Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation

Brian R. Branchford,[1,2] Peter Mourani,[3] Lalit Bajaj,[4] Marilyn Manco-Johnson,[1,2] Michael Wang,[1,2] and Neil A. Goldenberg[1,2,5]

[1]Department of Pediatrics, Section of Hematology/Oncology/Bone Marrow Transplantation, University of Colorado-Denver and Children's Hospital Colorado, Aurora, CO; [2]University of Colorado Hemophilia and Thrombosis Center, Aurora, CO; [3]Department of Pediatrics, Section of Critical Care, University of Colorado-Denver and Children's Hospital Colorado, Aurora, CO; [4]Department of Pediatrics, Section of Emergency Medicine, University of Colorado-Denver and Children's Hospital Colorado, Aurora, CO: and [5]Department of Medicine, Division of Hematology/Oncology/Bone Marrow Transplantation University of Colorado, and CPC Clinical Research, Aurora, CO, USA

ABSTRACT

Background
Studies evaluating risk factors for in-hospital venous thromboembolism in children are limited by quality assurance of case definition and/or lack of controlled comparison. The objective of this study is to determine risk factors for the development of in-hospital venous thromboembolism in children.

Design and Methods
In a case-control study at The Children's Hospital, Colorado, from 1st January 2003 to 31st December 2009 we employed diagnostic validation methods to determine pediatric in-hospital venous thromboembolism risk factors. Clinical data on putative risk factors were retrospectively collected from medical records of children with International Classification of Diseases, 9th edition codes of venous thromboembolism at discharge, in whom radiological reports confirmed venous thromboembolism and no signs/symptoms of venous thromboembolism were noted on admission.

Results
We verified 78 cases of in-hospital venous thromboembolism, yielding an average incidence of 5 per 10,000 hospitalized children per year. Logistical regression analyses revealed that mechanical ventilation, systemic infection, and hospitalization duration of five days or over were statistically significant, independent risk factors for in-hospital venous thromboembolism (OR=3.29, 95%CI=1.53-7.06, *P*=0.002; OR=3.05, 95%CI=1.57-5.94, *P*=0.001; and OR=1.03, 95%CI=1.01-1.04, *P*=0.001, respectively). Using these factors in a risk model, post-test probability of venous thromboembolism was 3.6%.

Conclusions
These data indicate that risk of in-hospital venous thromboembolism in children with this risk factor combination may exceed that of hospitalized adults in whom prophylactic anticoagulation is indicated. Substantiation of these findings via multicenter studies could provide the basis for future risk-stratified randomized control trials of pediatric venous thromboembolism prevention.

Key words: thrombosis, risk factors, case-control study.

Citation: Branchford BR, Mourani P, Bajaj L, Manco-Johnson M, Wang M, and Goldenberg NA. Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. Haematologica 2012;97(4):509-515. doi:10.3324/haematol.2011.054775

Acknowledgments: the authors thank Deborah Batson, Clinical Research Data Warehouse Architect at The Children's Hospital, Colorado, for her assistance with case and control group identification by ICD-9 codes and admission/discharge dates. B.B. is supported by a Clinical Fellowship Award from Baxter and the National Hemophilia Foundation. P.M. is supported in part by a career development grant from NIH (NIH career development grant (1K23RR021921). M.M-J. is supported in part by a Thrombophilia Pilot Project grant from the Centers for Disease Control and Prevention (U01DD00016). N.G. is supported in part by a career development award from the National Institutes of Health, National Heart Lung and Blood Institute (1K23HL084055).

Funding: B.R.B. is supported by a Clinical Fellowship Award from Baxter and the National Hemophilia Foundation. P.M. is supported in part by a career Development grant from NIH (NIH career development grant (1K23RR021921). M.M-J. is supported in part by a Thrombophilia Pilot Project grant from the Centers for Disease Control and Prevention (U01DD00016). N.A.G. is supported in part by a career development award from the National Institutes of Health, National Heart Lung and Blood Institute (1K23HL084055).

Manuscript received on September 9, 2011. Revised version arrived on November 2, 2011. Manuscript accepted on November 16, 2011.

Correspondence:
Brian R. Branchford, University of Colorado Hemophilia and Thrombosis Center P.O. Box 6507 Aurora, CO 80045-0507, USA.
E-mail: brian.branchford@childrens-colorado.org

Introduction

Venous thromboembolism (VTE), comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), affects an estimated 350,000 to 600,000 Americans each year, and together, DVT and PE are estimated to contribute to at least 100,000 deaths each year.[1] The recognition of the public health burden imposed by VTE, and the extent to which many cases (particularly hospital-acquired VTE) are preventable prompted a Call-to-Action by the United States Surgeon General in 2008.[1] As part of this effort, a Surgeon General's Working Group identified research into risk factors for development of VTE in children, and adverse outcomes of VTE in this population (such as the development of post-thrombotic syndrome following limb DVT) as an important priority.[2]

