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## Treatment and follow-up of venous thrombosis in the neonatal intensive care unit: A retrospective study

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### Abstract

**Objective**—The critically ill, premature patients of neonatal intensive care units are susceptible to venous thrombosis, an adverse event associated with short- and long-term morbidity. Venous thrombosis is frequently treated with low molecular weight heparins (LMWH) such as enoxaparin, but optimal dosing of LMWH must balance the morbidity of venous thrombosis with the potential adverse effects of anticoagulation. The optimal dosing of enoxaparin for premature infants is unclear. The objective of this study was to describe enoxaparin therapy and follow-up in critically ill neonates diagnosed with venous thrombosis.

**Study Design**—Retrospective medical record review in the neonatal intensive care unit (NICU) in a single tertiary care institution. Infants with venous thrombosis diagnosed in the NICU were identified using pre-existing quality improvement lists and medical records.

**Results**—Twenty-six infants with 30 venous thromboses were identified with a median gestational age of 31 weeks at birth. Eighteen (69%) infants received enoxaparin for venous thrombosis during their hospitalization, beginning with a median dose of 1.5 mg/kg every 12h. This dose was increased to a median 2.1 mg/kg every 12h to achieve target anti-factor Xa levels. The target dose was significantly higher in patients with a postmenstrual age less than 37 weeks. Enoxaparin treatment was documented after discharge in 12 patients, continuing for a median of 99 days. Four patients died during hospitalization and their deaths were not attributable to venous thrombosis or anticoagulation complication. Follow-up documentation between 6 and 24 months

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### Conflicts of Interest

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after venous thrombosis diagnosis revealed no major morbidity of venous thrombosis or enoxaparin therapy.

**Conclusions**—Our data reinforces the relative safety and necessity of enoxaparin doses above 1.5 mg/kg per 12 hours in most neonates. This was particularly true for infants at lower postmenstrual age.

### Keywords

anticoagulation; neonatal intensive care unit; low molecular weight heparin; critical care; venous thrombosis; central venous catheter

## INTRODUCTION

Venous thrombosis is a rare but increasingly identified adverse event in children<sup>1, 2</sup> and is associated with admission to critical care units, central venous catheterization (CVC), mechanical ventilation (MV), surgery, and age less than 1 year<sup>2, 3</sup>. Accordingly, the young, critically ill, and often catheterized patients of the neonatal intensive care unit (NICU) are at risk for venous thrombosis, with reported incidences ranging from 1.4 to 2.4 per 1000 NICU admissions<sup>2, 4</sup>. This increased risk is likely due to age-related differences in vasculature and hemostasis<sup>5, 6</sup>. Although direct mortality is low, identification of venous thrombosis remains important as neonates may suffer significant morbidity in the form of pulmonary embolism, embolic stroke, and post-thrombotic syndrome, a chronic condition consisting of limb swelling and skin induration<sup>2, 3, 7, 8</sup>. Morbidity and mortality are less well described in neonates compared to older children or adults, and in particular, there is less long-term follow-up data existing for neonates with venous thrombosis<sup>2</sup>.

Thrombosis in critically ill children is frequently treated with unfractionated heparin, low-molecular-weight heparins (LMWH) such as enoxaparin, and vitamin K-antagonists<sup>9</sup>. In recent years, anticoagulation with LMWH has become relatively standardized through the American College of Chest Physicians' (ACCP) guidelines for anticoagulation<sup>10</sup>. A growing body of evidence shows that preterm neonates require higher doses of LMWH to achieve anti-factor Xa levels within target ranges<sup>10, 11, 12, 13, 14, 15</sup>. However, in the absence of large randomized controlled trials, and with much of our current understanding of pharmacokinetics extrapolated from adult studies, ideal dosing for anticoagulation in critically ill neonates remains uncertain<sup>13, 16, 17, 18</sup>. This dosing will ultimately depend on accurate descriptions of the morbidities of venous thrombosis in neonates, as well as the risks associated with LMWH therapy at different doses<sup>9</sup>. Such data is currently lacking in the literature, particularly with respect to the long-term sequelae of venous thrombosis and enoxaparin therapy. In view of this need, we conducted a retrospective chart review of infants diagnosed with venous thrombosis in the Children's Hospital of Pittsburgh (CHP) NICU between 2005 and 2013 with the aim to describe the hospital course and long-term follow-up of critically ill infants diagnosed with venous thrombosis, as well as enoxaparin treatment in the NICU setting.

