Low Risk of Central Line–associated Bloodstream Infections in Pediatric Hematology/Oncology Patients

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Background: Central venous lines (CVLs) are essential for standard care of pediatric hematology/oncology patients providing safe administration of cytotoxic drugs and pain-free blood sampling. Central line–associated bloodstream infections (CLABSIs) cause significant morbidity. This study describes the epidemiology, microbiology, and risk factors for CLABSI in all children with malignancies in Iceland.

Methods: All children that were diagnosed with malignancy in Iceland and received a CVL during 2008–2017 were included in the study. Characteristics of CVLs and patients were registered, information on risk factors, and microbiology was collected. International standards were used for CLABSI definition.

Results: One hundred forty-three CVLs were placed in 94 children. Acute lymphoblastic leukemia was the most common underlying disease (31/94). Median age was 7 years. Implantable ports were the most commonly placed CVLs (82/143, 57%), tunneled lines were 39 (27%). Overall CLABSI rate was 0.24 infections/1000 line-days (14 episodes in 58,830 line-days), with little fluctuations. No CLABSI episodes occurred for 4 consecutive years (2012–2015). Staphylococci (of which 7 *Staphylococcus aureus*) were the cause of 10/14 episodes. Nine CLABSI episodes led to line removal, but no deaths were linked to CLABSIs.

Conclusion: We report very low CLABSI rates over a 9-year period at our hospital, with 4 consecutive CLABSI-free years. Even with the addition of episodes of possible CLABSI, rates were still very low and lower than most published reports.

Key Words: central venous catheters, CLABSI, children, malignancy, Staphylococcal infection

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Central venous lines (CVLs) are essential in the treatment of pediatric hematology/oncology patients for safe administration of cytotoxic drugs, parenteral nutrition, and pain-free blood sampling. Complications associated with CVLs are well known and include mechanical complications, thrombus formation, and infections.[1–3] Central line–associated bloodstream infections (CLABSIs) are a major cause of morbidity and lead to extended hospital stay, prolonged antibiotic use, and sometimes additional surgical interventions.[4–7] Furthermore, CLABSI's place a significant financial burden on health care systems.[4,8,9] CLABSI rates are traditionally expressed as events per 1000 line-days. The CLABSI rates vary between centers and countries, but commonly reported rates are between 0.7 and 3.4/1000 line-days.[5,10–13] Several factors have been associated with increased risk of CLABSI in children, including type of CVL, malnutrition, neutropenia at the time of line insertion, and hematologic malignancies.[8,14,15] The purpose of this study was to describe the epidemiology, microbiology, and risk factors for CLABSIs in children with malignant diseases in Iceland, with the aims of assessing need for improvement in care for pediatric hematology/oncology patients at the Children's Hospital Iceland.

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METHODS

Study Design

This was a retrospective descriptive study of central line–associated bloodstream infections in pediatric hematology/oncology patients at the Children's Hospital in Iceland. Children diagnosed with malignant diseases during the 10-year period 2008–2017 and received 1 or more CVL during that period were included in the study. CVLs included were nontunneled CVLs, Broviac/Hickman (tunneled) catheters, implantable ports, and peripherally inserted central catheters (PICCs). The study was approved by the hospital's research ethics committee (reference no. 26/2018) and the hospital's medical director.

Catheter Care

No antibiotic prophylaxis is given before or during the insertion of CVLs nor are preventive antimicrobial locks used in routine clinical care. Fewer than 10 assigned oncology nurses to take care of the catheters on a very regular basis, although all nurses at the inpatient ward are trained in catheter care guided by a hospital protocol. The dressings are changed every 7 days, more often if needed (eg, loose or wet dressings). Needles in ports are changed every 7 days. The dressings are changed both at the ward at the Children's Hospital and at home. Parents are trained in catheter care and home care is done by both parents and home nursing staff, usually the same nurses as in the Children's Hospital. Catheters are flushed with 20 mL of NaCl after every use. Ports are additionally flushed with 5 mL of heparin (100 ie/mL) after every use. For other catheters, a heparin flush is used in addition to NaCl if the catheter will not be used again within 24 hours. Connecting and disconnecting of the line is minimized and blood drawing combined with other line connections when possible. When thrombosis in the catheter is detected, urokinase is used for thrombolysis. Catheters are removed when *Staphylococcus aureus* is cultured from the CVL, and the device is replaced a few days later. The catheter care did not change over the study period.

