

# Prevalence and risk factors for venous thromboembolism in children with sickle cell disease: an administrative database study

Riten Kumar,<sup>1</sup> Joseph Stanek,<sup>2</sup> Susan Creary,<sup>1</sup> Amy Dunn,<sup>1</sup> and Sarah H. O'Brien<sup>1</sup>

<sup>1</sup>Division of Hematology/Oncology, Department of Pediatrics, The Ohio State University, Nationwide Children's Hospital, Columbus, OH; and <sup>2</sup>Division of Biostatistics, Nationwide Children's Hospital, Columbus, OH

## Key Points

- Adults with SCD have an increased incidence of VTE, but similar data in children are lacking.
- In this 7-year, multicenter retrospective study, 1.7% of children with SCD developed VTE.

A hypercoagulable state resulting in increased venous thromboembolism (VTE) has been described in adults with sickle cell disease (SCD), but similar data for children are lacking. The objective of this retrospective cohort study was to describe the rate of VTE and risk factors associated with VTE in children with SCD across tertiary-care children's hospitals in the United States between the years 2009 and 2015. We used the Pediatric Health Information System database to investigate all pediatric patients with SCD admitted to 1 of 48 participating institutions between 1 January 2009 and 30 September 2015. International Classification of Disease, Ninth Edition, Clinical Modification codes were used to identify index thromboembolic events and chronic medical conditions known to be associated with VTE. Billing codes were used to identify central venous line (CVL) placement and pharmaceutical billing codes to identify estrogen containing oral-contraceptive use. Logistic regression analysis was used to study the association among unique patient characteristics, VTE, and death. 10 454 eligible subjects with SCD were identified. Median age ( $\pm$ interquartile range) of study cohort was 10 ( $\pm$ 11) years. 181 subjects (1.7%) developed an index venous thromboembolic event during the study period. Median age at VTE diagnosis was 15.9 ( $\pm$ 7.4) years. On multivariable logistic regression analysis, CVL placement, chronic renal disease, history of stroke, female sex, length of hospitalization, intensive care unit utilization, and older age were associated with VTE. After adjusting for other variables, VTE was independently associated with death. In summary, VTE can occur in pediatric patients with SCD. CVL placement is a modifiable risk factor for VTE development.

## Introduction

Sickle cell disease (SCD) occurs secondary to homozygous or compound heterozygous mutations in the  $\beta$ -globin chain. The resulting valine to glutamic substitution at position 6 results in production of hemoglobin S (HbS),<sup>1</sup> which polymerizes in a concentration-dependent manner under conditions of hypoxia, resulting in symptoms of vaso-occlusion. In the United States, ~100 000 to 140 000 individuals are affected by this condition.<sup>2</sup>

A hypercoagulable state resulting in increased venous thromboembolism (VTE) has been well-described in adult patients with SCD.<sup>3</sup> Nearly a quarter of adults with SCD have a history of VTE.<sup>4</sup> Additionally, VTE is associated with a two- to fourfold increased risk of death in adults with SCD.<sup>4,5</sup> Etiology of this hypercoagulability in SCD includes both "traditional" and "sickle-cell specific" risk factors.<sup>3</sup>

**Table 1. ICD-9-CM codes used in the study**

Condition	Subcategories	ICD-9-CM codes
<b>Primary inclusion diagnosis</b>		
SCD	Sickle cell thalassemia	282.41, 282.42
	SCD	282.6x
<b>Diagnosis of interest</b>		
VTE	PE	415.1, 415.11, 415.12, 415.19
	DVT lower	451.11, 451.19, 451.2, 451.81, 453.40, 453.41, 453.42
	DVT upper	451.83, 451.84, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87
	Other VTE	325, 451.89, 451.9, 452, 453.0, 453.1, 453.2, 453.3, 453.8, 453.89, 453.9
<b>Comorbid diagnosis of interest</b>		
Congenital heart disease	Bulbus cordis anomalies; anomalies of cardiac septal closure	745.745.11, 745.12, 745.2, 745.3, 745.4, 745.5, 745.61, 745.69
	Other congenital anomalies of the heart	746.x
	Congenital anomalies of circulatory system	747.1x, 747.21, 747.22, 747.3x, 747.4x
Renal disease	Nephrotic syndrome	581.x
	Nephritis with membranous glomerulonephritis	583.1
	Chronic kidney disease	585.x
	History of nephrotic syndrome	V13.03
Inflammatory bowel disease	Enteritis	555.x
	Ulcerative colitis	556.0, 556.6, 556.8, 556.9
Stroke	Intracerebral hemorrhage	431, 432.x
	Occlusion and stenosis of precerebral arteries	433.x
	Occlusion of cerebral arteries	434.x
	Transient cerebral ischemia	435.x
	History of stroke	V12.54
Cancers/neoplasms	Renal tumors	189.0
	Brain tumors	191.x
	Leukemia	204.x, 205.x, 206.x, 207.x, 208.x
Bone marrow transplant	Bone marrow transplantation	41.0x
	Transfusion	99.01, 99.04, 99.74
Obesity	Obesity	278.0x