## MATERIALS AND METHODS

### Patient Population

This study was approved by the University of Pittsburgh Institutional Review Board. The CHP NICU is a tertiary referral center with 55-beds and approximately 1100 admissions per year. Infants who developed a venous thrombosis while treated at the CHP NICU between 2005 and 2013 were identified through a search conducted by the CHP Data Warehouse and the University of Pittsburgh's Center for Assistance in Research using eRecords (CARE) to identify patients with venous thrombosis by identifying all patients who underwent Doppler ultrasound and were subsequently treated with either unfractionated or low molecular weight heparin during the study period. This period represented all data available from the introduction of medical records up to the time of data collection. Additional infants were identified using an existing list of venous thrombosis maintained by the NICU for quality improvement purposes. All charts were then reviewed to confirm a diagnosis of venous thrombosis.

### Data Collection

For each subject, study personnel retrospectively examined charts for patient demographics including age, gestational age, sex, and race; medical history including surgeries prior to admission and diagnoses noted on admission notes; and hospital course and therapies such as surgeries, catheterization, mechanical ventilation, and venous thrombosis diagnosis and treatment. Hematology and other follow-up visits were noted between 6 months and 2 years after discharge.

### Central Venous Catheterization (CVC)

All CVCs in place prior to venous thrombosis development were noted and categorized as peripherally-inserted or centrally-inserted. Venous thromboses that developed in a limb that had been catheterized were classified as catheter-associated (CA-VT). All other venous thromboses were classified as noncatheter-associated (NCA-VT).

### Venous Thrombosis Diagnosis

In all study patients, documented radiologist ultrasound (US) readings were reviewed to confirm diagnosis of venous thrombosis and date of resolution, whenever available.

### Enoxaparin Treatment

In this retrospective study, enoxaparin treatment was performed according to hospital treatment recommendations and administered at the discretion of a Neonatologist or NICU Pharmacist. From 2005 – 2010, the hospital recommendation for initial treatment of thrombosis in patients < 2 months of age was 1.5 mg/kg/dose every 12 hours, which was consistent with the dosing recommended in the ACCP *Chest* 2001 and 2008 guidelines. However, in 2011, the hospital recommendations for initial treatment of thrombosis in patients < 2 months of age were adjusted to 1.7 mg/kg/dose every 12 hours for term infants and 2 mg/kg/dose every 12 hours for preterm infants in response to publications by Malowany et al. and Sanchez de Toledo et al., which validated the need for increased initial

enoxaparin doses in younger patients<sup>14, 19</sup>. Throughout the study period, anti-factor Xa levels were drawn 4 hours after the second dose of enoxaparin, then 4 hours after each subsequent dose change, then weekly for inpatients and monthly for outpatients to monitor efficacy.

The presence or absence of enoxaparin treatment between venous thrombosis diagnosis and hospital discharge was noted, along with daily enoxaparin dose and anti-factor Xa levels when applicable. The time between diagnosis and enoxaparin initiation was recorded, as well as the time to achieve target serum anti-factor Xa level and the total number of enoxaparin dose adjustments required to reach target levels. In addition, if enoxaparin was continued following discharge, the length of treatment as determined by hematology clinic follow-up notes was noted.

### **Additional Comparisons**

Patients who received enoxaparin during their hospital stay were compared according to gestational age at birth, as well as both chronologic and postmenstrual age at the time of enoxaparin initiation. Postmenstrual age was defined as gestational plus chronological age in weeks<sup>20</sup>. We also subdivided patients according to the presence or absence of diagnoses of thrombocytopenia, NEC, and congenital heart disease noted on admission.

### **Adverse Outcomes**

We reviewed medical records between 6 and 24 months following hospital discharge and identified hematology or other assessments containing complete reviews of systems and physical examinations. These notes were reviewed for any indication of adverse events including ongoing ischemia, mottling, swelling, limb amputation as well as side effects or complications of enoxaparin treatment such as bruising or bleeding.

### **Statistical Analysis**

All statistical analyses were performed using IBM SPSS (version 23; IBM Corp., Armonk, NY, USA). Continuous measures were summarized based on medians and interquartile ranges, while categorical measures were summarized by frequencies and percentages. Two-group comparisons of continuous variables were performed using Mann-Whitney U tests, and two-group comparisons of categorical variables were performed using Fisher's exact tests.