Chemotherapy is given to patients both as in- and outpatients. Selective gut decontamination is not given during neutropenia episodes.

Data Collection

The following information was collected from patient records: age, sex, underlying disease, type of central venous line, insertion date, insertion site, absolute neutrophil count (ANC) at insertion date, date of removal, reason for removal and number of days with catheter. Information was collected on positive blood

cultures as well as how many blood cultures were taken per CVL and per patient. Information was collected on ANC at time of positive blood culture and if the patient was neutropenic, the duration of neutropenia.

Definitions

Episodes of bacteremia were grouped in the following groups: (1) CLABSI, (2) possible CLABSI, (3) noncentral line BSI (non-CL BSI), and (4) contamination.

The CLABSI definition was based on the centers for disease control and prevention/National healthcare safety network (CDC/NHSN)[16] guidelines of laboratory confirmed bloodstream infections as (a) a positive blood culture with a recognized pathogen according to NHSN; or (b) ≥2 positive blood cultures with the same commensal organism at separate occasions within 48 hours and at least 1 of the following symptoms: fever >38.0°C, chills, or hypotension; or (c) for patients ≤1 year of age, ≥2 positive blood cultures with the same commensal organism at separate occasions within 48 hours and at least 1 of the following signs or symptoms: body temperature <36.0°C or >38.0°C, bradycardia, or apnea. To count as CLABSI, the bacteremia could not be related to an infection at another site and could not fulfill criteria for mucosal barrier injury laboratory confirmed bloodstream infection (MBI-LCBI).[16] MBI-LCBIs were categorized as non-CL BSIs. Possible CLABSI was defined as an episode of bacteremia with a common commensal organism that does not fulfill the CDC/NSHN criteria for CLABSI nor MBI-LCBI and was clinically treated as a CVL-associated bloodstream infection (antibiotics given or CVL removed). Possible CLABSI episodes were determined by 2 individual study team members (IK and VT) and required at least 1 positive blood culture and compatible clinical symptoms. If a second episode meeting CLABSI criteria occurred within 14 days in the same CVL and with the same microorganism, it was classified as the same event.

The number of line-days was counted from the day of insertion to the day of removal or until discontinuation of treatment at the Children's Hospital, death or end of study period. When insertion and removal dates were not clearly registered, the dates, and dwelling time were estimated from patient records. Each patient contributed 1 CVL-day, even if >1 CVL was in place at the same time.

Neutropenia was defined as ANC $\leq 0.5 \times 10^9$/L. ANC on the insertion date was noted but if not available, ANC within 2 calendar-days before or after was used.

2008 was used as a run-in year, registering insertion of lines and CLABSIs but not reporting CLABSI rate as accumulative line-days are lower in the first year of data collection.

Statistical Analysis

All CVLs were included for patients that had more than 1 CVL placed during the study period. All episodes of CLABSI from 2009 were included in calculations of incidence, expressed as rate per 1000 line-days. If >1 episode of CLABSI occurred in the same CVL, only the first episode was used in calculations for risk factors and time to event. Comparison between groups was done with Fisher's exact test and Mann-Whitney *U* test. CLABSI-free survival of CVLs was estimated with Kaplan-Meier estimate and log-rank test was used for comparison of survival curves of different CVL types. A *P* value of <0.05 was considered statistically significant. R (version 3.6.3) was used for statistical analysis.

RESULTS

During the 10-year period, 143 CVLs were placed in 94 of the 146 children diagnosed with malignancies in Iceland (Table 1). Those who did not receive a CVL had solid tumors and were treated surgically without chemotherapy. On 7 occasions, catheters were placed to treat relapse cases.

