The Incidence of Catheter-Associated Venous Thrombosis in Noncritically Ill Children

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KEY WORDS
central venous catheter (CVC), peripherally inserted central catheter (PICC), port-a-cath, thrombosis, deep vein thrombosis, venous thromboembolism

ABBREVIATIONS
CI: confidence interval
CVC: central venous catheter
IBD: inflammatory bowel disease
IQR: interquartile range
OR: odds ratio
PICC: peripherally inserted central catheter
SBS: short bowel syndrome
TPN: total parenteral nutrition

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abstract

OBJECTIVE: Previous studies estimated the incidence of catheter-associated venous thrombosis to be between 2% and 81%. Our goals were to define the incidence rate of catheter-related thrombosis in a hospitalized, noncritically ill, pediatric population and to determine modifiable factors that alter the risk of thrombosis.

METHODS: A retrospective cohort study was performed at the North Carolina Children’s Hospital from 2009 to 2012. Chart review was performed with extraction of patient characteristics and line-related variables. Presence of symptomatic catheter-associated venous thrombosis was the primary outcome. Bivariable analysis and multivariable logistic regression were used to explore associations between line-related variables and thrombosis.

RESULTS: A total of 1135 lines were placed in 815 patients for 118,023 catheter-days. Thirty-six were complicated by venous thrombosis (3.2%) yielding a rate of 0.3 events per 1000 catheter-days. In multivariable analysis, increasing age (odds ratio [OR] 1.08, 95% confidence interval [CI] 1.03–1.13; P = .002), renal dialysis (OR 3.2, 95% CI 1.09–9.66; P = .035), and a diagnosis of inflammatory bowel disease or short bowel syndrome (OR 4.3, 95% CI 1.2–15.0; P = .02) were associated with increased risk of thrombosis. Modifiable risk factors, such as line site, size, and lumens, were not significantly associated with thrombosis. No thromboembolic events were observed.

CONCLUSIONS: We observed a lower incidence rate of catheter-associated venous thrombosis than in most previous reports. No modifiable characteristics altered the risk of thrombosis. Additional investigation of measures to prevent thrombosis is warranted in higher-risk populations, such as patients undergoing dialysis or patients with inflammatory bowel disease.

More than 5 million central venous catheters (CVCs) are placed annually in the United States1 and are necessary in the treatment of pediatric patients. Central venous access is often required in children for total parenteral nutrition (TPN), prolonged antibiotics, chemotherapy, and frequent blood sampling.

Although these devices are essential in the care of patients, their use is associated with complications, such as infection, dysfunction, or obstruction. These complications have been reported in as many as 65% of central lines in pediatric patients.2 Additionally, the incidence of venous thrombosis is increasing among pediatric patients.3 More than 50% of venous thrombosis in children is related to CVCs, making catheter placement the single most significant risk factor for thrombus formation.
in children.\textsuperscript{4,5} Previously reported incidence rates of catheter-associated venous thrombosis in pediatric patients have been widely divergent, from 1.7\% to as high as 81.0\%.\textsuperscript{2,6–31} Many of these studies considered specific subpopulations of patients, such as those with hemophilia, cancer, or cystic fibrosis, or patients receiving TPN. Others included small-sample populations, primarily outpatients or critically ill patients (Table 1).

Line placement in intensive care settings is driven by an acute need for secure access and rapid medication administration. This risk-benefit balance shifts in patients with less-acute illness, necessitating a thoughtful discussion of the risks and benefits of line placement with the patient and the patient’s guardians. To better inform this discussion, we sought to determine the rate of catheter-associated venous thrombosis in noncritically ill patients who were hospitalized at the time of line placement at a tertiary pediatric hospital. Additionally, modifiable line characteristics, such as line type, line size, and location of placement were assessed to determine their relationship with thrombosis. Finally, we attempted to identify populations in whom line placement may carry increased risk.

