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Central line-associated bloodstream infection in infants admitted to a level lll neonatal intensive care unit

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ABSTRACT

Introduction. Central line (CL)-associated bloodstream infection (CLABSI) is one of the most common and yet preventable hospital-acquired infections in infants admitted to neonatal intensive care units (NICUs) and is associated with significant morbidity. The objectives of this retrospective study were to 1) determine the incidence rates of CLABSI in infants admitted to a level lll NICU and to 2) identify independent CLABSI risk factors in high-risk infants.

Methods. Data were collected from patient medical records, and incidence rates were calculated per 1,000 CL days and per 1,000 patient (PT) days. Univariate analyses were performed to identify potential risk factors associated with CLABSI, and those with a p-value ≤ 0.05 were assessed in multivariate analyses.

Results. The cohort represented 382 infants in whom 512 CLs were inserted. The CLABSI incidence rates per 1,000 CL days and per 1,000 PT days were 13.41 and 3.18, respectively. The only independent risk factor for CLABSI was prolonged CL dwell-time for the groups of umbilical catheters (adjusted odds ratio (aOR) = 1.42 per day (95% confidence interval (CI): 1.15-1.75)) and central venous catheters (aOR = 1.04 per day (95% CI: 1.01-1.07)).

Conclusion. Compared with other high-income countries, our overall incidence rate seems high. Since units of measurement and the definition used for CLABSI vary between studies, it is important to keep this in mind when comparing findings. Future research should focus on preventative measures in relation to CLs.

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Trial registration. not relevant.

Central lines (CLs) are widely used in neonatal intensive care units (NICUs) to ensure vascular access, which is necessary in many sick neonates and preterm infants. CLs include umbilical catheters (UVCs), central venous catheters (CVCs) and peripherally inserted central venous catheters (PCVCs) for providing nutrition, intravenous fluids and medications [1]. The use of CLs is associated with a risk of CL-associated bloodstream infection (CLABSI), which is one of the most common hospital-acquired infections and represents a significant and largely preventable cause of morbidity [2].

The association between CLs and patient characteristics, both of which are related to the occurrence of CLABSI, has been reported by various studies in the literature, especially in relation to preterm infants. These risk factors

include low birth weight [2-4], low gestational age [4-6], parenteral nutrition [2, 7], blood transfusion [7, 8], abdominal surgery [7, 9], prolonged admission to the NICU [7], prolonged CL dwell-time [2, 3, 5, 7, 8, 10, 11] and CL manipulations [4, 7]. In contrast, risk factors for surgically treated infants have rarely been investigated; yet a few studies have identified low gestational age [12] and prolonged CL dwell-time [11] for those exposed to abdominal surgery. Since multiple factors have regularly been shown to contribute to the pathogenesis of CLABSI, knowledge about this healthcare issue is important for implementing preventive measures in the NICUs. Therefore, the objectives of this study were to 1) determine CLABSI incidence rates in infants admitted to a level lll NICU and to 2) identify independent risk factors for developing CLABSI in high-risk infants with major health conditions including both prematurity and abdominal surgery.

METHODS

This retrospective study was conducted in a level lll NICU at Hans Christian Andersen Children's Hospital, Odense University Hospital (OUH), Denmark. In the period from November 2019 to February 2020, we collected data from patient medical records using procedural registrations for UVCs, PCVCs and CVCs. Furthermore, we collected data on the World Health Organization (WHO) International Classification of Diseases, tenth version (ICD-10) codes for prematurity, extremely low birth weight, CLABSI, septicaemia, hypoglycaemia and asphyxia, as well as procedural registrations for treatment with ventilator or continuous positive airway pressure and parenteral nutrition. The inclusion criteria were: 1) postmenstrual age < 44 weeks, 2) survival to at least the third day, 3) admission to the NICU and 4) CL insertion at the OUH within the period from 1 January 2015 to 31 December 2018. We used the Centre for Disease Control and Prevention's definition of clinical sepsis in infants ≤ 1 year of age [13] supplemented with the criterion: ≥ 7 consecutive days of antibiotic treatment [14]. Thus, a CLABSI event was defined as:

- at least one positive blood culture or seven consecutive days of antibiotic treatment

- the presence of at least one of the following clinical signs or symptoms with no other recognised cause: rectal temperature > 38 °C or < 37 °C, apnoea or bradycardia

- the onset of symptoms during the period from placement to removal of CL.