## **RESULTS**

### **Demographics**

Our search strategy identified 26 patients who developed 30 venous thromboses during their CHP NICU stay between 2005 and 2013. The demographics of these patients are described in Table 1. Twenty-four (92%) infants were admitted from an outside hospital. Their admission notes described a median 6 (IQR 3–7) different diagnoses. The most common admission diagnoses were sepsis (15 infants, 58%), necrotizing enterocolitis (11 infants, 42%), and thrombocytopenia (10 infants, 38%). Together 18 (69%) infants were diagnosed with respiratory conditions including respiratory distress syndrome, persistent pulmonary

hypertension, bronchopulmonary dysplasia, respiratory syncytial virus, aspiration, and pneumonia. Sixteen (62%) infants were diagnosed with infections including sepsis, urosepsis, and respiratory syncytial virus. Fourteen (54%) infants were diagnosed with gastrointestinal diagnoses including necrotizing enterocolitis (NEC), gastroschisis, omphalocele, and volvulus. Eight (31%) of infants were diagnosed with cardiac conditions including patent ductus arteriosus, atrial septal defect, ventricular septal defect, arrhythmia, heart block, coarctation of the aorta and patent foramen ovale. Five (19%) patients were diagnosed with renal conditions including hydronephrosis, renal caliectasis, renal agenesis, renal insufficiency, and renal failure, and one infant was admitted with the oncologic diagnosis of neuroblastoma. In addition, prior to the development of any thrombosis, 20 (77%) patients had received mechanical ventilation and 19 (73%) had undergone a surgical procedure before or during admission.

### **Venous Thrombosis and Catheterization**

Thirty venous thromboses were identified amongst the 26 infants in our study population. Data on the hospital course of each patient's initial thrombosis are outlined in Table 2.

Twenty-four (92%) patients had a CVC in place during their hospitalization prior to the diagnosis of any venous thrombosis, including one patient who received extracorporeal membrane oxygenation. Of the remaining 2 patients, 1 had documentation of a CVC placed in a prior admission and the final patient had no documentation of any central access.

Of 30 venous thromboses, 23 (76%) were classified as catheter-associated (CA-VT) based on previous or current catheter placement in the occluded vein. The remaining 7 (24%) thromboses were not found to be catheter-associated (NCA-VT), which we defined as any CVC placed that were either at a site remote to the point of thrombosis (n=5) or no CVC had been in place during hospitalization (n=2). Among the 26 initial venous thromboses for each patient, 20 (80%) were catheter-associated. Standard practice in our NICU is to remove the catheter after an associated venous thrombosis is discovered. As described in Table 2, among initial thromboses NCA-VT developed significantly earlier in the course of hospitalization compared to CA-VT (median 4 vs. 19 days, p=0.01).

### **Enoxaparin Treatment and the Effects of Gestational Age, Postmenstrual Age, and Comorbid Conditions**

Of the 26 patients with diagnosed venous thrombosis, 18 (69%) received enoxaparin therapy during their hospitalization. The 8 patients that did not receive enoxaparin therapy had comorbidities that contraindicated treatment with anticoagulation, such as significant intracranial hemorrhage (n=3), liver failure (n=2), or a recent operation (n=3). Of these 18 patients receiving enoxaparin, 14 (78%) had been delivered at less than 37 weeks. Seven (39%) were at a postmenstrual age of less than 37 weeks at the time of treatment. Eight (44%) treated patients were diagnosed with thrombocytopenia, 8 (44%) with necrotizing enterocolitis (NEC), and 6 (33%) with congenital heart disease. In 13 (72%) treated patients, their initial thrombosis was catheter associated. The treated patients received a median initial dose of enoxaparin 1.5 mg/kg (IQR 1.0–1.5) every 12h, beginning a median 1 (IQR 0–2.5)

day following diagnosis. In order to reach target anti-factor Xa levels of 0.5–1.0 units/mL, the enoxaparin dosage was increased in 17 (94%) patients.

