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From the Children's Healthcare Advancements in Thrombosis Consortium

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<https://escholarship.org/uc/item/21f5q8p1>

Journal

Pediatric Critical Care Medicine, 26(9)

ISSN

1529-7535

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Publication Date

2025-09-01

DOI

10.1097/pcc.0000000000003788

Peer reviewed

CLINICAL INVESTIGATION ARTICLE

Thromboprophylaxis for Critically Ill Adolescents: A Multicenter Case-Control Study From the Children’s Healthcare Advancements in Thrombosis Consortium

OBJECTIVES: To determine if thromboprophylaxis, including pharmacologic, mechanical, or in combination, is associated with a hospital-acquired venous thromboembolism (HA-VTE) risk reduction among critically ill adolescents.

DESIGN: Multicenter case-control study from the Children’s Healthcare Advancements in Thrombosis Consortium Registry and VTE risk-model validation study from January 2012 to July 2022.

SETTING: Thirty-two North American PICUs.

PATIENTS: Critically ill adolescents 12–19 years old including cases with radiographically confirmed HA-VTE (i.e., pulmonary embolism and deep venous thrombosis) and controls without HA-VTE.

INTERVENTIONS: Pharmacologic (i.e., prophylactic anticoagulation) and mechanical (i.e., intermittent pneumatic compression) thromboprophylaxis.

MEASUREMENTS AND MAIN RESULTS: Of 163 cases and 975 controls, 7.6% received pharmacologic, 23.5% mechanical, and 9.2% pharmacologic and mechanical thromboprophylaxis. Compared with controls, cases more frequently had central venous catheterization (89% vs. 21.1%), invasive ventilation (52.2% vs. 11.8%), longer median length of stay (29 d [interquartile range, 15–46 d] vs. 6 d [interquartile range, 3–10 d]), impaired mobility (72.6% vs. 22.1%), and infection (48.5% vs. 16%; all $p < 0.001$). Venous thromboembolism risk tiers (low, moderate, and high) were calculated using validated scoring criteria. Using multivariable logistic regression for HA-VTE risk accounting for additional prothrombotic covariates and among each VTE risk tier, pharmacologic and combined thromboprophylaxis, but not mechanical thromboprophylaxis alone, were independently associated with reduced HA-VTE risk.

CONCLUSIONS: Among critically ill adolescents, pharmacologic thromboprophylaxis alone or in combination with mechanical thromboprophylaxis, but not mechanical thromboprophylaxis alone, was associated with an HA-VTE risk reduction.

KEYWORDS: adolescents; hospital-acquired venous thromboembolism; pediatrics; thromboprophylaxis

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Contemporary epidemiologic data reveal a significant increase in the occurrence rate of pediatric hospital-acquired venous thromboembolism (HA-VTE) over the preceding 2 decades (1). Among critically ill children, HA-VTE is associated with morbidity and mortality occurring in as many as one in 50 hospitalized children (2, 3). Pediatric clinical trials have assessed the efficacy and safety of pharmacologic thromboprophylaxis in select subpopulations, including children with hematologic malignancy undergoing

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DOI: 10.1097/PCC.0000000000003788



RESEARCH IN CONTEXT

- Thromboprophylaxis, including pharmacologic and/or mechanical interventions, is prescribed for critically ill adolescents without prospective evidence regarding safety and efficacy in reducing hospital-acquired venous thromboembolism risk.
- In the multicenter case-control study using data from the Children's Healthcare Advancements in Thrombosis Consortium, we sought to determine if thromboprophylaxis (including pharmacologic, mechanical, or a combination thereof) is associated with a venous thromboembolism risk reduction among critically ill adolescents.

induction chemotherapy (4, 5), acquired and congenital heart disease (6), COVID-19-related illness (7), and following and throughout the course of central venous catheterization (CVC) (8, 9). However, the paucity of prospective studies evaluating thromboprophylaxis in critically ill children, coupled with a perception of heightened bleeding risk (10), contribute to wide variation observed in the use and modalities of VTE prevention across inpatient pediatric healthcare settings and populations (11–14).

Risk prediction models for HA-VTE among critically ill children are not sufficiently validated but have consistently identified salient risk factors including a prolonged length of stay (LOS), CVC, and a concurrent infectious or parainflammatory process as independent HA-VTE risk factors (15, 16). More recently, multinational collaboratives including the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee and the Children's Healthcare Advancements in Thrombosis (CHAT) Consortium have emphasized the urgent need for research aimed at identifying optimal thromboprophylaxis strategies to inform pediatric practice guidelines for hospitalized children, including multicenter observational data on VTE and bleeding outcomes associated with thromboprophylaxis in critically ill children (11). However, critical care providers have exhibited resistance to anticoagulant use based on the assumption of efficacy of mechanical thromboprophylaxis and risk of bleeding from anticoagulation (17).