Traditional risk factors for VTE include placement of central venous lines (CVL), frequent hospitalization, and immobilization for pain crisis and need for surgery.<sup>6-9</sup> Sickle cell-specific risk factors include platelet activation, chronic activation of coagulation secondary to externalization of the highly procoagulant phosphatidylserine on the sickled red blood cells, increased expression of tissue factor on circulating monocytes, and acquired deficiency of natural anticoagulants (proteins S and C).<sup>10-15</sup>

Previously, we reported a single-institution retrospective study of 414 pediatric patients (≤21 years) with SCD followed at Nationwide Children’s Hospital between 2009 and 2015.<sup>16</sup> Cumulative incidence of VTE was found to be 2.9% (12/414). Nine of the 12 VTE were CVL associated. On multivariable analysis, the presence of a CVL was identified as an independent risk factor for thrombosis (odds ratio [OR] [ $\pm$ 95% confidence interval (CI)], 33.8 [8.7-130.9]). The primary objective of the current multicenter cohort study was to review the rate of VTE in pediatric subjects with SCD across 48 tertiary-care children’s

hospitals in the United States over a 7-year period (2009-2015). Additionally, we investigated the risk factors associated with VTE in this cohort.

## Methods

### Data source

This retrospective, multicenter cohort study was deemed to be exempt by the Institutional Review Board at Nationwide Children’s Hospital. Administrative approval was obtained through the Children’s Hospital Association (Overland Park, KS). Data for this study was obtained from the Pediatric Health Information System (PHIS), an administrative database that contains data from inpatient, ambulatory surgery, emergency department, and observation encounters for 48 tertiary-care children’s hospitals in the United States.<sup>17,18</sup> Participating centers are heterogeneous for bed number, daily census, and geographic location. Data reliability and quality are assured through a joint effort between the participating hospitals and the Children’s

Hospital Association.<sup>19,20</sup> Data are deidentified at the time of submission and subject to a number of validity and reliability checks before being included in the dataset. For the purpose of this study, data from all 48 participating hospitals were included.

## Study population

International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) codes were used to identify subjects. Eligible subjects were  $\leq 21$  years of age (at last encounter), were admitted to one of the participating PHIS hospitals between 1 January 2009 and 30 September 2015 and had at least 2-SCD specific ICD-9-CM discharge codes (Table 1). Subjects who underwent hematopoietic stem cell transplant during the course of the study were excluded from the analysis. Baseline demographic variables including patient age, sickle cell genotype, sex, race/ethnicity, and mortality were abstracted. Venous thromboembolic events during the study period were identified using ICD-9-CM codes. Superficial vein thromboses (ICD-9-CM 451.0) were not considered to be VTE events. For patients with multiple hospitalizations with VTE codes, only the first thromboembolic event was included in the analysis.

Billing codes were used to identify CVL placement,<sup>21</sup> and pharmaceutical billing codes were used to identify estrogen-containing oral contraceptive use. Chronic medical conditions known to be associated with VTE (namely, congenital heart disease, inflammatory bowel disease, renal disease [including nephrotic syndrome], and history of cancer [leukemia, brain and renal tumors], stroke, and obesity) were also identified using ICD-9-CM codes (Table 1).<sup>22-26</sup> A diagnosis of these conditions was included in the analysis only if the subject had 2 disease-specific codes during the study period (eg, leukemia would only be included in the analysis if the subject had 2 ICD-9-CM codes specific for leukemia documented during the study period). To investigate age as a risk factor for VTE, we compared age at VTE (for patients with a history of thrombosis) to age at censoring (for those who did not develop VTE). Similarly, to assess the impact of “length of hospital stay” and “intensive care unit (ICU) utilization” on development of VTE, the hospital admission during which the VTE occurred (for patients with a history of thrombosis) was compared with last admission (for those without VTE).