This study was approved by the Danish Data Protection Agency (2012-58-0018).

Statistical methods

Data were stored in the database of Research Electronic Data Capture (REDCap) and analysed in Stata - version 16.1. Incidence rates were calculated per 1,000 CL days and per 1,000 patient (PT) days, and multiple CLABSI events associated with one CL were handled independently. We used the chi-squared test and the Mann-Whitney-U test to examine differences between categorical and continuous variables, respectively. Risk factors with a p-value ≤ 0.05 in the univariate analyses were considered statistically significant and assessed in multivariate analyses using unconditional logistic regression models, and adjusted odds ratios (aOR) were accomplished. In addition to two-sided p-values, statistical significance was determined using 95% confidence intervals (95% CI).

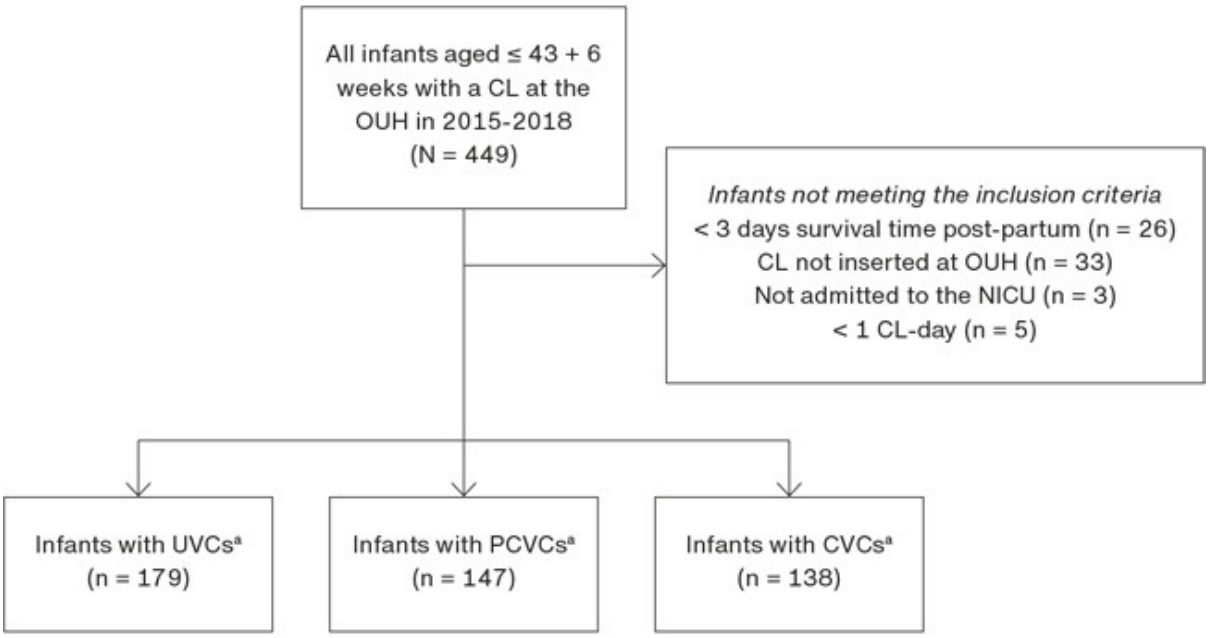
Trial registration: not relevant.

