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Secondary Anticoagulation Prophylaxis for Catheter-Related Thrombosis in Pediatric Intestinal Failure: Comparison of Short-Vs Long-Term Treatment Protocols

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Abstract

Introduction: Catheter-related thrombosis (CRT) is a devastating complication of central venous catheters in children with intestinal failure (IF), but the optimal preventive therapy of CRT is unknown. This study assessed the efficacy and safety of 2 protocols of secondary anticoagulation prophylaxis with low-molecular-weight heparin (LMWH).

Methods: This is a comparative cohort study of children from 2 IF programs who received secondary anticoagulation prophylaxis with LMWH for CRT. The short-term protocol group (N = 13) received therapeutic dosing until thrombus resolution or 3 months. In the long-term protocol group (N = 26), prophylactic dosing continued until line removal. Patients underwent routine annual vascular ultrasound and were followed for 1 year. The primary outcome was development of secondary thrombosis; post hoc analysis assessed rates of secondary thrombosis at 12 months.

Results: Patient demographics were similar between groups. Secondary thrombosis occurred in 8 of 13 (62%) patients in the short-term group and in 9 of 26 (35%) in the long-term protocol group ($P = .019$) in a median time of 144.5 and 689 days, respectively ($P = .01$). Secondary thrombosis

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within 12 months occurred in 7 of 13 (54%, short term) and 2 of 26 (8%, long term) patients ($P = .001$). Secondary thrombosis was associated with catheter replacements (23.5 vs 5.5 catheters per 1000 catheter days; $P = .016$) and longer daily parenteral nutrition (PN) infusion (24 vs 15.25 hours; $P = .044$). Compliance was good (>80% of doses) in 92% of patients.

Conclusions: Long-term secondary anticoagulation prophylaxis with LMWH reduces the incidence of secondary thrombosis and should be considered in children with CRT that require PN for prolonged periods of time.

Keywords

anticoagulation; central venous catheter; intestinal failure; low-molecular-weight heparin; pediatric; prophylaxis; treatment; vascular access; venous thrombosis

Introduction

Intestinal failure (IF) is a rare, clinically challenging condition that is frequently associated with significant morbidity and mortality. Children with IF require parenteral nutrition (PN) support and prolonged use of a central venous catheter (CVC) to maintain growth and development¹. The development of multidisciplinary intestinal rehabilitation programs and advances in neonatal, surgical, and nutrition management over the last 2 decades have contributed to a significant decrease in disease-specific and overall mortality,² with survival rates > 90% in many specialized centers³⁻⁶. Prolonged survival resulted in a growing population of children that require PN support via CVC for many years. Catheter-related venous thrombosis is a devastating and severe complication of CVC use. In cases in which multiple central veins are thrombosed, PN infusion is jeopardized and intestinal transplantation is required to avoid patient death^{7,8}.

IF patients are at an increased risk of catheter-related thrombosis (CRT)⁹ because of multiple factors, including prolonged and daily use of CVCs; disruption to blood flow and injury to the endothelium by the catheter; acquired low levels of natural anticoagulant inhibitors, such as antithrombin, protein C, and protein S;¹⁰ and specific components of the PN solution, such as dextrose and calcium, that favor hypercoagulation¹¹. Several studies have examined CRT in IF, and although improvements in catheter care reduced the incidence of CRT over time,^{6,11} it is still reported as 0.2 to 1.7 episodes per 1000 catheter days, with a prevalence of 20%–57%^{10,12-14}. The prevalence varies, depending on the diagnostic imaging modality, study design, and whether routine screening is done. CRT has been reported in as many as 85% of patients undergoing routine vascular screening,^{15,16} and only a portion of the patients are symptomatic. This highlights the importance of routine surveillance for CRT in children with IF. Beyond the loss of a vascular access site, venous thrombosis may be associated with severe complications, such as infection, pulmonary embolism, limb edema, venous congestion, and superior vena cava syndrome¹⁷.