TABLE 1. Characteristics of 143 CVLs Placed in 94 Children Diagnosed With Malignant Diseases at the Children's Hospital in the 10-year Period 2008–2017

	CVLs, N = 143	Patients, N = 94
Age at diagnosis, median (range)		7 (0–17)
Age at insertion of CVL, median (range)	7 (0-17)	
Sex, n (%)		
Male	93 (65)	59 (62.8)
Female	50 (35)	35 (37.2)
Underlying condition, n (%)		
Hematologic malignancy	94 (65.7)	58 (61.7)
Solid tumor	49 (34.3)	36 (38.3)
Insertion site, n (%) *		
Subclavian vein	131 (94.9)	
Jugular veins	6 (4.35)	
Femoral vein	1 (0.72)	
CVL dwell time (days), median (range)	202 (5–2142)	
Broviac/Hickman	120 (7–430)	
Nontunneled CVL	10.5 (5–23)	
Port	550.5 (12–2142)	

*Data missing on insertion site for 5 CLs.
CLs indicates central lines; CVLs, central venous lines.

Acute lymphoblastic leukemia was the most common underlying disease (31/94), followed by lymphoma (18/94) and sarcoma (11/94). The median age at diagnosis was 7 years and 63% (59/94) of the patients were male. Implantable ports were the most commonly placed device (82/143, 57.3%). Forty-nine (34.3%) Broviac/Hickman catheters were placed during the study period and 12 nontunneled CVLs (8.4%). No PICCs were placed. The subclavian vein was the most common insertion site (131/138, 94.9%) but insertion site could not be determined for 5 CVLs. Information on number of lumens was available for 45 catheters (31.5%) and of those, 38 were double lumen catheters, 6 were single lumen, and 1 had 4 lumens. None of the studied variables were found to be significantly associated with risk of CLABSI when comparing CVLs in which CLABSIs occurred and CLABSI-free CVLs, apart from number of blood cultures taken [median 5.5 (range 2–37) vs. 2 (range 0–40), $P = 0.02$].

Fourteen episodes of CLABSI occurred during the 10-year period, in 11 different CVLs. If possible CLABSIs were included, 20 episodes occurred in 13 CVLs. Overall CLABSI rate was 0.24 infections per 1000 line-days (14 episodes in 58,830 line-days). If possible CLABSIs are included the infection rate was 0.32 infections per 1000 line-days (19 events in 58,830 line-days). The highest infection rate was in the year 2011 with 0.54 CLABSIs per 1000 line-days (Fig. 1). No CLABSI episodes were confirmed during 4 consecutive calendar years (2012–2015). No child had an episode of CLABSI in more than 1 separate CVLs. Three implantable ports had 2 distinct CLABSI episodes, in all instances the same pathogen was identified in both episodes [*Corynebacterium* species in 1 port, coagulase-negative staphylococci (CoNS) in another and methicillin sensitive *S. aureus* (MSSA) in the third port]. Neutropenia was present in 2 CLABSI episodes with CoNS, which occurred in the same port. The patient had been neutropenic for 7 days and 1 day, respectively, before the CLABSI episodes. The median time from insertion to first CLABSI episode was 85 days (range 2–279 days) and the median interval between subsequent infections was 37 days (range 29–136). In all cases, the latter infection resulted in CVL removal. In total, 10 CLABSI episodes and 2 episodes of possible CLABSI

