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BRIEF REPORT

Hospital-acquired venous thromboembolism among critically ill children with diabetic ketoacidosis: a multicenter, retrospective cohort study

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Abstract

Background: Critically ill children and young adults with diabetic ketoacidosis are thought to be in a prothrombotic state. However, the rate of hospital-acquired venous thromboembolism and associated risk factors in this population have not been identified.

Objectives: Children hospitalized for diabetic ketoacidosis (DKA) may be at increased risk of hospital-acquired venous thromboembolism (HA-VTE). We sought to estimate the incidence of HA-VTE and identify unique prothrombotic risk factors in this population.

Methods: We performed a multicenter, retrospective cohort study using the Pediatric Health Information Systems registry including patients aged 0 to 21 years hospitalized for DKA from January 2017 to December 2023 within 48 participating centers. The primary outcome was the frequency of HA-VTE. Secondary outcomes were rates of cerebral edema, central venous catheterization (CVC), invasive mechanical ventilation (IMV), infection, and length of stay (LOS). An adjusted logistic regression was employed to identify potential HA-VTE risk factors.

Results: Of the 27,613 patients studied, 93 (0.3%) developed a HA-VTE. Compared with those without HA-VTE, those with HA-VTE had a greater median LOS (10 [IQR, 5-21] vs 2 [IQR, 2-3] days) and rates of cerebral edema (25.8% vs 6.6%), CVC (23.7% vs 1.1%), infection (72% vs 23.5%), and IMV (39.8% vs 1.4%; all $P < .001$). In an adjusted logistic model, factors independently associated with increased HA-VTE were CVC (adjusted odds ratio [aOR], 3.04; 95% CI, 1.49-6.19), infection (aOR, 4.61; 95% CI, 2.81-7.56), IMV (aOR, 9.24; 95% CI, 4.83-17.56), and increasing LOS (aOR, 1.05; 95% CI, 1.02-1.06; all $P < .01$).

Conclusion: The frequency of HA-VTE among critically ill children and young adults hospitalized for DKA was 0.3%. After prospective validation, putative risk factors (ie,

CVC, IMV, infection, and extended LOS) may be incorporated into the design of forthcoming pediatric thromboprophylaxis trials.

KEYWORDS
deep venous thrombosis, diabetic ketoacidosis, hospital-acquired condition, intracranial sinus thrombosis, pediatric critical care medicine, pediatric intensive care unit, pediatrics, pulmonary embolism

Essentials

- Hospital-acquired venous thromboembolism (HA-VTE) in pediatric diabetic ketoacidosis is ill-defined.
- In a multicenter study, HA-VTE rate and risk factors for children in acute diabetic ketoacidosis (DKA) were studied.
- Among 27,613 cases of pediatric DKA from 48 United States hospitals, the HA-VTE frequency was 0.3%.
- Overall, HA-VTE among critically ill children with DKA was less frequent than anticipated.

1 | INTRODUCTION

Hospital-acquired venous thromboembolism (HA-VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common cause of pediatric morbidity and mortality occurring in more than 1 in 50 critically ill children [1]. General pharmacologic thromboprophylaxis guidelines exist for critically ill adults without a contraindication to anticoagulants [2]. Yet, outside of unique clinical contexts, such as COVID-19 infection and multisystem inflammatory syndrome in children [1–3], universal pediatric thromboprophylaxis guidelines do not exist. Several HA-VTE risk models have been proposed [4] to identify at-risk pediatric subpopulations that may benefit most from anticoagulation. Establishing at-risk subgroups for HA-VTE remains a priority in selecting optimal study populations for thromboprophylaxis trials in children.