**METHODS**

We conducted a retrospective cohort study to determine the rate of catheter-associated thrombosis and the risk factors for venous thrombosis development in children who had undergone placement of central venous lines. Billing data were queried by using current procedural terminology codes (Supplemental Table 5) to identify all pediatric patients (<18 years old) who had a central line placed from 2009 through 2011. Outcomes were assessed for a year after the placement time frame, through December 2012. Patients were excluded if they were critically ill at the time of line placement, defined by the unit to which the patient was admitted and the service providing their care or if they were outpatient status when the line was placed. Chart review was performed for each identified patient with extraction of baseline patient characteristics (age, gender, underlying diagnosis, and reason for line placement) and line-related variables (type of line, size and location of placement). Subsequent clinical outcomes were assessed with the primary outcome being the presence of symptomatic catheter-associated venous thrombosis whether located in either a superficial or deep vein. Both occlusive and nonocclusive thromboses were considered a positive outcome. Imaging was obtained in evaluation

**TABLE 1** Previous Studies Reporting the Incidence of Catheter-Associated Venous Thrombosis in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Patient Population</th>
<th>Catheter-Associated Thrombosis Incidence Rate, %</th>
<th>Thrombosis/1000 Catheter-Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aitken et al 2000</td>
<td>65</td>
<td>Children with cystic fibrosis</td>
<td>16</td>
<td>0.06</td>
</tr>
<tr>
<td>Beck et al 1998</td>
<td>93</td>
<td>Critically ill children</td>
<td>18</td>
<td>0.06</td>
</tr>
<tr>
<td>Casado-Flores et al 2001</td>
<td>268</td>
<td>Critically ill children</td>
<td>2.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Cotogni et al 2013</td>
<td>254</td>
<td>Children with cancer receiving TPN</td>
<td>1.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Diamanti et al 2007</td>
<td>60</td>
<td>Children with intestinal failure on TPN</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>Dubois et al 2007</td>
<td>214</td>
<td>PICC placed in consecutive children by radiology</td>
<td>9.4</td>
<td>3.85</td>
</tr>
<tr>
<td>Deerojananwong et al 1998</td>
<td>44</td>
<td>Children with cystic fibrosis and ports</td>
<td>9</td>
<td>0.06</td>
</tr>
<tr>
<td>Ettingshausen et al 2002</td>
<td>25</td>
<td>Children with hemophilia</td>
<td>32</td>
<td>0.06</td>
</tr>
<tr>
<td>Faustino et al 2013</td>
<td>101</td>
<td>Critically ill children</td>
<td>15.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Glaser et al 2001</td>
<td>24</td>
<td>Children with cancer</td>
<td>50</td>
<td>0.06</td>
</tr>
<tr>
<td>Hanslik et al 2008</td>
<td>90</td>
<td>Children with congenital heart disease</td>
<td>28</td>
<td>0.06</td>
</tr>
<tr>
<td>Journeycake et al 2001</td>
<td>15</td>
<td>Children with hemophilia</td>
<td>53</td>
<td>0.06</td>
</tr>
<tr>
<td>Journeycake et al 2006</td>
<td>287</td>
<td>Children with cancer</td>
<td>7</td>
<td>0.06</td>
</tr>
<tr>
<td>Kakzanov et al 2008</td>
<td>1321</td>
<td>Infants and children receiving long-term TPN</td>
<td>9.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Kanin and Young 2013</td>
<td>6915</td>
<td>Hospitalized children</td>
<td>2.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Male et al 2002</td>
<td>66</td>
<td>Children with leukemia</td>
<td>26</td>
<td>0.06</td>
</tr>
<tr>
<td>Male et al 2003</td>
<td>85</td>
<td>Children with leukemia</td>
<td>34</td>
<td>0.06</td>
</tr>
<tr>
<td>Male et al 2005</td>
<td>158</td>
<td>Children with central line placement</td>
<td>13</td>
<td>0.06</td>
</tr>
<tr>
<td>Pinon et al 2009</td>
<td>748</td>
<td>Children with hematolgy/oncology or immune disease</td>
<td>2</td>
<td>0.06</td>
</tr>
<tr>
<td>Price et al 2004</td>
<td>16</td>
<td>Children with hemophilia</td>
<td>81</td>
<td>0.06</td>
</tr>
<tr>
<td>Revel-Vilk et al 2010</td>
<td>262</td>
<td>Children with cancer</td>
<td>4.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Takemoto et al 2014</td>
<td>238</td>
<td>Hospitalized children</td>
<td>28</td>
<td>0.06</td>
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<tr>
<td>Vegting et al 2009</td>
<td>26</td>
<td>Children receiving TPN</td>
<td>32</td>
<td>0.06</td>
</tr>
<tr>
<td>Zitomersky et al 2013</td>
<td>104</td>
<td>Hospitalized children with IBD</td>
<td>3.8</td>
<td>0.06</td>
</tr>
</tbody>
</table>