None of the analyzed aspects of enoxaparin treatment (time from venous thrombosis to enoxaparin treatment, initial dose, dose to achieve target anti-factor Xa levels, days of treatment to achieve target levels, and dose changes to achieve target levels) varied significantly based on gestational age. Patients of postmenstrual age <37 weeks required higher doses to achieve target anti-factor Xa levels (2.5 vs. 1.8 mg/kg/day,  $p<0.01$ ). Thrombocytopenia, necrotizing enterocolitis (NEC), and congenital heart disease (CHD), did not show a significant effect on enoxaparin treatment based on univariate analysis. Enoxaparin treatment also did not vary based on catheter-association of venous thromboses.

### Discharge and follow-up

Figure 1 describes the long-term follow-up of patients diagnosed with venous thrombosis. Patients were discharged or died a median 27 (IQR 14–67) days after diagnosis, by which time 7 patients experienced complete resolution and were discharged off anticoagulation ( $n=6$ ) or died during hospitalization ( $n=1$ ). Four patients (15.4%) died during their stay and their causes of death were listed as prematurity ( $n=2$ ), congenital neuroblastoma ( $n=1$ ), and Tetralogy of Fallot ( $n=1$ ). One of these patients had already experienced thrombosis resolution. None of these deaths was directly or indirectly attributable to venous thrombosis.

Sixteen patients were discharged without documented thrombus resolution. Twelve of these patients received enoxaparin treatment as outpatients, which continued for a median 99 (IQR 38–138) days. Of the remaining 4 patients not receiving outpatient enoxaparin treatment, 2 were discharged to outside hospitals and were thus lost to follow-up at our institution. Enoxaparin treatment was contraindicated in one patient because of a recent intraparenchymal hemorrhage, and one patient's venous thrombosis was improving on ultrasound examination, so enoxaparin was never initiated and the thrombosis was not subsequently examined. Among patients discharged with venous thrombosis, resolution was documented in 5 (31%) patients a median 60 (IQR 42–297) days following diagnosis. Two (11%) patients had documented collateralization, and 9 (47%) patients had no documented resolution, either because they received no further therapy or monitoring after discharge (2, 11%), they were transferred back to their referring hospital (2, 11%), or were otherwise lost to follow-up prior to thrombus resolution (5, 26%).

Of the 22 patients discharged from our hospital, follow-up appointments with hematology or other healthcare providers between 6 and 24 months after discharge were identified in 18 (82%) patients and occurred a median 251 (IQR: 190–414) days following discharge. At the time of reassessment two patients (11%) had documented minor sequelae of venous thrombosis: one patient had mild asymmetry in size between the venous thrombosis-affected and opposing limb, and another patient with history of collateralized internal jugular thrombosis had prominent superficial chest vasculature. Neither patient was symptomatic. No patients, either during hospitalization or on follow-up, were noted to have documented complications of enoxaparin therapy.

## DISCUSSION

### Enoxaparin Dosing

The data from this retrospective study shows that enoxaparin reached target levels at doses greater than initial ACCP guidelines in most patients, with even higher doses required in infants of low postmenstrual age. We also described the conditions and treatments comorbid with venous thrombosis in the tertiary NICU population and found a low incidence of minor sequelae of venous thrombosis in 6 to 24 month follow-up.

This study adds to the existing body of literature calling for higher enoxaparin dosing in neonates<sup>14</sup>. Median initial enoxaparin doses in our study were below hospital recommendations, but matched current ACCP guidelines, likely reflecting individual physicians' familiarity with or preference for the latter. Nevertheless, almost all patients required gradual increases in enoxaparin dosage, a process that took several days. Our finding that patients of low postmenstrual age require even higher doses of enoxaparin is novel; although prior studies have examined enoxaparin dosing in NICU patients as a function of chronological or gestational age, they have not combined the two<sup>11, 21, 22</sup>. By accounting for maturation of an infant's vasculature and physiology before and after birth, postmenstrual age may better identify overall maturity than either gestational or chronological age alone. Additional work is required to better understand the molecular physiologic pathways regulating vasculature development in the premature infant.

In addition to these alternative approaches to patient age, we assessed several other factors for potential effects on enoxaparin treatment or activity. We did not find a significant effect on enoxaparin treatment of comorbid thrombocytopenia, congenital heart disease (CHD), necrotizing enterocolitis (NEC), or CA-VT. In contrast, Streif et al. found that patients with CHD required significantly lower doses of enoxaparin to achieve target anti-factor Xa levels<sup>21</sup>.