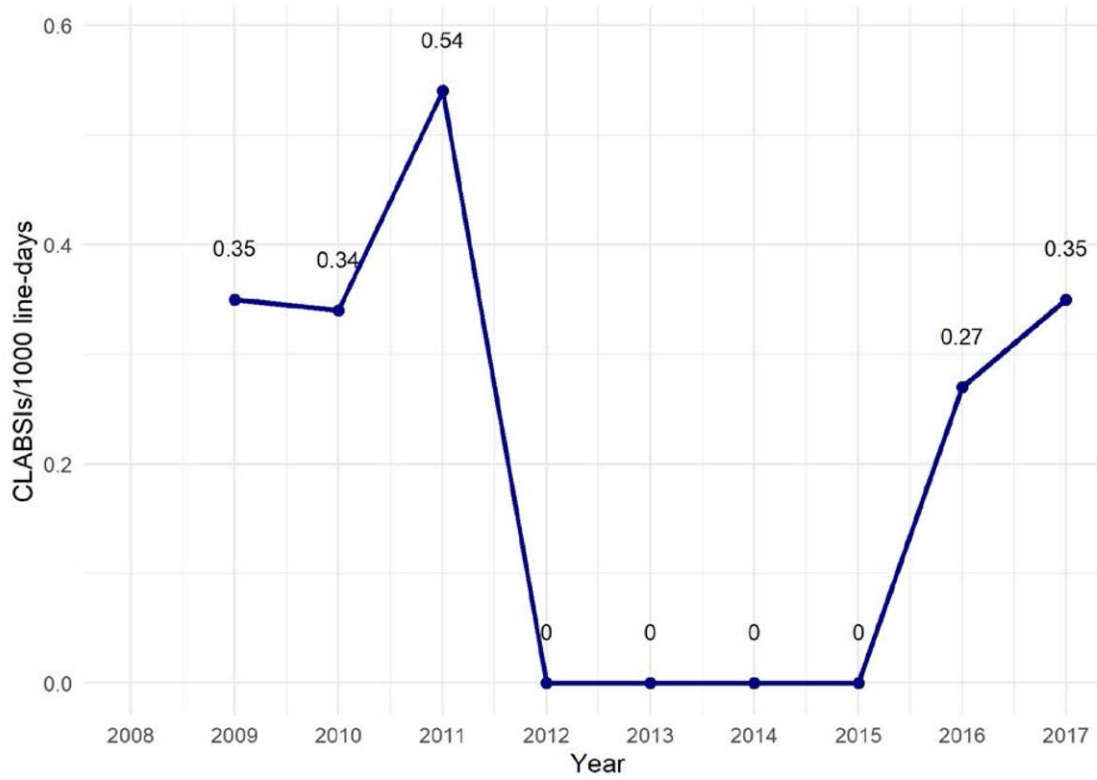

FIGURE 1. The figure shows CLABSI rates/1000 line-days over the study period 2009–2017. No CLABSI rate reported for 2008, as it was used as a run-in year. CLABSI indicates central line–associated bloodstream infections. full color online

resulted in CVL removal. In addition, 5 CVLs were removed due to suspected infection despite negative cultures. Other reasons for removal, besides end of treatment, were malfunctions or mechanical complications. One CVL was removed due to a thrombus. No CLABSI episodes resulted in death. In 1 CLABSI episode IV contrast had been given within 3 days before CLABSI episode and in none of the possible CLABSI episodes.

S. aureus (all MSSA) was the most common pathogen, causing 7/14 CLABSI episodes, of which 5 episodes occurred in the last 2 years of the study period. Before 2016, only 2 episodes of CLABSI with *S. aureus* occurred, both in the same implantable port with just over a month between episodes. Coagulase-negative staphylococci were the second most common pathogens, causing 3/14 of CLABSI episodes and 5/6 of possible CLABSI episodes. Other pathogens causing CLABSI were *Corynebacterium* species, *Candida parapsilosis* and *Enterobacter cloacae*. Ten episodes of bacteremia were defined as non-CL BSI, of which 80% were caused by Gram-negative bacteria (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E389).

The overall CLABSI-free line survival at 6 months was 92.2% (95% CI: 87.3–97.3%). Six-month CLABSI-free line survival was 95% for Broviac/Hickman catheters (95% CI: 87.5–100%) and 92.1% for implantable ports (95% CI: 86.2–98.4%). Twelve-month CLABSI-free line survival was 78.8% for Broviac/Hickman catheters (95% CI: 54.7–100%) and 90.5% for implantable ports (95% CI: 84.0–97.5%) (Fig. 2).

DISCUSSION

We report very low CLABSI rates (0.24/1000 line-days) in a cohort of pediatric hematology/oncology patients over a 10-year study period, with *S. aureus* as the most common pathogen followed by coagulase-negative staphylococci.

