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BRIEF REPORT

Outcomes in infants with unprovoked venous thromboembolism: A retrospective cohort study

Hilary Whitworth MD, MSCE[1] | Lauren A. Beslow MD, MSCE[2] | Rebecca A. Hubbard PhD[3] | Charles E. Leonard PharmD, MSCE[4,5] | Rebecca Scobell MD, MSCE[6] | Char Witmer MD, MSCE[1] | Leslie Raffini MD, MSCE[1]

[1]Division of Hematology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Division of Neurology, Children's Hospital of Philadelphia, Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]Center for Real-World Effectiveness and Safety of Therapeutics, Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[6]Division of Nephrology, Children's Hospital of Philadelphia, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Hilary Whitworth, 13569 Hub for Clinical Collaboration, 3501 Civic Center Blvd, Philadelphia, PA 19104, USA.
Email: whitworthh@chop.edu

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Abstract

Background: Although children aged <1 year have a relatively high rate of venous thromboembolism (VTE) compared to older children, most have additional prothrombotic risk factors. Unprovoked VTE is rare, and little is known about this population, particularly the risk of recurrent VTE.

Objectives: We aimed to determine the rate of recurrent VTE in infants with prior unprovoked VTE and evaluate long-term, end-organ outcomes for infants with renal and intracranial vein thrombosis.

Methods: Infants <1 year of age with an unprovoked VTE between 2003 and 2021 at a single institution were included. Time to recurrent event and anticoagulation duration were summarized using the Kaplan-Meier estimator. Neurologic outcomes were summarized with the pediatric stroke outcome measure for infants with cerebral sinovenous, medullary, or cortical vein thrombosis. Kidney outcomes were summarized with estimated glomerular filtration rates for infants with renal vein thrombosis. Anticoagulation was summarized.

Results: Forty infants with intracranial, renal, portal, and extremity VTE met the inclusion criteria and were followed for a median of 4.7 years (IQR, 2.1-8.5). Most VTE events occurred during the first month of life. There was 1 recurrent event in 237 person-years of follow-up (incidence rate, 4 per 1000 [95% CI, 0.6-29.9] person-years). In outpatient follow-up, 40% of infants with intracranial thrombosis met criteria for moderate or severe neurologic outcomes and two-thirds of infants with a prior renal vein thrombosis had abnormal kidney function (estimated glomerular filtration rate < 90 mL/min/1.73 m^2).

Conclusion: There is a low rate of recurrent VTE but significant end-organ morbidity in infants with unprovoked VTE.

KEYWORDS
infant, newborn, pediatrics, thrombosis, venous thromboembolism

Essentials

- Unprovoked venous thromboembolism (VTE) is rare and understudied in infants.
- We evaluated recurrent VTE and neurologic and kidney outcomes after unprovoked VTE in infants.
- There is a low rate of early recurrent VTE in early childhood; late recurrence remains unknown.
- There remains significant end-organ morbidity in infants with renal and intracranial thrombosis.

1 | INTRODUCTION

Thrombotic events in children are mostly associated with provoking risk factors such as central venous catheters (CVCs), critical illness, or other comorbidities [1–3]. The incidence rate of pediatric venous thromboembolism (VTE) is biphasic, with a peak in infants aged <1 year and a second peak during adolescence [4]. Unprovoked VTE is uncommon in pediatrics, and we recently reported a high rate of recurrent VTE in children aged ≥1 year with unprovoked VTE (104 recurrent VTE events per 1000 person-years [95% CI, 71-153]) [5]. In this study, we evaluated recurrent VTE in infants <1 year of age who had index VTE not associated with a CVC, surgery, prothrombotic comorbidity, or other known major provoking factors, hereafter referred to as unprovoked VTE. We hypothesized that these events may be partly related to the prothrombotic nature of the maternofetal environment, which may be a unique "provoking" factor and that the rate of recurrent VTE would be low compared to older children with unprovoked VTE. Recognizing that a high proportion of infants with unprovoked VTE have renal vein thrombosis (RVT) or cerebral sinovenous thrombosis (CSVT), we collected data on long-term kidney and neurologic outcomes.