While the incidence of VTE is considerably lower in children than adults, and has been estimated at 5 per 10,000 per year from the National Hospital Discharge Survey,[3] more recent data suggest that pediatric VTE incidence may be dramatically increasing.[4] At the same time, the consequences of DVT and PE in children are substantial. Sixteen to 20% of children with VTE have objectively confirmed PE,[5] and retrospective data from the Hospital for Sick Children indicated a VTE-specific mortality rate of 9% among pediatric PE cases.[6] The risks of long-term pulmonary insufficiency and of chronic thromboembolic pulmonary hypertension following PE in children remain undefined. Additionally, a systematic review of the pediatric literature has demonstrated that at least 20% of children with limb DVT develop post-thrombotic syndrome (PTS), a syndrome of chronic venous insufficiency often associated with limitation in age-appropriate physical activities that are critical to normal growth and development.[7]

Recommendations for prevention of hospital-acquired VTE in adults are well established[8] and have been informed by evidence from randomized controlled clinical trials. In pediatrics, such recommendations and data are largely lacking, historically attributable to the rarity of VTE in this population. A non-selective (i.e. non-risk-stratified) approach to VTE prevention in hospitalized children through prophylactic anticoagulation would undoubtedly expose an excess of these young patients to bleeding risks in order to prevent relatively few deaths and long-term sequelae from VTE. While registries and cohort studies have identified central venous catheterization and infection as highly prevalent among pediatric VTE cases, few well-designed case-control studies employing diagnostic validation have been published that establish a significant increase in odds of VTE associated with these or other candidate risk factors for a selective approach to VTE prevention in hospitalized children. The development of such evidence, and its substantiation via subsequent multicenter studies, would provide the basis for future risk-stratified RCTs of pediatric VTE prevention.

Accordingly, the objective of this work was to determine risk factors for the development of in-hospital VTE in children, in the context of a single institution case-control study. We employed diagnostic validation methods to overcome the limitations of International Classification of Diseases, 9th edition (ICD-9) codes in pediatric VTE (for which evidence of validity and diagnostic performance has not been published), as well as the challenge of distinguishing pre-hospital *versus* in-hospital onset of VTE.

Design and Methods

Subjects

We retrospectively reviewed medical records of consecutive children (age birth through to 21 years old) hospitalized at the Children's Hospital Colorado, a 300-bed, tertiary care pediatric referral center with approximately 20 subspeciality sections, from 1st January 2003 to 31st December 2009 in whom ICD-9 diagnosis codes at discharge included VTE (cases), as well as records of children in whom these diagnoses were absent (contemporaneous controls). The pertinent ICD-9 codes were 453.2 (inferior vena cava thrombus), 453.4 (venous thromboembolism of deep vessels of the lower extremity), 453.8 (embolism or thrombosis of other specified veins), 453.9 (embolism and thrombosis of unspecified site), and 415.1 (pulmonary embolism and infarction). Case definition of in-hospital VTE was further refined by the following validation criteria: 1) supporting radiological evidence of VTE, as previously defined[9] (using compression ultrasonography with Doppler imaging for objective confirmation of extremity DVT, with CT or MRI for suspected extension into deep pelvic or abdominal veins, and spiral CT for PE confirmation), no sooner than Day 2 of hospitalization; 2) absence of documentation of signs or symptoms consistent with VTE in the admission history and physical exam; 3) length of hospitalization at least two days. Presence of risk factors (including central venous catheters, CVCs), was defined according to the admission history, and hence preceded the diagnosis of VTE (as per criterion #1 above). Controls were selected from a patient database provided by the institution's Clinical Research Data Warehouse based upon stated eligibility criteria, and then matched with cases on age (exact year-matching), gender, and hospital unit location (pediatric intensive care unit, PICU; neonatal intensive care unit, NICU; cardiac intensive care unit, CICU; and non-ICU floor) at time of VTE diagnosis. Subsequently, controls were assigned a study ID number, and for each case, 2 controls were randomly selected, using a web-based random number generator program. Definition of hospitalized controls was further refined by duration of hospitalization of at least two days, and the validation criterion of absence of an impression of VTE among reports in the radiological record. Case and control criteria were confirmed by 2 independent reviewers (BB and NAG). The study was approved by the Colorado Multiple Institutional Review Board.

