n = 4037)	2011 (n = 3819)	2012 (n = 4144)	2013 (n = 4140)	2014 (n = 4110)	2015 (n = 3887)	2016 (n = 4007)	*P* value*
Neonates with hospital-acquired infection,† n (%)	572 (14.2)	547 (14.3)	477 (11.5)	498 (12.0)	439 (10.7)	403 (10.4)	370 (9.2)	<.01
Type of infection								
1 CLABSI, n (%)	301 (7.5)	228 (6.0)	242 (5.8)	233 (5.6)	224 (5.5)	219 (5.6)	199 (5.0)	<.01
>1 CLABSI, n (%)	69 (1.7)	85 (2.2)	51 (1.2)	49 (1.2)	60 (1.5)	49 (1.3)	57 (1.4)	.01
1 non-CLABSI, n (%)	138 (3.4)	171 (4.5)	147 (3.6)	177 (4.3)	117 (2.9)	108 (2.8)	88 (2.2)	<.01
>1 non-CLABSI, n (%)	24 (0.6)	24 (0.6)	12 (0.3)	17 (0.4)	19 (0.5)	14 (0.4)	8 (0.2)	<.01
Both CLABSI and non-CLABSI, n (%)	40 (1.0)	39 (1.0)	25 (0.6)	22 (0.5)	19 (0.5)	13 (0.3)	18 (0.5)	<.01
≥1 CLABSI,‡ n (%)	410 (10.2)	352 (9.2)	318 (7.7)	304 (7.3)	303 (7.3)	281 (7.2)	274 (6.8)	<.01
≥1 non-CLABSI,§ n (%)	202 (5.0)	234 (6.1)	184 (4.4)	216 (5.2)	155 (3.8)	135 (3.5)	114 (2.9)	<.01
Meningitis	49 (1.2)	32 (0.8)	26 (0.6)	31 (0.8)	23 (0.6)	24 (0.6)	30 (0.8)	<.01
Central line-associated meningitis	36 (0.9)	21 (0.5)	14 (0.3)	19 (0.5)	14 (0.4)	13 (0.3)	23 (0.6)	.02
Non–central line-associated meningitis	13 (0.3)	11 (0.3)	12 (0.3)	12 (0.3)	9 (0.2)	11 (0.3)	7 (0.2)	.22
Hospital-acquired infection per 1000 patient-days								
Number of hospital-acquired infections	776	747	593	607	561	500	476	N/A
Total patient-days	176 871	169 979	180 655	180 221	182 983	177 057	183 026	N/A
Hospital-acquired infection per 1000 patient-days	4.39	4.39	3.28	3.37	3.07	2.82	2.60	<.01
Etiologic agent								
Gram-positive cocci, n (%)	609 (78.5)	568 (76.0)	443 (74.7)	484 (79.7)	419 (74.7)	375 (75.0)	349 (73.3)	.06
Gram-negative organisms, n (%)	122 (15.7)	143 (19.1)	124 (20.9)	98 (16.1)	121 (21.6)	104 (20.1)	106 (22.3)	<.01
Fungi, n (%)	34 (4.4)	25 (3.4)	18 (3.0)	19 (3.1)	14 (2.5)	14 (2.8)	14 (2.9)	.08
Viruses, n (%)	11 (1.4)	11 (1.5)	8 (1.4)	6 (1.0)	7 (1.3)	7 (1.4)	7 (1.5)	.90

N, number of neonates with hospital-acquired infections in group; *n*, number of neonates in the subgroup.
**P* values from Cochran-Armitage trend tests and linear regression model tests.
†Hospital-acquired infection includes 1 CLABSI, >1 CLABSI, 1 non-CLABSI, >1 CLABSI, and CLABSI and non-CLABSI categories.
‡One or more CLABSI includes 1 CLABSI, >1 CLABSI, and both CLABSI and non-CLABSI categories.
§One or more non-CLABSI includes1 non-CLABSI, >1 non-CLABSI, and both CLABSI and non-CLABSI categories.

www.jpeds.com). When we examined rates of both CLABSIs and non-CLABSIs by gestational age, there was a significant decrease in the percent of neonates 27-30 weeks of gestation who developed CLABSIs and non-CLABSIs across the study period, whereas the decrease in infections in infants <27 weeks of gestation was not as marked (**Table IV**; available at www.jpeds.com).