Reports on CRT in children with IF consist primarily of descriptive studies on prevalence and outcome⁹. Interventional studies using systemic anticoagulation for the prevention of CRT are scarce and limited to 3 reports^{15,18,19}. The treatment protocols in 2 of these studies included anticoagulation for all patients, whether they had a previously identified

thrombus (secondary prophylaxis) or not (primary prophylaxis), whereas in the third study,¹⁸ only secondary prophylaxis was used. Although the results of these experiences indicate reduction of thrombotic events, treatment protocols varied and the studied populations were small, with insufficient evidence to establish specific recommendations^{1,20}.

Considering the scarcity of data on this important issue, we aimed to assess the efficacy and safety of 2 distinct institutional protocols of secondary prophylaxis for CRT with low-molecular-weight heparin (LMWH) in children with IF receiving long-term PN and to assess their impact on the progression and recurrence of CRT.

Methods

Study Design and Population

We conducted a retrospective cohort study of children diagnosed with IF who received secondary anticoagulation prophylaxis with LMWH for CRT, comparing 2 different regimens. Children aged <18 years who were managed by the Intestinal Rehabilitation Program either at SickKids Hospital, Toronto, Canada, or at Seattle Children's Hospital, Seattle, USA, between January 1, 2006, and January 31, 2017, were included in the study. IF was defined as the need for PN support for ≥42 days via a CVC. All patients followed by these programs undergo routine annual venous imaging screening of the neck, upper extremities, and groin with an ultrasound doppler after the insertion of the first CVC. Children met the study inclusion criteria once a first CRT was identified and secondary prophylaxis therapy with LMWH was initiated. CRT was identified during either routine annual ultrasound surveillance or on imaging in cases of clinical suspicion of thrombosis. Patients were excluded from the study if they had previous exposure to anticoagulant therapy, had an inherited bleeding disorder, were lost to follow-up before completing the first year of follow-up, or when the initial thrombotic event was diagnosed at a different center.

Patients were followed for ≥12 months after the diagnosis of venous thrombosis, until development of a secondary venous thrombosis, patient death, intestinal transplantation, discontinuation of PN with catheter removal, considered lost to follow-up after 12 months, or completion of the study observation period on January 31st, 2017. Development of a secondary venous thrombosis was defined as development of a new vascular thrombus or progression of the first thrombus²¹.

The primary outcome was the development of secondary venous thrombosis at any time during follow-up. A post hoc analysis for the development of secondary venous thrombosis at 12 months after the initial CRT diagnosis was done to assess short-term efficacy in the whole cohort and mitigate patient censoring over time.

Data collection included patient demographics (age, sex, diagnosis, and intestinal anatomy); CVC history (number and type of catheters, insertion sites, and use of a catheter locking solution); characteristics of the first and secondary thrombotic event (date, location of the CVC and thrombus, and presence of symptoms); serum albumin level and daily PN infusion hours (within 3 months of the thrombotic event, at 1 year and at censoring); doses

and duration of anticoagulation; and side effects of and compliance with anticoagulation. Bleeding episode severity was classified as defined by Schulman et al²² and Kaatz et al²³: A major bleeding is a fatal bleeding and/or symptomatic bleeding in a critical area or organ. Clinically relevant nonmajor bleeding (CRNMB) is a bleeding episode that does not fulfill criteria for a major bleeding and requires medical intervention by a healthcare professional and/or leads to hospitalization or an increased level of care and/or prompts a face-to-face evaluation. A minor bleeding is any sign or symptom of hemorrhage that does not fulfill the above criteria. Adherence to medication was assessed through documentation in clinical notes when reported by the family and classified as defined by Brown et al²⁴.