## Statistical analysis

Standard statistical methods were used to summarize the variables (frequency and percent for categorical parameters and mean [ $\pm$  standard deviation (SD)], median, and range for ordinal or continuous scaled parameters). Multivariable logistic regression models were fit using stepwise and backward variable selection methods to identify unique patient characteristics associated with VTE. Similarly, logistic regression analysis was used to investigate the association between VTE and death after adjusting for cancer, renal disease, stroke, congenital heart disease, and inflammatory bowel disease. Due to the low event rate of VTE, logistic regression models were corrected using the Firth method.<sup>27</sup> Associations were summarized by calculating ORs and corresponding 95% CIs. To assess the correlation between number of CVLs placed and number of SCD patients encountered per hospital, Pearson correlation coefficients were used. Analyses were performed using

**Table 2. Baseline demographic information**

Characteristics	n (%)
Total unique patients	10 454
Male sex	5424 (51.9)
<b>Race</b>	
African American/black	9411 (90.0)
White	274 (2.6)
Asian	15 (0.1)
Pacific Islander	4 (0.04)
American Indian	15 (0.1)
Other	482 (4.6)
Missing/unknown	253 (2.4)
<b>Ethnicity</b>	
Hispanic/Latino	441 (4.2)
Not Hispanic/Latino	8999 (86.1)
Unknown	1014 (9.7)
<b>Any VTE diagnosis*</b>	181 (1.7)
Pulmonary embolism	43 (0.4)
Lower DVT	41 (0.4)
Upper DVT	75 (0.7)
Other VTE	53 (0.5)

\*Some patients had >1 VTE diagnosis code at first occurrence.

SAS version 9.3 (SAS Institute, Cary, NC). All calculated *P* values were 2 sided, and *P* < .05 was considered statistically significant.

## Results

A total of 10 454 eligible subjects with SCD (5030 females) underwent 67 122 admissions between 1 January 2009 and 30 September 2015 (median, 4 admissions/patient; range, 2-101 admissions). Median age ( $\pm$  interquartile range [IQR]) at last encounter during study period was 10 ( $\pm 11$ ) years. Baseline demographic information is elaborated in Table 2. During the study period, 1987 CVLs were placed in 1522 subjects (458 peripherally inserted central catheters [PICCs], 349 tunneled externalized catheters [eg, Broviac and Hickman catheters], 353 totally implantable catheters [eg, mediports and portacaths], and 827 unspecified catheters [including dialysis catheters and jugular and femoral vein catheters]).<sup>21</sup>

One hundred eighty one subjects (1.7%) developed an index venous thromboembolic event during the study period. One hundred thirty six out of 181 subjects (75.1%) had HbSS genotype, 14 (7.7%) had HbS- $\beta$  thalassemia genotype, 16 (8.8%) had HbSC genotype, and 15 (8.3%) were unspecified. Median age ( $\pm$ IQR) at VTE diagnosis was 15.9 ( $\pm 7.4$ ) years. Forty three out of 181 (23.8%) subjects had a pulmonary embolism code at diagnosis. Median age (range) of this subcohort was 18.4 ( $\pm 4.1$ ) years. Ninety seven out of 1522 patients (6.4%) who underwent a CVL placement developed a thromboembolic event (23/97 patients with CVL-associated VTE had an additional pulmonary embolism diagnosis code). Median (range) time interval between the most recent CVL placement and VTE development was 4 weeks (same admission, 4.2 years).