To assess potential risk reduction of HA-VTE among critically ill adolescents who received thromboprophylaxis including those who received mechanical thromboprophylaxis, pharmacologic thromboprophylaxis, or both, we performed a case-control study within the CHAT Consortium Registry and CHAT prospective, multicenter risk-model validation study of critically ill children. We aimed to preclassify cases with HA-VTE and non-HA-VTE controls by thrombotic risk strata as defined by Arlikar et al (15) (i.e., low-, moderate-, and high-risk tiers). We hypothesized that among patients classified as a priori high risk for HA-VTE, pharmacologic thromboprophylaxis would be associated with reduced odds of HA-VTE.

MATERIALS AND METHODS

Study Design and Eligibility Criteria

We conducted a case-control study of critically ill adolescents previously enrolled into two CHAT Consortium studies: 1) the “CHAT Registry” and 2) the CHAT ICU risk-model validation study (referred to as “CHAT 1901 Study”). The CHAT Registry, previously described in detail (18), is a registry of children younger than 22 years old diagnosed with a HA-VTE from January 2012 to June 2021 at eight participating U.S. pediatric quaternary referral centers. Cases were drawn from the CHAT Registry and included patients from 12 years old or older to younger than 19 years admitted to a participating PICU between January 2012 and June 2021 with a radiographically confirmed HA-VTE (defined below). Exclusion criteria included a HA-VTE diagnosis before or on the date of PICU admission. The CHAT 1901 Study was a prospective observational study of randomly selected children younger than 22 years old admitted to a PICU at 32 institutions in the United States from January 2020 to July 2022 (including the centers participating in the CHAT Registry). Controls drawn from the CHAT 1901 study included those 12 years old or older to younger than 19 years admitted to a participating PICU who did not develop a HA-VTE.

The study protocol described herein was reviewed and approved by the Johns Hopkins University Institutional Review Board (IRB: 00396103, approved: July 7, 2023) and the CHAT Scientific Review and Publications Committee. All participating CHAT sites were granted a waiver of consent by their respective

IRBs (see www.chatconsortium.org for a full listing of centers). The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. The article was formatted for consistency with Strengthening the Reporting of Observational Studies in Epidemiology reporting of case-control studies.

Data Collection, Management, and Quality Assurance

Data were collected using standardized collection forms completed by trained personnel at each participating site using a secure electronic data capture system. Data capture forms including demographic data, clinical data, details regarding known or putative prothrombotic risk factors, and HA-VTE characteristics used identical data fields and definitions between the CHAT Registry and CHAT 1901 Study. Monthly quality assurance reports were sent to participating sites' research staff and principal investigators to verify and correct missing or flagged data. Study variables were captured retrospectively for HA-VTE cases identified within the CHAT Registry and prospectively for non-HA-VTE controls from the CHAT 1901 Study.

Study Outcomes and Definitions

The primary exposure variables of interest were pharmacologic and mechanical thromboprophylaxis. The former was defined as prescription of unfractionated heparin, low-molecular-weight heparin (LMWH), or direct oral anticoagulants (DOACs) at prophylactic pediatric dosing regimens at the discretion of study sites. The latter was defined as intermittent or sequential pneumatic compression devices that include either thigh or calf-compression locations. The primary outcome of interest was HA-VTE, defined as pulmonary embolism and/or limb/neck/abdominal deep venous thrombosis (DVT) confirmed either by Doppler ultrasonography, CT, venography, echocardiography, or MRI at the discretion of the participating center. The HA-VTE events recorded in the CHAT Registry are predominantly clinically symptomatic as routine

radiographic screening for VTE is not standard care at participating centers. Recorded HA-VTE characteristics included timing of diagnosis after hospitalization, the location (i.e., specific vascular bed), and relationship (yes/no) to an ipsilateral indwelling CVC or CVC insertion within the preceding period of hospitalization. Recorded symptoms of HA-VTE included pain, limb swelling, limb temperature and/or color change, mental status change, hypoxemia, shortness of breath, vomiting, CVC malfunction, and tissue plasminogen activator use for CVC malfunction/occlusion. Recorded characteristics of pharmacologic thromboprophylaxis included start/stop dates. Cases drawn from the CHAT registry did not have ISTH-defined bleeding data available for analysis (19).