To explain the decrease in CLABSIs, we assessed changes in the use of central lines and duration of central lines in neonates eligible for the study (**Table V**). There was a significant increase in the number of UVCs, but not in the duration of UVC use. There was a significant decrease in the rate and duration of peripherally inserted central catheters ($P < .01$ and $P = .01$) and rate and duration of any central lines ($P = .01$) across the study period. The decreasing trend also was consistent for duration of CVLs, although not statistically significant. Number of neonates who had surgical CVLs decreased. Probiotics use steadily increased over study years. Prophylactic fluconazole use remained stable over the last 5 years in our network, with about 4% of neonates receiving fluconazole every year. Data for age at first feeding were available for only the last 3 years of the study and has remained stable at a median of 2 days of age.

The etiologic agents of the majority of hospital-acquired infections were gram-positive cocci (76.2%) and specifically CoNS (n = 2334; 54.8% of total infections; **Table VI** [available at www.jpeds.com]). After CoNS, the 2 most common organisms were *S aureus* (n = 528) and *E coli* (n = 385). For CLABSIs, the most common organisms were CoNS (n = 1662), *E coli* (n = 295), and *S aureus* (n = 216). For non-CLABSIs, the most common organisms were CoNS (n = 672), group B *Streptococcus* (n = 105), and *S aureus* (n = 92). There was a decreasing trend of hospital-acquired infections owing to both gram-positive cocci and fungi as a proportion of the total infection episodes throughout the study period (**Table II**). The percent of infections owing to gram-negative organisms (out of total infections during that year) significantly increased during the study period, whereas the proportion of infections owing to viruses per year remained unchanged throughout the study period (**Table II**, **Table VI**, and **Figure 5** [available at www.jpeds.com]). During the entire study period, the majority of gram-negative organisms causing hospital-acquired infection were *E coli* (47.4%), *Klebsiella* species (23.7%), and *Enterobacter* species (12.5%). Following the CNN confidentiality policy, specific organisms per year were not reported when the number of organisms in a subcategory was <5.

Table V. Central line use, central line duration, and other practices

Practices	Admission year 2010 (n = 4037)	2011 (n = 3819)	2012 (n = 4144)	2013 (n = 4140)	2014 (n = 4110)	2015 (n = 3887)	2016 (n = 4007)	*P* value*
Central line use and duration in days								
Neonates who had UVC, n (%)	1946 (48)	1878 (49)	2014 (49)	2074 (50)	2166 (53)	2178 (56)	2286 (57)	<.01
Duration of UVC, median (IQR)	7 (4-9)	6 (4-9)	7 (4-9)	7 (4-9)	7 (4-9)	7 (4-8)	6 (4-8)	.70
Neonates who had a PICC, n (%)	1747 (43)	1597 (42)	1617 (39)	1644 (40)	1607 (39)	1541 (40)	1524 (38)	<.01
Duration of PICC, median (IQR)	13 (8-23)	13 (9-24)	13 (8-23)	12 (8-22)	12 (8-23)	12 (8-21)	11 (7-23)	.01
Neonates who had a surgical CVL, n (%)	113 (3)	81 (2)	56 (1)	40 (1)	50 (1)	43 (1)	56 (1)	<.01
Duration of surgical CVL, median (IQR)	14 (7-32)	14 (7-24)	15 (5-27)	17 (7.5-28)	14.5 (7-30)	12 (6-27)	11 (4-32)	.36
Neonates who had any central line,† n (%)	2539 (63)	2381 (62)	2530 (61)	2578 (62)	2629 (64)	2567 (66)	2645 (66)	<.01
Duration of any central line,† median (IQR)	13 (8-23)	13 (8-23)	11 (8-21)	11 (7-19)	11 (7-20)	10 (7-19)	10 (7-18)	.01
Other practices								
Probiotics, n (%)	35 (1)	105 (3)	223 (5)	241 (6)	376 (9)	1048 (27)	1420 (35)	<.01
Prophylactic fluconazole, n (%)	NA	31 (1)	153 (4)	182 (4)	205 (5)	186 (5)	162 (4)	<.01
Age at first day of feeding (days); any milk or formula, median (IQR)	NA	NA	NA	NA	2 (2-1)	2 (1-3)	2 (1-3)	NA

N, number of neonates with hospital-acquired infections; *n*, number of neonates in each central line category; NA, not applicable; *PICC*, peripherally inserted catheter.
**P* value was calculated using the Mann-Kendall trend test. Median was used for each year and the number of observations per year was not accounted for.
†Central line was defined as any of UVC, surgical CVL, or PICC.