Treatment Protocols

Following the diagnosis of CRT, patients received anticoagulation with LMWH according to each institution's protocol. Patients in the short-term protocol received therapeutic dosing of Enoxaparin (initial dose: 1 mg/kg/dose twice daily, with a target anti-Xa level of 0.6–1.0 IU/ml) for 30 days followed by repeat imaging. If the thrombus had resolved, dosing was changed to prophylaxis (twice daily dosing, with a target level of 0.2–0.4 IU/ml) to complete 3 months of treatment. Otherwise, therapeutic dosing was continued, with reimaging at 3 months. Anticoagulation was stopped if the clot was stable (no changes in appearance or extension) or resolved at the 3-months' imaging, and no long-term prophylactic anticoagulation was given. Patients managed in the long-term protocol were started on LMWH (Enoxaparin or Tinzaparin) either at therapeutic dosing (initial dose equivalent to 1 mg/kg/dose of Enoxaparin twice daily, with a target anti-Xa level of 0.5–1.0 IU/ml), for 3 months followed by prophylactic dosing (equivalent to 1 mg/kg/dose of Enoxaparin once daily and no level monitoring), or at prophylactic dosing from the start of treatment. The decision whether to use the therapeutic dose at the initiation of treatment was based on the discretion of the treating thrombosis team and frequently influenced by the size, location, thrombus calcification by imaging denoting chronicity, and date of the CVC insertion in the absence of symptoms. Prophylactic treatment was continued indefinitely until achievement of enteral autonomy and CVC removal. Heparin was not added to the PN solution in any group.

Statistical Analysis

Descriptive statistics used median and interquartile range (IQR) for continuous variables. Frequencies with proportions were used for categorical variables. The protocol groups were compared using Student *t*-test for continuous variables and χ^2 test for categorical variables. Kaplan-Meier survival curve was used for the primary outcome, with the subjects stratified by their secondary anticoagulation treatment protocol and compared using the log-rank test. Patients were censored when follow-up was terminated as per the indications described previously. An α value of <0.05 was considered significant. All analysis was completed using GraphPad Prism 8.0.1 (San Diego, CA).

Results

Study Cohort and Demographics

A total of 388 charts were screened and 39 patients were included in the final analysis (Figure 1), with 13 in the short-term protocol group and 26 in the long-term protocol group. Median overall follow-up time was 398 days (IQR, 152–747.5).

Patient demographics and characteristics of the first CRT episode are shown in Tables 1 and 2, respectively. Etiology and residual bowel length were similar between the groups, with a minor difference in the presence of a stoma at study entry (46% of patients in the long-term group vs 15% in the short-term group). There were no differences in patient characteristics at first CRT. For the whole cohort, median age at first CRT was 7 months and median time to first CRT since initiation of PN was 5.3 months. When considering the previous CVCs used, peripherally inserted central catheters and tunneled CVCs had similar incidence of CRT in both protocol groups. All but 1 were silicone or polyurethane CVCs. Patients that were receiving cycled PN for > 20 hours used heparin as a locking solution. Overall, 4 patients had some exposure to ethanol locks, and this was associated with the first CRT in 2 of them. Median time to first CRT since the last CVC insertion was 70 days (IQR, 8–117) in the short-term group and 16 days (IQR, 9–58) in the long-term group; however, this difference was not statistically significant ($P = .654$). Most thrombi (92%) were identified in a central location (proximal to and/or within internal jugular, subclavian, and iliac veins), regardless of the type of line used. There was no significant difference in serum albumin levels, average daily PN infusion hours, and presence of symptoms between protocol groups at the time of first CRT. Symptoms included fever or persistent bacteremia (33.3%), limb swelling (25.6%), and persistent thrombocytopenia without other cause (5.1%). No patient had symptomatic pulmonary embolism or superior vena cava syndrome.

Primary and Secondary Outcome

The primary outcome, secondary venous thrombosis, occurred in 8 (62%) patients in the short-term group and in 9 (35%) patients in the long-term protocol group (log-rank [$P = .019$]) in a median time of 144.5 days (IQR, 53–258.25) and 689 days (IQR, 567–1052), respectively ($P = .01$). The thrombosis-free survival curve is shown in Figure 2. Most of the thrombi (76%) were identified in a central location in both groups (88% vs 67%; $P = .312$), with no difference between body sides.