**Table 3. Univariate and multivariable analysis investigating association of patient characteristics with VTE**

Characteristics	VTE diagnosis, n (%)		Unadjusted OR		Adjusted OR	
	Yes (n = 181)	No (n = 10 273)	Estimate (95% CI)	P	Estimate (95% CI)	P
<b>SCD type</b>						
HbSS	136 (75.1)	7 196 (70.1)	—	—		
HbS-B	14 (7.7)	886 (8.6)	0.86 (0.50-1.49)	.5950		
HbSC	16 (8.8)	1 305 (12.7)	0.67 (0.40-1.2)	.1219		
Unspecified	15 (8.3)	886 (8.6)	0.92 (0.54-1.57)	.7634		
<b>Stroke</b>						
No	137 (75.7)	9 598 (93.4)	—	—	—	—
Yes	44 (24.3)	675 (6.6)	4.60 (3.25-6.51)	<.0001	2.19 (1.45-3.21)	<.0001
<b>Congenital heart disease</b>						
No	177 (97.8)	10 194 (99.2)	—	—		
Yes	4 (2.2)	79 (0.8)	3.25 (1.24-8.55)	.0168		
<b>IBD</b>						
No	180 (99.5)	10 257 (99.8)	—	—		
Yes	1 (0.5)	16 (0.2)	5.16 (0.92-29.03)	.0624		
<b>Chronic renal disease</b>						
No	173 (95.6)	10 239 (99.7)	—	—	—	—
Yes	8 (4.4)	34 (0.3)	14.54 (6.70-31.53)	<.0001	4.32 (1.69-11.07)	.0023
<b>Cancer</b>						
No	181 (100.0)	10 261 (99.9)	—	—		
Yes	0 (0.0)	12 (0.1)	2.25 (0.12-43.08)	.5893		
<b>Obese</b>						
No	161 (89.0)	9 942 (96.8)	—	—		
Yes	20 (11.0)	331 (3.2)	3.81 (2.37-6.11)	<.0001		
<b>Sex</b>						
Male	75 (41.4)	5 349 (52.1)	—	—	—	—
Female	106 (58.6)	4 924 (47.9)	1.53 (1.14-2.06)	.0049	1.60 (1.17-2.20)	.0035
<b>OCP</b>						
No	178 (98.3)	10 224 (99.5)	—	—		
Yes	3 (1.7)	49 (0.5)	4.05 (1.34-12.22)	.0131		
<b>Any CVL</b>						
No	84 (46.4)	8 848 (86.1)	—	—	—	—
Yes	97 (53.6)	1 425 (13.9)	7.16 (5.32-9.64)	<.0001	3.47 (2.49-4.83)	<.0001
<b>ICU stay</b>						
No	124 (68.5)	9 874 (93.8)	—	—	—	—
Yes	57 (31.5)	638 (6.2)	5.42 (4.02-7.30)	<.0001	3.16 (2.13-4.69)	<.0001
Median age at VTE or censoring	15.9 y	10.6 y	1.10 (1.07-1.13)	<.0001	1.08 (1.05-1.11)	<.0001
Median length of hospital stay	8 d	3 d	1.08 (1.07-1.10)	<.0001	1.05 (1.04-1.06)	<.0001

—, Reference; IBD, inflammatory bowel disease; OCP, estrogen-containing oral contraceptive pill.

Results of univariate and multivariable logistic regression analysis investigating the association of CVL placement, sickle cell genotype, length of hospitalization, ICU utilization, chronic medical conditions, and VTE are elaborated in Table 3. In summary, on multivariable logistic regression analysis, any catheter placement (OR [95% CI],  $P = 3.47 [2.49-4.83]$ ,  $P < .0001$ ), chronic renal disease ( $4.32 [1.69-11.07]$ ,  $P = .0023$ ), history of stroke ( $2.19$

$[1.45-3.21]$ ,  $P < .0001$ ), female sex ( $1.60 [1.17-2.20]$ ,  $P = .0035$ ), ICU utilization ( $3.16 [2.13-4.69]$ ,  $P < .0001$ ), older age ( $1.08 [1.05-1.11]$ ,  $P < .0001$ ), and length of hospitalization ( $1.05 [1.04-1.06]$ ,  $P < .0001$ ) were associated with VTE.