Discussion

In this large, population-based retrospective cohort study, we identified a significant decrease in hospital-acquired infections, both for CLABSIs and non-CLABSIs, in Canadian NICUs from 2010 through 2016. There was an associated significant decrease in the duration of central catheter usage, which may account for the reduction in CLABSIs rates. The rates of hospital-acquired infections owing to gram-positive cocci decreased over the study period, although they are still responsible for the majority of hospital-acquired infections. The percent of infections owing to gram-negative organisms did not change significantly over the study period.

The decrease in CLABSIs observed in our study is consistent with previous studies. Sinha et al reported a reduction in late-onset sepsis and CLABSIs from 2007 to 2012 after implementation of specific practices: appointment of a hospital specialist vascular device nurse, a change in the mode of administration of vancomycin, standardization of the hospital disinfection policy for skin and catheter hub, and the introduction of a venous infusion phlebitis scoring system.[14] CoNS infection rates lowered in this study as well.[14] Previous studies established that catheter duration is a risk factor for infection,[15] indicating that decreasing duration of catheter usage in Canadian NICUs could account for some of the decrease in CLABSIs. Although the majority of the infections in our study were CLABSIs (72%), it is clear from our results that non-CLABSIs continue to make up a significant component of hospital-acquired infections.

Rates of non-CLABSIs and specific interventions targeted at decreasing non-CLABSIs are not well-described in the literature. Our study suggests that general interventions packaged within CLABSI prevention bundles such as hand hygiene, sterile or clean procedures for handling noncatheter devices, and so on, may have played a role in the decrease in non-CLABSIs. The decrease in hospital-acquired infections coincides with a national quality improvement project running in Canada in which hospital-acquired infections are among the targets.[16] Interestingly, the trend of hospital-acquired infection decrease was observed despite a decrease in the mean gestational age of preterm birth by approximately 1 week. This outcome was the result of widespread and close attention to infection as a priority for preventable morbidity. We do not have an explanation for the increase in rates of premature rupture of membranes. The increase in the rates of chorioamnionitis could be due to better detection; however, we do not have data to prove this assumption. Between 2013 and 2017, changes in several infection-related practices were introduced by various units at varying times (**Table VII**; available at www.jpeds.com). The use of probiotics has increased during the study period, which may have contributed to the decrease in infections; however, we have observed that the increase in the use of probiotics was not different among infants who developed hospital-acquired infections vs those who did not develop hospital-acquired infections. Fluconazole prophylaxis has not been implemented widely in Canada because of a relatively low rate of fungal infection.[17] We believe that a multitude of interventions directed at several processes are needed to decrease the number of hospital-acquired infections.

Studies on hospital-acquired infections have commonly identified that the majority of infections are due to CoNS.[3,18-22] However, gram-negative organisms are recognized as an important source of infection and have been noted as the major causative organisms in some NICUs.[2,23] Gram-negative organisms are particularly virulent compared with other organisms, and there is documented increasing development of multidrug-resistant gram-negative bacilli in NICUs.[18] It is possible that the majority of packages or bundles of interventions to prevent CLABSIs are directed at preventing the direct spread of

organisms from procedures, skin commensals, and contact, which usually are gram-positive organisms. Although there has been evidence that some gram-negative infections are caused by a translocation of gut flora,[24,25] the source of gram-negative infections can be untraceable. This factor makes developing specific recommendations for reducing gram-negative infections challenging. It is possible that human milk feeding and antibiotic stewardship may help, but further evidence is necessary regarding their role in preventing gram-negative infections. The consistent percentage of hospital-acquired infections from gram-negative organisms observed in Canadian NICUs across the study period is worrisome and identifies the need for the development of preventative measures that specifically target gram-negative organisms.

