Pediatric Surgery International (2019) 35:487–493
https://doi.org/10.1007/s00383-018-4418-y

ORIGINAL ARTICLE

Venous thromboembolism risk factors in a pediatric trauma population

Louis A. Carrillo[1] · Akshita Kumar[1] · Matthew T. Harting[1] · Claudia Pedroza[2] · Charles S. Cox Jr[1]

Accepted: 12 November 2018 / Published online: 19 November 2018

Abstract

Purpose New guidelines have been proposed for venous thromboembolism (VTE) prophylaxis in pediatric trauma patients. This paper seeks to evaluate risk factors associated with VTE that might further guide patient selection for prophylaxis.

Methods Review of a tertiary children's academic hospital's trauma database for VTE events and associated risk factors from 2005 to 2016.

Results 15,306 pediatric trauma patients were identified and reviewed. During this time period there were 6191 admissions (40.4%), of which 20 developed a VTE (0.3%) including two pulmonary emboli. Primary outcome was comparison of risk factors for developing a VTE that were identified in the literature. Age stratification revealed the highest incidence of VTE in children under the age of 2 (0.7%), which increased with CVC placement when compared to children aged 2–12 and 13–15 (0.036 Fisher's exact test).

Conclusions VTE after pediatric trauma is rare, and may be more uncommon than previously reported. CVC placement was the strongest predictor of VTE, particularly in infant and toddler patients which can explain their higher overall incidence compared to other pediatric age groups. Identifying high-risk patients is important to optimize screening and prophylaxis of VTE in pediatric trauma patients while minimizing risks of anticoagulation.

Keywords Trauma · Thrombus · Venous thromboembolism · VTE · Anticoagulation prophylaxis · Pediatric trauma · CVC · Central venous catheter · PICC · Peripherally inserted central catheter

Introduction

Pediatric venous thromboembolism (VTE) is a worsening problem as incidence continues to rise in hospitalized children [1]. One cohort study found an approximately 70% increase in incidence between 2001 and 2007 and an almost tenfold increase compared to the incidence identified in the 1990s by the Canadian registry study [1, 2]. Multiple studies have identified risk factors for VTE in pediatric patients such as age, hospital stay, and need for surgical procedures [3, 4]. The most prevalent risk factor appears to be use of central venous catheters (CVC). One study by Takemoto et al., found that half of the pediatric patients with a VTE had a CVC, and the majority of the VTEs that occurred formed in the same vessel the CVC was placed [3].

Venous thromboembolism also has significant costs to society and families, as well as morbidity for pediatric patients. These patients have a higher risk of in-hospital death, emboli migrating to the brain or lung, and of developing post-thrombotic syndrome (PTS) [5]. Another study found that pediatric patients who developed a VTE during admission, stayed an average of 8.1 days longer and had an increased cost of $27,686 when compared to matched controls [6]. The lack of FDA approved treatment options for pediatric patients [7] also creates a burden on families as Warfarin is the only oral anticoagulant for children. This option can be challenging for younger children as there is no available liquid formulation and the frequent INR monitoring. Enoxaparin injection is the only other current treatment option, as oral anticoagulants are being studied in clinical trials.

✉ Louis A. Carrillo
Louis.a.carrillo@uth.tmc.edu

[1] Department of Pediatric Surgery, McGovern Medical School at University of Texas Health Science Center at Houston, 6431 Fannin St, MSB 5230, Houston, TX 77030, USA

[2] Department of Pediatrics, McGovern Medical School at University of Texas Health Science Center at Houston, 6431 Fannin St, MSB 5230, Houston, TX 77030, USA

Traumatic injury is another identified risk factor associated with VTE in the pediatric population [3]. A review of the American College of Surgeons' (ACS) National Trauma Databank found a VTE diagnosis in 0.4% of patients less than 21 years of age [8]. Studies of pediatric trauma patients have demonstrated an increased incidence of VTE in older children, patients with higher injury severity score (ISS), CVC placement, blood transfusions, hemodynamic instability, and major vascular injuries [8–11]. The identification of these risk factors are being utilized to create standardized systems to stratify high-risk patients. One such trial at the Children's Hospital of Wisconsin saw a 65% reduction in VTE incidence in a high-risk group of patients admitted to the pediatric intensive care unit after trauma, involving applying sequential compression devices (SCD), chemical prophylaxis and ultrasound screening based on VTE and bleeding risks [12]. In early 2017, the Eastern Association for the Surgery of Trauma (EAST) and the Pediatric Trauma Society published guidelines recommending the use of chemical prophylaxis in certain subsets of the pediatric trauma population such as children over 15 and post pubescent children with ISS > 25. However, the guidelines note the need for further pediatric trauma VTE research and having to extrapolate information from adult studies for the pediatric population to develop these guidelines [13]. The goal of our study is to contribute data from our pediatric trauma population to the growing cohort of literature aiming to characterize VTE risk factors in the pediatric trauma population.