Data collection

Demographic data were extracted on age, gender, date of admission, and hospital unit location. In addition, clinical data on putative risk factors for VTE were retrospectively collected on cases and controls, including duration of hospitalization and presence/absence (and details) of the following: mechanical ventilation, systemic infection, central venous catheterization, chronic inflammatory disease, malignancy, surgery, dehydration, and obesity (measured as body mass index > 95th percentile for age, using CDC criteria).[10] Chronic inflammatory disease included Crohn's disease (n=1), ulcerative colitis (n=1), graft-*versus*-host-disease (n=1), autoimmune encephalitis (n=1) and necrotizing enterocolitis (n=1). Dehydration was identified based upon its notation in the admission history, and infection was noted based upon a description of systemic (non-localized) infection present in the admission or discharge history. Presence of central venous catheter (CVC) was divided into long-term CVC (Broviac, Mediport, etc.) *versus* short-term CVC (PICC line, temporary internal jugular or femoral line, etc.).

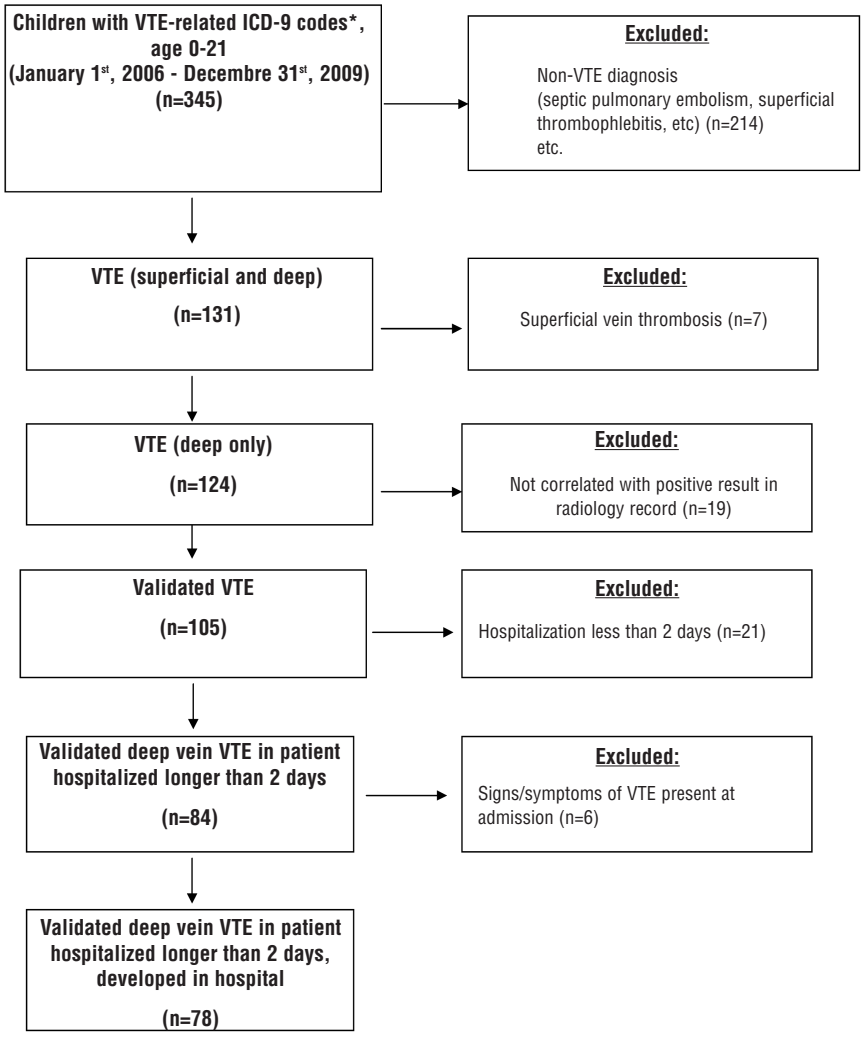
Statistical analyses

Descriptive statistics were used to define distributions of con-

tinuous variables and frequencies and proportions of categorical variables, which were then compared between cases and controls via Mann-Whitney U and χ^2 tests, respectively. Fisher's exact test was used in lieu of χ^2 in instances of a two-by-two table with a frequency value of 5 or under in at least one cell. Univariate and multiple logistic regression was employed to evaluate for unadjusted and adjusted associations between putative risk factors and case/control status; results were expressed as odds ratios (ORs), with accompanying 95% confidence intervals (95% CIs) calculated by the Wald method. A significance threshold defined *a priori* as $P<0.2$ was used for inclusion of explanatory variables into multiple logistic regression. Otherwise, for all hypothesis testing, $P<0.05$ was considered statistically significant. All hypothesis tests were two-tailed. χ^2 tests were performed using Epi Info version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA), and all other hypothesis tests were conducted using SAS 9.1 statistical software (SAS Institute, Cary, NC, USA). Positive likelihood ratios were calculated as sensitivity + (1-specificity), and negative likelihood ratios were calculated as specificity + (1-sensitivity), with corresponding confidence intervals determined as previously described.[11]