The strengths of our study include a large and robust sample, national population-based data, meticulous data collection, and clearly defined CLABSIs and non-CLABSIs. However, our data have important limitations. First, NICUs across Canada have variable practices; therefore, the change in infection rates could not be attributed to ≥1 specific clinical changes. Second, to be consistent with the CNN definition of late-onset sepsis, we assumed that all infections manifesting after 2 days of age were hospital acquired, which may overcount the number of hospital-acquired infections relative to other definitions for separating early-onset sepsis (3, 5, or 7 days of age) from late-onset sepsis in the literature. Given a frequent definition of late-onset sepsis in the literature is an event after 3 days of age, we examined the number of infants who had a positive culture between 2 and 3 days of age and identified only 31 neonates suggesting any overcounting is minimal. Third, obtaining only 1 blood culture could also lead to an overestimation of hospital-acquired infection rates in our cohort (and particularly non-CLABSI CoNS cases); however, in our study, a hospital-acquired infection was only counted if the neonate was suspected clinically of having an infection and was treated for ≥5 days with antibiotics. Finally, this study may not fully account for the number of hospital-acquired infections caused by viruses. We only included viral infections identified in blood and cerebrospinal fluid culture and did not include infections confirmed by nasopharyngeal swabs.

Despite our findings of decreasing CLABSIs and non-CLABSIs in Canadian NICUs, our study demonstrates that the rate of hospital-acquired infections remains high. Gram-positive cocci continue to cause the majority of hospital-acquired infections and highlight that further preventative efforts are needed. Stable rates of infections from Gram-negative organisms suggest that new and unique practices may need to be developed to specifically target these organisms. Our study highlights the importance of strengthening existing infection reduction approaches and developing novel approaches to prevent both CLABSIs and non-CLABSIs. ■

*We acknowledge all site investigators and abstractors of the Canadian Neonatal Network (CNN; **Appendix**). We thank Sarah Hutchinson, PhD, from the Maternal-Infant Care (MiCare) Research Centre at Mount Sinai Hospital, Toronto, ON for editorial assistance in the preparation of this manuscript and other MiCare staff for organizational support of the CNN and this project.*

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Relapse of *Hemophilus influenzae* Type b Meningitis during Intravenous Therapy with Ampicillin

Coleman SJ, Auld EB, Connor JD, Rosenman SB, Warren GH. J Pediatr 1969;74:781-4

Coleman et al describe a child with *Hemophilus influenzae* meningitis who initially improved on ampicillin (150 mg/kg/d, low by today's standards) only to relapse after 5 days despite retained susceptibility of the organism to the antibiotic. The authors speculated that drug entry through the blood–brain barrier decreased as meningeal inflammation resolved, resulting in recrudescent infection.

One year before the current report, The National Committee for Clinical Laboratory Standards, later known as the Clinical and Laboratory Standards Institute (CLSI), was incorporated. One of the goals of this organization was to establish best practices for antimicrobial susceptibility testing through standardized measurement of minimal inhibitory concentrations (MICs), the lowest concentration of antibiotic needed to suppress the growth of a clinical isolate in vitro. The actual MIC is not helpful to most clinicians. Hence, CLSI establishes "breakpoint MICs," above which the organisms are judged resistant ("R") to a particular drug and below which they are interpreted as susceptible ("S"). CLSI recommends breakpoint MICs based on a consensus of physicians, microbiologists, pharmacologists, and members of the pharmaceutical industry. MIC breakpoints are neither static nor sacrosanct. They are revised in response to new studies and emerging resistance patterns. Furthermore, it should be noted that antibiotic pharmacokinetics vary significantly, particularly in critically ill children, affecting the predictive power of the S and R judgments, and that MICs may be increased in high-burden infections. Indeed, it is remarkable that the predictive power of antibiotic susceptibility testing is as accurate as it is.

An additional nuance of susceptibility testing, relevant to the case reported by Coleman et al, is that most assigned breakpoints are based on antibiotic concentrations achievable in serum and extracellular fluid. When the infection occupies a body space in which antibiotic distribution is limited, such as the central nervous system, prediction of clinical success becomes more dicey. In *Streptococcus pneumoniae* infections, CLSI breakpoints are adjusted if the organism is isolated from the cerebrospinal fluid, but in most other instances they are not, and in such cases the clinician should consult with an infectious disease expert to insure choice of the proper drug and dose, rather than depend on a quick perusal of the S and R judgments reported by the microbiology laboratory.