In the post hoc analysis of secondary venous thrombosis at 12 months from the initial CRT, 7 (54%) patients in the short-term group and 2 (8%) in the long-term group (log-rank [$P = .001$]) had recurrence or progression of CRT. The 1-year thrombosis-free survival curve is shown in Figure 3. Median time to secondary venous thrombosis was 108 days (IQR, 47–204) in the short-term group and 42.5 days (IQR, 33.3–51.8) in the long-term protocol group ($P = .098$). When excluding patients that achieved enteral autonomy in this period ($N = 8$), recurrence remained significantly lower in the long-term protocol group (10% vs 64% in the short-term group; $P = .002$).

Risk Factors for Second CRT at 12 Months

Univariate analysis for CRT recurrence or progression at 12 months is shown in Table 3. Patients with secondary venous thrombosis did have more frequent catheter replacements (23.5 vs 5.5 catheters per 1000 catheter days; $P = .016$). Diagnosis, bowel anatomy, presence of symptoms or complete vessel occlusion at the first CRT episode, and frequency of central line-associated bloodstream infections (CLABSIs) between CRT episodes were not associated with an increased risk of secondary thrombosis at 12 months after the initial episode. Only 1 patient (11%) had a CLABSI at the time of the second CRT compared with 33% of patients at first CRT. The duration of therapeutic dose anticoagulation was also not associated with a lower risk for CRT recurrence.

Throughout the study period, a trend of a decrease in average daily PN infusion hours and an increase in serum albumin level was observed. At 1 year, patients without a second CRT had lower PN infusion hours (15.3 vs 24 hours in those with second CRT; $P = .044$). This difference remained significant after exclusion of patients who had achieved enteral autonomy and weaned off PN (16 vs 24 hours in those with second CRT; $P < .001$). At the time of censoring, serum albumin levels were not different between patients with and without second CRT within 12 months.

Safety

One patient in the long-term protocol group died during the study period. This was not related to the thrombosis or anticoagulation therapy, and the patient did not have a secondary CRT at the time of death.

Among patients in the short-term protocol, 4 (31%) experienced side effects. Two patients (15%) had CRNMB events and 2 had (15%) minor bleeding events. In the long-term protocol, 10 patients (38%) had 1 side effect, 4 while on therapeutic anticoagulation and 6 on prophylactic anticoagulation. Two patients (8%) had CRNMB, 3 patients (12%) had minor bleeding events, 3 patients (12%) had presumed heparin-induced thrombocytopenia, 2 patients (8%) reported bruises at the site of injection, and 1 patient (4%) had a mild allergic reaction (rash) to a preservative and was switched to a preservative-free formulation. One patient discontinued long-term prophylaxis following a gastrointestinal CRNMB bleeding event. There was no significant difference in the occurrence of side effects between protocol groups.

Medication Compliance

Based on the reported information in the patient chart, compliance to anticoagulation was good (>80% of recommended doses taken²⁴) in 93.3% of patients in the short-term protocol group and in 92% of patients in the long-term protocol group ($P = .879$). Anticoagulation was stopped because of difficulties with or discomfort of the subcutaneous injections by 3 (11%) patients on therapeutic dosing and 2 patients (7%) on prophylactic dosing.

Discussion

The treatment approach to CRT in children with IF is poorly studied and undefined. Our study provides the first comparison between 2 secondary prophylaxis anticoagulation protocols for CRT in PN-dependent children. We found that long-term anticoagulation was more effective in preventing recurrence or progression of central venous thrombus at 12 and beyond 12 months of follow-up. Repeated replacements of CVCs and longer daily PN infusion were associated with a higher risk of secondary venous thrombosis.

The protection and salvage of central venous access is highly important for the prognosis and long-term outcome of patients with IF receiving long-term PN; however, international guideline recommendations are inconsistent. In adults with CVCs,^{25,26} and in most studies of CRT in neonatal and pediatric patients,²⁷⁻³⁰ prophylactic anticoagulation has not demonstrated consistent benefit, with no distinction between primary and secondary prophylaxis. The American College of Chest Physicians guideline for children and neonates³¹ recommends secondary prophylactic anticoagulation for patients with CRT if the catheter is functioning and required, until it is removed, and primary prophylaxis with vitamin K antagonists in children receiving home PN. The most recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on PN²⁰ from 2009 do note that daily subcutaneous LMWH is effective in patients at high risk for thrombosis, being therefore reasonable in patients with malignancies, chronic inflammatory diseases, or a medical or family history of idiopathic thrombotic events. However, it does not mention past history of CRT as a high-risk category. Pediatric IF was also not addressed specifically.

