Hospital-Associated Venous Thromboembolism in Children: Incidence and Clinical Characteristics

Clifford M. Takemoto, MD[1], Sajeet Sohi, MD[1], Kruti Desai, MD[1], Raman Bharaj, MD[1], Anuj Khanna, MD[1], Susan McFarland, MD[2], Sybil Klaus, MD[2], Alia Irshad, MD[2], Neil A. Goldenberg, MD, PhD[1,3], John J. Strouse, MD, PhD[1,4], and Michael B. Streiff, MD[4]

Objective To determine incidence and clinical characteristics of hospital-associated venous thromboembolism (VTE) in pediatric patients.

Study design A retrospective analysis of patients with hospital-associated VTE at the Johns Hopkins Hospital from 1994 to 2009 was performed. Clinical characteristics of patients aged 21 years and younger who developed VTE symptoms after 2 days of hospitalization or <90 days after hospital discharge were examined. *International Classification of Diseases, Ninth Revision* codes were used to categorize patients with complex chronic medical conditions and trauma.

Results There were 270 episodes of hospital-associated VTE in 90 485 admissions (rate 30 per 10 000 admissions). Young adults (18-21 years) and adolescents (14-17 years) had significantly increased rates of VTE compared with children (2-9 years) (incidence rate ratio [IRR] 7.7, 95% CI 5.1-12.0; IRR 4.3, 95% CI 2.7-6.8, respectively). A central venous catheter (CVC) was present in 50% of patients, and a surgical procedure was performed in 45% of patients before VTE diagnosis. For patients without a CVC, trauma was the most common admitting diagnosis. CVC-related VTE was diagnosed most frequently in infants (<1 year old) and in patients with malignancy. Renal and cardiac diseases were associated with the highest rates of VTE (51 and 48 per 10 000, respectively). Rates were significantly higher among those with ≥4 medical conditions compared with those with 1 medical condition (IRR 4.0, 95% CI 1.4-8.9).

Conclusion Older age and multiple medical conditions were associated with increased rates of hospital-associated VTE. These data can contribute to the design of future clinical trials to prevent hospital-associated VTE in high-risk children. *(J Pediatr 2014;164:332-8)*.

Hospital-associated venous thromboembolism (VTE), which encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality.[1] The estimated incidence of hospital-associated VTE in adult medical or general surgical patients without appropriate prophylaxis ranges from 10% to 40%.[2] In comparison, studies of national administrative data sets of pediatric patients have reported an overall incidence of VTE of 0.2%-0.6% of hospitalizations.[3-5] Although VTE is much less common in children compared with adults, the incidence of VTE in pediatric patients has increased during the past decade.[3] Specific diseases have been associated with increased VTE rates,[6] with VTE diagnosed in 5% of hospitalized adolescents and young adults with malignancy (most often associated with presence of a central venous catheter [CVC][7]) and 0.25%-0.6% in pediatric trauma patients.[8,9] A number of other conditions that also occur in children are associated with an increased risk of VTE in adults, including inflammatory bowel disease, nephrotic syndrome, and systemic infection[6]; however, the incidence of hospital-associated VTE in children with these and other diagnoses has not been examined carefully.

Evidence-based guidelines for VTE thromboprophylaxis are well established for adults,[10-12] but there is no consensus on VTE prophylaxis in children, in large part due to a paucity of evidence.[13] Indiscriminant use of pharmacologic prophylaxis could needlessly expose low-risk children to excessive risk of bleeding and heparin-induced thrombocytopenia; conversely, omission of prophylaxis in high-risk children may result in preventable episodes of VTE. Consequently, development of an evidence-based approach to risk stratification is essential to identify patients who would benefit from thromboprophylaxis. Central to the appropriate use of VTE prophylaxis in children is the identification of the highest-risk patients, based on readily available clinical data

CCC	Complex chronic condition
CVC	Central venous catheter
DVT	Deep venous thrombosis
HLHS	Hypoplastic left heart syndrome
ICD-9	*International Classification of Diseases, Ninth Revision*
IRR	Incidence rate ratio
PE	Pulmonary embolism
VTE	Venous thromboembolism

From the [1]Division of Pediatric Hematology, [2]Division of Quality and Safety, Department of Pediatrics, Johns Hopkins University, Baltimore, MD; [3]Pediatric Thrombosis Program, All Children's Hospital—Johns Hopkins Medicine, St. Petersburg, FL; and [4]Division of Adult Hematology, The Johns Hopkins Hospital, Baltimore, MD

The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.10.025

including principal diagnosis and age. The most common clinical factor associated with VTE in children is the presence of a CVC.[14] However, it appears that the majority of children with CVCs do not develop VTE, and pediatric trials demonstrating the safety and efficacy of pharmacologic prophylaxis of CVC-related VTE are lacking.[15] Even though a number of studies have reported the incidence of VTE in hospitalized children, relatively few published studies focus on the subset of patients with hospital-associated VTE.[16] The purpose of this retrospective study was to determine clinical characteristics associated with the development of hospital-associated VTE.