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Appendix

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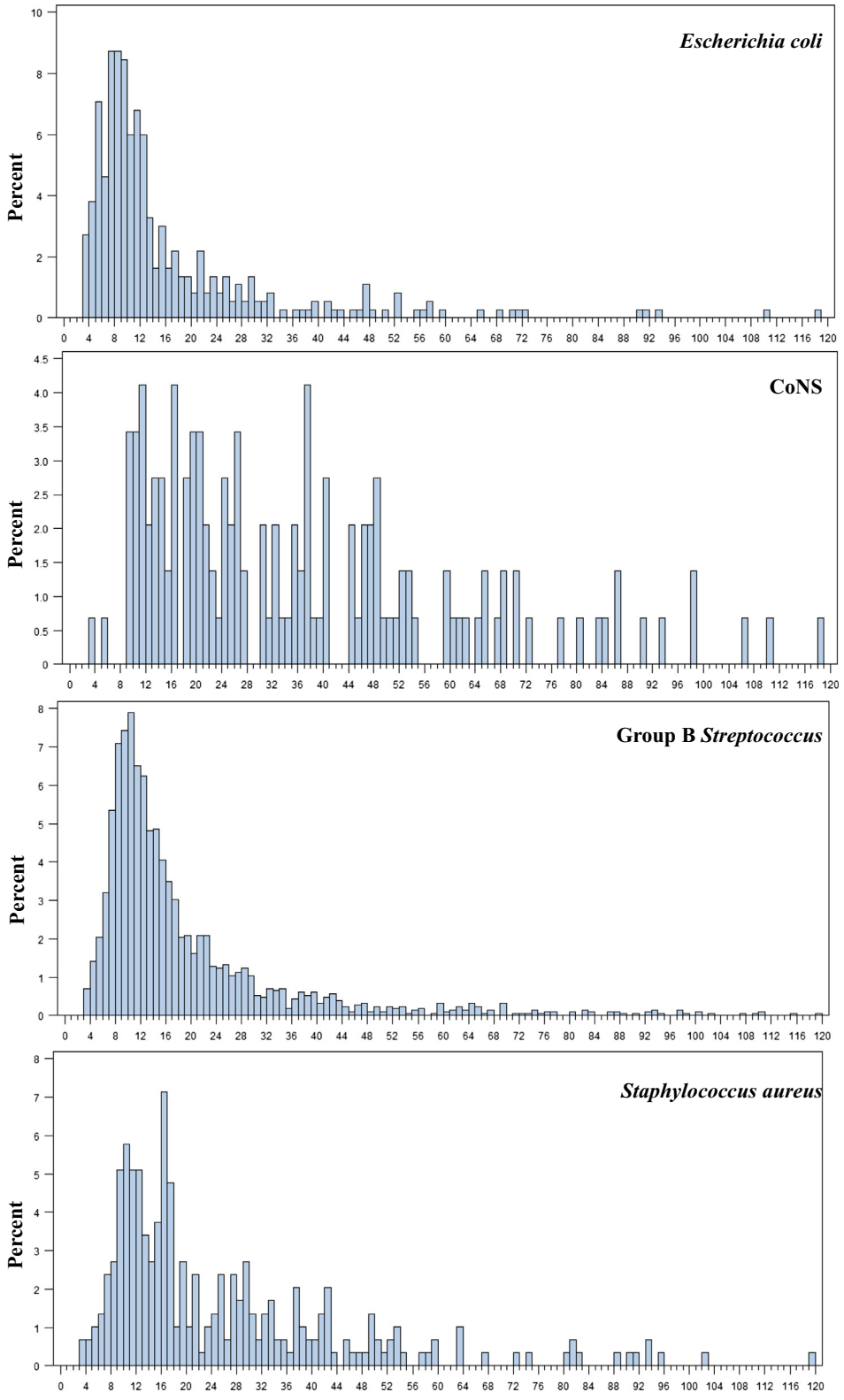

Figure 1. Age at diagnosis of first infection by common organisms.