Results

Seventy-eight cases of in-hospital VTE were confirmed during the 7-year period of observation, after application of the validation criteria (see *Design and Methods* section). Figure 1 provides a flow diagram of case selection. Notably, the discharge diagnosis ICD-9 codes used to identify cases were found to have a specificity of 38% (131 of 345) for VTE, and of 23% (78 of 345) for in-hospital (i.e. hospital-acquired) VTE, in children. Given 22,094 hospitalizations of at least two days during the seven years of the study, this yielded an average in-hospital VTE incidence of 5 per 10,000 hospitalized children per year. Cases were matched by age, gender, date of hospitalization, and hospital unit location (PICU, CICU, NICU, and non-ICU floor) to 160 randomly selected controls. Demographic characteristics and frequency of putative risk factors for VTE are shown in Table 1 for cases *versus* controls. Peak VTE frequency was observed in infancy. The median time from hospital admission to VTE diagnosis was seven days (range 1-73 days). Nearly 80% of cases were mechanically ventilated, and the prevalence of sys-



*Qualifying ICD-9 codes included 453.2 (inferior vena cava thrombus), 453.4 (venous thromboembolism of deep vessels of the lower extremity), 453.8 (embolism or thrombosis of other specified veins), 453.9 (embolism and thrombosis of unspecified site), and 415.1 (pulmonary embolism and infarction).

Figure 1. Flow diagram showing the inclusion and exclusion criteria for selection of case subjects. This figure demonstrates how the 345 subjects initially identified by ICD-9 discharge diagnosis codes for thrombosis were reduced to 78 cases identified for final statistical analysis.

temic infection was approximately 60%. Long-term CVCs (Broviacs, Mediports, etc.) were identified in fewer than 20% of catheterized patients, with the remainder having short-term CVCs (PICC lines, temporary internal jugular or femoral lines, etc.). Short-term catheterization was present in approximately 50% of cases and in 27% of controls. No difference in the presence of long-term catheterization was noted between the cases and controls. The proportion of children that had three or more putative risk factors for VTE was significantly greater among cases than controls (80% *vs*. 38%, respectively; $P<0.001$). This corresponded to an OR of 6.06 (95%CI 3.22-11.4; $P<0.001$) for VTE development during hospitalization in patients who have three or more risk factors. Rate of previous hospitalization within 30 days was similar between cases and controls (13% *vs.* 14%; $P=1.00$).

Table 2 presents the results of unadjusted and adjusted odds of VTE associated with putative risk factors among all subjects, from univariate and multiple logistical regression. In univariate analyses, mechanical ventilation, a central venous catheter, systemic infection, and length of hospitalization were identified as statistically significant risk factors for development of in-hospital VTE. In multiple logistic regression, mechanical ventilation, systemic infection, and length of hospitalization served as statistically significant, independent risk factors for development of in-hospital VTE (OR=3.29, 95%CI=1.53-7.06, $P=0.002$; OR=3.05, 95%CI=1.57-5.94, $P=0.001$; and OR=1.03, 95%CI=1.01-1.04, $P=0.001$, respectively). The odds ratio for length of hospitalization indicated that, with each additional day of hospitalization, the odds of in-hospital VTE increases by 3%.

Subgroup analyses of risk factor profiles by hospital unit location revealed no statistically significant VTE risk factors for patients in the CICU. In the NICU, univariate analyses identified surgery and length of hospitalization as statistically significant risk factors for the development of in-hospital VTE (OR=4.22, 95%CI=1.25-14.3, $P=0.02$; and OR=1.02, 95%CI=1.00-1.04, $P=0.006$, respectively). In multiple logistic regression, however, only length of hospitalization of five days or more was a statistically significant, independent risk factor (OR=1.02, 95%CI=1.003-1.04, $P=0.02$). In the PICU, mechanical ventilation, systemic infection, cancer, and length of hospitalization were each shown to be statistically significant, independent risk factors for in-hospital VTE (OR=4.96, 95%CI=0.97-25.4, $P=0.005$; OR=12.6, 95%CI=2.86-55.8, $P<0.001$; OR=45.8, 95%CI=1.51-999, $P=0.03$; and OR=1.08, 95%CI=1.03-1,12, $P=0.001$, respectively).

The combination of mechanical ventilation, systemic infection, and length of hospitalization of five days or over had a hospital-wide sensitivity of 45% (95%CI: 34-57%) and a specificity of 95% (95%CI: 90-98%) for development of in-hospital VTE. Using these factors in a risk model, post-test probability of VTE was 3.1%. This same combination of risk factors when applied specifically in the PICU setting had a sensitivity of 47% (95%CI: 31-64%) and a

Table 1. Demographic characteristics and frequency of putative risk factors for VTE among cases *versus* controls. Statistically significant differences are shown in bold.