Great variations are reported in CLABSI rates in published literature, ranging from 0.35 to 6.7 infections/1000 line-days.[10,15,17,18] The low incidence of CLABSI in our study might in part be explained by the high number of implantable ports used during the study period (56.6% of CVLs inserted). Previous studies have shown implantable ports to have the lowest incidence rate of CLABSI[8,10,11,13,19] and PICCs the highest,[10] although our study did not show CVL type to be associated with CLABSI risk. Variations in definitions of CLABSIs[20] play an important part in reported CLABSI rate differences. With the addition of MBI-LCBI in CDC/NHSN definitions, episodes that would have previously been classified as CLABSI are now defined as MBI-LCBI, thus potentially lowering CLABSI rates in newer studies and ours.[16] The 2018 CDC/NHSN definitions were utilized for this study and to fulfill CLABSI criteria for commensal organisms, 2 separate and positive blood cultures taken within 48 hours are required. Furthermore, the definition of line-days will impact CLABSI rates/1000 line-days. We counted line-days from insertion to removal, as has been done in other studies,[5,11,21] which will contribute to lower rates. This includes days without a needle in the port when infection risk is low. In some other studies, only inpatient line-days are counted, according to CDC/NHSN surveillance guidelines,[16,22,23] resulting in a lower denominator and potentially higher infection rates. However, the infection risk remains in outpatient and home care for CVLs. The possibility for over- or underestimation remains either way.[24] The low CLABSI rate observed might partly be explained by number of blood cultures obtained. In a few cases, only 1 blood culture was obtained and thus some CLABSI episodes might have been missed. In an effort to correct for the effects of

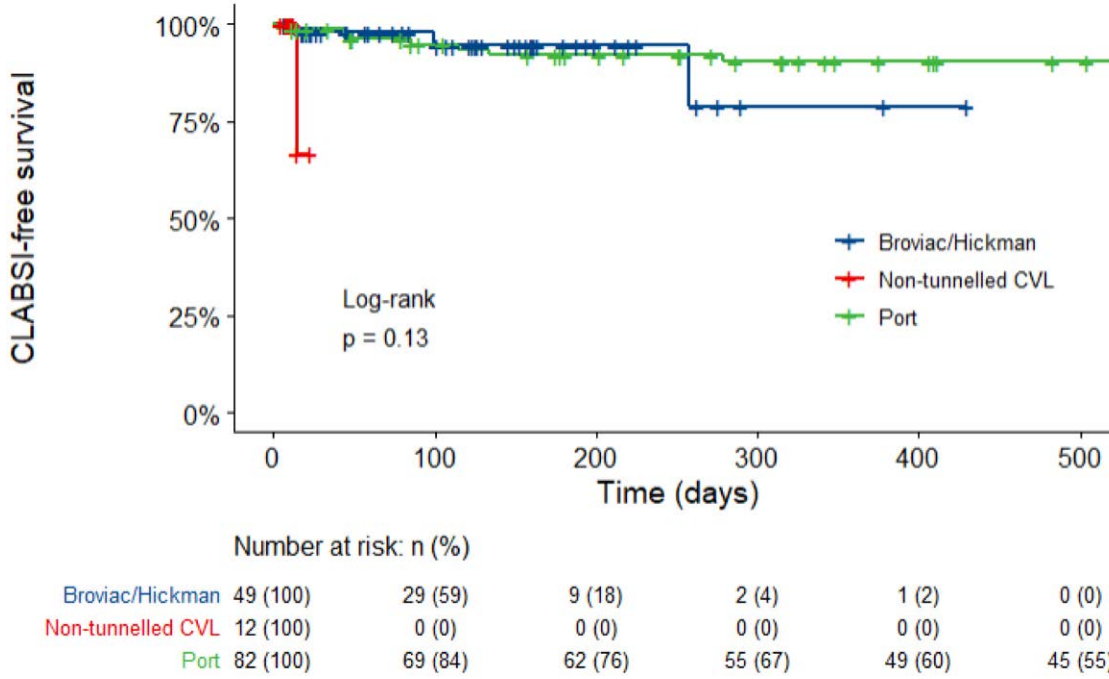

FIGURE 2. Survival curves showing CLABSI-free survival of CVLs based on Kaplan-Meier estimates. No CLABSIs occurred after 415 days from insertion, thus the x-axis has been restricted to 500 days. Broviac/Hickman: Tunneled CVL. Port: Implantable venous access system. CLABSI indicates central line–associated blood stream infection; CVL, central venous line. full color online

lack of repeated blood cultures on CLABSI rates, we included the definition of possible CLABSIs. Even after the addition of possible CLABSI cases, the overall CLABSI rate remains lower than most reported CLABSI rates (0.34/1000 line-days). Patients requiring bone marrow transplantation, a high-risk group for CLABSIs, are however partly treated abroad. CLABSI episodes occurring within the first weeks after transplantation before returning back to Iceland, are therefore missing from our data. If this has occurred, the number will be small and have minimal effects on total CLABSI rates. Effective staff training and a relatively small group that handles all CVLs is also likely to contribute to low CLABSI rates.