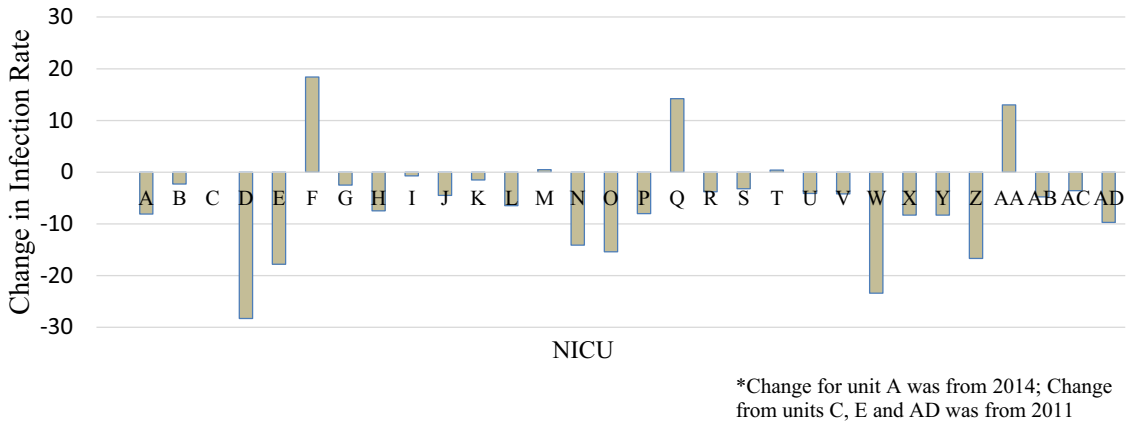

Figure 3. Change in hospital-acquired infection rate from 2010 to 2016 by NICU.

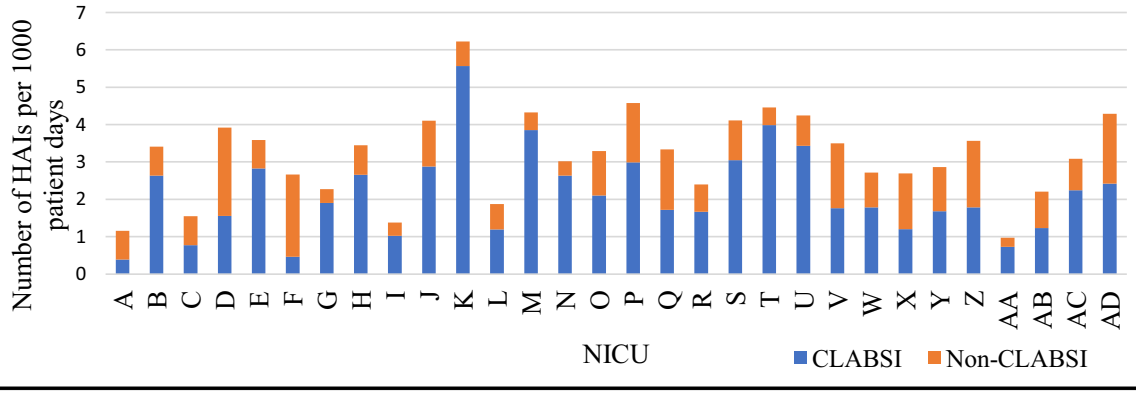

Figure 4. Number of hospital-acquired infections per 1000 patient-days by NICU.

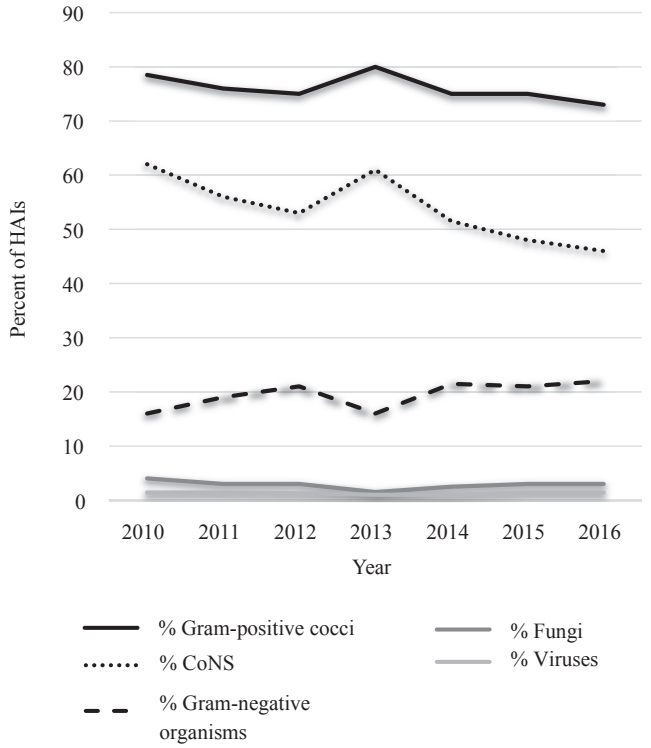

Figure 5. Change in organisms causing hospital-acquired infections.