2 | METHODS

We conducted a single center, retrospective cohort study of infants aged <1 year who had an index VTE without provoking risk factors between January 1, 2003, and August 1, 2021 and who had at least 1 hematology outpatient encounter in the Children's Hospital of Philadelphia (CHOP) electronic medical record (EMR). This study was deemed exempt from review by the CHOP Institutional Review Board. The cohort identification process was previously described [5]. Subjects <21 years of age were identified as possibly having a VTE based on EMR data. Those with provoking risk factors and ≥1 year of age at index VTE were then excluded by both automated and manual review of EMR data [5].

Subject demographics, VTE clinical characteristics, laboratory testing, anticoagulation, and long-term neurologic and kidney outcomes were collected via manual chart review and stored in the Research Electronic Data Capture software [6,7]. The index VTE date was defined as the date of the imaging study that identified the VTE. Recurrent VTE, inherited thrombophilia, and bleeding were defined as previously described [5]. Inherited thrombophilia included prothrombin G20210A, factor V Leiden, antithrombin deficiency, protein C deficiency, and protein S deficiency. Protein deficiencies were based on laboratory values interpreted by their hematologist to be consistent with a diagnosis of protein S, C, or antithrombin deficiency.

The pediatric stroke outcome measure (PSOM) [8] was used to assess neurologic outcomes of infants with a CSVT, medullary, or cortical vein thrombosis who had an outpatient CHOP neurology visit. The PSOM includes left and right sensorimotor, expressive and receptive language, and cognitive/behavioral categories. It ranges from 0 (no deficits) to 10 and has been validated to use retrospectively [8,9]. The PSOM was retrospectively calculated from the examination documented at the last neurology visit within the study period by a licensed pediatric neurologist (L.B.). The PSOM was then categorized into normal/mild, moderate, and severe outcome severity based on a previously validated severity classification scheme (PSOM-SCS) [10]. For infants with RVT, kidney function at last follow-up was calculated using the U25 CKiD equation [11]. and was defined as abnormal if estimated glomerular filtration rate (eGFR) was <90 mL/min/1.73 m^2.

Baseline demographics and clinical characteristics were summarized using descriptive statistics. The incidence rate of recurrent VTE was estimated as the number of recurrent events divided by the total cohort person-time and its 95% CI was estimated based on an approximation to Poisson distribution. Recurrent VTE was defined as occurring at least 7 days after the index VTE, as was done in prior studies [5,12,13]. Therefore, the start of follow-up time for the recurrent VTE analysis was set at 7 days after the index event. Total therapeutic anticoagulation duration was summarized using the Kaplan-Meier estimator, as previously described [5]. Subjects were followed until the first recurrent event or censoring, either at the end of the study period (August 1, 2021), death, or the date of their last contact in the CHOP EMR.

3 | RESULTS AND DISCUSSION

The cohort identification process is described in the Figure. Between January 1, 2003, and August 1, 2021, there were 40 eligible infants. The Table summarizes the characteristics of the cohort, including thrombus locations. The median age at diagnosis of first VTE was 5 days (IQR, 3-11), and 39 of 40 (98%) events occurred within the first 30 days of life. There was a slight male predominance (26 of 40, 65%).