The subclavian vein was the most common insertion site (131/138, 94.9%). Previous studies have shown conflicting results regarding the safest insertion site, with 1 reporting increased risk of CLABSI with insertion in the subclavian vein[10] and other not showing insertion sites to be associated with CLABSI incidence.[5] Although some studies have shown increased CLABSI risk if the line is inserted at time of severe neutropenia,[3,15] we did not find any such association, which is in accordance with a study by Junqueira et al[18] on neutropenia and CLABSI risk.

Gram-positive bacteria were the dominant causative organisms, causing 87% of the CLABSI episodes. That is slightly higher than previous studies have reported, with Gram-positive bacteria causing 55–72% of episodes, Gram-negative 20–32%, and fungi 3–10%.[8,10,12] *S. aureus* was the most common pathogen, with a significant increase in the last 2 years of our study, followed by CoNS, causing 21.4% of CLABSI episodes. CoNS are frequently the most common bacteria causing CLABSIs.[1,8,18,25] In our study, 5/6 episodes of possible CLABSI were caused by CoNS and they would have been the most common pathogen had they been included as CLABSIs. The difference in the most common CLABSI pathogens is likely explained by differences in definitions, although epidemiologic variability between countries and centers could also partly explain the difference. *Candida parapsilosis* has been reported as the most common fungi isolated from CLABSI[2,12,25] and it was the only confirmed fungal bloodstream infection in our study.

There are some limitations to the study. Despite the study period being relatively long, due to the small population in Iceland only 143 CVLs were placed in children with malignancies. It is possible that insertion of some CVLs (most likely PICCs) may have been missed due to lack of registration and a separate electronic record keeping software utilized in the intensive care unit for a part of the study period. However, all blood cultures from the study group during the study period were included, so it is highly unlikely that any CLABSIs were missed for these reasons. As previously mentioned, some CLABSIs may have been missed by not repeating blood cultures within 48 hours of positive ones but even when including possible CLABSIs, the CLABSI rates remained very low.

CONCLUSION

CLABSI rates in children with malignancies in Iceland are low. Efficient staff training, few and selected members of staff providing CVL care and high numbers of implantable ports are potential explanations. Studies on CLABSI rate and risk factors are highly variable due to different study populations, CVL types included, and definitions of infections, making comparison difficult. We will continue to closely monitor the CLABSI rates in our hospital and place emphasis on continuous staff training in handling CVLs in immunocompromised patients.

REFERENCES

1. van den Bosch CH, van der Bruggen JT, Frakking FNJ, et al. Incidence, severity and outcome of central line related complications in pediatric oncology patients; a single center study. *J Pediatr Surg*. 2019;54:1894–1900.
2. Cesaro S, Cavaliere M, Pegoraro A, et al. A comprehensive approach to the prevention of central venous catheter complications: results of 10-year prospective surveillance in pediatric hematology-oncology patients. *Ann Hematol*. 2016;95:817–825.