-- not reported.
of symptoms, such as pain, swelling, erythema, or line dysfunction, according to standard clinical decision-making. Based on previous definitions, venous thrombosis was considered line-associated if it occurred in an anatomic location in proximity to the site of the line.\textsuperscript{10,18} All venous thromboses were confirmed radiographically by using Doppler ultrasound, venogram, echocardiogram, or magnetic resonance venography. Findings were confirmed by radiologists or cardiologists. Lines are not imaged as a standard to find asymptomatic venous thrombosis; all venous thromboses presented with symptoms first, followed by confirmation with imaging. The duration of line placement was recorded in number of days. Bivariable analysis and multivariable logistic regression were used to explore associations between line-related variables and venous thrombosis. Linear regression was used to explore associations between line-related variables and duration of line placement. The generalized estimating equation approach was used for all linear and logistic regression analyses to account for clustering induced by multiple lines per patient. All statistical analyses were performed by using Stata data analysis and statistical software (StataCorp, College Station, TX) or SAS 9.3 statistical software (SAS Institute, Inc, Cary, NC).

The study was approved by the University of North Carolina Institutional Review Board and the Ethics Committee (Institutional Review Board number 12–1988).

**RESULTS**

A total of 1604 central line placements were identified during the 3-year time period. Of these, 469 placements were excluded because the patients were in an ICU (333), the coding was incorrect (75), the billed procedure was a line removal or revision instead of placement (24), the patient was an outpatient (20), the placement was unsuccessful (13), or the patient was admitted on an adult medical service (4). The 1135 included lines were placed in 815 unique subjects. Mean age was 8 years (SD 6), and 55% of subjects were boys. Lines were in place for a total of 118,023 catheter-days with a median of 22 days (range 0–1393, interquartile range [IQR] 13–55). Additional patient and thrombosis characteristics are included in Table 2.

Most lines were nurse-placed peripherally inserted central catheters (PICCs) and were positioned in the brachial or cephalic vein. Median line size was 4 Fr with more than half of the catheters <5 Fr. The size of 4 lines was unable to be determined. Most lines were used for prolonged antibiotic administration placed in patients with a diagnosis of infection. As expected, subcutaneous ports were in place significantly longer than any other line type \((P < .0001)\), with an average of 481 catheter-days per port. Lines in the subclavian vein were in place longer than those at other sites (mean 260 days per line \([P < .0001]\)). Patients with a diagnosis of cancer had lines in place longer than children with other diagnoses (mean 318 days per line \([P < .0001]\)).

Thirty-six catheter-associated venous thromboses were identified in 33 unique patients, 5 in superficial veins, and 31 in deep veins, yielding an incidence rate of 3.2% of lines and a rate of 0.3 thromboses per 1000 catheter-days. Three patients each had 2 catheter-associated thromboses. One patient was receiving chemotherapy for cancer, 1 was receiving TPN with underlying inflammatory bowel disease (IBD), and 1 was receiving antibiotics for cystic fibrosis. In each case, the patient had developed an upper extremity thrombus associated with a PICC. Each subsequent thrombus occurred in the contralateral arm after line placement in that arm. The median time from line placement to venous thrombosis diagnosis was 6 days. No thromboembolic events were observed. The rates of venous thrombosis are further summarized in Table 3. Increasing patient age (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.03–1.14; \(P = .002\)), an underlying diagnosis of either IBD or short bowel syndrome (SBS) (OR 5.4, 95% CI 2.2–13.2; \(P < .001\)), a diagnosis of end-stage renal disease (OR 3.9, 95% CI 1.2–12.4; \(P = .02\)), receipt of TPN (OR 2.9, 95% CI 1.2–7.3; \(P = .02\)), and renal dialysis (OR 5.2, 95% CI 1.6–16.8; \(P = .01\)) were all associated with higher risk of venous thrombosis. In the multivariable logistic regression model, a statistically significant increased risk for venous thrombosis persisted for increasing age (OR 1.07, 95% CI 0.99–1.15).
1.02–1.13;  \( P = .005 \) ), patients undergoing dialysis (OR 3.2, 95% CI 1.09–9.66;  \( P = .035 \) ), and an underlying diagnosis of IBD or SBS (OR 4.7; 95% CI 2.01–11.18;  \( P = .0004 \) ) (Table 4).

**DISCUSSION**

Negotiating the risks and benefits of line placement in pediatric patients can be challenging. A clearer understanding of the risks associated with line placement for noncritically ill children will hopefully enable pediatricians to counsel patients and families more effectively as well as make more informed decisions regarding the use of these devices. Previous studies have considered small patient populations, particularly subgroups of patients (patients with cancer or receiving TPN) or populations including critically ill patients. We assessed a noncritically ill pediatric patient population because we believe this population likely has a very different risk of venous thrombosis. Patients with all diagnoses were considered. Our study evaluated a large, diverse population of children with CVCs, including 1135 lines, 815 patients, and 118,000 catheter-days. Additionally, we present a direct comparison of line types (PICC, tunneled, nontunneled, and port) and location of placement.