The most common index VTE location was intracranial thrombosis, including CSVT, medullary, and cortical veins (23 of 40, 58%), followed by RVT (11 of 40, 28%), portal vein (3 of 40, 7.5%), and lower

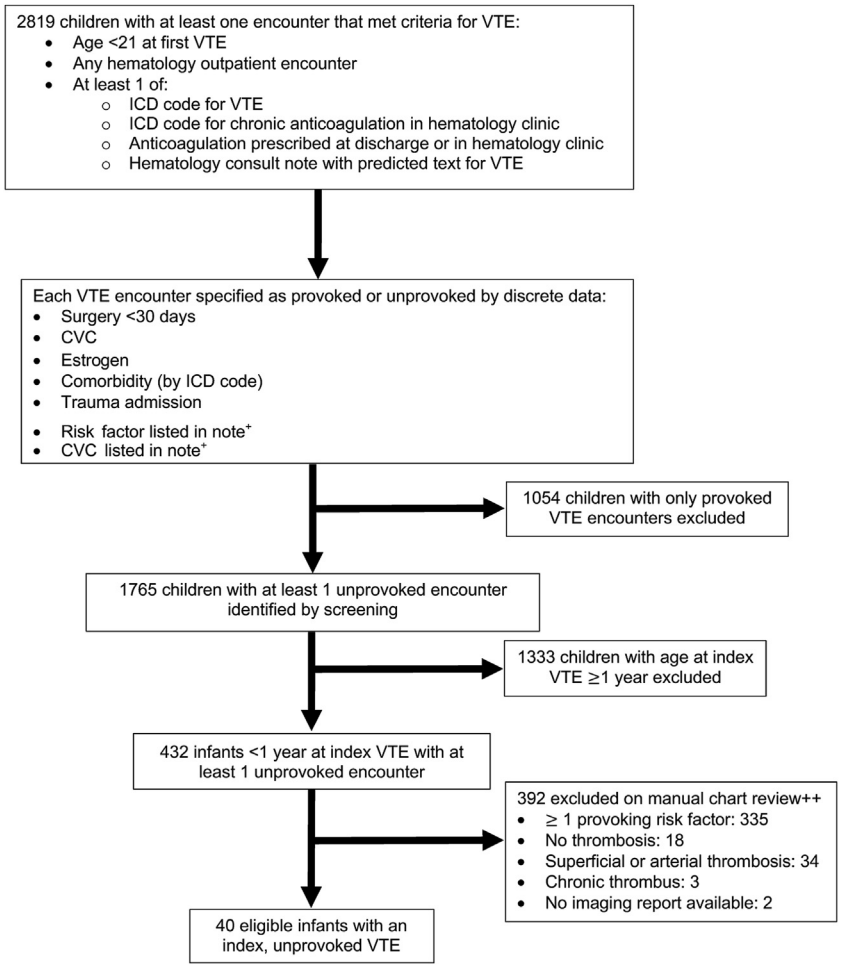

FIGURE Flow diagram of infants aged <1 year evaluated for inclusion between January 1, 2003, and August 1, 2021. +Identified using Structured Query Language using predictable, structured text in hematology consult note. ++The first identified exclusion criterion on chart review is the listed reason for exclusion. Thus, each participant has only 1 exclusion criteria listed here (first evaluated for chronic provoking risk factors; then excluded if VTE did not occur, was chronic, not in deep vein, or imaging report was not available; and then excluded if acute provoking risk factors were present at the time of VTE). CVC, central venous catheter; ICD, International Classifications of Diseases; VTE, venous thromboembolism.

extremity (3 of 40 7.4%). The median duration of follow-up after index VTE was 4.7 (IQR, 2.1-8.5) years. About half of the subjects (55%, 22 of 40) were censored at the end of the study period; 16 were censored for lost to follow-up in the EMR, 1 was censored for death unrelated to thrombosis, and 1 had a recurrent event (Supplementary Table). The majority (38 of 40, 95%) of subjects had at least a partial thrombophilia evaluation. Seven (18%) were diagnosed with a single inherited thrombophilia and 2 (5%) with 2 inherited thrombophilias.