RESULTS

Among 449 infants assessed for eligibility within the four-year study period (2015-2018), 67 were excluded for not meeting the inclusion criteria (**Figure 1**). The final cohort of 382 infants, in which boys were marginally

overrepresented (**Table 1**), included 512 CLs: UVCs (n = 187), PCVCs (n = 169) and CVCs (n = 156). Eighty-two infants were in need of several CLs during admission, and the most frequent combination was UVC substituted by PCVC (64.13%). Among infants with CVCs, the majority were term-born (37.1 (34.6-38.7) weeks) and had abdominal surgery (91.03%) due to gastrointestinal malformations with omphalocele/gastroschisis (33.80%) and oesophagus atresia (20.42%) as the most common conditions. In contrast, the groups of UVCs and PCVCs consisted mostly of preterm infants with an average gestational age of 33.6 (27-39.1) and 27.7 (26-30.3) weeks, respectively. Further infant characteristics are shown in Table 1.

FIGURE 1 Study population.



CL = central line; CVCs = central venous catheters; NICU = neonatal intensive care units; OUH = Odense University Hospital; PCVCs = peripherally inserted central venous catheters; UVCs = umbilical catheters.
a) Infants with > 1 type of CL were included in several groups (n = 82).

TABLE 1 Characteristics of the study population.

	UVC (n = 187)	PCVC (n = 169)	CVC (n = 156)
Baseline			
Sex: boys, n (%)	107 (57.22)	93 (55.03)	88 (56.41)
Birth: sectio, n (%)	124 (66.31)	114 (67.46)	63 (40.38)
Gestational age, wks, median (IQR)	33.6 (27-39.1)	27.7 (26-30.3)	37.1 (34.6-38.7)
Birth weight, g, median (IQR)	2,150 (892-3,290)	974 (725-1,359)	2,730 (2,065-3,295)
Diagnosis, n (%)			
Medical:			
Prematurity	92 (55.76)	109 (86.51)	4 (28.57)
Asphyxia	30 (18.18)	-	-
Infection	8 (4.85)	5 (3.97)	4 (28.57)
Hypoglycaemia	11 (6.67)	1 (0.79)	-
Necrotising enterocolitis	-	6 (4.76)	-
Other[a]	24 (14.55)	5 (3.95)	6 (42.85)
Subtotal	165 (88.24)	126 (74.56)	14 (8.97)
Surgical:			
Oesophagus atresia	4 (18.18)	5 (11.63)	29 (20.42)
Bowel atresia	1 (4.55)	6 (13.96)	20 (14.08)
Omphalocele/gastroschisis	-	3 (6.98)	48 (33.8)
Diaphragmatic hernia	11 (50)	2 (4.65)	13 (9.15)
Necrotising enterocolitis	2 (9.09)	22 (51.16)	13 (9.15)
Other[b]	4 (18.18)	5 (11.64)	19 (13.39)
Subtotal	22 (11.76)	43 (25.44)	142 (91.03)
Blood transfusion, n (%)	72 (38.5)	91 (53.85)	30 (19.23)
Central line			
Dwell-time, days, median (IQR)	4 (2-6)	8 (5-12)	12 (8-19.5)
Postmenstrual age at insertion, wks, median (IQR)	33.7 (27.4-39.6)	28.6 (26.9-32.1)	37.8 (36.7-40.4)
Parenteral nutrition, n (%)	109 (58.29)	163 (96.45)	141 (90.38)
Admission			
Length of hospital stay, days, median (IQR)	14 (6-45)	39 (15-83)	20 (13-37.5)
Discharged alive, n (%)	168 (89.84)	153 (90.53)	153 (90.08)

CVC = central venous catheter; IQR = interquartile range; PCVC = peripherally inserted central venous catheter; UVC = umbilical catheter.
a) Hydrops foetalis, rhesus isoimmunisation, small for gestational age, heart diseases, respiratory distress, hyperbilirubinaemia, genetic diseases.
b) Hirschsprung disease, intestinal malrotation, pyloric stenosis, meconium ileus.