Characteristics	VTE cases (n=78)	Controls (n=160)	*P* value
Demographics			
Sex*			
Male	39 (50%)	82 (51%)	n/a
Female	39 (50%)	78(49%)	
Age*			
Median (range)	1 (0-21)	1 (0-21)	n/a
Birth - 1 y	34 (44%)	70 (44%)	
1 - 5 y	17 (22%)	35 (22%)	
6 - 10 y	6 (8%)	14 (9%)	
11 - 15 y	9 (12%)	20 (13%)	
16 - 21 y	12 (15%)	20 (13%)	
Hospital unit location*			
Floor	18 (23%)	37 (23%)	n/a
PICU	33 (42%)	66 (41%)	
NICU	17 (22%)	35 (22%)	
CICU	10 (13%)	22 (14%)	
Putative risk factors			
Mechanical ventilation	60 (77%)	57 (35%)	**<0.001**
Short-term central venous catheter	38 (49%)	44 (27%)	**0.001**
Long-term central venous catheter	5 (6%)	11 (7%)	0.57
Infection	49 (63%)	34 (21%)	**<0.001**
Surgery	23 (29%)	21(13%)	**0.002**
Malignancy	7 (9%)	9(6%)	0.33
Obesity	2 (3%)	5 (3%)	1.00
Dehydration	4 (5%)	4 (3%)	0.44
** Inflammatory disease	5 (6%)	0 (0%)	**0.004**
Hosp. days, median (range)	28 (4-233)	4 (2-139)	**<0.001**
Prior hospitalization within 30 d	10 (13%)	22 (14%)	1.00
# Putative risk factors			
Median (range)	4 (0-7)	2 (0-5)	0.18
0	0 (0%)	8 (5%)	--
1 only	3 (4%)	55 (34%)	**<0.001**
2 only	13 (16%)	37 (23%)	0.25
3 or more	62 (80%)	60 (38%)	**<0.001**

*VTE: venous thromboembolism; PICU: Pediatric Intensive Care Unit; NICU: Neonatal Intensive Care Unit; CICU: Cardiac Intensive Care Unit. * Controls were matched for cases on these factors. ** Included: Crohn's disease (n=1), ulcerative colitis (n=1), graft-versus-host disease (n=1), autoimmune encephalitis (n=1), and necrotizing enterocolitis (n=1).*

Table 2. Unadjusted and adjusted risk factors for development of in-hospital VTE in children (all hospital unit locations), from univariate and multiple logistical regression. Independent risk factors, as determined by the results of multivariate analysis, are shown in bold. See Table 1 for *P* values of unadjusted risk factors.

Risk factor	Unadjusted		Adjusted		
	OR	95% CI	OR	95% CI	*P* value
Mechanical ventilation *	6.36	3.4-11.8	3.29	1.53-7.06	0.002
Central venous catheter *	3.81	2.16-6.75	1.44	0.70-2.97	0.33
Systemic infection *	3.88	2.19-6.89	3.05	1.57-5.94	0.001
Surgery	1.49	0.81-2.76	--	--	--
Malignancy	1.65	0.59-4.62	--	--	--
Dehydration	2.11	0.51-8.66	--	--	--
Inflammatory disease	NE	NE	--	--	--
Obesity	0.82	0.16-4.30	--	--	--
Hospitalization >/=5 d*	1.04	1.03-1.06	1.03	1.01-1.04	<0.001
Prior hospitalization within 30d	1.73	0.81-3.68	--	--	--

*VTE: venous thromboembolism; OR: odds ratio; CI: confidence interval; NE: not evaluable. *Univariate P value met the criterion for inclusion in multivariate analysis (see also* Design and Methods *section).*

specificity of 88% (95%CI: 77-94%) for development of in-hospital VTE. The post-test probability of in-hospital VTE using these factors in a risk model was 0.95% in the specific setting of the PICU. Corresponding likelihood ratios and pre- and post-test probabilities using the model from multivariate data in Table 2 are shown in Table 3.

Table 3. Sensitivity, specificity, and pre-test probability to post-test probability changes for the risk factor model in all hospitalized patients and patients in the PICU.

Risk factor model *	Hospital-wide	PICU-specific
Sensitivity	45% (95%CI: 34-57%)	47% (95%CI: 31-64%)
Specificity	95% (95%CI: 90-98%)	88% (95%CI: 77-94%)
Pre-test probability	0.35%	0.45%
Positive likelihood ratio	9	2.13
Negative likelihood ratio	1.73	1.66
Post-test probability**	3.1%	0.95%

** Consisted of mechanical ventilation + systemic infection + length of hospitalization >/= 5 days (see multivariate data from Tables 2 and 3). Given lack of precision stemming from rarity of cancer patients, cancer was not included in the PICU model despite its statistical significance. **Assumes pre-test probabilities of 0.35% (hospital-wide) and 0.45% (PICU), based upon frequencies of 78 cases among 22,094 hospital-wide admissions of more than 2 days and 17 cases among 3,804 PICU admissions.*

Discussion

The present work provides unique data on risk factors for development of pediatric in-hospital VTE, by means of a case-control study employing diagnostic validation. It reveals that patients who possess any three or more putative risk factors shown in Table 1 have a 6-fold increase in odds of in-hospital VTE. A specific risk factor model, based upon the statistically significant independent risk factors of in-hospital VTE in children identified in this study, comprises mechanical ventilation, systemic infection, and length of hospitalization greater than or equal to five days. This risk factor model is 45% sensitive and 95% specific for in-hospital VTE with a post-test probability of VTE of 3.1% in a hospital-wide setting, and 0.95% in the PICU setting.