About half (22 of 40, 55%) of the subjects received no anticoagulation for the index VTE (RVT, *N* = 5; CSVT, *N* = 5; medullary vein, *N* = 5; medullary and cortical vein, *N* = 2; portal vein, *N* = 3; and lower extremity deep vein thrombosis, *N* = 2). Documented reasons for not starting anticoagulation include concomitant or high risk of bleeding (in 12 of 22, 55%), unilateral RVT (in 2 of 22, 9%), minimal or no acute symptoms, and/or thought to have occurred *in utero* (in 8 of 22, 36%). Four subjects were prescribed unfractionated heparin followed by enoxaparin, and 14 received enoxaparin only. In the cohort of 18 subjects who received anticoagulation, the median duration of therapeutic anticoagulation was 106 days (95% CI, 78-138). Two infants had bleeding while being prescribed anticoagulation. One infant with an RVT and very mild thrombocytopenia (117 000/uL) had an adrenal hemorrhage while being prescribed therapeutic enoxaparin, although the anti-Xa was subtherapeutic, and anticoagulation was stopped. A second infant presented to the emergency department for mild gastrointestinal bleeding while prescribed therapeutic enoxaparin. Her hemoglobin and platelet count were normal, a random anti-Xa was subtherapeutic, and anticoagulation was not changed.

There was 1 recurrent VTE event in 237 person-years of follow-up (incidence rate, 4 per 1000 [95% CI, 0.6-29.9] person-years). This was a pulmonary embolism that occurred 16 years after an index RVT with inferior vena cava involvement in an adolescent with antithrombin deficiency and factor V Leiden. The subject had been recently switched from therapeutic intensity anticoagulation to decreased dose rivaroxaban (10 mg) prior to the recurrence.

The majority of infants with intracranial thrombosis had associated intracranial hemorrhage (ICH) at the time of the index VTE (78%, 18 of 23). ICH was present in 12 of 16 infants with CSVT, 4 of 5 with isolated medullary vein thrombosis, and 2 of 2 with medullary and cortical vein thrombosis. Ten (56%) of the 18 infants with ICH and intracranial thrombosis did not receive anticoagulation. Outpatient neurology data were available for 20 of 23 (87%) infants with intracranial thrombosis with a median of 2.5 (IQR, 0.2-5.3) years of neurology follow-up. The median total PSOM at last neurology visit was 0.5 (IQR, 0-3.8). Based on PSOM-SCS [10], 12 of 20 (60%) infants

TABLE Infants with unprovoked venous thromboembolism.

Characteristics	*N* = 40
Duration of follow-up (y), median (IQR)	4.7 (2.1-8.5)
Age at first VTE (d)	
0-3	14 (35)
>3-7	11 (27.5)
>7-30	14 (35)
>30	1 (2.5)
Age at first VTE (d), median (IQR)	5 (3-11)
Sex, *N* (%)	
Male	26 (65)
Female	14 (35)
Race, *N* (%)	
White	30 (75)
Black/African American	6 (15)
Other/Unknown	4 (10)
Ethnicity, *N* (%)	
Hispanic	4 (10)
Non-Hispanic	36 (90)
Inherited thrombophilia, *N* (%)	
Not evaluated	2 (5)
No inherited thrombophilia	29 (72.5)
Single	7 (17.5)
Protein C deficiency (*N* = 36)	2
Protein S deficiency (*N* = 37)	0
Antithrombin deficiency (*N* = 37)	1
FV Leiden heterozygote (*N* = 34)	2
Prothrombin G20210A heterozygote (*N* = 35)	2
Double	2 (5)
Antithrombin deficiency + FV Leiden heterozygote	1
Prothrombin G20210A homozygote + FV Leiden heterozygote	1
Maternal history of diabetes, *N* (%)	6 (15)
Birth weight (kg), median (IQR)	3.1 (2.6-3.3)
Gestational age (wk), median (IQR)	38 2/7 (35 5/7-39 4/7)
Location, *N* (%)	
Lower extremity DVT	2 (5)
Lower extremity DVT + IVC	1 (2.5)
Intracranial	23 (57.5)
CSVT	16
Medullary vein	5
Medullary + cortical vein	2
Portal	3 (7.5)
Renal vein	11 (27.5)
Bilateral	4
Without IVC involvement	4
With IVC involvement	4
With IVC + lower extremity DVT	3
Therapeutic anticoagulation, *N* (%)	
None	22 (55)
Unfractionated heparin followed by enoxaparin	4 (10)
Enoxaparin	14 (35)
Therapeutic anticoagulation duration[a] (d), median (95% CI)	106 (78-138)