Established and putative HA-VTE risk factors collected included CVC data (i.e., timing of insertion, vessel location, catheter size, number of lumens, and type), hospital and critical care LOS, concurrent infections (including pathogen and timing during hospitalization), perioperative care (including timing and procedural details), proinflammatory conditions (including systemic lupus erythematosus, celiac disease, inflammatory bowel disease, and juvenile rheumatoid arthritis), invasive mechanical ventilation (IMV) data, comorbid critical congenital heart disease, degree of acute immobility (as measured by Braden Q mobility [20] values at the time of admission and HA-VTE diagnosis), and history or current diagnosis of thrombophilia (i.e., positive testing for antiphospholipid antibodies, antithrombin deficiency, protein C or S deficiency, factor V Leiden, prothrombin gene mutation, plasminogen activator inhibitor-1 mutation, and elevated homocysteine levels). Sociodemographic data included age at admission, sex at birth, and historically marginalized race and ethnicity categories. Additional clinical outcomes recorded for study were hospital LOS and in-hospital mortality.

Statistical Analysis Plan

Statistical analyses were performed by the CHAT Consortium Data Coordinating Center at the Johns Hopkins All Children Hospital Institute for Clinical and Translational Research. Demographic data and baseline characteristics for cases and controls were summarized with counts (percentages) for categorical variables and means $\pm$ SD or

medians (interquartile range [IQR]) for quantitative variables depending on data distribution and normalcy. Comparative analyses between cases and controls for descriptive features and variables of interest were assessed using chi-square tests for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables. Unadjusted and adjusted associations between purported risk factors and HA-VTE were assessed using logistic regression models. Cases and controls were further classified into HA-VTE risk tiers (low, moderate, and high) as defined by Arlikar et al (15) for critically ill children based upon the relative weighting of the following covariates during hospitalization (and before HA-VTE among cases): CVC presence (8 points), LOS greater than or equal to 4 days (6 points), and hospitalization for sepsis/infection (1 point). For each tier, multivariable logistic regression was employed to assess the potential association between thromboprophylaxis and risk of HA-VTE. Covariates not already included in the model by Arlikar et al (15) as listed above were selected a priori based upon established pediatric HA-VTE risk factors, including patient age, IMV, acute immobility, congenital heart disease, hematologic malignancy, and parainflammatory conditions, yielding adjusted odds ratios (aORs) for HA-VTE with corresponding Wald 95% CIs. Backward elimination was applied to generate final models for each HA-VTE risk tier. All testing was two-sided, type I error was set at less than 0.05, and missing data were not imputed. A statistical analysis code check was performed by an independent biostatistician to ensure validity and reproducibility of all outputs. Statistical analyses were completed using SAS software, Version 9.4.3 (SAS Institute, Cary, NC).

RESULTS

Study Sampling

A study population flow chart is provided in **Figure 1**. For cases with HA-VTE, 1273 participants were identified in the CHAT Registry of which 175 were hospitalized in the PICU. Twelve were excluded based on having a VTE present on PICU admission, leaving 163 eligible for this study. Non-HA-VTE controls from the CHAT 1901 study were selected from a total of 3221

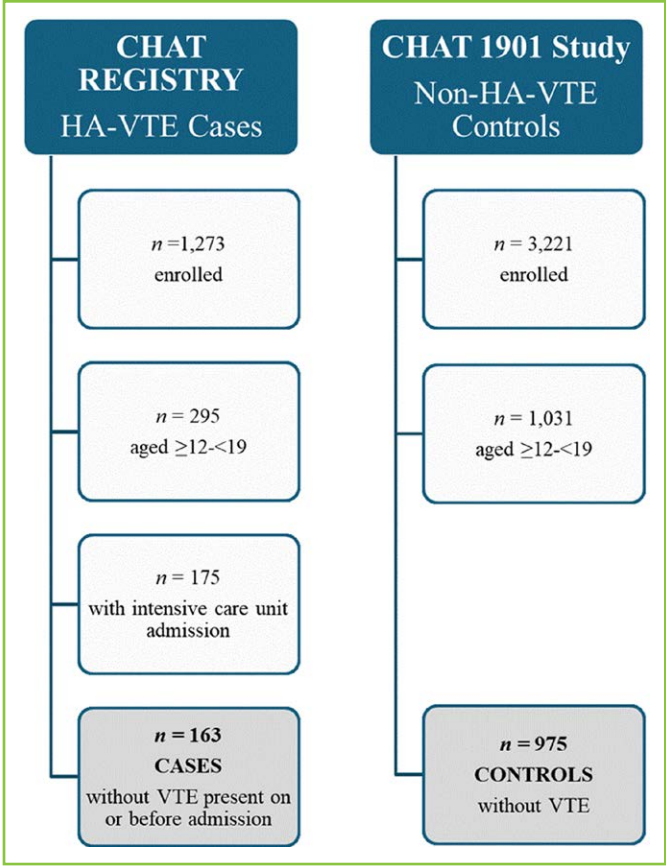


Figure 1. A study sampling flow chart. Cases with radiographically confirmed hospital-acquired venous thromboembolism (HA-VTE) were drawn from the Children's Healthcare Advancements in Thrombosis (CHAT) Consortium Registry. Controls without venous thromboembolism were drawn from the CHAT Consortium ICU Risk Validation Study.