One subpopulation of interest is critically ill children and young adults hospitalized for diabetic ketoacidosis (DKA). Children with DKA classically present with severe dehydration, hyperosmolarity secondary to hyperglycemia, and severe metabolic acidosis [5,6]. *Ex vivo* analyses of thrombus microstructures using samples from cases and controls with and without DKA, respectively, suggest that both acidosis and dehydration are associated with the degree of clot permeability and an acquired prothrombotic state [7]. Published estimates for HA-VTE risk among critically ill children and young adults with DKA are lacking. Further, potential prothrombotic risk factors within this subpopulation, such as the severity of disease (eg, the presence of cerebral edema, the severity of acidosis, and dehydration), have yet to be established.

We sought to estimate the frequency of HA-VTE occurrence among children and young adults hospitalized for DKA and evaluate clinical characteristics as putative HA-VTE risk factors using a large administrative registry, the Pediatric Health Information Systems (PHIS) database. We hypothesized that the rate of HA-VTE in this population would be higher than previously reported for the general pediatric intensive care unit (PICU) population (~2.2%) [1]. We also hypothesized that central venous catheterization (CVC), invasive mechanical ventilation (IMV), concurrent infection, cerebral edema, and prolonged hospital length of stay (LOS) would each be associated with increased odds of HA-VTE.

2 | METHODS

2.1 | Data source

We performed a multicenter, retrospective cohort study using the PHIS registry. The PHIS registry is an administrative database that includes 49 children's hospitals in the United States. Each encounter encompasses demographic data and up to 41 International Classification of Diseases, Tenth Revision (ICD-10) and Clinical Modification diagnostic codes. The registry includes Clinical Transaction Classification codes used to identify pharmaceutical, laboratory, procedural, and supply-related billing for each unique encounter. Encounters can be characterized by type (observation, inpatient, and outpatient) and level of service (eg, PICU). This study was reviewed and approved by the institutional review board (IRB#: 00392505, approved: 06/07/2023).

2.2 | Sampling criteria and study cohorts

Study criteria and cohort features were identified using ICD-10 codes (see Supplementary Table). Inclusion criteria were patients aged 0 to 21 years and an admission diagnosis for DKA. The study period included those with an admission date between January 1, 2017, and December 31, 2023. Exclusion criteria were perinatal encounter classification and the presence of a VTE diagnosis on admission. Children with nonketotic hyperglycemic hyperosmolarity were not studied. Comparative cohorts were defined by the presence or

TABLE 1 General encounter characteristics and clinical outcomes for those children and young adults (aged 0-21 years) hospitalized for diabetic ketoacidosis with and without hospital-acquired venous thromboembolism.

Variable	Overall *N* = 27,613 *n* (%)[a]	HA-VTE *n* = 93 *n* (%)[a]	No HA-VTE *n* = 27,520 *n* (%)[a]	*P* value
Age (y), mean ± SD	12.2 ± 4.6	12.5 ± 5.4	12.2 ± 4.6	.67
Race and ethnicity categories				
American Indian	114 (0.4)	0 (0)	114 (0.4)	>.999
Asian	389 (1.4)	0 (0)	389 (1.4)	.64
Black	7921 (28.7)	37 (39.8)	7884 (28.7)	.02
Latino	4870 (17.6)	12 (12.9)	4858 (17.7)	.27
Other	3048 (11)	9 (9.7)	3039 (11)	.87
Pacific Islander	118 (0.5)	0 (0)	118 (0.4)	>.999
White	15,420 (55.8)	43 (46.2)	15,377 (55.9)	.07
Gender at birth				
Female	14,400 (52.2)	57 (61.3)	14,343 (52.1)	.08
Male	13,213 (47.9)	36 (38.7)	13,177 (47.9)	
Type of HA-VTE				
Cerebral sinovenous thrombosis	-	11 (11.8)	-	-
Limb and neck VTE	-	75 (80.7)	-	-
PE	-	15 (16.1)	-	-
Putative HA-VTE risk factors				
CVC	327 (1.2)	22 (23.7)	305 (1.1)	<.001
Infection	6532 (23.7)	67 (72)	6465 (23.5)	<.001
Malignancy	69 (0.3)	0 (0)	69 (0.3)	>.999
Medical technology dependent	2334 (8.5)	22 (23.7)	2312 (8.4)	<.001
Ventilation (invasive)	433 (1.6)	37 (39.8)	396 (1.4)	<.001
Cerebral edema	1844 (6.7)	24 (25.8)	1820 (6.6)	<.001
LOS, median (IQR)	2 (2-3)	10 (5-21)	2 (2-3)	<.001
In-hospital mortality	54 (0.2)	0 (0)	54 (0.2)	>.999