Methods

We performed a chart review of pediatric patients (aged ≤21 years) who were hospitalized at the Johns Hopkins Hospital from 1994 to 2009. We identified patients with VTE using *International Classification of Diseases, Ninth Revision* (ICD-9) codes for DVT (451.11, 451.19, 45.12, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9, 453.2, 453.8, 453.9, 671.30, 671.31, 671.33, 671.40, 671.42, 671.44, 671.90, 671.91, 671.92, 671.93, 671.94) and PE (415.11, 415.19, 634.6, 634.61, 634.62, 635.60, 635.61, 635.62, 636.60, 636.61, 636.62, 637.60, 637.61, 637.62, 638.60, 638.61, 638.62, 673.20, 673.21, 673.22, 673.23, 673.24, V1251). The study was approved by the Johns Hopkins institutional review board. Hospital records were reviewed for objective documentation of VTE, the presence and onset of symptoms associated with VTE, principal and secondary diagnoses, a history of previous hospitalizations, and the presence of CVCs. We defined hospital-associated VTE as follows: (1) signs, symptoms, and diagnosis of VTE developing after 2 days of hospitalization or (2) diagnosis of VTE ≤90 days from a hospital discharge.[1] VTE episodes were defined as thrombosis of a new vascular territory or significant extension of a previous thrombus objectively documented with compression ultrasound with duplex Doppler, computed tomography angiography, magnetic resonance venography, or conventional venography.[17] A high-probability ventilation-perfusion scan was also considered objective confirmation of a new PE. We defined CVC-related VTE as a DVT within the same vessel as the CVC. ICD-9 codes for complex chronic conditions (CCCs) as previously published were used to determine medical diagnoses for 90 485 patients.[18] ICD-9 codes for the trauma as previously published were used to identify trauma patients.[9]

Hospital records were reviewed to confirm diagnoses of VTE. Individuals with chronic VTE (defined as previously diagnosed VTE and unchanged compared with previous imaging study) were excluded, as were patients with non–hospital-associated VTE, arterial thrombosis, and superficial vein thrombosis.

Incidence rate ratio (IRR) was calculated using exact methods as the ratio of patients with VTE per year to the total number of hospitalized patients per year. *P* values were calculated with the Student *t*-test and the χ^2 test; $P \leq .05$ was considered significant.

Results

We identified 238 patients who were 21 years and younger with 270 episodes of hospital-associated VTE among 90 485 total patient admissions from 1994 to 2009. This resulted in a total rate of 30 per 10 000 admissions, or 0.3%. One hundred eighty-five episodes of VTE were diagnosed within 90 days of a hospital discharge (rate of 20 per 10 000 or 0.2%); in 203 episodes, VTE was diagnosed after 2 days of hospital admission (rate of 22 per 10 000 or 0.2%). Hospital-associated VTE comprised 60% of all episodes of VTE diagnosed in hospitalized patients. In the 40% of episodes of VTE that did not meet the definition of hospital-associated VTE, patients had chronic VTE, asymptomatic VTE, and diagnosis of VTE within 48 hours of admission and no previous hospitalizations within 90 days. The demographics of patients with hospital-associated VTE are shown in Table I. Patients with hospital-associated VTE were significantly older and more often female compared with all hospitalized patients. There was no difference in the distribution of race between those with and without hospital-associated VTE. Hospital-associated VTE was also associated with a significant increase in the length of hospital stay compared with all hospitalized patients; for the subset of patients with hospital-associated VTE (diagnosed after 2 days of hospital admission), the length of hospital stay was even longer (median 10 days compared with 8 days).

We found a bimodal age distribution for patients with hospital-associated VTE, with the largest number among infants >1 year of age and adolescents through young adults 14-21 years of age, combined (Figure 1, A). When these data were adjusted for the number of admissions per age group, the rate of hospital-associated VTE was highest in older adolescents and young adults (Figure 1, B and Table II). IRR of hospital-associated VTE was nearly 8-fold that of children aged 2-9 years (Table II). We found that young women had the greatest rate of hospital-associated VTE at 117 per 10 000; this rate was 2-fold higher than that of

Table I. Demographics of patients with hospital-associated VTE in pediatric patients

	Hospital-associated VTE episodes (n = 270)	All hospital admissions (N = 90 485)	*P* value
Age, yr (median; IQR)	16; 8-19	8; 1-15	<.0001
Female sex, %	58	45	<.0001
Race, %			.2
White	48	53	
Black	45	40	
Other	7	7	
Length of stay, days (median; IQR)	All hospital-associated 8; 3-18 VTE diagnosed ≥2 days after hospital admission 10; 4–23 days	3; 2-17 days	<.0001