A systematic review published by Barco et al in 2017⁹ found few low-quality studies on the prevention and treatment of CRT in adults and children receiving either short-term or long-term PN. Only 1 high-quality pediatric study¹⁵ compared anticoagulation (nadroparin or acenocoumarol) with no treatment in patients receiving home PN. CRT-free survival almost doubled (from 160.9 to 351.7 days) after initiation of routine anticoagulation. However, the studied cohort was small (N = 8) and patients were not routinely reimaged; therefore, only catheter occlusions or symptomatic thrombi were captured on follow-up. McLaughlin et al¹⁸ used long-term anticoagulation as secondary prophylaxis in children with IF, with resolution of 43% of thrombi. Our results suggest that long-term secondary prophylaxis with LMWH can delay and reduce the recurrence of both symptomatic and occult CRT.

Pediatric IF patients are probably at a high risk for CRT. Gonzales-Hernandes et al¹⁰ compared children with IF for potential risk factors for CRT. Lower levels of natural anticoagulant proteins (antithrombin, protein S, and protein C), as well as elevated factor VIII levels, were associated with higher risk of CRT, with liver insufficiency and chronic inflammation suggested as potential causes. Patients with thrombosis also had significantly lower serum albumin levels, reflecting gastrointestinal losses of protein that may also include anticoagulation proteins. In our cohort, patients with CRT recurrence had a trend towards lower levels of serum albumin; however, anticoagulation proteins were not studied. In contrast to the findings by Gonzales-Hernandes, minor or major thrombophilia was not identified as a risk factor for recurrence in a large pediatric cohort with CRT³². It is

unclear how many of those were IF patients, and thus the relevance of these findings to our population is unclear.

Frequent catheter replacements and infections are additional risk factors for CRT in IF patients, highlighting the importance of proper catheter management. In our cohort, the first CRT occurred in a median of 25 days after insertion of a CVC, with 49% of patients being diagnosed within 1 month of insertion. Additionally, patients with secondary thrombosis within 12 months had more frequent catheter replacements. These findings are consistent with reports in other patient populations^{15,33} and suggest that endothelial damage due to catheter insertion acutely increases the risk for thrombosis. Prospective nonrandomized studies have suggested that minimizing the number of insertion attempts and damage to the vein wall, as obtained with ultrasound guidance, helps to yield a lower rate of subsequent thrombotic events. Therefore, many recommendations regarding CRT prevention, both in IF and non-IF populations, account for insertion technique^{20,34-36} and minimization of catheter replacement as much as possible. These suggest that efforts toward salvaging the catheter involved in the thrombosis without its removal might be beneficial. Patients with a second CRT within 12 months also had a longer requirement for daily PN infusion hours, which may suggest a more severe IF phenotype, with inability to wean off PN. Although anatomy and remaining bowel length was not identified as a risk factor for CRT in our study, this difference in PN needs suggests a potential difference in bowel function.

Both centers in this study have adopted a routine practice of an annual ultrasound of central veins to detect asymptomatic CRT. This allows early detection of thrombosis for timely intervention and for identification of patients that may require intestine transplantation^{7,8}. Ultrasound is a simple-to-use, noninvasive, readily available modality and, as such, was selected as the preferred modality in our centers. However, it is important to acknowledge that ultrasound might not be the ideal method to diagnose CRT, as it is operator dependent and therefore subject to bias, and the sensitivity for central vein thrombosis (subclavian, brachiocephalic, and superior vena cava) is lower than other modalities^{11,30}. Although venography has traditionally been the gold standard for CRT detection, computed tomography and magnetic resonance have been more widely used recently, especially in adult populations^{37,38}. Their role in children with IF is not yet fully established, but they may be beneficial for children with already known CRT for more accurate mapping of their vasculature.