Of note, subjects with VTE had a median of 8.5 hospitalizations during the study period (compared with a median of 4 hospitalizations for those without VTE [ $P < .0001$ ]). Fifty-seven of the 181

thromboembolic admissions (31.5%) had a simultaneous code for ICU admission. Thirty-nine subjects died during the study period, and 5 of these subjects (12.8%) encountered a thromboembolic event prior to death. Four out of 5 deaths occurred during the same admission as VTE diagnosis, and 1 death occurred shortly after (<1 month) the VTE diagnosis. After adjusting for underlying comorbid conditions, VTE was independently associated with death (OR [95% CI];  $P = 8.95$  [3.55-22.56];  $P < .0001$ ).

Lastly, given that CVL placement was a strong predictor of VTE development, we investigated interhospital variability between CVL placement and VTE development. After excluding 10 hospitals that admitted <75 patients with SCD throughout the study period, we did not identify a significant, positive correlation between CVLs placed per 1000 patient encounters and VTEs per 1000 SCD patients ( $r = -0.01$ ,  $P = .97$ ).

## Discussion

In this retrospective, multicenter PHIS study, over a 7-year period, nearly 2% of patients with SCD developed VTE. CVL placement, chronic renal disease, history of stroke, female sex, length of hospitalization, ICU utilization, and older age were all independently associated with VTE development. When comparing our results to other administrative database studies, the rate of VTE in children with SCD was found to be lower than the rate of VTE in pediatric cancer patients (5%),<sup>26</sup> comparable to VTE rate in children with congenital heart disease undergoing cardiac surgery (2.7%),<sup>28</sup> but higher than the VTE rate in children with trauma and lower-extremity fractures (0.05% to 0.2%).<sup>29,30</sup> The current work supports our recent, single-institution study, where the cumulative incidence of VTE in children with SCD followed at Nationwide Children's Hospital was estimated to be 2.9%,<sup>16</sup> and it adds to a growing body of literature.

Thromboembolism is thought to be common in adults with SCD. In the largest study of VTE in SCD, Paul Stein and colleagues evaluated 1 804 000 SCD admissions between 1979 and 2003, using the National Hospital Discharge Survey. They estimated the prevalence of PE to be 3.5 times higher in patients <40 years of age with SCD than in African American controls.<sup>31</sup> Although the prevalence of deep vein thrombosis (DVT) was similar in both cohorts, patients with SCD and DVT were significantly younger than controls (31 years vs 54 years). In a single-institution, cross-sectional study by Rakhi Naik and colleagues, 25% (101/404) patients with SCD had a history of VTE, with a median age of diagnosis of 29.9 years.<sup>4</sup> After adjusting for multiple variables, non-catheter-related VTE was associated with a 3.6-fold increased hazard ratio (HR) of death. The same group subsequently used data from the Cooperative Study of Sickle Cell Disease to estimate incidence rate for first VTE.<sup>5</sup> They studied 1523 SCD patients  $\geq 15$  years of age and estimated the cumulative incidence of VTE by 40 years of age to be 11.3% (95% CI, 8.3-15.3). Individuals with HbSS/S $\beta^0$  had the highest incidence of VTE; additionally, SCD patients with VTE had a 2.3-fold increased HR of death as compared with those in whom thromboembolism did not develop. Ann Brunson and colleagues retrospectively evaluated 6237 patients with SCD using the Patient Discharge Database for the State of California.<sup>32</sup> By 40 years of age, the cumulative incidence of VTE was 12.5% (95% CI, 11.5-13.6). Additionally, VTE was associated with a 2.9-fold increased HR of death. In summary, adult studies have consistently demonstrated an 11% to 12% cumulative

incidence of VTE in patients with SCD by 40 years of age, in addition to reporting a significant association between thromboembolism and death.

