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Perioperative neutropenia is not an independent risk factor for infectious complications of central venous line placement in children: A propensity score-matched analysis☆,☆☆,★

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ABSTRACT

Background: The infectious risk of central venous line (CVL) placement in children with neutropenia (absolute neutrophil count [ANC] <500/mm^3) is not well defined. This study aims to investigate the early (≤30 days) and late (>30 days) infectious complications of CVLs placed in pediatric patients with and without neutropenia.
Methods: A retrospective review was conducted of all CVLs placed by pediatric surgeons at two institutions from 2010 to 2017. Multivariable logistic regression was performed to identify risk factors for line infection. Propensity score-matched cohorts of patients with and without neutropenia were compared in a 1:1 ratio. Wilcoxon rank-sum, Chi-square, Fisher's exact, and log-rank tests were also performed.
Results: Review identified 1,102 CVLs placed in 937 patients. Fifty-four patients were neutropenic at the time of placement. Multivariable analysis demonstrated tunneled catheters and subclavian access as associated with line infection. The propensity score-matched cohort included 94 patients, 47 from each group. Demographic and pre-operative data were similar between the groups ($p > 0.05$). Patients with neutropenia were no more likely to develop early (4.3% vs. 2.1%, $p = 1.000$) or late (19.1% vs. 17.0%, $p = 1.000$) infectious complications than patients without neutropenia, with similar median time to infection (141 vs. 222 days, $p = 0.370$).
Conclusion: A policy of selective CVL placement in neutropenic patients with standardized postoperative line maintenance is safe. Future directions include defining criteria by which neutropenic patients could be prospectively selected for safe CVL placement.
Level of Evidence: II – Retrospective cohort study.

Placing durable central venous access in immunocompromised children has been associated with an elevated risk of adverse events [1]. Specifically, children with neutropenia (absolute neutrophil count [ANC] <500/mm^3) are felt to be at a higher risk for infection, traditionally resulting in the postponement of invasive procedures until recovery of neutrophils [2]. However, the practice of delaying central venous line (CVL) placement during periods of neutropenia may be associated with delays in chemotherapy [3], multiple venipunctures or complications from alternative forms of venous access [4]. Ideally, tunneled or implantable CVLs should be performed as soon as possible, but this must be balanced with the infectious risk associated with neutropenia in these patients.

The true rate of infectious complications following CVL placement in children with neutropenia is not well defined. Clinical precedent and level III evidence have propagated the concern that neutropenia at the time of placement is a significant risk factor for central line infection [5,6], fostering the current pediatric surgical practice of avoiding placement of a semi-permanent catheter in these patients. Recent studies have challenged this practice and demonstrate that neutropenia at the time of CVL placement may not be a risk factor for early infectious complications [7,8]. A crucial part of the ongoing debate lies within the

Abbreviations: CVL, Central Venous Line; ANC, Absolute Neutrophil Count; CDC, Center for Disease Control & Prevention; NHSN, National Health Safety Network; PSM, Propensity Score-Matched; AUROC, Area Under the Receiver Operating Characteristic Curve; IQR, Inter-Quartile Range.

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heterogeneous nature of the neutropenic pediatric population, making direct translation to clinical practice difficult.

In this study, we investigate the association between neutropenia at the time of CVL placement and early or late infectious complications in immunocompromised children. Specifically, we perform a retrospective multivariable analysis to identify risk factors for line infection, followed by a propensity score-matched analysis of children with and without neutropenia at two pediatric hospitals over an 8-year period in an effort to compare two groups of patients with similar baseline characteristics. We hypothesize that neutropenia at the time of CVL placement is not an independent risk factor of early infectious complications in immunocompromised children.

1. Material and methods

1.1. Data source and patient selection

After institutional review (Oregon Health & Science University IRB #16777, Legacy Emanuel Hospital IRB #1496), children who underwent CVL placement during the study period (January 2010 – June 2017) were retrospectively identified based on Common Procedural Terminology codes (36555–36561), which correspond to centrally inserted, tunneled and non-tunneled, central venous catheters, with and without a subcutaneous port. All tunneled catheters without a subcutaneous port were cuffed (e.g. Broviac, Hickman, Leonard). Our institutional practice has historically been to selectively place central venous catheters in children with neutropenia on a case by case basis. Electronic medical records were reviewed for demographic information, type of CVL, vessel accessed, indications for line placement, preoperative absolute neutrophil count, postoperative infectious complications, clinical outcomes, duration of line and indication for removal. Central venous lines placed by 15 pediatric surgeons, each with at least 2 years of pediatric surgical experience, at two pediatric institutions were included. Lines placed by interventional radiology, those that were peripherally inserted, CVLs placed in the lower extremities or those with inadequate documentation were excluded from analysis.