The primary outcomes measured were the incidence rate by using simple proportions and rate per 1000 catheter-days. The incidence rate observed in our patient population (3.2) is lower than that reported in most previous studies; however, such comparison of incidence must be interpreted...
A catheter-associated venous thrombosis incidence of 2.5% in PICCs and 3.0% in tunneled lines (OR 0.83). The observed incidence rates are similar to those observed in our cohort. We observed no differences in risk of thrombosis with type of line, size, location, and method of placement. Although not statistically significant, an increased risk of thrombosis was observed in PICCs placed by vascular interventional radiology (P = .09). This finding is likely confounded, as patients requiring line placement by vascular interventional radiology often have more complex medical conditions or a history of line placement failure. Increased attempts at line placement lead to increased endothelial injury that could increase thrombogenesis and venous thrombosis risk.

Significant differences in venous thrombosis risk were noted for certain characteristics that cannot be altered. For example, increasing patient age was associated with increased risk of thrombus formation. This is contrary to previous studies that have reported an increased incidence of line-associated venous thrombosis in younger children. Increased rates of venous thrombosis have been known to occur in adults, which has been attributed to higher rates of risk factors, such as obesity, smoking, and the use of thrombogenic medications. These comorbidities were not assessed in the current study. Our study may have failed to capture extremely young patients with central lines, as these patients often receive care in the ICU setting. Additionally, very young patients are unable to report subtle symptoms, which may lead to underdiagnosis in this population.

In our study, patients undergoing renal dialysis were observed to have a higher cautionsly because of the heterogeneity of these previous studies. The marked variation in patient populations, characterization of deep vein thromboses, and disease acuity considered in previous studies led to the development of this current study.

Two specific reasons likely explain why we observed a lower rate of thrombosis. Our study excluded critically ill patients and did not capture asymptomatic thromboses. Studies including asymptomatic thrombosis that used systematic screening for thrombosis have reported incidence rates as high as 81% in critically ill patients. Three of these studies included primarily critically ill patients. There are a variety of reasons that critically ill patients have a higher risk for thrombosis, including higher acuity, more medical comorbidities, inability to ambulate, increased inflammation, and other factors. A fourth study of critically ill patients that did not include asymptomatic thrombosis reported an incidence rate of 2.7%, similar to the rate we observed. This finding suggests that being critically ill may represent less of a risk factor for catheter-associated thrombosis. More often, symptomatic thromboses alter clinical decision-making; however, it is important to note that asymptomatic venous thromboses can be associated with significant morbidity, such as thromboembolism, infection, and postthrombotic syndrome. Our study is limited to reporting symptomatic thrombosis, as routine imaging to assess for asymptomatic line-associated thrombosis is generally not performed. Although we did not capture asymptomatic thrombosis in our review, there were no cases of thromboembolism.

Reviewing the rates of catheter-associated thrombosis reported in the literature, it is difficult to compare among studies because of the disparate cohorts considered. We demonstrate that noncritically ill inpatients have a venous thrombosis risk very similar to that previously demonstrated in pediatric outpatients. Our observed incidence rate is quite similar to that recently reported by Kanin and Young (2.6%), a study considering a comparable patient population and perhaps the largest number of hospitalized pediatric patients with central lines reviewed in such a study.

Limitations in imaging may lead to false-negatives and underdiagnosis of catheter-associated thrombosis. Although Doppler ultrasound has been shown to be reliable for detection of thrombosis in distal veins (jugular, axillary, brachial, femoral), venography has better sensitivity for imaging of central veins (subclavian, brachiocephalic, and superior vena cava). It is possible that any estimate of the incidence of catheter-associated thrombosis could be affected by imaging limitations and false-negative results.

We also attempted to identify modifiable characteristics that may affect the rate of venous thrombosis with lines. Previous studies have reported increased incidence rates of venous thrombosis with PICCs compared with tunneled and nontunneled central venous lines, lines with more than a single lumen, femoral lines, jugular compared with subclavian placement, and placement on the left side of the body. In a comparable patient population to our study, Kanin and Young demonstrated no significant difference in thromboembolic complications between PICC lines and tunneled lines. Nearly 7000 lines were observed in this study, with
risk of thrombosis. An increased risk of thrombosis in patients with underlying renal disease was recently reported by Takemoto and associates. The underlying etiology of the increased thrombotic risk in this population is unclear. This increased risk does not appear to be associated with the larger French of dialysis catheters, as catheter size was not associated with increased thrombosis in our study, regardless of underlying diagnosis.