CVC, central venous catheterization; HA-VTE, hospital-acquired venous thromboembolism; LOS, length of stay; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]Unless otherwise specified.

absence of HA-VTE identified after admission, including limb and neck DVT, PE, and cerebral sinovenous thrombosis.

2.3 | Study outcomes and definitions

The primary study outcome was the frequency of HA-VTE occurrence, characterized further by calendar year and participating center. Secondary outcomes included clinical characteristics hypothesized or previously described as prothrombotic [3,8,9]. These factors included the presence of cerebral edema, CVC, concurrent infection, hematologic malignancy, chronic medical technology dependence, IMV, and hospital LOS. Cerebral edema was a composite feature including corresponding ICD-10 codes, pharmaceutical and service codes for hyperosmolar treatments such as hypertonic saline and mannitol, and cerebral imaging service codes for head computed tomography or brain magnetic resonance imaging as surrogate markers of cerebral edema (see Supplementary Table). CVC and IMV were identified using procedural and Clinical Transaction Classification coding. Chronic medical technology dependence is a composite variable available through the PHIS registry and includes the presence of tracheostomy and gastrostomy tubes suggestive of chronic medical complexity. Concurrent infection was defined as a prespecified composite variable within PHIS that includes sepsis, septic shock, and bacteremia

diagnoses. Other descriptive data included demographics (ie, age, gender, and historically disparate race and ethnicity categories) and general clinical outcomes (ie, in-hospital mortality rate).

2.4 | Statistical analysis

Descriptive statistics were employed to characterize the study sample, cases were defined by the presence of HA-VTE, and controls did not develop an HA-VTE. These included percentages with proportions, means with SDs, or medians with associated IQR, depending on the type of data and their distribution. Normality was assessed using Shapiro–Wilk testing. The annual trends for HA-VTE occurrence frequencies were examined using linear and nonlinear approaches. The correlation between HA-VTE occurrence frequencies and center-specific DKA admission volumes was assessed using Pearson's correlation. Putative factors associated with HA-VTE risk were initially assessed using unadjusted logistic regression. Variables with significate associations in univariate models (ie, P value < .05) were then included as covariates in an adjusted logistic model. All statistical tests were 2-sided, and type I error was set at .05. Encounters were used as the unit of analysis and assumed independent. Missing data were not imputed. Analyses were completed using Stata v15.1 software (Stata Corporation).

3 | RESULTS

3.1 | General sample characteristics

General descriptive data for the overall study sample and those with and without HA-VTE can be found in Table 1. A total of 27,613 patient encounters were eligible for the study from 48 participating United States PICUs (1 center was excluded for recorded data within the study period). Of those included in the study, 93 (0.3%) participants experienced an HA-VTE. For the overall sample, the mean age of participants was 12.2 ± 4.6 years, with a slight female predominance (52.2%). No differences in demographic features were noted between those with and without HA-VTE.

3.2 | Frequency of HA-VTE occurrence

The mean annual frequency of HA-VTE occurrence was 0.3% ± 0.1%, with little variation observed throughout the study period (Figure). Most HA-VTE was represented as DVT of the limbs and neck (80.7%), with the remainder as PE (16.1%) and cerebral sinovenous thrombosis (11.8%). Compared with those without HA-VTE, those who developed HA-VTE more frequently underwent CVC (23.7% vs 1.1%), had a concurrent infection (72% vs 23.5%), underwent IMV (39.8% vs 1.4%), had chronic medical technology dependence (23.7% vs 8.4%), and experienced cerebral edema (25.8% vs 6.6%; all P < .001). The median LOS among those with a HA-VTE was greater than those without a HA-VTE (10 [IQR, 5-21] vs 2 [IQR, 2-3] days; P < .001). The overall inpatient mortality rate was low at 0.2% (n = 54) and not detectably different for those with and without a HA-VTE.