The presence of a central venous catheter was statistically significant in univariate analyses and has been consistently shown in the literature to be clinically important as a risk factor for VTE in children.[12] However, since CVC are frequently placed temporarily in hospitalized children for blood sampling, fluid resuscitation, and medication or blood product administration, and yet the incidence of VTE in children is rather low, it was not surprising that the presence of a short-term CVC was only shown in unadjusted analyses to be a significant risk factor for pediatric in-hospital VTE, and not as an independent risk factor in analyses adjusted for other demonstrated risk factors. While our analysis did not support long-term CVC as an independent risk factor for in-hospital VTE, it is possible that there may still be an independent association for outpatient VTE in children.

Prior data on risk factors for in-hospital VTE in unselected children are limited to a few studies. In a recent restrospective analysis using the Kids' Inpatient Database, independent risk factors for development of DVT in hospitalized children included age 15 years or over, obesity, inflammatory bowel disease, hematologic malignancy, and thoraco-abdominal or orthopedic surgery.[13] By contrast, in a retrospective analysis of the Riley Children's Hospital experience, Sandoval and colleagues observed no consistent trend of increasing VTE risk with age, but rather a bimodal distribution of age with respect to hospital-acquired DVT, with peaks in infancy and adolescence.[14] In one of the only prospective studies of in-hospital DVT, Rohrer and colleagues observed one case of in-hospital DVT in 59 at-risk children (defined by the presence of two risk factors, including surgery, trauma, immobility, stroke, cancer, sepsis, femoral venous catheterization, prior VTE, and known thrombophilia), from among 1,779 consecutive hospitalized children over a 6-month period at the University of Massachusetts Medical Center.[15] This finding emphasizes the need for further risk-stratification (*i.e.* greater selection) in identifying those hospitalized children at appreciably increased risk of VTE; yet, such efforts are hindered by the lack of evidence substantiating risk factors for in-hospital VTE from well-designed pediatric case-control studies.

Review of pediatric trauma-specific literature reveals many of the same VTE risk factors determined in the present work. A recent study from the Children's Hospital of Wisconsin PICU demonstrated increased VTE risk in trauma patients with multiple risk factors such as immobility, poor perfusion, and CVC, with a median of nine days until VTE diagnosis, suggesting that it is critical to identify children at highest risk for VTE.[16] This study found that each additional risk factor caused a 3-fold increase in risk for VTE development, which is similar to our findings, as shown in Table 1. An analysis of the 2003 Healthcare Cost and Utilization Project Kids' Inpatient Database showed that VTE was identified in 2.7 per 1,000 pediatric trauma discharges (using ICD-9 codes for trauma definitions) and, using ICD-9 codes or procedure codes for risk factor identification, also demonstrated that VTE risk was strongly correlated with surgery, CVC, and severity of injury.[17] The use of a risk score to identify patients more likely to develop VTE may help mitigate the increased resource utilization by these patients by targeting them for preventative measures.

The lack of published data regarding validity of ICD-9 codes in pediatric VTE and the registry structure of data collection in pediatric VTE poses challenges to data quality of the existing literature on risk factors for VTE. Indeed, the discharge diagnosis ICD-9 codes used to identify cases in our study had a specificity of only 38% for VTE, and of only 23% for in-hospital VTE, in children. Among the aforementioned studies, only Sandoval *et al.* utilized radiological confirmation of VTE as a validation criterion for ICD-9-based VTE diagnosis, and of in-hospital (*vs.* pre-hospital) VTE based upon absence/presence of these ICD-9 codes among the admission diagnoses.[14] Unfortunately, while that study showed a high prevalence of CVC, infection, surgery, and malignancy among children with in-hospital DVT, it did not establish an increased risk in VTE associated with these predisposing conditions, via comparison of their frequencies among a control group of hospitalized children who did not develop VTE in the hospital. We employed a similar validation criteria approach to Sandoval and colleagues,[14] but further evaluated each admission record for the presence of signs and symptoms (unilateral limb pain/swelling) compatible with limb DVT, in order to exclude pre-hospital DVT episodes in which

diagnosis was delayed.