A total of 66 CLABSIs occurred in 57 infants, among whom eight suffered from several events. Among those, two infants had two and one infant had three events associated with one CL (PCVC and CVCs). Most CLABSIs were confirmed by a positive blood culture, identifying that 91.11% were caused by gram-positive microorganisms, in particular *Staphylococcus epidermidis*/*S. capitis* (30.71%) and coagulase-negative staphylococci (26.83%) (**Table 2**). We identified six independent cases caused by *S. epidermidis*/*S. capitis* with CL removal and antibiotic treatment for 2-4 days without relapse, which also applied to three coagulase-negative staphylococci cases. They were, however, treated with antibiotics for four to six days. The average antibiotic treatment duration was seven days (Table 2).

TABLE 2 Microorganisms identified in blood cultures and antibiotic treatment.

	UVC (n = 14)	PCVC (n = 24)	CVC (n = 28)
CLABSI			
Postmenstrual age, wks, median (IQR)	29.5 (27.4-31.7)	28.15 (27-31.3)	39.7 (37-41.75)
Blood cultures, n (%)	13 (92.86)	20 (83.33)	26 (92.86)
Positive blood cultures, n (%)	12 (92.31)	13 (65)	19 (73.08)
Type of microorganisms, n (%)			
Gram-positive microorganisms:			
Coagulase-negative staphylococci	1 (10)	7 (58.33)	3 (15.79)
Enterococcus faecalis/ Enterococcus faecium	-	-	5 (26.32)
Streptococci	-	1 (8.33)	-
Staphylococcus aureus	3 (30)	2 (16.67)	2 (10.53)
Staphylococcus epidermidis/ Staphylococcus capitis	6 (60)	1 (8.33)	6 (31.58)
Micrococcus luteus	-	-	2 (10.53)
Bacillus cereus	-	1 (8.33)	1 (5.26)
Subtotal	10 (83.33)	12 (85.71)	19 (100)
Gram-negative microorganisms:			
Escherichia coli	1 (50)	1 (50)	-
Enterobacter cloacae	1 (50)	-	-
Klebsiella pneumoniae	-	1 (50)	-
Subtotal	2 (16.67)	2 (14.29)	
Antibiotic treatment			
Antibiotics, n (%):			
Penicillin	2 (3.51)	-	-
Gentamicin	16 (28.07)	8 (29.63)	10 (15.15)
Ampicillin	5 (8.77)	3 (11.11)	2 (3.03)
Meropenem	2 (3.51)	4 (14.81)	7 (10.61)
Vancomycin	7 (12.28)	2 (7.41)	20 (30.30)
Metronidazole	7 (12.28)	1 (3.7)	9 (13.64)
Cefuroxime	18 (31.58)	9 (33.33)	18 (27.27)
Length of antibiotic treatment, days, median (IQR)	7 (5-8)	7 (4-8)	7 (5.5-10)

CLABSI = central line-associated bloodstream infection; CVC = central venous catheter; IQR = interquartile range; PCVC = peripherally inserted central venous catheter; UVC = umbilical catheter.

In all groups, a higher number of boys than girls developed CLABSI (**Table 3**). A significantly lower birth weight (UVCs: 920 versus 2,270 g, PCVCs: 697 versus 1,003.5 g and CVCs: 2,100 versus 2,790 g) and a lower gestational age (PCVCs: 26.25 versus 27.95 weeks and CVCs: 35.85 versus 37.3 weeks) were recorded for infants with CLABSI. In addition, they had a significantly longer CL dwell-time (UVCs: 6.5 versus four days and CVCs: 18 versus 11 days), more blood transfusions (UVCs: 64.29 versus 36.42% and CVCs: 46.43 versus 15.27%), a greater need of parenteral nutrition (UVCs: 85.71 versus 56.07%) and longer hospital stay (UVCs: 57 versus 13 days, PCVCs: 60 versus 35 days and CVCs: 42 versus 18 days). In the multivariate analyses, only prolonged CL dwell-time retained the significant association with CLABSI for infants with UVCs (aOR = 1.42 per day (95% CI: 1.15-1.75)) and infants with CVCs (aOR = 1.04 per day (95% CI: 1.01-1.07)) (Table 3).