In stark contrast to adult literature, pediatric data on SCD and VTE are largely limited to case reports<sup>33,34</sup> and case series investigating the risk of CVL placement in children with SCD.<sup>6,35,36</sup> The first attempt to systematically study VTE in pediatric patients with SCD was made by Tiago de Oliveira Boechat and colleagues in 2015.<sup>37</sup> They performed a retrospective study of 1063 patients followed at the State Institute of Hematology of Rio de Janeiro between the years 2000-2012.<sup>37</sup> Twenty subjects (1.8%) underwent CVL placement (usually for acute management of sepsis and acute chest syndrome). Two subjects (0.2%; median age: 6 years) developed DVT after placement of femoral lines (median duration of CVL: 5 days) for management of acute chest syndrome. The difference in the VTE rate between the State Institute of Hematology of Rio de Janeiro and PHIS datasets are likely secondary to increased CVL placement in the institutions included in the PHIS study (1.8% vs 14.5%, respectively). Since the publication of the stroke prevention (STOP) trial in 1998,<sup>38</sup> chronic transfusions have become the standard of care for children with SCD and abnormal transcranial Doppler results. Nearly 20% of pediatric SCD patients in the United States are on chronic transfusion therapy.<sup>39</sup> Iron overload, the inevitable consequence of chronic transfusion therapy, may be prevented by erythrocytapheresis.<sup>40,41</sup> We hypothesize that increased use of erythrocytapheresis in children with SCD managed in tertiary care centers in the United States has required increased placement of CVLs and consequently greater thrombosis risk.

The rate of PE observed in our cohort (24%) was higher than the PE rate previously reported in a PHIS study investigating the epidemiology of VTE in an unselected cohort of children (11%).<sup>42</sup> A high prevalence of PE in patients with SCD or SC trait has been previously noted in adult studies,<sup>43-45</sup> and is hypothesized to result from in situ pulmonary artery thrombosis. Interestingly, even though the majority of thrombotic events occurred in the setting of CVLs, VTE was associated with an increased HR of death. CVL placement is often required in children with SCD who have additional comorbidities, such as history of stroke, abnormal transcranial Doppler findings, recurrent vaso-occlusive crisis, and acute chest syndrome, possibly indicating a severe sickle cell phenotype. The fact that subjects with VTE had significantly greater number of admissions over the study period (median of 8.5 admissions vs 4 admissions for those without VTE) lends support to this hypothesis.

The current work represents the largest VTE study in pediatric patients with SCD. Limitations of the current study include use of an administrative database, which relies on accurate documentation of diagnosis using ICD-9-CM codes. Also, given limitations of ICD-9-CM coding, we were unable to distinguish patients with HbS- $\beta^0$  thalassemia from those with HbS- $\beta^+$  thalassemia, even though both conditions have very different phenotypes. Patients were eligible only if they had 2 disease-specific ICD-9-CM codes, whereas this may have excluded some patients with SCD/chronic medical conditions, we believe this was important to ensure validity of the data. Additionally, we only investigated inpatient data, because we thought it was very unlikely for a pediatric patient with SCD and VTE to be managed on an outpatient basis. It was difficult to determine a temporal relationship between CVL placement/chronic medical

condition development and VTE, and therefore, this study documents association between these factors and not causality. It was also technically challenging to estimate how many CVLs were placed for acute indications vs chronic conditions. We only studied patients between the years 2009 and 2015; it is possible that several patients who developed VTE before 2009 were missed. The study therefore documents the VTE rate over a specified period of time and not the cumulative prevalence of VTE in children with SCD. A prospective study is needed to confirm our findings, but this would be hard to accomplish. Because there was significant overlap between CVL billing codes, we were unable to confidently investigate the impact of CVL subtype of VTE development. We were also unable to assess the duration/complications of anticoagulation since the PHIS pharmacy data does not differentiate between therapeutic and prophylactic anticoagulation use. Lastly, our data, though generalizable to academic tertiary care pediatric centers, may not be representative of nonfreestanding hospitals.

In summary, our findings document that VTE can occur in children with SCD, particularly adolescents and young adults. In addition, the VTE diagnosis is associated with an increased HR of death. Lastly, CVL placement was identified as a modifiable risk factor for VTE development. A risk–benefit assessment should be undertaken in every SCD patient before CVL placement, and thrombosis/

need for anticoagulation should be discussed as a risk factor. The collection of prospective data, though difficult, would be critical in confirming our findings and eventually to develop a risk prediction model to identify patients at highest risk of VTE, who may benefit from prophylactic anticoagulation.

## Acknowledgments

R.K. is the recipient of the Hemostasis and Thrombosis Research Society, Mentored Research Award (2016-2018), which was supported by an educational grant from Bioerativ Therapeutics.

## Authorship

Contribution: R.K. and J.S. designed the research study, analyzed the data, and wrote the manuscript; and S.C., S.H.O., and A.D. analyzed the data and critically reviewed the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profile: R.K., 0000-0001-8004-4190.