In addition to enoxaparin, ACCP guidelines recommend the situational use of several other interventions, including thrombectomy, thrombolytics, and vitamin K antagonists.<sup>10</sup> These are not routinely used at our institution and therefore were not analyzed in this study. Furthermore, in our cohort, prothrombotic evaluations were not consistently evaluated.

### Catheterization

Many studies have reported that the majority of venous thromboses in children are associated with CVC placement<sup>2, 3, 23, 24</sup>. Here, we compared the qualities of catheter-associated and noncatheter-associated thromboses, which to our knowledge have not been analyzed in the past. As in previous studies, we found that CA-VT form several weeks into hospitalization<sup>25</sup>. In contrast, NCA-VT occurred significantly earlier, for unclear reasons. It is possible that these patients are predisposed to thrombosis due to less time-dependent factors such as inherited clotting disorders, which was not analyzed in this study. Future research might assess whether early or NCA-VT warrants screening for inherited clotting disorders, which remains controversial in neonates<sup>8</sup>.

## Venous thrombosis sequelae and enoxaparin adverse effects

This study aimed to expand the existing body of knowledge on short- and long-term complications of venous thrombosis and enoxaparin therapy. In the short-term, our data is consistent with prior studies finding low direct mortality, but relatively high all-cause mortality in critically ill infants with venous thrombosis<sup>2, 3, 21</sup>. In the long term, none of the 18 patients for whom we had adequate follow-up documentation showed documented major sequelae of their venous thromboses, and only two showed minor sequelae of mild limb swelling and visible superficial vasculature. In contrast, other studies have found rates of post-thrombotic syndrome (limb pain, swelling, and induration) as high as 63% in children with venous thrombosis, although most of these cases were also mild<sup>2</sup>. This discrepancy may reflect a difference in the natural history of venous thrombosis in the NICU and pediatric ICU populations, the difficulty of diagnosing pain in neonates, or incomplete follow up in our neonatal population.

Our review found no record of any adverse events due to enoxaparin therapy, either at discharge or in follow-up. We feel confident that any major adverse events such as intracerebral hemorrhage or compartment syndrome would have been noted in discharge and follow-up notes. However, some of our patients may have experienced undocumented minor bleeding events such as oozing at the injection site, epistaxis, or bruising, given rates as high as 75% in other studies<sup>14, 22</sup>.

The existing literature on venous thrombosis and enoxaparin treatment in this population includes some large registries, but still relies heavily on relatively small cohort studies such as this one, and few studies have described long-term follow-up. However, small, retrospective studies such as ours are not ideally suited to identify subtle consequences of venous thrombosis or its treatment. Our sample size leaves open the possibility that we could not detect some trends in venous thrombosis development and treatment, and by identifying patients retrospectively through tests and treatment related to venous thrombosis, we may have missed some cases. Larger, prospective studies are needed to assess subtle and rare morbidities of both venous thrombosis and enoxaparin therapy.

## CONCLUSIONS

This retrospective, single-institution study found that most NICU patients with a venous thrombosis require enoxaparin doses higher than those suggested by the ACCP. Infants of low postmenstrual age require significantly even higher doses. Short- and long-term adverse events associated with both venous thrombosis and enoxaparin therapy are rare, and will require more extensive prospective study for accurate quantification.