1.2. Definitions and Outcomes

All patient records were reviewed until the CVL was removed, the patient was lost to follow-up, the study end date or patient death. Neutropenia was defined as an absolute neutrophil count (ANC) less than 500/mm^3. Preoperative neutropenia was determined based on the most recent laboratory data prior to central line placement. If the most recent ANC available was collected greater than 7 days prior the procedure, the data was noted as missing. Central line infections were determined based on the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) definition of central line-associated bloodstream infection [9]. A single positive blood culture identifying an organism that is not related to infection at another site or two positive blood cultures identifying the same commensal bacteria in the setting of clinical signs of infection generally satisfy this definition. Central line infections identified within 30 days of placement were categorized as early, and any line infection identified greater than 30 days from placement was categorized as late.

The tunneled central venous catheters placed in this study were placed in the operating room with image guidance. Postoperatively, CVLs were maintained according to institutional protocol. Subcutaneous ports were accessed in a clean fashion and access was changed weekly. Tunneled catheters were similarly accessed in a clean fashion, needleless connectors were changed every 96 hours, and overlying dressings were changed every 48 hours or weekly depending on the dressing type.

The primary outcome of interest in this study was the incidence of early and late central line infections in children with and without neutropenia. Secondary outcomes include median time to central line infection and rate of CVL removal for infectious reasons.

The population of children who receive central venous access at our institutions is a considerably heterogeneous group with varying indications for line placement and incidences of neutropenia. To decrease the potential bias present in a direct comparison of children with and without neutropenia sourced from the entire cohort, propensity score-matching was employed to identify a group of subjects with similar baseline characteristics to our subjects with neutropenia.

1.3. Multivariable analysis

Bivariate analysis was performed to identify preoperative risk factors associated with subsequent central line infection. Risk factors included in the multivariable analysis were identified based on a bivariate $p < 0.20$. Association of risk factors with subsequent line infection was determined by multivariable logistic regression, with significance defined as $p < 0.05$.

1.4. Propensity score matching

Propensity score-matching (PSM) was performed with a non-parsimonious logistic regression model based on six demographic, operative and clinical variables. The outcome of the model was neutropenia with two levels (yes/no). Matching variables were chosen from available preoperative demographic data based on ability of said variable to contribute to the likelihood of neutropenia at the time of CVL placement or the likelihood of postoperative line infection. The independent variables used for matching were hospital where the procedure was performed, age, gender, vessel (internal jugular or subclavian vein), procedure (subcutaneous port or subcutaneously tunneled external central venous catheter), and indication for line placement (acute lymphoblastic leukemia, acute myeloid leukemia, solid organ malignancy, malignant neoplasm of the bones, aplastic anemia, myelodysplastic syndrome or primary immunodeficiency). Patients with and without neutropenia were matched in a 1:1 fashion. Patients missing data in the propensity score estimation were excluded from matching. Patient matching occurred through a nearest neighbor search and patients who were propensity score outliers, where a match could not be identified, were excluded from analysis.

1.5. Statistical analysis

Descriptive statistics were tabulated. Non-parametric data are reported as medians with interquartile ranges (IQR). Continuous variables were not normally distributed, and therefore differences between neutropenic groups were compared using a Wilcoxon rank-sum test. Differences in the time (days) to central line infection between groups was compared with a log-rank test from a Kaplan–Meier. Categorical variables were analyzed with a chi-square test for independence or Fisher Exact test for small samples. Significance was defined at $p < 0.05$. Analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY, USA).