participants, of whom 975 met all study criteria by patient age.

General Characteristics and HA-VTE Data

Descriptive characteristics and clinical outcomes for HA-VTE cases and non-HA-VTE controls are listed in **Table 1**. Cases and controls exhibited comparable demographic and anthropometric data, with a study sample mean ($\pm$ SD) age of 15.4 ± 1.9 years upon admission, slight male predominance (51.5%), and median body mass index of 22.5 kg/m^2 (IQR, $19.1\text{--}27.9 \text{ kg/m}^2$). Compared with controls, cases more commonly had a CVC (89% vs. 21.1%), experienced a longer median LOS (29 d [IQR, 15–46 d] vs. 6 d [IQR, 3–10 d]), more frequently underwent IMV for greater than or equal to 1 day (52.2% vs. 11.8%), were more frequently treated for infection (48.5% vs. 16%), had a comorbid history

TABLE 1.
General Characteristics and Clinical Outcomes for Cases and Controls

Study Variables	HA-VTE Cases (<i>n</i> = 163)	Non-HA-VTE Controls (<i>n</i> = 975)	<i>p</i>
Age at admission (yr), mean (SD)	15.8 (1.8)	15.3 (1.9)	0.007
Sex at birth, <i>n</i> (%)			0.089
Female	69 (42.3)	481 (49.5)	
Male	94 (57.7)	490 (50.5)	
Historically disparate race categories, <i>n</i> (%)			< 0.001
Asian	6 (3.7)	23 (2.7)	
Black	18 (11)	172 (17.6)	
White	73 (44.8)	586 (14.2)	
Other	9 (5.5)	138 (14.2)	
Unknown	57 (35)	56 (5.7)	
Historically disparate ethnic categories, <i>n</i> (%)			0.05
Hispanic	44 (27)	185 (19)	
Non-Hispanic	102 (62.6)	692 (71)	
Not listed	17 (10.4)	98 (10.1)	
History of thrombophilia, <i>n</i> (%)	45 (27.6)	20 (2.1)	< 0.001
Sepsis/infection, <i>n</i> (%)	79 (48.5)	156 (16.0)	< 0.001
Hematologic cancer, <i>n</i> (%)	13 (8.0)	26 (2.7)	0.001
Congenital heart disease, <i>n</i> (%)	16 (9.8)	32 (3.3)	< 0.001
Parainflammatory conditions, <i>n</i> (%)	6 (3.7)	13 (1.3)	0.043
Underwent surgical procedure, <i>n</i> (%)	14 (8.6) ^a	252 (29)	< 0.001
Thromboprophylaxis, <i>n</i> (%)			0.001
None	80 (49.1)	600 (61.5)	
Mechanical	41 (25.2)	226 (23.2)	
Pharmacologic	15 (9.2)	71 (7.3)	
Both mechanical and pharmacologic	27 (16.6)	78 (8)	
Central venous catheterization, <i>n</i> (%)	145 (89.0)	206 (21.1)	< 0.001
Ventilation duration (d), median (IQR)	8 (4–15)	1 (1–3)	< 0.001
Duration ≥ 1 d, <i>n</i> (%)	85 (52.2)	114 (11.8)	< 0.001
Hospital length of stay (d), median (IQR)	29 (15–46)	6 (3–10)	< 0.001
Duration ≥ 4 d, <i>n</i> (%)	160 (99.4)	635 (73.8)	< 0.001
Braden Q immobility score, <i>n</i> (%)			
Completely immobile/very limited	90 (72.6)	161 (22.1)	< 0.001
HA-VTE risk tier, <i>n</i> (%)			< 0.001
Low risk	9 (5.5)	706 (72.4)	
Moderate risk	86 (52.8)	208 (21.3)	
High risk	68 (41.7)	61 (6.3)	
In-hospital mortality, <i>n</i> (%)	0 (0)	18 (1.8)	0.08

HA-VTE = hospital-acquired venous thromboembolism, IQR = interquartile range.