Correspondence: Riten Kumar, Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205; e-mail: [riten.kumar@nationwidechildrens.org](mailto:riten.kumar@nationwidechildrens.org).

## References

1. Wun T, Brunson A. Sickle cell disease: an inherited thrombophilia. *Hematology Am Soc Hematol Educ Program*. 2016;2016:640-647.
2. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38(4 Suppl):S512-S521.
3. Naik RP, Streiff MB, Lanzkron S. Sickle cell disease and venous thromboembolism: what the anticoagulation expert needs to know. *J Thromb Thrombolysis*. 2013;35(3):352-358.
4. Naik RP, Streiff MB, Haywood C Jr, Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med*. 2013;126(5):443-449.
5. Naik RP, Streiff MB, Haywood C Jr, Segal JB, Lanzkron S. Venous thromboembolism incidence in the Cooperative Study of Sickle Cell Disease. *J Thromb Haemost*. 2014;12(12):2010-2016.
6. Abdul-Rauf A, Gauderer M, Chiarucci K, Berman B. Long-term central venous access in patients with sickle cell disease. Incidence of thrombotic and infectious complications. *J Pediatr Hematol Oncol*. 1995;17(4):342-345.
7. Adam S, Jonassaint J, Kruger H, et al. Surgical and obstetric outcomes in adults with sickle cell disease. *Am J Med*. 2008;121(10):916-921.
8. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288-1294.
9. Raj A, Bertolone S, Bond S, Burnett D, Denker A. Cathlink 20: a subcutaneous implanted central venous access device used in children with sickle cell disease on long-term erythrocytapheresis—a report of low complication rates. *Pediatr Blood Cancer*. 2005;44(7):669-672.
10. Ataga KI, Orringer EP. Hypercoagulability in sickle cell disease: a curious paradox. *Am J Med*. 2003;115(9):721-728.
11. Noubouossie D, Key NS, Ataga KI. Coagulation abnormalities of sickle cell disease: Relationship with clinical outcomes and the effect of disease modifying therapies. *Blood Rev*. 2016;30(4):245-256.
12. Piccin A, Murphy C, Eakins E, et al. Protein C and free protein S in children with sickle cell anemia. *Ann Hematol*. 2012;91(10):1669-1671.
13. Setty BN, Key NS, Rao AK, et al. Tissue factor-positive monocytes in children with sickle cell disease: correlation with biomarkers of haemolysis. *Br J Haematol*. 2012;157(3):370-380.
14. Shah N, Thornburg C, Telen MJ, Ortel TL. Characterization of the hypercoagulable state in patients with sickle cell disease. *Thromb Res*. 2012;130(5):e241-e245.
15. Wright JG, Malia R, Cooper P, Thomas P, Preston FE, Serjeant GR. Protein C and protein S in homozygous sickle cell disease: does hepatic dysfunction contribute to low levels? *Br J Haematol*. 1997;98(3):627-631.
16. Woods G, Sharma R, Creary S, et al. Venous thrombo-embolism (VTE) in children with sickle cell disease (SCD): an institutional experience. *J Thromb Haemost*. 2015;13:58.
17. Lo JY, Minich LL, Tani LY, Wilkes J, Ding Q, Menon SC. Factors Associated With Resource Utilization and Coronary Artery Dilatation in Refractory Kawasaki Disease (from the Pediatric Health Information System Database). *Am J Cardiol*. 2016;118(11):1636-1640.