Table III. CLABSIs per 1000 catheter-days in study period

Year	CLABSIs	Catheter days	CLABSIs/1000 catheter-days
2010	410	49 684	8.25
2011	352	44 146	7.97
2012	318	44 480	7.15
2013	304	43 393	7.01
2014	303	45 298	6.69
2015	281	42 302	6.64
2016	274	42 536	6.44

P value for trend: $P < .01$ (for testing the slope of best fit straight line through all 7 years = 0).

Table IV. CLABSIs and non-CLABSIs by gestational age

Gestational ages (weeks)	Category	Admission year 2010	2011	2012	2013	2014	2015	2016	*P* value*
<24	Number of infants	64	60	69	77	64	92	80	
	≥1 CLABSI,† n (%)	22 (34)	20 (33)	25 (36)	25 (33)	16 (25)	30 (33)	35 (44)	.53
	≥1 non-CLABSI,‡ n (%)	5 (8)	5 (8)	3 (4)	7 (9)	5 (8)	6 (7)	5 (6)	.75
24	Number of infants	164	140	158	180	195	159	188	
	≥1 CLABSI,† n (%)	61 (37)	52 (37)	49 (31)	47 (26)	55 (28)	46 (29)	58 (31)	.06
	≥1 non-CLABSI,‡ n (%)	17 (10)	20 (14)	15 (10)	16 (9)	21 (11)	19 (12)	15 (8)	.41
25	Number of infants	267	228	269	249	231	230	259	
	≥1 CLABSI,† n (%)	80 (31)	72 (32)	60 (22)	59 (24)	56 (24)	60 (26)	49 (19)	.04
	≥1 non-CLABSI,‡ n (%)	30 (11)	25 (11)	23 (9)	26 (10)	19 (8)	17 (7)	22 (9)	.12
26	Number infants	329	305	275	258	312	269	260	
	≥1 CLABSI,† n (%)	52 (16)	61 (20)	49 (18)	41 (16)	51 (16)	54 (20)	42 (16)	1.00
	≥1 non-CLABSI,‡ n (%)	25 (8)	42 (14)	17 (6)	22 (9)	15 (5)	15 (6)	21 (8)	.04
27	Number infants	387	311	340	351	329	295	352	
	≥1 CLABSI,† n (%)	71 (18)	43 (14)	44 (13)	49 (14)	45 (14)	21 (7)	41 (12)	<.01
	≥1 non-CLABSI,‡ n (%)	30 (8)	25 (8)	26 (8)	25 (7)	19 (6)	20 (7)	11 (3)	.01
28	Number of infants	373	378	404	424	387	400	408	
	≥1 CLABSI,† n (%)	45 (12)	32 (9)	26 (6)	37 (9)	27 (7)	21 (5)	21 (5)	<.01
	≥1 non-CLABSI,‡ n (%)	21 (6)	41 (11)	17 (4)	35 (8)	16 (4)	17 (4)	12 (3)	<.01
29	Number of infants	462	458	482	452	498	465	417	
	≥1 CLABSI,† n (%)	31 (7)	31 (7)	26 (5)	20 (4)	21 (4)	20 (4)	8 (2)	<.01
	≥1 non-CLABSI,‡ n (%)	20 (4)	29 (6)	27 (6)	27 (6)	17 (3)	18 (4)	7 (2)	<.01
30	Number of infants	585	526	598	614	563	529	531	
	≥1 CLABSI,† n (%)	28 (5)	17 (3)	22 (4)	9 (2)	12 (2)	17 (3)	8 (2)	<.01
	≥1 non-CLABSI,‡ n (%)	22 (4)	20 (4)	16 (3)	25 (4)	18 (3)	11 (2)	6 (1)	.01
31	Number of infants	654	618	704	715	710	649	691	
	≥1 CLABSI,† n (%)	9 (1)	14 (2)	11 (2)	9 (1)	13 (2)	8 (1)	9 (1)	.45
	≥1 non-CLABSI,‡ n (%)	19 (3)	13 (2)	20 (3)	15 (2)	16 (2)	6 (1)	11 (2)	.02
32	Number of infants	752	795	845	820	821	799	821	
	≥1 CLABSI,† n (%)	11 (2)	10 (1)	6 (1)	8 (1)	7 (1)	4 (1)	3 (0.4)	.01
	≥1 non-CLABSI,‡ n (%)	13 (2)	14 (2)	20 (2)	18 (2)	9 (1)	6 (1)	4 (0.5)	<.01

n, Number of infants in infection category.
*Cochrane Armitage trend test.
†Includes infants with 1 CLABSI, >1 CLABSI, and infants who had both CLABSI and non-CLABSI.
‡Includes infants with 1 non-CLABSI, >1 non-CLABSI, and infants who had both CLABSI and non-CLABSI.