2. Results

2.1. Demographic data

Retrospective review identified 1,102 central venous lines placed in 937 patients during the study period. Patients were subsequently excluded from multivariable analysis and propensity score matching based on their likelihood of neutropenia prior to CVL placement (Fig. 1). Ultimately, 590 patients underwent bivariate and multivariable analysis. Demographic data for this cohort can be found in Table 1. Fifty-four (9%) patients in the cohort were neutropenic at the time of placement. In this group, 87 (15%) patients developed a

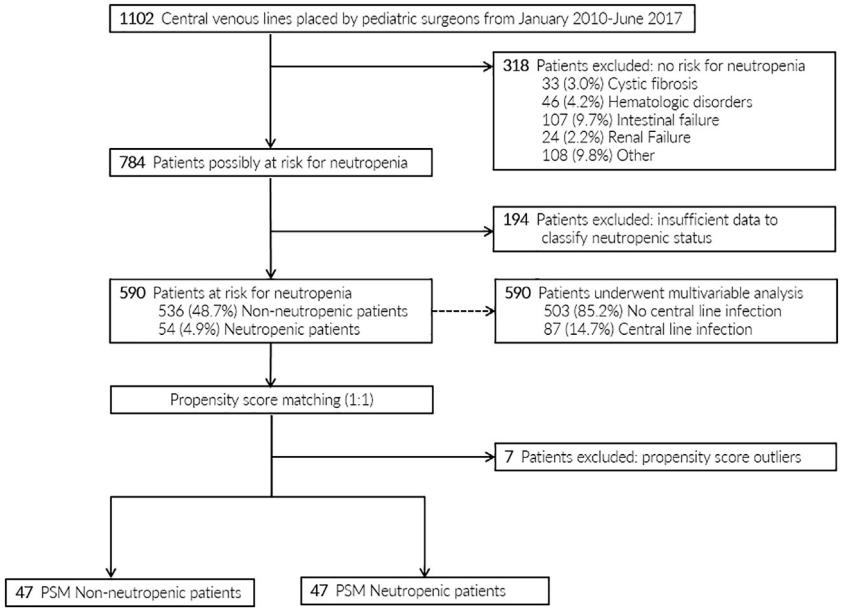

Fig. 1. Flowchart of patient selection for propensity score matching (PSM) and multivariable analysis. Neutropenic patients (absolute neutrophil count <500/mm^3) were identified from an initial cohort of 1,102 children who underwent central line placement. Those at risk for neutropenia underwent multivariable regression analysis and PSM. To identify PSM cohorts, neutropenic patients were matched 1:1 with non-neutropenic patients who were at a similar risk of neutropenia based on a non-parsimonious logistic regression model.

central line infection over the course of their treatment, while their line was in place.

2.2. Bivariate and multivariable analysis results

Bivariate analysis identified age ($p = 0.018$), vessel ($p = 0.032$), indication ($p < 0.001$), procedure ($p < 0.001$), and neutropenia ($p = 0.001$) as significant risk factors for central line infection (Table 1). These variables were chosen for inclusion in the multivariable logistic regression model to identify risk factors for line infection. Regression analysis identified only two variables as significantly associated with line infection (Table 2); tunneled central lines (e.g. Hickman, Broviac) increased the risk of subsequent infection (OR 4.9, 95% CI 2.9–8.4) and jugular vein access was protective (OR 0.5, 95% CI 0.3–0.8).

Further investigation of these findings, with propensity score matching, was employed to control for multiple covariates and analyze the risk factor of interest, neutropenia at the time of line placement.

2.3. Propensity score matching demographics

Five hundred ninety patients underwent PSM to identify a 1:1 sample of neutropenic and non-neutropenic patients. Forty-seven patients in each group comprise the PSM sample. Six patients with neutropenia were excluded from the PSM sample as propensity score outliers. Prior to matching, age, indication and procedure were statistically different between the neutropenic and non-neutropenic groups (Table 3). After PSM, the baseline characteristics between neutropenic and non-neutropenic groups were not significantly different (Table 4). The propensity score model generated a c-statistic (area under the receiver operating characteristic curve [AUROC]) of 0.81, indicating a strong ability by the model to discriminate between the two groups.

Median time of follow-up was 258 days (IQR 136–851 days) and no differences were noted in the neutropenic and non-neutropenic PSM

Table 1
Patient characteristics of those at risk for neutropenia. Preoperative characteristics compared for those who did and did not develop a central venous line (CVL) infection. IQR: Inter-quartile range.