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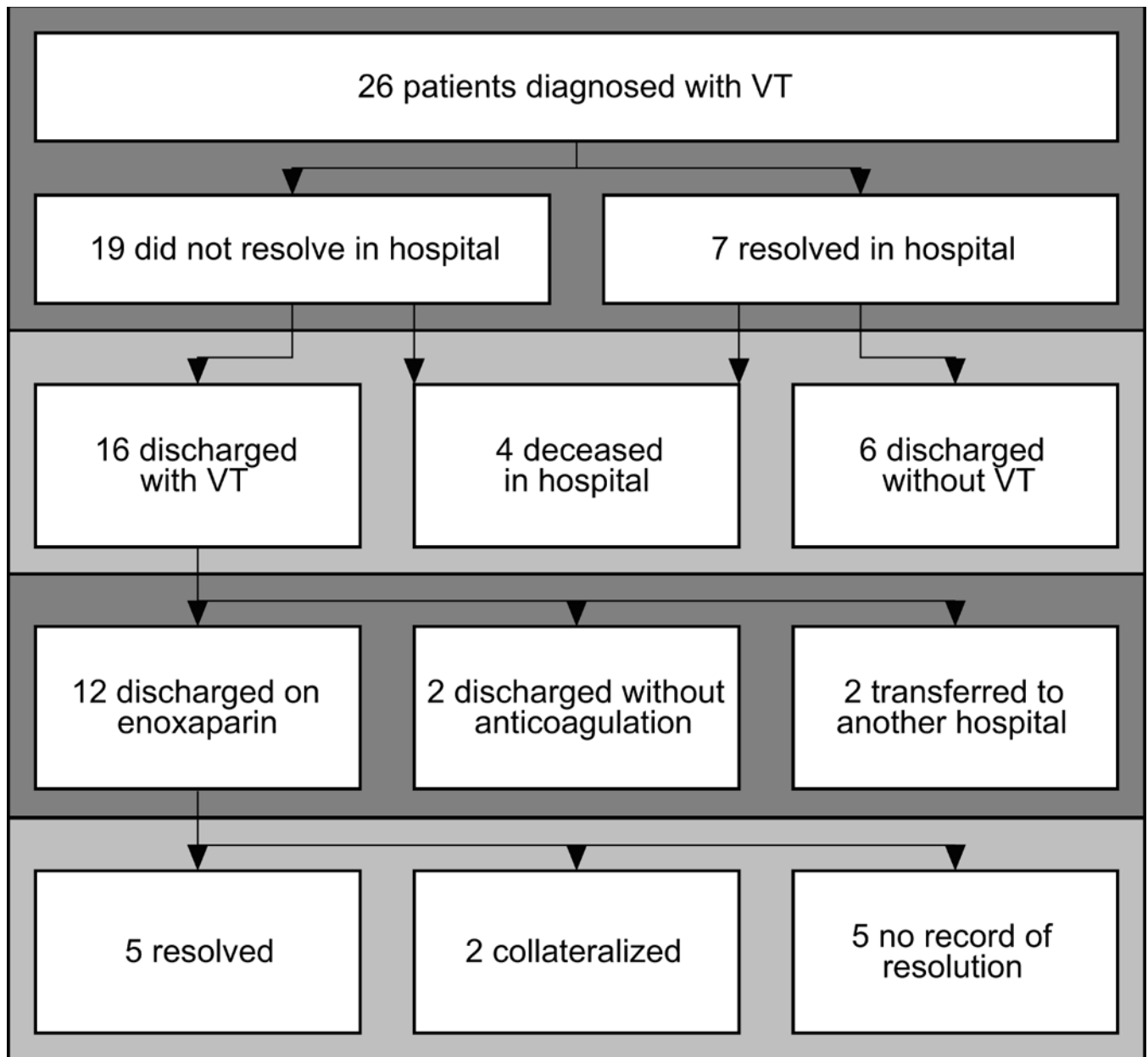


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**Figure 1. Clinical course and follow-up of patients with venous thromboses**

Resolution refers to ultrasound-confirmed resolution of all venous thromboses in a given patient. VT=venous thrombosis.

**Table 1**

Demographic data of infants diagnosed with venous thrombosis.

	<b>Median (IQR)</b>	<b>Percent (number)</b>
Age at admission (days)	9 (0–23)	
Gestational age (weeks)	31 (27–38)	
Postmenstrual age (weeks)	35 (29–39)	
Gender: Male		55% (15)
Race: African American		19% (5)
Asian		4% (1)
Caucasian		58% (15)
Hispanic		8% (2)
Unknown		12% (3)

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**Table 2**

Effects of catheter association on hospitalization length and course.

	Admission to VT (days)	VT to Discharge (days)	Total stay (days)	Documented resolution	Time to resolution (days)
All patients (n=26)	13 (6-37)	27 (14-67)	58 (23-143)	46% (12)	22 (8-59)
Catheter-Associated					
Yes (n=20)	19 (6-45)	27 (14-75)	68 (25-147)	45% (9)	29 (8-58)
No (n=6)	4 (2-7)	28 (14-76)	31 (16-80)	50% (3)	15 (8- <sup>**</sup> )
p value	0.01	0.92	0.27	1.0	1.0

Data are reported as median (interquartile range) or as percentage (n). Time intervals are reported in days. VT=venous thrombosis.

<sup>\*\*</sup> = Could not be calculated.