Materials and methods

Study population and VTE diagnosis

All pediatric trauma patients (age 15 and younger) evaluated from January 2005 to August 2016 at Children's Memorial Hermann Hospital by the trauma or pediatric surgery services were eligible. This patient population consisted of all trauma code activations. Exclusions included patients who were in the hospital for less than 24 h and patients who expired soon after arrival to the trauma bay. The criteria and numbers are seen in Fig. 1. The decision was made to exclude patients who were admitted for less than 24 h for two reasons. First, if they developed a VTE, it would not be considered a hospital acquired VTE due to their short stay. Secondly, their short time in the hospital is a reflection of their overall non-critical condition and creates statistical relationships where there is no clinical relationship. Data was extracted using the institution's Trauma Registry of the American College of Surgeons (TRACS) with approval of the University of Texas Health Science Center at Houston and Memorial Hermann Hospital Institutional Review Board (HSC-GEN-18-0056). This included demographics, injury severity score, CVC placement, ICU admission status, length of stay, and intubation/ventilation requirements. Patients found to have a VTE had their charts reviewed to document pertinent information about the VTE such as location and treatment course.

VTE events were defined as the documentation, coding, and/or billing of a deep venous thrombus (DVT)

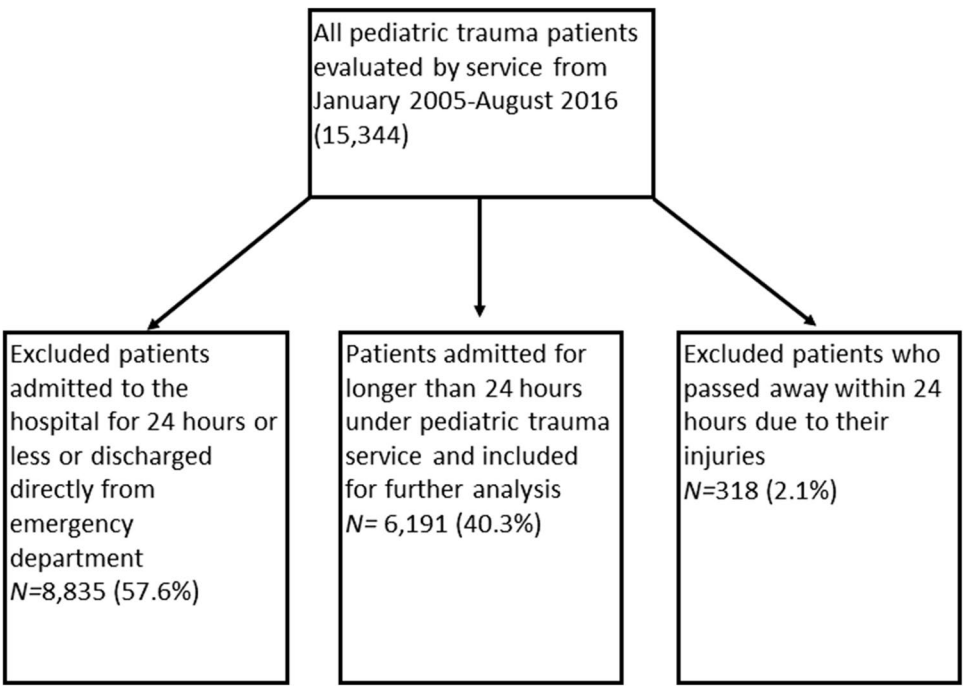

Fig. 1 Inclusion and exclusion criteria for pediatric trauma cohort Jan 2005-Aug 2016

diagnosis detected by duplex ultrasonography and/or pulmonary embolism (PE) detected by helical computed tomography angiography (CTA) of the chest during the hospital stay or at readmission. These tests were ordered at the provider's discretion typically due to concerns for a VTE due to symptoms such as a swollen extremity or dyspnea after prolonged immobility. All patients who had developed a documented VTE had their chart reviewed for location of thrombus, treatment, and a short overview of their admission.