TABLE 3 Analyses of risk factors associated with central line-associated bloodstream infection.

	Univariate analysis, potential risk			Multivariate analysis, significant risk, aOR (95% CI)
	CLABSI events	no CLABSI events	p-value	
UVC				
N	14	173		
Sex: boys, n (%)	8 (57.14)	99 (57.23)	0.995	-
Birth: sectio, n (%)	9 (64.29)	115 (66.47)	0.868	-
Gestational age, wks, median (IQR)	28.65 (27-36.3)	34.1 (27-39.6)	0.2103	-
Birth weight, g, median (IQR)	920 (578-2,160)	2,270 (937-3,300)	0.0212	1.00 (0.99-1.00)
Diagnosis: medical, n (%)	11 (78.57)	154 (89.02)	0.243	-
Central line dwell-time, days, median (IQR)	6.5 (4-7)	4 (2-6)	0.0003	1.42 (1.15-1.75)*
Parenteral nutrition, n (%)	12 (85.71)	97 (56.07)	0.03	
Yes[a]				1.00
No				1.17 (0.13-10.51)
Blood transfusion, n (%)	9 (64.29)	63 (36.42)	0.039	
Yes[a]				1.00
No				0.48 (0.12-1.96)
Length of hospital stay, days, median (IQR)	57 (15-74)	13 (6-38)	0.0068	1.00 (0.99-1.01)
Discharged alive, n (%)	13 (92.86)	155 (89.60)	0.698	-
PCVC				
N	24[b]	146		
Sex: boys, n (%)	13 (54.17)	80 (54.79)	0.954	-
Birth: sectio, n (%)	12 (50)	44 (30.14)	0.06	-
Gestational age, wks, median (IQR)	26.25 (24.75-27.8)	27.95 (26.3-30.7)	0.005	1.12 (0.83-1.51)
Birth weight, g, median (IQR)	697 (549-1,000)	1,003.5 (770-1,410)	0.0022	1.00 (0.99-1.00)
Diagnosis: medical, n (%)	19 (79.17)	108 (73.93)	0.587	-
Central line dwell-time, days, median (IQR)	9.5 (7-14.5)	8 (5-12)	0.0825	-
Parenteral nutrition, n (%)	23 (95.83)	141 (96.58)	0.855	-
Blood transfusion, n (%)	15 (62.5)	77 (52.74)	0.7908	-
Length of hospital stay, days, median (IQR)	60 (19.5-108)	35 (14-81)	0.0518	1.00 (0.99-1.01)
Discharged alive, n (%)	22 (91.67)	132 (90.41)	0.845	-
CVC				
N	28[b]	131		
Sex: boys, n (%)	18 (64.29)	71 (54.2)	0.329	-
Birth: sectio, n (%)	7 (25)	56 (42.75)	0.081	-
Gestational age, wks, median (IQR)	35.85 (31.65-37.35)	37.3 (35.9-38.7)	0.0078	1.03 (0.80-1.32)
Birth weight, g, median (IQR)	2,100 (1,476-3,195)	2,790 (2,265-3,300)	0.0094	1.00 (0.99-1.00)
Diagnosis: medical, n (%)	2 (7.14)	12 (9.16)	0.732	-
Central line dwell-time, days, median (IQR)	18 (12-34)	11 (7-18)	0.0004	1.04 (1.01-1.07)*
Parenteral nutrition, n (%)	27 (96.43)	117 (89.31)	0.242	-
Blood transfusion, n (%)	13 (46.43)	20 (15.27)	< 0.00001	
Yes[a]				1.00
No				0.37 (0.13-1.10)
Length of hospital stay, days, median (IQR)	42 (23-82.5)	18 (12-29)	< 0.00001	1.00 (0.99-1.02)
Discharged alive, n (%)	27 (96.43)	129 (98.47)	0.47	-

aOR = adjusted odds ratio; CI = confidence interval; CL = central line; CLABSI = central line-associated bloodstream infection; CVC = central venous catheter; IQR = interquartile range; PCVC = peripherally inserted central venous catheter; UVC = umbilical catheter.
*) $p < 0.05$.
a) Reference.
b) Including 3 independent cases in whom CLABSI was associated with 1 CL.