CSVT, cerebral sinovenous thrombosis; DVT, deep vein thrombosis; FV, factor V; IVC, inferior vena cava; VTE, venous thromboembolism.
[a]Based on the Kaplan-Meier estimator including 18 subjects who received anticoagulation.

met criteria for normal/mild, 4 of 20 (20%) met criteria for moderate, and 4 of 20 (20%) met criteria for severe outcomes.

Outpatient nephrology data were available for 9 of 11 (82%) infants with RVT with a median duration of nephrology follow-up of 7.8 years (IQR, 2.6-14.8 years). The median eGFR at last follow-up was 82 (IQR, 68-112) mL/min/1.73 m^2. Three of 9 subjects with nephrology follow-up had normal eGFR (≥90 mL/min/1.73 m^2); 5 had an eGFR between 60 and 90 mL/min/1.73 m^2, consistent with stage 2 chronic kidney disease (CKD); and 1 had an eGFR of 45 mL/min/1.73 m^2, consistent with stage 3 CKD. Six subjects had a urinalysis and none had protein detected. Renal bladder ultrasound data were available for 10 of 11 infants with RVT at a median of 5.4 years (IQR, 1.9-9.4 years) after index VTE. Nine (90%) subjects had findings of abnormal kidney appearance and/or significant abnormalities in kidney growth, with complete unilateral kidney atrophy in 5 children.

The low incidence rate of recurrence in this study contrasts with our prior work that demonstrated a high incidence rate of recurrent VTE in children aged ≥1 year, particularly adolescents [5]. Notably, the only recurrent event in this infant cohort occurred during adolescence and the median duration of follow-up in this study was 4.7 years, about 2.5 years shorter than the median time to recurrent VTE in our older cohort (7.3 years) [5]. The relatively short duration of follow-up in this study is partly related to a large proportion (40%) of subjects who were lost to follow-up before the end of the study period. While the risk of recurrent VTE in the early childhood period is low in this cohort, there is insufficient follow-up to evaluate whether infants with unprovoked VTE are at increased risk for recurrence during

adolescence, particularly in patients with inherited thrombophilia, which was identified as a potential risk factor for recurrent VTE in older children and adolescents [5]. The slight male predominance (65%) observed in our cohort is consistent with prior infant thrombosis cohorts, particularly those with RVT and CSVT [14–16].

Another explanation for the low rate of recurrence in this cohort is that infants are affected by prothrombotic maternofetal factors, including gestational diabetes, placental insufficiency, or birth trauma, which resolve with age and distinguish this population from older children with unprovoked VTE [1]. We did not have access to maternal records to confirm these risk factors and relied on documentation in the infant's chart, which may be incomplete or biased by the clinical scenario. While we included infants <1 year of age, most of this cohort represents neonatal thrombosis, with 25 of 40 (63%) diagnosed in the first week of life. Because the date of index VTE was defined as the date of the first imaging study to identify the VTE, the diagnosis may have been delayed, especially in infants who may have been too sick for definitive imaging, such as those with intracranial thrombosis who initially presented with hemorrhage and/or seizure. Four subjects with VTE diagnosed at relatively older ages (17-24 days) had dehydration documented as possibly contributing to their VTE risk. The infant with the oldest age at index VTE (RVT) had prenatally diagnosed asymmetric kidneys but did not get postnatal imaging until postnatal day 66. We are limited by the retrospective review of charts and incomplete maternal records, which may not fully capture the exact timing of VTE development. However, this cohort is distinct from infants with clear provoking risk factors such as CVCs, cardiac disease, or surgery, and it is important to understand the long-term implications of thrombosis in this particular population.