^aSurgery in cases were counted only if occurred before or on the date of VTE diagnosis.

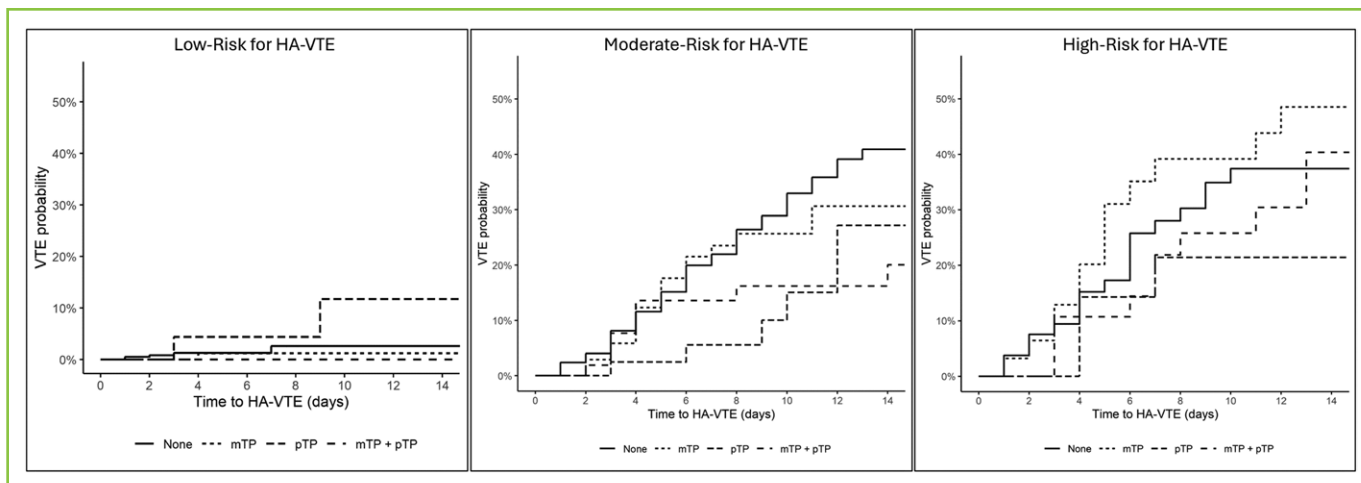


Figure 2. Survival curves for hospital-acquired venous thromboembolism (HA-VTE) by thromboprophylaxis regimens applied to a priori venous thromboembolism risk tiers. mTP = mechanical thromboprophylaxis, pTP = pharmacological thromboprophylaxis.

of thrombophilia (27.6% vs. 2.1%), and more commonly acutely experienced complete immobility or very limited mobility upon admission (72.6% vs. 22.1%; all $p < 0.001$). Among the 163 HA-VTE cases, 145 (89%) had DVT of the neck/limbs/abdomen and 16 (9.8%) had pulmonary embolism. Ninety-five (58.3%) of HA-VTE events were CVC-related (64.5% of CVC were classified as percutaneous IV central catheters, 27% percutaneous CVCs, and 10.5% tunneled CVCs). The HA-VTE cases were clinically identified at a median of 7 days (IQR, 4–14 d) after hospitalization.

Thromboprophylaxis and HA-VTE Risk

For the entire study cohort, 59.8% were not given thromboprophylaxis of any type, 23.5% received mechanical thromboprophylaxis alone, 7.6% pharmacologic thromboprophylaxis alone, and 9.2% a combination of pharmacologic and mechanical thromboprophylaxis (Table 1). Median time to initiation of pharmacologic thromboprophylaxis was 1 day (IQR, 0–6 d) and mechanical thromboprophylaxis was 1 day (IQR, 0–2 d). Regarding a priori HA-VTE risk tiers, cases with HA-VTE were more frequently classified as high risk (41.7% vs. 6.3%) and moderate risk (52.8% vs. 21.3%), as compared with low risk (5.5% vs. 72.4%; $p < 0.001$) as compared with controls. Survival curves (i.e., time to HA-VTE) by risk tiers are presented in **Figure 2**. As compared with non-HA-VTE controls, cases were more frequently provided one or more forms

of thromboprophylaxis (50.9% vs. 38.5%; $p < 0.001$); however, no differences were detected after regrouping cohorts by HA-VTE risk tiers.