18. Witmer CM, Lambert MP, O'Brien SH, Neunert C. Multicenter cohort study comparing U.S. management of inpatient pediatric immune thrombocytopenia to current treatment guidelines. *Pediatr Blood Cancer*. 2016;63(7):1227-1231.
19. Blevins EM, Glanz K, Huang YS, Raffini L, Shinohara RT, Witmer C. A multicenter cohort study of inferior vena cava filter use in children. *Pediatr Blood Cancer*. 2015;62(12):2089-2093.
20. Lavery AM, Banwell BL, Liu G, Waldman AT. Hospital admission rates for pediatric multiple sclerosis in the United States using the Pediatric Health Information System (PHIS). *Mult Scler Relat Disord*. 2016;9:5-10.
21. Orgel E, Ji L, Pastor W, Schore RJ. Infectious morbidity by catheter type in neutropenic children with cancer. *Pediatr Infect Dis J*. 2014;33(3):263-266.
22. Gentilomo C, Huang YS, Raffini L. Significant increase in clopidogrel use across U.S. children's hospitals. *Pediatr Cardiol*. 2011;32(2):167-175.
23. Kerlin BA, Smoyer WE, Tsai J, Boulet SL. Healthcare burden of venous thromboembolism in childhood chronic renal diseases. *Pediatr Nephrol*. 2015;30(5):829-837.
24. Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. *Pediatr Blood Cancer*. 2012;59(2):258-264.
25. Wedekind MF, Dennis R, Sturm M, Koch T, Stanek J, O'Brien SH. The effects of hospital length of stay on readmissions for children with newly diagnosed acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2016;38(5):329-333.
26. O'Brien SH, Klima J, Termuhlen AM, Kelleher KJ. Venous thromboembolism and adolescent and young adult oncology inpatients in US children's hospitals, 2001 to 2008. *J Pediatr*. 2011;159(1):133-137.
27. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80(1):27-38.
28. Silvey M, Hall M, Bilynsky E, Carpenter SL. Increasing rates of thrombosis in children with congenital heart disease undergoing cardiac surgery. *Thromb Res*. 2017;162:15-21.
29. Candrilli SD, Balkrishnan R, O'Brien SH. Effect of injury severity on the incidence and utilization-related outcomes of venous thromboembolism in pediatric trauma inpatients. *Pediatr Crit Care Med*. 2009;10(5):554-557.
30. Murphy RF, Naqvi M, Miller PE, Feldman L, Shore BJ. Pediatric orthopaedic lower extremity trauma and venous thromboembolism. *J Child Orthop*. 2015;9(5):381-384.
31. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. *Am J Med*. 2006;119(10):897.
32. Brunson A, Lei A, Rosenberg AS, White RH, Keegan T, Wun T. Increased incidence of VTE in sickle cell disease patients: risk factors, recurrence and impact on mortality. *Br J Haematol*. 2017;178(2):319-326.
33. Alli NA, Wainwright RD, Mackinnon D, Poyiadjis S, Naidu G. Skull bone infarctive crisis and deep vein thrombosis in homozygous sickle cell disease: case report and review of the literature. *Hematology*. 2007;12(2):169-174.
34. Villanueva H, Kuril S, Krajewski J, Sedrak A. Pulmonary thromboembolism in a child with sickle cell hemoglobin d disease in the setting of acute chest syndrome. *Case Rep Pediatr*. 2013;2013:875683.
35. Jeng MR, Feusner J, Skibola C, Vichinsky E. Central venous catheter complications in sickle cell disease. *Am J Hematol*. 2002;69(2):103-108.
36. Shah N, Landi D, Shah R, Rothman J, De Castro LM, Thornburg CD. Complications of implantable venous access devices in patients with sickle cell disease. *Am J Hematol*. 2012;87(2):224-226.
37. Boechat TO, do Nascimento EM, Lobo CL, Ballas SK. Deep venous thrombosis in children with sickle cell disease. *Pediatr Blood Cancer*. 2015;62(5):838-841.
38. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339(1):5-11.
39. Vichinsky EP, Ohene-Frempong K; Transfusion Committee. Approaches to transfusion therapy and iron overload in patients with sickle cell disease: results of an international survey. *Pediatr Hematol Oncol*. 2011;28(1):37-42.
40. Hilliard LM, Williams BF, Lounsbury AE, Howard TH. Erythrocytapheresis limits iron accumulation in chronically transfused sickle cell patients. *Am J Hematol*. 1998;59(1):28-35.
41. Lee MT, Piomelli S, Granger S, et al; STOP Study Investigators. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood*. 2006;108(3):847-852.
42. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001-1008.
43. Austin H, Key NS, Benson JM, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. *Blood*. 2007;110(3):908-912.
44. Folsom AR, Tang W, Roetker NS, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. *J Thromb Haemost*. 2015;13(1):2-9.
45. Mekontso Dessap A, Deux JF, Abidi N, et al. Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med*. 2011;184(9):1022-1029.