3. Nam SH, Kim DY, Kim SC, et al. Complications and risk factors of infection in pediatric hemato-oncology patients with totally implantable access ports (TIAPs). *Pediatr Blood Cancer*. 2010;54:546–551.
4. Goudie A, Dynan L, Brady PW, et al. Attributable cost and length of stay for central line-associated bloodstream infections. *Pediatrics*. 2014;133:e1525–e1532.
5. Moon HM, Kim S, Yun KW, et al. Clinical characteristics and risk factors of long-term central venous catheter-associated bloodstream infections in children. *Pediatr Infect Dis J*. 2018;37:401–406.
6. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis*. 2009;49:1–45.
7. Hecht SM, Ardura MI, Yildiz VO, et al. Central venous catheter management in high-risk children with bloodstream infections. *Pediatr Infect Dis J*. 2020;39:17–22.
8. Wylie MC, Graham DA, Potter-Bynoe G, et al. Risk factors for central line-associated bloodstream infection in pediatric intensive care units. *Infect Control Hosp Epidemiol*. 2010;31:1049–1056.
9. Wilson MZ, Rafferty C, Deeter D, et al. Attributable costs of central line-associated bloodstream infections in a pediatric hematology/oncology population. *Am J Infect Control*. 2014;42:1157–1160.
10. Carter JH, Langley JM, Kuhle S, et al. Risk factors for central venous catheter-associated bloodstream infection in pediatric patients: a Cohort Study. *Infect Control Hosp Epidemiol*. 2016;37:939–945.
11. Adler A, Yaniv I, Steinberg R, et al. Infectious complications of implantable ports and Hickman catheters in paediatric haematology-oncology patients. *J Hosp Infect*. 2006;62:358–365.
12. Kelly M, Conway M, Wirth K, et al. Moving CLABSI prevention beyond the intensive care unit: risk factors in pediatric oncology patients. *Infect Control Hosp Epidemiol*. 2011;32:1079–1085.
13. Allen RC, Holdsworth MT, Johnson CA, et al. Risk determinants for catheter-associated blood stream infections in children and young adults with cancer. *Pediatr Blood Cancer*. 2008;51:53–58.
14. Viana Taveira MR, Lima LS, de Araújo CC, et al. Risk factors for central line-associated bloodstream infection in pediatric oncology patients with a totally implantable venous access port: a cohort study. *Pediatr Blood Cancer*. 2017;64:336–342.
15. Berrueco R, Rives S, Català A, et al. Prospective surveillance study of blood stream infections associated with central venous access devices (port-type) in children with acute leukemia: an intervention program. *J Pediatr Hematol Oncol*. 2013;35:e194–e199.
16. CDC/NHSH Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central line-associated Bloodstream Infection). Centers for Disease Control and Prevention, and the National Healthcare Safety Network. 2018.
17. Miliaraki M, Katzilakis N, Chranioti I, et al. Central line-associated bloodstream infection in childhood malignancy: single-center experience. *Pediatr Int*. 2017;59:769–775.
18. Junqueira BL, Connolly B, Abla O, et al. Severe neutropenia at time of port insertion is not a risk factor for catheter-associated infections in children with acute lymphoblastic leukemia. *Cancer*. 2010;116:4368–4375.
19. Rinke ML, Chen AR, Bundy DG, et al. Implementation of a central line maintenance care bundle in hospitalized pediatric oncology patients. *Pediatrics*. 2012;130:e996–e1004.
20. Tomlinson D, Mermel LA, Ethier MC, et al. Defining bloodstream infections related to central venous catheters in patients with cancer: a systematic review. *Clin Infect Dis*. 2011;53:697–710.
21. Rinke ML, Milstone AM, Chen AR, et al. Ambulatory pediatric oncology CLABSIs: epidemiology and risk factors. *Pediatr Blood Cancer*. 2013;60:1882–1889.
22. Bundy DG, Gaur AH, Billett AL, et al.; Children's Hospital Association Hematology/Oncology CLABSI Collaborative. Preventing CLABSIs among pediatric hematology/oncology inpatients: national collaborative results. *Pediatrics*. 2014;134:e1678–e1685.
23. Gaur AH, Bundy DG, Werner EJ, et al.; Children's Hospital Association Childhood Cancer & Blood Disorders Network (CCBDN). A prospective, holistic, multicenter approach to tracking and understanding bloodstream infections in pediatric hematology-oncology patients. *Infect Control Hosp Epidemiol*. 2017;38:690–696.
24. Simon A, Furtwängler R, Graf N, et al. Surveillance of bloodstream infections in pediatric cancer centers—what have we learned and how do we move on? *GMS Hyg Infect Control*. 2016;11:Doc11.
25. Advani S, Reich NG, Sengupta A, et al. Central line-associated bloodstream infection in hospitalized children with peripherally inserted central venous catheters: extending risk analyses outside the intensive care unit. *Clin Infect Dis*. 2011;52:1108–1115.