Unadjusted and adjusted logistic regression models for HA-VTE are shown in **Table 2**. Clinical features found to be associated with HA-VTE included extended hospital LOS (aOR, 1.06; 95% CI, 1.04–1.07; $p < 0.001$), prescription of a combination of pharmacologic and mechanical thromboprophylaxis (aOR, 0.41; 95% CI, 0.20–0.86; $p = 0.02$), CVC (aOR, 9.3; 95% CI, 4.99–17.45; $p < 0.001$), complete immobility or very limited mobility by Braden Q values at admission (aOR, 3.9; 95% CI, 2.14–7.11; $p < 0.001$), congenital heart disease (aOR, 3.87; 95% CI, 1.47–10.17; $p = 0.006$), and infection (aOR, 2.62; 95% CI, 1.57–4.36; $p < 0.001$). Multivariable logistic regression models for HA-VTE at each stratum of a priori HA-VTE risk revealed pharmacologic thromboprophylaxis (aOR, 0.18; 95% CI, 0.04–0.78; $p = 0.02$) and combined pharmacologic/mechanical thromboprophylaxis (aOR, 0.20; 95% CI, 0.06–0.66; $p = 0.008$), but not mechanical thromboprophylaxis alone, were associated with reduced risks of HA-VTE among those children in the high-risk tier (and among those in the moderate-risk tier; **Table 3**). In addition, IMV exposure (aOR, 4.25; 95% CI, 1.63–11.03; $p = 0.003$) and complete immobility/very limited mobility (aOR, 3.72; 95% CI, 1.4–9.88; $p = 0.008$) were independently associated with HA-VTE risk among participants within the high-risk tier and among those in the moderate-risk tier (Table 3).



AT THE BEDSIDE

- In this report, 7.6% of the study participants received pharmacologic thromboprophylaxis, 23.5% mechanical thromboprophylaxis, and 9.2% a combination of both thromboprophylaxis strategies.
- In a multivariable model applied in three venous thromboembolism risk tiers, pharmacologic and combined thromboprophylaxis, but not mechanical thromboprophylaxis alone, were independently associated with reduced hospital-acquired venous thromboembolism risk.

DISCUSSION

In this observational multicenter study, we demonstrated that pharmacologic thromboprophylaxis with or without mechanical thromboprophylaxis was associated with a risk reduction in HA-VTE among critically ill adolescents considered to be at moderate and high VTE risk. These findings, along with the identification of acute IMV exposure and impaired mobility as additional HA-VTE risk factors, are critical to inform design of much-needed interventional trials of thromboprophylaxis in critically ill children. Furthermore, the findings suggest that, among critically ill adolescents, mechanical thromboprophylaxis alone may be insufficient for primary VTE prevention.

Prescribed in as many as 12–24% of critically ill adolescent patients (12–14), mechanical thromboprophylaxis is thought to lower HA-VTE risk by reducing venous stasis through dynamic compression of extremity veins and releasing endogenous mediators of anticoagulation from the venous endothelium (21–23). However, evidence in support of mechanical thromboprophylaxis is derived solely from adult trials (24–26). Our recent report by Betensky et al (27) evaluated data from a multicenter administrative registry to assess for associations between mechanical thromboprophylaxis and HA-VTE risk among critically ill adolescents. Although that report was not able to account for pharmacologic thromboprophylaxis exposure, our data confirmed their observations of no detectable association between mechanical thromboprophylaxis and decreased HA-VTE risk across the

low-, moderate-, and high-risk tiers. Given the lack of evidence for a decrease in VTE risk in association with mechanical thromboprophylaxis, the use of mechanical thromboprophylaxis may impede the use of a theoretically more effective strategy of pharmacologic thromboprophylaxis.

In critically ill adults, the American College of Physicians recommends routine provision of pharmacologic thromboprophylaxis at hospitalization, with use of mechanical thromboprophylaxis in those with an absolute contraindication to anticoagulation (28). Yet, the scarcity of pediatric trial-derived evidence for both pharmacologic and mechanical thromboprophylaxis represents an impediment to the development of universal pediatric thromboprophylaxis guidelines for critically ill children. As highlighted in our study findings, the risk of HA-VTE among critically ill children remains multifactorial and is associated with iatrogenic factors (i.e., CVC, immobility, and IMV), inherited thrombophilia, and underlying proinflammatory disease (e.g., oncologic processes and infection) (29–31).