Additionally, patients with certain underlying gastrointestinal illnesses had increased risk of venous thrombosis. Patients with IBD or SBS had higher rates of line-associated venous thrombosis compared with patients with other underlying diagnoses. Two recent studies also reported increased risk of venous thrombosis in patients with IBD. A relative risk of 2.4 for thromboembolic event was observed in a study. Catheter placement was cited as an additional thrombogenic risk factor in addition to older age, parenteral nutrition, and coinciding hypercoagulable state. An additional study included 532 children hospitalized with IBD. Of the patients with a central line, 3.8% developed an associated venous thrombosis during the hospitalization.

The increased rates of venous thrombosis in the setting of IBD could be due to the high level of inflammation at the time of line placement. Often these patients are admitted during an active IBD flare or for surgery, leading to a period of increased inactivity. This is different from the line placement for patients with cancer, for instance, who require long-term central access for ongoing maintenance chemotherapy, even when the underlying disease is in remission. Patients admitted for infection requiring central venous access will often receive antibiotics through a peripheral line for 2 to 3 days until blood cultures are sterile. This delay in line placement during the period of most active inflammation potentially leads to lower rates of thrombosis. In our cohort, the median time to thrombus diagnosis was 6 days, suggesting that thrombogenesis likely starts soon after line placement. Other studies also have reported that the risk of thrombosis is highest soon after catheter placement. Whether this is due to elevated levels of inflammation in the earlier stages of illness or due to the proximity of timing for the endothelial injury from line placement is uncertain. Additional investigation of delayed versus routine central line placement would be informative.

Thrombosis prophylaxis in high-risk patient populations with central lines has been considered. For most patients with short- or medium-term central lines, thromboprophylaxis is not recommended. In patients with cancer, daily warfarin prophylaxis was not associated with decreased risk of catheter-related thrombosis. Routine thrombosis prophylaxis is not recommended for patients with cancer and central lines. For patients with central lines who have certain risk factors, such as undergoing dialysis or receiving TPN, prophylaxis for thrombosis is recommended.

A recent small prospective cohort study has established the safety and efficacy of venous thrombosis chemoprophylaxis in patients receiving TPN. For patients with IBD who are being admitted for a flare or surgery, prophylactic anticoagulation has been used based on risk stratification, including such variables as history of previous thromboembolic event, an inherited hypercoagulable condition, family history of thrombosis, CVC placement, parenteral nutrition, or limited mobility. Further prospective trials of the benefit of chemoprophylaxis in high-risk populations is needed.

We present one of the largest studies to date examining the incidence rate of catheter-associated venous thrombosis in pediatric patients. Although limited by its retrospective design and the consideration of only symptomatic line-associated thromboses, the strength of the study includes its consideration of a large, diverse pediatric population at a tertiary care pediatric hospital. Because our pediatric hospital has an institution-wide line-care policy (standardized flushing, dressing changes, obstruction clearance), it is unlikely that patient service or hospital location contributed to the differences observed in thrombosis rates among patient populations. We believe the data are also applicable to patients who are discharged from the hospital with a central line, as many of the patients in this study carried their lines into the ambulatory setting. We directly compared thrombosis incidence rates among all types of CVCs and their associated modifiable characteristics. Although no modifiable risk factors were associated with an increased risk of venous thrombosis, we did observe an increased risk in patients with IBD, SBS, and in those undergoing dialysis. Because of the increased incidence rates of thrombosis in these populations, we believe that further prospective studies evaluating the benefits of thrombosis prophylaxis in high-risk populations are warranted. Additionally, we believe that the findings in this study will improve the clinical care of pediatric patients requiring central venous access by better
informing medical providers regarding the risks associated with these devices.

CONCLUSIONS
The incidence rate of catheter-associated venous thrombosis in a diverse, hospitalized pediatric population of non-critically ill patients is lower than most previous reports and approaches that reported in outpatient populations. No modifiable line characteristics that altered the risk of venous thrombosis were identified. Increasing age, dialysis, and the diagnosis of IBD or SBS are associated with higher incidence rates of line-associated venous thrombosis. Further investigation is needed to understand the underlying etiology for the increased thrombosis risk in these patients and of the benefit and safety for chemoprophylaxis in these high-risk populations.

REFERENCES