	Total (%)	No line infection (%)	Line infection (%)	*p*
	N = 590	N = 503	N = 87	
Age, median (IQR), years	5.2 (2.6–10.9)	5.5 (2.8–11.2)	3.8 (1.8–8.8)	0.018
Male	342 (58.0)	296 (58.8)	46 (52.9)	0.297
Vessel				0.032
Jugular	351 (59.5)	310 (61.6)	41 (47.1)	
Subclavian	239 (40.5)	193 (38.4)	46 (52.9)	
Indication				<0.001
Acute lymphoblastic leukemia	234 (39.7)	209 (42.0)	25 (28.7)	
Acute myeloid leukemia	109 (18.5)	93 (18.7)	16 (18.4)	
Solid organ malignancy	151 (25.6)	43 (8.6)	17 (19.5)	
Malignant neoplasm of the bones	50 (8.5)	44 (8.8)	6 (6.9)	
Aplastic anemia	16 (2.7)	11 (2.2)	5 (5.7)	
Myelodysplastic syndrome	9 (1.5)	6 (1.2)	3 (3.4)	
Primary immunodeficiency	18 (2.8)	10 (2.0)	6 (6.9)	
Procedure				<0.001
Subcutaneous port	419 (71)	385 (77.0)	34 (39.1)	
Tunneled CVL	168 (28.5)	115 (23.0)	53 (60.9)	
Neutropenic at time of placement	54 (9.2)	38 (7.6)	16 (18.4)	0.001

Table 2
Results of the multivariable analysis. Multivariable logistic regression was performed using risk factors for line infection identified on bivariate analysis. CVL: central venous line. 95% CI: 95% confidence interval.

	OR	95% CI	*p*
Age	0.981	0.935–1.029	0.426
Tunneled CVL	4.898	2.853–8.411	<0.001
Neutropenia at the time of placement	1.529	0.727–3.213	0.263
Jugular vein access	0.515	0.313–0.847	0.009
Indication			
Acute lymphoblastic leukemia	0.679	0.187–2.467	0.557
Acute myeloid leukemia	0.552	0.149–2.040	0.373
Solid organ malignancy	0.864	0.231–3.240	0.829
Malignant neoplasm of the bones	0.883	0.191–4.068	0.873
Myelodysplastic syndrome	1.067	0.168–6.798	0.945
Primary immunodeficiency	1.379	0.274–6.955	0.697

Table 3
Patient characteristics prior to propensity score matching. Age, sex, vessel accessed, indication for central venous line, and type of catheter implanted are reported. Data is stratified based on preoperative neutropenia, defined as an absolute neutrophil count less than 500 per cubic millimeter. Significance is defined at $p < 0.05$. IQR: inter-quartile range. CVL: central venous line. ANC: absolute neutrophil count. mm^3: cubic millimeters.

	Total (%)	ANC >500/mm^3 (%)	ANC <500/mm^3 (%)	p
	N = 590	N = 536	N = 54	
Age, median (IQR), years	5.2 (2.6–10.9)	5.3 (2.8–11.1)	3.6 (1.2–9.35)	0.012
Male	342 (58.0)	314 (58.6)	28 (51.9)	0.342
Vessel				0.584
Jugular	351 (59.5)	324 (60.5)	27 (50.0)	
Subclavian	239 (40.5)	212 (39.5)	27 (50.0)	
Indication				<0.001
Acute lymphoblastic leukemia	234 (39.7)	211 (39.4)	23 (42.6)	
Acute myeloid leukemia	109 (18.5)	99 (18.5)	10 (18.5)	
Solid organ malignancy	151 (25.6)	148 (27.7)	3 (5.7)	
Malignant neoplasm of the bones	50 (8.5)	48 (9.0)	2 (3.7)	
Aplastic anemia	16 (2.7)	8 (1.5)	8 (14.8)	
Myelodysplastic syndrome	9 (1.5)	5 (0.9)	4 (7.4)	
Primary immunodeficiency	18 (2.8)	12 (2.3)	4 (7.5)	
Procedure				<0.001
Subcutaneous port	419 (71)	397 (74.1)	22 (40.7)	
Tunneled CVL	168 (28.5)	136 (25.4)	32 (59.3)	

groups (280 vs. 248 days, $p = 0.266$). During the study period, 14 subjects (14.9%) died with a CVL in place (5 neutropenic vs. 9 non-neutropenic, $p = 0.247$) and 7 CVLs (7.4%) were in place at the end of the study period (3 neutropenic vs. 4 non-neutropenic, $p = 0.694$). Four subjects (4.3%) were lost to follow-up (2 neutropenic vs. 2 non-neutropenic, $p = 1.000$).

Table 4
Patient characteristics after propensity score matching. Age, sex, vessel accessed, indication for central venous line, and type of catheter implanted are reported. Data is stratified based on preoperative neutropenia, defined as an absolute neutrophil count less than 500 per cubic millimeter. Significance is defined at $p < 0.05$. IQR: inter-quartile range. CVL: central venous line. ANC: absolute neutrophil count. mm^3: cubic millimeters.