Given the inherent trade-off between VTE risk reduction and bleeding risk-increase in clinical decision making on anticoagulation, the evaluation of use of pharmacologic thromboprophylaxis must consider a priori bleeding risk. Critically ill children are at elevated risk of major bleeding relative to noncritically ill hospitalized children (32, 33). However, meta-analyses have yielded an estimated risk of clinically relevant bleeding of 0.6–2.3% among hospitalized children receiving LMWH as thromboprophylaxis (34, 35). Indeed, a growing body of prospective study data suggests the relative safety and efficacy of LMWH and DOACs as primary thromboprophylaxis in pediatric subpopulations, including those with critical illnesses. Clinical trials assessing pharmacologic thromboprophylaxis in specific pediatric subpopulations, including children with COVID-19 (7), those with a newly placed CVC (8, 9), acquired and congenital heart disease (6), and acute lymphoblastic leukemia (4, 5) have collectively observed no difference in rates of clinically relevant bleeding for children who received LMWH or DOACs when compared with standard care (4–9). Given the heterogeneity in regard to critically ill and noncritically ill patients in these studies, and their individual restriction to specific disease states or a single risk factor for VTE (e.g., CVC) among multiple known risk factors, clinical trials of pharmacologic thromboprophylaxis as

TABLE 2.**Unadjusted and Adjusted Odds Ratios and 95% CIs for Hospital-Acquired Venous Thromboembolism**

Independent Variables	Hospital-Acquired Venous Thromboembolism			
	Unadjusted OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
Age	1.13 (1.03–1.24)	0.007	1.1 (0.99–1.28)	0.077
Sex				
Female	Reference		Reference	
Male	0.75 (0.54–1.05)	0.089	1.01 (0.63–1.65)	0.95
Hospital length of stay (d)	1.09 (1.08–1.11)	< 0.001	1.06 (1.04–1.07)	< 0.001
Thromboprophylaxis				
None	Reference		Reference	
Mechanical	1.36 (0.91–2.04)	0.14	0.67 (0.36–1.22)	0.19
Pharmacologic	1.59 (0.87–2.90)	0.14	0.45 (0.20–1.02)	0.056
Mechanical and pharmacologic	2.60 (1.58–4.26)	< 0.001	0.41 (0.20–0.86)	0.018
Central venous catheterization				
No	Reference		Reference	
Yes	30.07 (18.0–50.25)	< 0.001	9.3 (4.99–17.45)	< 0.001
Invasive mechanical ventilation				
None or < 1 d	Reference		Reference	
> 1 d	8.17 (5.68–11.77)	< 0.001	1.38 (0.80–2.39)	0.25
Braden Q immobility score				
No/slight limitations	Reference		Reference	
Completely immobile/very limited	9.32 (6.05–14.35)	< 0.001	3.90 (2.14–7.11)	< 0.001
Hematologic malignancy				
No	Reference		Reference	
Yes	3.16 (1.59–6.29)	0.001	0.75 (0.29–1.93)	0.56
Parainflammatory condition				
No	Reference		Reference	
Yes	2.83 (1.06–7.55)	0.038	3.72 (0.92–15.15)	0.066
Active treatment for infection				
No	Reference		Reference	
Yes	4.94 (3.47–7.02)	< 0.001	2.62 (1.57–4.36)	< 0.001

OR = odds ratio.

primary VTE prevention in critically ill children are urgently needed.

Case-control studies are limited in their capacity to evaluate therapeutic interventions, and we can only infer causality. We studied adolescents as they have highest risk of HA-VTE and commercially available mechanical thromboprophylaxis is anecdotally used. As we did not study infants and young children and mechanical thromboprophylaxis sizes are

limited, our study findings cannot be generalized to that population. The specific agent and dosing schema for pharmacologic thromboprophylaxis were not recorded in CHAT; for this reason, and due to limitations in power, it was not possible to assess associations between anticoagulant types and VTE risks. Nevertheless, other studies have shown that the predominant agent used as pharmacologic thromboprophylaxis among critically ill children is LMWH (11).

TABLE 3.

Multivariable Logistic Regression for the Association Between Hospital-Acquired Venous Thromboembolism and Thromboprophylaxis Regimen for a Priori Classified Hospital-Acquired Venous Thromboembolism Risk-Tier Classification (20)