Previous work has also evaluated risk factors for pediatric VTE outside a hospital setting, focusing on specific medical conditions. VTE risk factors identified in children with nephrotic syndrome have included age over 12 years, severity of proteinuria, and prior history of VTE.[18] In addition, among children with acute lymphoblastic leukemia undergoing induction chemotherapy, a meta-analysis has identified *E. coli*-derived L-asparaginase, concomitant corticosteroid use, presence of a CVC, and genetic thrombophilia as putative risk factors for VTE development.[19] A subsequent multicenter European cohort study confirmed that higher risk scores (based upon greater number of these risk factors) were associated with heightened VTE risk in pediatric ALL, and on an exploratory basis suggested that use of enoxaparin prophylaxis during induction in these children reduced the risk of VTE.[20]

Anticoagulant primary prevention against VTE in hospitalized adults is well established both with respect to surgical and medical prophylaxis.[21] By contrast, evidence for efficacy and safety of anticoagulant primary prophylaxis against VTE in hospitalized children is largely lacking. The few clinical trials that have evaluated anticoagulant prevention against VTE in hospitalized children,[22] and those that have involved both inpatient and outpatient settings,[23,24] have generally failed to show efficacy; this is likely due in large part to the need for greater risk-stratification of these populations (pediatric cardiac surgery patients with a central venous catheter, pediatric cancer patients with a central venous catheter, etc.). The recent findings of Raffini and colleagues from the Children's Hospital of Philadelphia, demonstrating increased use of VTE prophylaxis in high-risk patients by using risk-based guidelines,[25] are a testament to the importance of risk evaluation as a basis for appropriate prevention strategies. Our present findings, if substantiated by further prospective studies, provide the basis for greater risk stratification for pediatric in-hospital VTE.

Key limitations of the present work include the retrospective nature of the analysis, the lack of follow up after hospital discharge to determine if any symptoms of VTE had developed beyond hospitalization (hence the pertinence of our findings to "in-hospital" rather than "hospital-acquired" VTE), and the heterogeneity of the patient population. It should be recognized that restriction of case identification to the period of hospitalization is likely to underestimate the magnitude of the problem. Also, the sensitivity of ICD-9 discharge diagnosis codes for VTE in children has not been established, and therefore the rate of VTE identified in the present work may be an underestimate. To that end, we have addressed the suboptimal utility of sensitivity of ICD-9 discharge diagnosis codes for clinical research in pediatric VTE in a separate manuscript via a different study design (prospective inception cohort) involving known thrombosis patients followed longitudinally via our subspeciality thrombosis clinic.

In addition, given the limitations posed by the number of cases identified, most risk factors were analyzed as broad categories (e.g. surgery, inflammatory condition), such that differential risk within these groupings (e.g. orthopedic surgery *vs.* thoraco-abdominal surgery, systemic lupus erythematosus *vs.* inflammatory bowel disease, emergent *vs*. elective central venous catheterization) was not analyzed, and should be evaluated in larger cooperative studies. Similarly, given the small numbers of patients with cancer, the magnitude of this risk factor shown to be significant in the PICU setting is imprecise. We were unable to discern risk factor profiles in the CICU, likely due in part to frequent use of prophylactic anticoagulation in the post-operative period in the CICU at our institution in children weighing less than 10 kg with a CVC in place. Furthermore, we had only limited ability to discern risk factors in the NICU. While patient heterogeneity is a potential limitation of the study, it can also be perceived as advantageous with regard to external validity (i.e. generalizability) of our findings to the pediatric in-hospital VTE population at large. Nevertheless, our data from the Children's Hospital Colorado, are most applicable to pediatric tertiary care hospitals, and may not be generalizable to community hospitals where children are admitted.

A few more minor limitations are also noteworthy. While we were unable to readily determine usage of prophylactic anticoagulation given the limitations of pharmacy data (including dosing, duration, and indication), it should be noted that prophylactic anticoagulation was not the standard of care at our institution, except in the post-operative subgroup of CICU patients as mentioned above. In addition, because length of hospitalization cannot be precisely known at the time of admission, this identified risk factor presents challenges for implementation in a VTE prevention algorithm upon hospital admission. Indeed, this limitation is shared by many studies in the VTE risk factor literature, which have consistently implicated length of stay as an important risk factor. At the same time, the number and severity of problems/underlying conditions noted on admission are often used clinically to grossly estimate anticipated duration of hospitalization for patient disposition purposes. Therefore, the use of a length of hospitalization threshold of at least five days in the present risk model is felt to be pragmatic for future application based upon anticipated length of stay. Alternatively, prophylactic anticoagulation could be withheld until the length of hospitalization reaches five days (in the presence of the other described risk factors), recognizing that such an approach may not prevent VTE in cases in which the pathophysiological process has begun soon after admission.