	Total (%)	ANC >500/mm^3 (%)	ANC <500/mm^3 (%)	p
	N = 94	N = 47	N = 47	
Age, median (IQR), years	4.4 (1.7–8.7)	4.5 (2.3–7.0)	3.9 (1.2–10.1)	0.642
Male	57 (60.6)	30 (63.8)	27 (57.4)	0.527
Vessel				0.588
Jugular	46 (48.9)	24 (51.1)	22 (46.8)	
Subclavian	48 (51.1)	23 (48.9)	25 (53.2)	
Indication				0.603
Acute lymphoblastic leukemia	44 (46.8)	22 (44.9)	22 (44.9)	
Acute myeloid leukemia	14 (14.9)	5 (10.6)	9 (19.1)	
Solid organ malignancy	8 (8.5)	5 (10.6)	3 (6.4)	
Malignant neoplasm of the bones	4 (4.3)	2 (4.3)	2 (4.3)	
Aplastic anemia	8 (8.5)	6 (12.8)	2 (4.3)	
Myelodysplastic syndrome	5 (5.3)	1 (2.1)	4 (8.5)	
Primary immunodeficiency	9 (9.6)	5 (10.6)	4 (8.5)	
Other	2 (2.1)	1 (2.1)	1 (2.1)	
Procedure				0.409
Subcutaneous port	48 (51.1)	26 (55.3)	22 (46.8)	
Tunneled CVL	46 (48.9)	21 (44.7)	25 (53.2)	

2.4. Outcomes

Early infectious complications, following CVL placement, were uncommon and no more likely to develop in patients with neutropenia (4.3% with neutropenia vs. 2.1% without, $p = 1.000$) (Table 5). Similarly, late infectious complications, greater than 30 days from placement, were no more likely to occur in our neutropenic cohort (19.1% with neutropenia vs. 17.0% without, $p = 0.370$). Ultimately, 9 CVLs were removed for infectious complications, without an observed significant difference between neutropenic and non-neutropenic groups (5 vs. 4, $p = 1.000$). Median time to infection (149 days [50–279], IQR) was also similar between the groups in our PSM cohort (Fig. 2).

3. Discussion

In this study we demonstrate that the incidence and rate of early or late infectious complications following CVL placement is statistically similar between well-matched neutropenic and non-neutropenic groups. These findings are in concordance with other studies on the topic [8,10] but represent the first multicenter, propensity score-matched analysis of this kind in this population.

This study adds to a growing collection of evidence that suggests that neutropenia at the time of central venous access is not an independent risk factor for postoperative infectious complications. It is notable that our early infectious rate of 4.3% in neutropenic patients is considerably lower than the widely reported rate of 9–15% in this population [7,8,10,11]. We suspect this difference is due to the rigid adherence to a standard central line maintenance policy at our two institutions. Additionally, while our late infectious rate of 19% in neutropenic patients is comparable to similar studies [10], it is clear that patients with neutropenia are at a higher risk of infection over the life of a CVL when compared to the non-immunocompromised population, as the rate of late infections is reported at 12.8% in immunocompetent children [12]. The additional risk in neutropenic patients appears to not be associated with the clinical situation at the time of placement – as evidenced by a median time to infection of 141 days in our study – but rather the additional infectious hazard of an internal foreign body in the setting of future transient bacteremia, as proposed by some studies [7]. Lastly, central line removal for infectious reasons represents a nuanced decision made in the presence of many variables, as evidenced by the wide range reported in the literature of 5–44% [8,10,11] to which our overall rate of 9.6% appears to be comparable. Despite broad agreement with prior studies, our PSM study design uniquely allowed us to isolate the risk factor of neutropenia, in ideally matched populations, so that a direct comparison on postoperative infectious complications can be made. Ultimately, this confirmed the study's hypothesis that preoperative neutropenia is not an independent risk factor for subsequent CVL infection.

Table 5
Infection rates following central venous line placement in a propensity score-matched cohort of children with and without neutropenia. Incidence of central line infection before and after 30 days from placement is noted. Additionally, rate of line removal for infectious reasons and median time to line infection are reported. Significance is defined at $p < 0.05$. IQR: inter-quartile range. ANC: absolute neutrophil count. mm^3: cubic millimeters. CVL: central venous line.