Table VI. Etiologic organisms by year for hospital-acquired infections

Organisms	2010	2011	2012	2013	2014	2015	2016	Total
Gram-positive cocci								3247
CoNS	481	420	313	371	289	240	220	2334
Staphylococcus aureus	77	76	71	67	76	79	82	528
Enterococcus species	30	39	23	22	25	21	19	179
Group B *Streptococcus*	15	24	33	20	22	31	18	163
Other*	6	9	NR	NR	7	NR	10	43
Gram-negative bacilli								812
Escherichia coli	46	57	61	53	66	51	51	385
Klebsiella species	29	29	35	20	25	29	27	194
Enterobacter species	24	20	13	11	12	9	13	102
Serratia marcescens	8	17	7	8	5	NR	NR	52
Pseudomonas species	8	9	4	NR	6	7	7	42
Other†	7	11	NR	5	7	NR	5	43
Fungi								138
Candida species	29	19	16	18	14	12	14	122
Other‡	5	6	NR	NR	NR	NR	NR	16
Viruses								57
Cytomegalovirus species	5	6	5	3	7	7	5	38
Other§	6	5	NR	NR	NR	NR	NR	19
Total	776	747	593	607	561	500	476	4260

NR, Not reported.
The CNN does not report numbers when the cell size is <5 for confidentiality reasons.
*Included *Streptococcus pneumoniae*, *Streptococcus* species unspecified, and *Staphylococcus* species unspecified.
†Included *Acinetobacter* species, *Citrobacter* species, and *Proteus* species, *Haemophilus influenzae, Moraxella* species, and *Ureaplasma* species.
‡Included *Malassezia furfur,* and *Candida* species unspecified.
§Included *Enterovirus* species, *Herpes simplex,* and *Parainfluenza* species.

Table VII. Practice changes by sites to prevent hospital-acquired infections

Domains	Intervention
Hand hygiene	Easy access to alcohol-based hand rinse
	Implemented clothing/jewelry policy
	Trained of the 5 (or 6) moments for hand hygiene
	Established a culture of safety in which staff and families are empowered to speak up when there are breaches in technique
	Performed regular hand hygiene audits in the NICU
	Provided hospital-grade skin moisturizing agents
	Established and identify zones around the patient
Feeding	Obtained colostrum from mothers of premature
	Ensured that mothers of newly born NICU patients begin regular pumping within 6 hours of birth
	Fed exclusively with mother's milk
	Used banked human milk if mother's milk is not available
	Instituted minimal enteral feedings on day 1
	Used standardized feeding guidelines
Line insertion	Avoided use of femoral lines
	Used standardized line cart or line tray
	Used a dedicated line insertion team
	Shielded area and restrict traffic during procedure
	Used a checklist for all line insertions
	Performed audits to assess compliance with accepted insertion procedure
	Used maximal sterile barrier precautions during procedure
	Used double-glove for skin prep and draping
	Used 2% chlorhexidine solution for skin preparation
	Used clean introducer for each attempt (skin break)
	Restricted attempts to 2 per operator
	Critically reviewed insertion site q shift
	Used a closed, needleless fluid and medication administration system
Line management/maintenance	Assembled and prime infusion tubing using sterile technique
	Performed audits to assess compliance with accepted line assembly
	Used dedicated line team for connecting new infusion sets
	Changed line tubing every 96 hours (bag and lipids q 24 hours)
	Added heparin to TPN to a concentration of 0.5 IU/mL
	Considered Use of alcohol-impregnated caps over unused ports
	Scrub the hub with 70% alcohol
	Used prefilled syringes for line flushes
	Performed regular line connection/line entry audits
	Considered prophylactic fluconazole for infants with central catheters
	Considered switching from UVC to PICC before 7 days of age if needed
Line removal	Removed line when enteral intake reaches 120 mL/kg/day
	Used standardized template to investigate factors possibly contributing to the development of the BSI
	Evaluated need for central line daily
Review of infections by multidisciplinary team	Considered any blood stream infection to be an adverse event
	Convened a multidisciplinary team to investigate each BSI
	Used standardized template to investigate factors possibly contributing to the development of the BSI

PICC, peripherally inserted central catheter.