Notwithstanding these limitations, the validation criteria employed toward the definition of in-hospital VTE in the present work provide high-quality retrospective data on risk factors for development of in-hospital VTE in children. Our findings identify a combination of clinical risk of factors that has prognostic utility for the development in-hospital VTE in children. Their substantiation via subsequent prospective multicenter studies would provide the basis for a future pilot study of safety and preliminary efficacy of primary prophylactic anticoagulation in the highest-risk group of patients. If this pilot study yields favorable results, a more definitive multicenter risk-stratified RCT of pediatric VTE prevention could be performed.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. http://www.surgeongeneral.gov/topics/deepvein/calltoaction/call-to-action-ondvt-2008.pdf. Accessed 22 December 2010.
2. The Surgeon General's Workshop on Deep Venous Thrombosis. Manco-Johnson MJ and Goldenberg NA. Thrombosis in the pediatric patient: unique risk factors, diagnosis, and management issues. 2006; Bethesda, MD, pp. 8-9.
3. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr. 2004;145(4):563-5.
4. Raffini L, Huang Y-S, 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):1001-8.
5. Journeycake J, Manco-Johnson MJ. Thrombosis during infancy: what we know and what we do not know. Hematol Oncol Clin North Am. 2004;18(6):1315-38.
6. Biss TT, Brandão LR, Kahr WH, Chan AK, Williams S. Clinical Features and Outcome of Pulmonary Embolism in Children. Br J Haem. 2008;142(5):808-18.
7. Goldenberg NA, Donadini MP, Kahn SR, Crowther M, Nowak-Göttl U, Manco-Johnson MJ. Post thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. Haematologica. 2010;95(11):1952-9.
8. Geerts WH. Prevention of venous thromboembolism: A key patient safety priority. J Thromb Haemost. 2009;7(Suppl 1):1-8.
9. Goldenberg NA, Bernard TJ. Venous thromboembolism in children. Hematol Oncol Clin North Am. 2010;24(1):151-66.
10. http://apps.nccd.cdc.gov/dnpabmi. Accessed 7 December 2010.
11. Simel DL, Sansa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol. 1991;44(8):763-70.
12. Male C, Chait P, Andrew M, Hanna K, Julian J, Mitchell L; PARKAA Investigators. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. Blood. 2003;101(11):4273-8.
13. Vu LT, Nobuhara KK, Lee H, Farmer DL. Determination of risk factors for deep venous thrombosis in hospitalized children. J Pediatr Surg. 2008;43(6):1095-9.
14. Sandoval JA, Sheehan MP, Stonerock CE, Shafique S, Rescorla FJ, Dalsing MC. Incidence, risk factors, and treatment patterns for deep venous thrombosis in hospitalized children: an increasing population at risk. J Vasc Surg. 2008;47(4):837-43.
15. Rohrer MJ, Cutler BS, MacDougall E, Herrmann JB, Anderson FA Jr, Wheeler HB. A prospective study of the incidence of deep venous thrombosis in hospitalized children. J Vasc Surg. 1996;24(1):46-9.
16. Hanson SJ, Punzalan RC, Greenup RA, Liu H, Sato TT, Havens PL. Incidence and risk factors for pediatric thromboembolism in critically ill children after trauma. J Trauma. 2010;68(1):52-6.
17. Candrilli SD, Balkrishnan R, O'Brien SH. Effect of injury severity on the incidence and utilization-related outcomes of venous thromboembolism in pediatric trauma patients. Pediatr Crit Care. 2009;10(5):554-7.
18. Kerlin BA, Blatt NB, Fuh B, Zhao S, Lehman A, Blanchong C, et al. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. J Pediatr. 2009;155(1):105-10.
19. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood. 2006;108(7):2216-22.
20. Mitchell L, Lambers M, Flege S, Kenet G, Li-Thiao-Te V, Holzhauer S, et al. Validation of a predictive model for identifying an increased risk for thromboembolism in children with acute lymphoblastic leukemia: results of a multicenter cohort study. Blood. 2010;115(24):4999-5004.
21. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). Chest. 2008:133(6 Suppl):381S-453S.
22. Schroeder AR, Axelrod DM, Silverman NH, Rubesova E, Merkel E, Roth SJ. A continuous heparin infusion does not prevent catheter-related thrombosis in infants after cardiac surgery. Pediatr Crit Care Med. 2007;11(4):489-95.
23. Massicotte P, Julian J, Gent M, Shields K, Marzinotto V, Szechtman B, et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. Thromb Res. 2003;109(2-3):101-8.
24. Ruud E, Holmstrom H, De Lange C, Hogstad EM, Wesenberg F. Low-dose warfarin for the prevention of central line-associated thromboses in children with malignancies: a randomized, controlled study. Acta Paediatr. 2006;95(9):1053-9.
25. Raffini L, Trimarchi T, Beliveau J, Davis D. Thromboprophylaxis in a Pediatric Hospital: A patient-safety and quality improvement initiative. Pediatrics. 2011;127(5):e1326-32.