The total number of CL days was 4,921, which provided an overall (including both laboratory-confirmed and non-laboratory-confirmed CLABSIs) incidence rate of 13.41 per 1,000 CL days. Limited to CLABSI events caused by bacteraemia (laboratory-confirmed), the rate decreased to 8.94. Moreover, we calculated an overall rate of 3.18 (2.12 for laboratory-confirmed CLABSIs) per 1,000 PT days as the total number of PT days was 20,747.

DISCUSSION

In the study period (2015-2018), we found overall CLABSI incidence rates in the NICU at the OUH of 13.41

(laboratory-confirmed: 8.94) per 1,000 CL days and 3.18 (laboratory-confirmed: 2.12) per 1,000 PT days. Furthermore, we found that for the groups of UVCs (aOR = 1.42 per day (95% CI: 1.15-1.75)) and CVCs (aOR = 1.04 per day (95% CI: 1.01-1.07)) prolonged CL dwell-time was an independent risk factor for CLABSI.

Our overall incidence rate (13.41) is high if compared with the rates reported in most of the literature (range: 2.01-9.3) [2-5, 15, 16]. However, a few aspects should be considered. We used a broader CLABSI definition, which includes all potential CLABSI events as cases. This may have led to an overestimation of CLABSI in our study, making the comparison with the target literature difficult. Our rate of laboratory-confirmed CLABSI events (8.94) may therefore provide a more meaningful comparison and rank close to the rates of Zingg et al. (8) [2] and Mitt et al. (8.6) [15]. A Danish study, comparable in population and CLABSI definition, reported a rate of 13.3 per 1,000 CL-days [17], which is similar to ours (13.41). We, however, rank lower when comparing rates per 1,000 PT days (3.18 versus 5.1 [17]), which is also true for comparisons with the data reported by Wo&;jkowska-Mach et al. (6.7) [6] and by Leighton et al., (6) [18]. The differences observed across studies may be partly attributable to the variability between hospitals in patient characteristics and management of patient courses.

Our result showing 42% (aOR = 1.42) increased odds of CLABSI for every UVC day is roughly in line with the data reported by Zingg et al. (OR = 1.2) [2] and lower than those reported by Butler-O'Hara et al. (OR = 5.46 beyond the first seven days) [4]. We found no significant differences converting CL dwell-time into categories of less than and beyond seven days, which may be due to reduced statistical power. In line with Smith et al. [19], we did not identify a prolonged PCVC dwell-time as an independent risk factor; yet, this runs contrary to the findings of Zingg et al. (within the first seven days) [2]. UVCs are mostly the first choice to obtain fast vascular access in sick new-borns, and they are removed after a relatively short period of time. If long-term intravenous therapy is needed, our results indicate that early substitution of UVCs with a PCVC or a CVC is necessary to reduce the risk of CLABSI. However, further research in standardised settings is required.

In our study, most CLABSIs were caused by skin flora; and among these, we identified the fewest days of antibiotic treatment, which may possibly indicate that antibiotic treatment was adapted to clinical symptoms as recommended in the Danish national guideline [14]. We should draw attention to the management of CLs: use of appropriate dressings, careful and sterile CL access techniques and also limitation of CL manipulations, and therefore we suggest that future research should focus on this topic.

CONCLUSION

The overall CLABSI incidence rate in our NICU appears high compared with incidence rates reported in other high-income countries. This is due, in part, to differences in CLABSI definitions, units of measurement and differences between infants and hospitals. Despite some limitations, this study offers a starting point for improving CL handling in clinical practice and engaging in further clinical research projects on this topic in our NICU.

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