The use of daily injection with LMWH to prevent CRT in children is not trivial and may impact quality of life, especially if used chronically. This population of patients has already been demonstrated to have lower health-related quality of life scores compared to healthy and chronically ill controls³⁹. Additionally, delivery of LMWH through subcutaneous injections may impact adherence²⁴. Beyond the discomfort of the subcutaneous administration, it adds to the already extensive and highly complex treatment plan reliant on parents. The burden of medication cost is another factor to be considered, as it might be prohibitive, especially if used long term. However, cost-effectiveness analysis on this treatment aspect does not exist. There were no events of major bleeding in our cohort. This is in keeping with reports of an incidence of only 0.7%–5.6% in children^{40,41}. Nonmajor bleeding events (CRNMB and minor bleeding), on the other hand,

are common (up to 75.6% of patients)^{41,42}, which was also the finding in our cohort (23%). Previous studies of anticoagulation prophylaxis in pediatric IF have not reported any bleeding events^{15,18,19}; however, clear definitions were not reported, and minor bleeding complications were not always included in the reports. It is important to note that only 1 patient in our cohort discontinued the treatment because of a bleeding episode.

Three (11%) patients in this cohort stopped anticoagulation during twice daily therapeutic dosing and 2 (7%) during once daily prophylaxis on the grounds of a child's or parent's refusal to inject given the discomfort and impact on quality of life. Family support and education on the merits of a secondary prophylaxis treatment by the treating team can potentially improve adherence and minimize discontinuation of LMWH. In cases of poor adherence, treatment with Warfarin, or a similar derivate, can be an alternative. However, Warfarin absorption in IF patients is inconsistent and unpredictable and it may also compete with vitamin K absorption. Therefore, drug monitoring is a challenge, with increased risk for either overanticoagulation or underanticoagulation.

This retrospective study has several limitations. Although this is the largest study to date to assess anticoagulation as secondary prophylaxis for CRT in children with IF, the overall number of patients is still relatively small – an ongoing challenge in this rare pediatric disease. Treatment protocols were well established in each center; however, management of the CVC when a thrombotic event was identified and follow-up practices varied. Additionally, data were collected retrospectively and, therefore, prone to higher bias, especially regarding information about adherence to medication. These limitations were mitigated as much as possible by specific definitions and careful data collection.

In conclusion, long-term secondary anticoagulation prophylaxis with LMWH reduces the incidence of secondary thrombosis within 12 and after 12 months of follow-up compared with short-term anticoagulation. Secondary long-term prophylaxis may be influenced by a declining adherence over time and accumulating costs. However, because of the long-term implications of venous thrombosis on PN delivery, long-term anticoagulation prophylaxis is a viable option for children requiring PN therapy for prolonged periods of time. Additionally, efforts should be made to minimize the frequency of catheter replacement, including salvaging the catheter involved in the thrombotic episode, when possible. Further studies with a larger sample size are needed to determine long-term outcomes.

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Clinical Relevancy Statement

Children with intestinal failure (IF) are at increased risk for catheter-related thrombosis (CRT), a devastating complication of prolonged parenteral nutrition therapy. Anticoagulation prophylaxis with low-molecular-weight heparin (LMWH) may reduce CRT, but the optimal preventive protocol is unknown. This study compared 2 protocols of secondary anticoagulation prophylaxis with LMWH (short- and long-term protocol) and found that long-term prophylactic anticoagulation until line removal was associated with lower recurrence or progression of CRT.

Figure 1.

Patient flow chart. AC, anticoagulation; CRT, catheter-related thrombosis; LMWH, low-molecular-weight heparin.

Figure 2. Overall thrombosis-free survival in the long-term and short-term anticoagulation treatment protocols.

Figure 3. One-year thrombosis-free survival in the long-term and short-term anticoagulation treatment protocols.

Table 1.

Characteristics of Children With IF and Need for Secondary Anticoagulation Prophylaxis.