3.3 | Putative risk factors

Univariable logistic regression was employed to assess putative HA-VTE risk factors (summarized in Table 2). The following clinical features were associated with HA-VTE risk in unadjusted analyses: IMV, infectious disease, CVC, medical technology dependence, cerebral edema, and increasing LOS (all P < .001). In adjusted logistic regression analyses, factors that remained associated with HA-VTE risk included IMV (adjusted odds ratio [aOR], 9.24 [95% CI, 4.83-17.56]; P < .001), infectious disease (aOR, 4.61 [95% CI, 2.81-7.56]; P < .001), CVC (aOR, 3.04 [95% CI, 1.49-6.19]; P = .002), and increasing LOS (aOR, 1.05 [95% CI, 1.02-1.06]; P < .001).

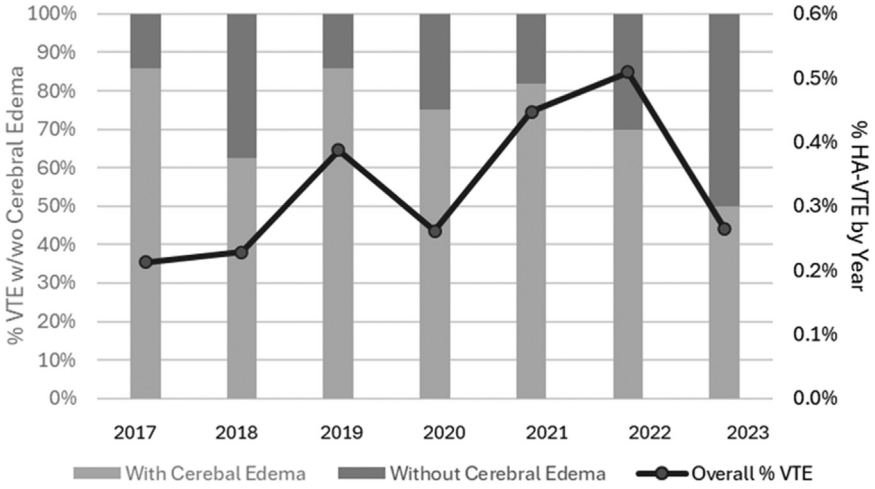

FIGURE Annual frequencies of occurrence of hospital-acquired venous thromboembolism (HA-VTE) among children and young adults (aged 0-21 years) hospitalized for diabetic ketoacidosis. Proportionally stacked bar graphs represent thromboembolism that occurred in children with (light gray) and without (dark gray) a diagnosis of or surrogate markers (ie, mannitol, 3% saline, and cranial imaging) for cerebral edema. VTE, venous thromboembolism.

TABLE 2 Results of univariate and multivariate-adjusted logistic regression analyses for hospital-acquired venous thromboembolism among children and young adults aged 0-21 years of age hospitalized for diabetic ketoacidosis.

	Univariate analysis			Multivariate analysis		
Independent variables	**OR**	**95% CI**	***P* value**	**aOR**	**95% CI**	***P* value**
CVC	6.93	16.91-45.19	<.001	3.04	1.49-6.19	.002
Cerebral edema	4.91	3.08-7.83	<.001	0.99	0.52-1.88	.99
Infectious disease	8.39	5.33-13.21	<.001	4.61	2.81-7.56	<.001
IMV	45.26	29.53-69.36	<.001	9.24	4.83-17.56	<.001
LOS (increasing)	1.09	1.08-1.11	<.001	1.05	1.02-1.06	<.001
Medical technology dependent	1.09	1.08-1.11	<.001	1.72	0.94-3.13	.08

aOR, adjusted odds ratio; CVC, central venous catheterization; IMV, invasive mechanical ventilation; LOS, length of stay; OR, odds ratio.