	Total (%)	ANC >500/mm^3 (%)	ANC <500/mm^3 (%)	p
	N = 94	N = 47	N = 47	
Any infection	20 (21.3)	9 (19.1)	11 (23.4)	0.802
Infection <30 days	3 (3.2)	1 (2.1)	2 (4.3)	1.000
Infection >30 days	17 (18.1)	8 (17.0)	9 (19.1)	1.000
Time to infection, median (IQR), days	148.5 (50.0–278.5)	222.0 (80.0–311.0)	141.0 (41.0–217.0)	0.370

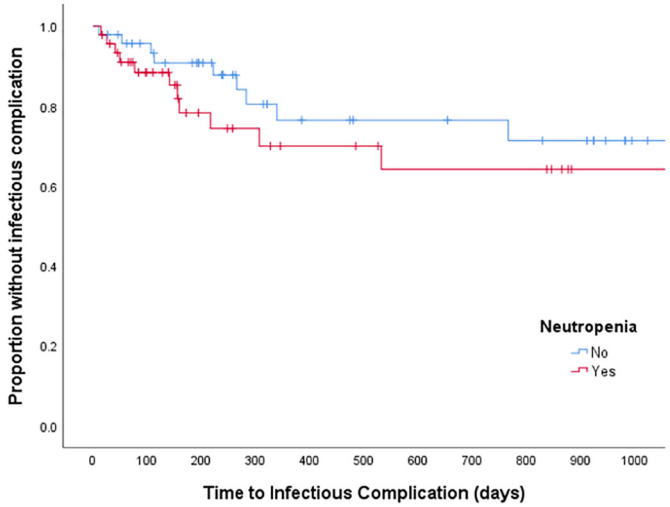

Fig. 2. Time to infectious complications in neutropenic propensity score-matched cohort. Time to infectious complication was plotted in neutropenic (red) and non-neutropenic (blue) patients on a Kaplan–Meier curve. Median time to infection was 141 vs. 222 days ($p = 0.370$), in neutropenic and non-neutropenic patients, respectively. Neutropenia is defined as absolute neutrophil count $<500/mm^3$.

We recognize that there are some limitations with our study, notably concerning our retrospective study design. Propensity score-matching was chosen specifically to limit the influence of confounders inherent in our total population; however, this may have increased the influence of random error in our analysis. A reduction in sample size after PSM can theoretically increase this risk, but we suspect the overall advantage gained from PSM is greater than the possible disadvantage of subsequent random error bias. Despite a rigorous PSM process, the possibility of persistent imbalance in the baseline characteristics of the cohorts remains. While this risk, either from incomplete matching or from unmeasured demographic variables, cannot be eliminated, we believe that significant risk factors for postoperative infection (hospital where the procedure was performed, age, vessel accessed, type of device placed and preoperative diagnosis) have been considered. Unfortunately, due to the considerable variety and number of pediatric surgeons performing the procedures, surgeon was unable to be used as a matching variable and we recognize that this omission may expose the analysis to a persistent confounder. The identification of a source of bacteremia in patients undergoing chemotherapy with a CVL in place is often difficult. Practical clinical care decisions further confound this process, leading to a number of NHSN-classified line infections in our study where cause was attributed to the catheter, though the possibility is high that bacterial translocation from a mucosal barrier defect was the pathogenesis. For this reason, even the reported rate of infectious complications in our study is likely an over-estimate of the true CVL infectious rate attributable to preoperative factors. Lastly, we recognize that there exists an inherent selection bias evident in the small percentage of patients with neutropenia who underwent central venous access in our study. The retrospective nature of our study precludes complete omission of this bias, but our study design, to include PSM, was chosen in an attempt to reduce this bias.

4. Conclusions

Our findings did not demonstrate an association between preoperative neutropenia and subsequent early or late central line infections. Therefore, we believe a policy of selective CVL placement in children with neutropenia, in the setting of standardized postoperative line maintenance, is safe. Future investigation is needed in this topic to define criteria by which neutropenic patients could be prospectively selected for safe line placement.

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Patient consent

This study was exempted from obtaining individual patient consent as approved by the Oregon Health & Science University and Legacy Emanuel Hospital Institutional Review Boards. This report does not contain any personal information that could lead to identification of any patients.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Conflict of interest

The following authors have no financial disclosures: AJC, KVM, ED, SK, MWB, DN, MCH, NAH.

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