Independent Variables	Venous Thromboembolism	
	Adjusted OR (95% CI)	<i>p</i>
Low HA-VTE risk tier (cases [<i>n</i> = 9], controls [<i>n</i> = 703])		
Thromboprophylaxis		
None	Reference	
Mechanical	0.52 (0.06–4.58)	0.56
Pharmacologic	8.59 (1.83–40.27)	0.006
Both mechanical and pharmacologic	1.70 (0.08–38.33)	0.74
Invasive mechanical ventilation		
None or < 1 d	Reference	
> 1 d	7.39 (1.65–35.12)	0.009
Moderate HA-VTE risk tier (cases [<i>n</i> = 86], controls [<i>n</i> = 205])		
Thromboprophylaxis		
None	Reference	
Mechanical	0.63 (0.31–1.27)	0.20
Pharmacologic	0.36 (0.14–0.92)	0.03
Both mechanical and pharmacologic	0.44 (0.20–1.00)	0.04
Age	1.20 (1.03–1.39)	0.02
Invasive mechanical ventilation		
None or < 1 d	Reference	
> 1 d	1.50 (0.83–2.71)	0.18
Braden Q immobility score		
No/slight limitations	Reference	
Completely immobile/very limited	5.77 (2.82–11.81)	< 0.001
High HA-VTE risk tier (cases [<i>n</i> = 68], controls [<i>n</i> = 61])		
Thromboprophylaxis		
None	Reference	
Mechanical	0.49 (0.16–1.46)	0.20
Pharmacologic	0.18 (0.04–0.78)	0.02
Both mechanical and pharmacologic	0.20 (0.06–0.66)	0.008
Invasive mechanical ventilation		
None or < 1 d	Reference	
> 1 d	4.25 (1.63–11.03)	0.003
Braden Q immobility score		
No/slight limitations	Reference	
Completely immobile/very limited	3.72 (1.40–9.88)	0.008

HA-VTE = hospital-acquired venous thromboembolism, OR = odds ratio.

In addition, the duration and magnitude of mechanical thromboprophylaxis exposure are not collected, preventing our ability to evaluate for a potential “dose-response” in VTE risk reduction in association with mechanical thromboprophylaxis. Nevertheless, our study provides a basis to proceed with randomized interventional studies of thromboprophylaxis in this high-risk setting. Although research personnel underwent training sessions before data entry and quality assurance checks to optimize data collection, the possibility of misclassification bias cannot be excluded. CHAT Registry and the 1901 Study did not collect data for bleeding outcomes as a mandatory field for all subjects unless they received pharmacologic thromboprophylaxis. As such, we cannot speak to the net clinical benefit of pharmacologic thromboprophylaxis balancing both the risk of HA-VTE and bleeding. Time to event analyses (yielding adjusted hazard ratios) could address the implication of timing of thromboprophylaxis as it relates to HA-VTE prevention but were not performed as part of this research. Although we can only speculate as to local institutional practices, prothrombotic workup data were likely only collected on patients who had a VTE during hospitalization and may explain the observed differences in rates for inherited hypercoagulability between cases and controls. Planned pediatric trials of thromboprophylaxis in critically ill children must evaluate these factors.

CONCLUSIONS

In this multicenter observational study, we found that pharmacologic thromboprophylaxis, alone or in combination with mechanical thromboprophylaxis, is associated with a decreased risk of HA-VTE among critically ill adolescents who were assessed a priori to have moderate and high risks of HA-VTE. In addition, we identified prolonged IMV exposure and acute immobility as additional HA-VTE risk factors. These findings are important in informing the design of urgently needed clinical trials of thromboprophylaxis in critically ill adolescents.

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This research was supported by the Johns Hopkins All Children's Foundation.

Dr. Jaffray's institution received funding from the National Institutes of Health (NIH) (1K23HL163330)/the National Center for Advancing Translational Sciences, the Hemostasis and Thrombosis Research Society, and the National Heart, Lung, and Blood Institute; she received funding from Octapharma, Genentech, and HEMA Biologics. Drs. Jaffray and Goldenberg received funding from Bayer. Drs. Jaffray's, Krava's, and Goldenberg's institutions received funding from Boehringer-Ingelheim. Drs. Stillings, Krava, and Goldenberg received support for article research from the NIH. Dr. Branchford received funding from Novo Nordisk, Bioproducts Laboratories/Kedrion, Sana Biological, and ROMTech; he received support for article research from the Versiti Blood Research Institute Foundation; and he disclosed off-label use of pediatric pharmacologic thromboprophylaxis. Dr. Betensky disclosed off-label use of low-molecular-weight heparin; she received funding from the NIH (1K23HL084055). Drs. Stillings' and Krava's institution received funding from the Health Resources and Services Administration (340B), the NIH (KL2, K23), and the Hemostasis & Thrombosis Research Society. Dr. Goldenberg received funding from Johnson & Johnson, CPC Clinical Research, and Anthos Therapeutics for advisory committee and data and safety monitoring committee activities for antithrombotic trials; his institution received funding from Chiesi and Pfizer; and he disclosed off-label use of anticoagulant in children. Dr. Sochet received support for article research from the Johns Hopkins All Children's Foundation; he disclosed off-label use of anticoagulants as pharmacologic thromboprophylaxis; and he received funding from the NIH (1K23HL177270). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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