4 | DISCUSSION

Previously published estimates for HA-VTE rates among critically ill children vary between 0.3% and 2.2% depending on HA-VTE definition and study populations [1,8–10]. In this multicenter retrospective cohort study of critically ill children and young adults hospitalized for DKA, we observed a lower-than-anticipated HA-VTE rate of 0.3%. Prior to this report, only case series were available describing the potential relationship between HA-VTE and DKA. Among critically ill children, the presence of a CVC, prolonged LOS (>4 days), and a concurrent infection are thought to be the greatest contributors to HA-VTE risk [8]. In our study population, these features were less common, with only 1.2% undergoing CVC, a median LOS of 2 (IQR, 2-3) days, and a rate of current infection of 23.7%. While we hypothesized that the severity of illness specific to DKA measured by the presence and treatment of cerebral edema would be a prothrombotic risk factor for this population, a significant association was not observed after adjusting for other salient prothrombotic risk factors. For those children and young adults hospitalized for DKA, risk factors for HA-VTE appear to be consistent with those described in critically ill subpopulations and include CVC, IMV, infectious comorbidity, and prolonged LOS [1,3,10–17]. As such, these features could be applied to construct anticoagulant thromboprophylaxis trial conditions.

Children with DKA are thought to be at risk for thromboembolism, given changes in blood rheology secondary to disease-induced dehydration and hyperglycemic hyperosmolarity [18]. In general, the coagulation and fibrinolytic systems represent a balance between the physiologic maintenance of hemostasis and the development of a prothrombotic state [19]. DKA has been shown to induce markers of activation of the coagulation cascade, complement pathway, and platelets, as well as the release of prothrombotic factors from endothelia [20,21]. Laboratory evidence of coagulative dysfunction for those with and without DKA exists as measured by clot formation and permeability analyses [7]. Further, patients hospitalized with DKA may experience a prothrombotic state from oxidative stress [6,22]. In conjunction with the prospective evaluation of coagulative function among those hospitalized for DKA, risk-stratified clinical trials of pharmacologic thromboprophylaxis in this subpopulation are also needed.

4.1 | Limitations

There are limitations to consider with this research. The PHIS registry lacks patient-level granularity, including the timing of covariate interventions such as the presence or absence of pharmacologic thromboprophylaxis, laboratory data (eg, blood gas analysis data, plasma osmolarity, and glucose results hyperglycemia), and mental status indices (eg, Glasgow Coma Scale). While cerebral edema was defined by both ICD-10 coding and surrogate markers of cerebral edema, this composite feature may still underrepresent clinically significant cerebral edema. Prospective research utilizing laboratory results and neurologic examination documentation could overcome this limitation. Within PHIS, erroneous coding could lead to misclassification, sampling bias, and misinterpretation of primary findings. Billing documentation does not include the related date or time of service. Therefore, the sequence of events and interventions can only be inferred. While we excluded children with a VTE diagnosis if qualified as present on admission, it is possible that these diagnoses were initially asymptomatic as no universal screening practices, including ultrasonography or other forms of imaging, are recommended for critically ill children.

5 | CONCLUSIONS

The frequency of HA-VTE occurrence among critically ill children and young adults with DKA among 48 United States pediatric referral centers from 2017 to 2023 was 0.3% ± 0.1%. The development of a HA-VTE was associated with increasing LOS and comorbid IMV, CVC, and infection. If validated in prospective observational studies, these findings suggest that the severity of illness, measured by the presence of identified risk factors, should be applied as study inclusion criteria in the design of forthcoming pediatric thromboprophylaxis trials.

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AUTHOR CONTRIBUTIONS

K.M.D. participated in substantial contributions to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. E.E.H. participated in substantial contributions to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. M.B. participated in substantial contributions to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published. N.A.G. participated in substantial contributions to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published.

A.A.S. participated in substantial contributions to concept and design, analysis and/or interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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