Parameter	Short-term protocol (n = 13)	Long-term protocol (n = 26)	P-value
Sex (male), %	46	62	.361
Etiology, n (%)			.508
NEC	6 (46)	10 (38)	
Abdominal wall defect	4 (31)	7 (27)	
Volvulus	1 (8)	2 (8)	
Atresia	1 (8)	3 (12)	
Other ^a	1 (8)	4 (15)	
Residual bowel anatomy ^{a3}			
% Of expected SB length (median)	43	39	.969
Total colon resected, n (%)	1 (8)	4 (15)	.535
% Of expected colon length (median)	100	99.5	.640
Presence of stoma, %	15	46	.042
ICV present, %	38	38	.513
Catheter history before first CRT			
Number of previous central lines, median (IQR)	3 (3–4)	3 (2–5)	.802
Catheter days, median (IQR)	274 (65–339)	125 (56.5–496.75)	.501
Follow-up time, median (IQR), d	199 (5–1595)	531.5 (24–3255)	.051

CRT, catheter-related thrombosis; ICV, ileocecal valve; IQR, interquartile range; NEC, necrotizing enterocolitis; SB, small bowel.

^aPerforation, long-segment Hirschsprung disease.

Table 2.**Patient and Line Characteristics at First CRT.**

Parameters	Short-term protocol (n = 13)	Long-term protocol (n = 26)	P-value
Patient characteristics at first CRT			
Age, median (IQR), mo	10 (4–11)	6 (2–23.5)	.277
Time since PN start, median (IQR), d	283 (135–339)	116 (45–479)	.466
Time from last catheter insertion, median (IQR), d	70 (8–117)	16 (9–58)	.654
Serum albumin level, median (IQR), g/L	28.5 (24.75–32.75)	27.5 (23.25–34)	.992
Average daily PN infusion hours, median (IQR)	24 (20–24)	20 (18–24)	.301
Line type and location at first CRT			
PICC, n (% of CVC history)	3 (10)	15 (25)	.088
Tunneled catheter, n (% of CVC history)	10 (26)	11 (42)	.602
Right, n (% of CVC history)	7 (18)	18 (24)	.458
Left, n (% of CVC history)	6 (21)	7 (19)	.901
Characteristics of first CRT episode			
Central location of thrombus n (%)	10 (100)	23 (88)	.202
Presence of symptoms ^a (n, %)	8 (62)	15 (58)	.818

CRT, catheter-related thrombosis; CVC, central venous catheter; IQR, interquartile range; PICC, peripherally inserted central catheter; PN, parenteral nutrition.

^aSymptoms include limb swelling, fever/bacteremia, and thrombocytopenia.

Table 3.
Risk Factors for Second CRT at 12 Months After Initiation of Low-Molecular-Weight Heparin Treatment.

Parameter	Second CRT (n = 9)	No second CRT in 1 year (n = 27)	P-value
Symptoms at first CRT, n (%)	4 (44)	15 (50)	.770
Complete vessel occlusion at first CRT, n (%)	6 (67)	16 (53)	.479
Catheter replacements			
Number of catheters 1 year after first CRT, median (IQR)	2 (1–3)	1.5 (1–3)	.667
Number of catheters per 1000 days, median (IQR) ^a	23.5 (14.6–33.3)	5.5 (2.7–8.8)	.016
CLABSI per 1000 catheter days, median (IQR)	0 (0–5.5)	0 (0–5.5)	.461
Serum albumin level, median (IQR), g/L	32 (24–33)	36 (32.3–40.8)	.100
Average daily PN infusion hours, median (IQR)	24 (24–24)	15.3 (9.5–18)	.044
Therapeutic anticoagulation			
>29 d, n (%)	6 (67)	16 (53)	.479
>12 wk, n (%)	1 (11)	12 (40)	.107

CLABSI, central line-associated bloodstream infection; CRT, catheter-related thrombosis; IQR, interquartile range; PN, parenteral nutrition.

^aOne patient with thrombosis recurrence in 5 days is an outlier and was excluded from the analysis.