We report that 40% (8 of 20) of infants with prior intracranial thrombosis and neurology follow-up have moderate or severe neurologic outcome, based on the PSOM-SCS, which has been validated to correlate with quality of life and functional outcomes [10]. This is consistent with prior literature reporting a high percentage of unfavorable neurologic outcomes in infants with CSVT [3,14]. We also demonstrated poor outcomes after RVT. Two-thirds of infants with a prior RVT and outpatient nephrology follow-up had decreased kidney function, which is consistent with prior literature demonstrating increased risk of CKD after neonatal RVT [17]. These poor outcomes may be confounded by more data being available for those with more severe disease; however, outpatient data were available for >80% of infants with either RVT or intracranial thrombosis. These findings demonstrate concerning long-term, nonthrombotic outcomes that should be evaluated in future studies of this population and argue for longer duration of follow-up for infants with unprovoked VTE.

Our study is limited by the small sample size and inability to perform formal statistical testing or control for confounding. We may have missed recurrent events that occurred at other institutions; however, we censored subjects at their last encounter in the CHOP system in order to increase the likelihood that events occurring during the follow-up period were captured in the CHOP EMR. Additionally, the short duration of follow-up for some subjects may have limited our ability to capture recurrent VTE in adolescence, and thus, the low rate of recurrence in this study should be interpreted with caution. It is possible that the use of EMR data as part of our cohort definition may create a selection bias and we may have missed infants with VTE. To limit this, we used broad criteria to define potential VTE. Our study is strengthened by the manual validation of the cohort and the outcome, which limits misclassification.

In this single institution, retrospective cohort study, we describe the unique population of infants with unprovoked VTE. We demonstrate a low incidence rate of recurrent VTE in early childhood, but those with RVT and intracranial thrombosis had significant morbidity. This study highlights the importance of long-term follow-up and the inclusion of nonthrombotic outcomes in future research to fully assess the clinical impact of pediatric VTE.

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AUTHOR CONTRIBUTIONS

H.W. collected the data and drafted the manuscript. L.B. collected, analyzed, and interpreted neurologic outcomes. R.S. interpreted renal outcomes. All authors contributed to study design, analysis, and interpretation and revised and approved the manuscript.

RELATIONSHIP DISCLOSURE

L.R. serves as a consultant for Janssen and Boeringer Ingelheim. C.E.L. is an executive committee member of the University of Pennsylvania's Center for Real-World Effectiveness and Safety of Therapeutics, which receives funds from Pfizer and Sanofi to support pharmacoepidemiology education. C.E.L. recently received honoraria from the American College of Clinical Pharmacy Foundation, the University of Florida, the University of Massachusetts, the Scientific and Data Coordinating Center for the National Institutes of Health–funded Chronic Renal Insufficiency Cohort Study, Health Canada, and the Consortium for Medical Marijuana Clinical Outcomes Research. C.E.L. is also a special government employee of the US Food and Drug Administration and consults for their Reagan-Udall Foundation. C.E.L. consults for TriNetX Limited Liability Company. C.E.L. receives travel support from John Wiley & Sons. C.E.L.'s spouse is an employee of Merck; neither C.E.L. nor his spouse owns stock in the company. R.W. has received grants to institution from Pfizer, Merck, and Johnson & Johnson in the past 3 years. R.A.H. received funding from Pfizer, Merck, and Johnson & Johnson. The remaining authors, H.W. and C.W., have no competing interests to disclose.

TWITTER

Hilary Whitworth @hilarywhitworth
Rebecca A. Hubbard @rhubbBstat
Charles E. Leonard @CE_leonard
Rebecca Scobell @BeckyScobell
Leslie Raffini @leslie_raffini

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SUPPLEMENTARY MATERIAL

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