Peripherally Inserted Central Catheters (PICCs) are not included in the institutions TRACS database as a CVC. Chart review of the VTE patients found them to be the sole central catheter placed, with thrombi developing on the PICCs in some cases. The decision was made to include these patients into the CVC category. To account for the database not tracking PICC line placement, an incidence rate of PICC line placement was determined. Pediatric trauma patients with length of stays over 1 week who did not have a CVC documented were identified. From this subgroup 100 patients were randomly selected and the incidence of PICC lines was determined via retrospective medical chart review. These incidence rates were used to calculate an estimated total number of catheters for each age group.

Statistical analyses

Comparison of incidence and risk factors in patients with and without a VTE were performed with two sample *t* tests for mean values and the Mann-Whitney *U* test for median values including GCS and ISS. Both tests were conducted on GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA). These tests were repeated with the ICU population. Additionally admitted patients were stratified into age groups. The cohort was analyzed by comparing patients aged 13–15 years to the rest of the study population via incidence rates and Chi-square tests. Further stratification was performed due to the high number of VTE events in children under the age of two. This resulted in three strata for further statistical analysis: those patients under two, patients aged 2–12 and patients aged 13–15. These strata were compared via their incidence of VTE development, CVC placement, and VTE with CVC placement. These rates were analyzed using Fisher's exact test to compare the 3 groups simultaneously on StataCorp. 2017. (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Fisher's exact test was also performed for the adjusted totals including PICC lines. Lastly, a logistic regression of the age groups and CVC placement isolated the relationship of the catheters.

Results

At Children's Memorial Hermann Hospital, a total of 15,344 pediatric trauma patients were evaluated from January 2005 to August 2016. Of the total number of patients, 6191 were included in analysis. The other 9153 patients included 8835 (57.6%) who were discharged within 24 h and 318 (2.1%) who did not survive past 24 h. Of the 6191 patients included in analysis 20 developed a VTE (0.3%). Two of these twenty included pulmonary emboli with one patient developing a VTE in their injured extremity as well as the pulmonary emboli. The differences between patients who developed a VTE and did not are seen in Table 1. The patients who experienced a VTE event ranged in age from 1 month to 15 years with no difference in average age ($p=0.88$) and no statistical difference in gender distribution ($p=0.77$) compared to the patients who did not develop a VTE. The VTE patients, when compared to the patients who did not develop a VTE, had a higher median injury severity scores (ISS) (17 vs 9 $p<0.001$), lower Glasgow Coma Scale (GCS) scores on arrival to the trauma bay (5 vs 15, $p<0.001$). They were more likely to require an intensive care unit (ICU) admission (95% vs 29.8%, $p<0.001$), and require mechanical intubation (90% vs 12.80%, $p<0.001$). These patients were more likely to have an ISS > 15 (70% vs 15%, $p<0.001$) signifying at least one severe injury or multiple moderate/mild injuries. Concurrent with other studies a higher incidence of CVC placement is noted in VTE patients (85% vs 5.70%, $p<0.001$) in the VTE population.Analysis of the 1860 ICU patients is seen in Table 2 and Chart 1, demonstrating no statistical difference in the median ISS (17 vs 17 $p=0.46$) and the duration of mechanical ventilation (7.24 days vs 4.46

Table 1 Demographics and Characteristics of Pediatric Trauma Patients ($n=6191$)

Variable	VTE patients ($n=20$)	Non- VTE patients ($n=6171$)	*p*
Age (years)	6.72	6.56	0.88
Males (%)	60	63.4	0.77
ED GCS (median)	5	15	< 0.001
Admitted LOS (Days)	21.19	5.817	< 0.001
ICU admissions (%)	95	29.8	< 0.001
Intubation (%)	90	7.8	< 0.001
CVC placement (%)	85	5.7	< 0.001
Average ISS (median)	17	9	< 0.001
ISS > 15 (%)	70	15	< 0.001

Mann–Whitney *U* test perform on GCS and ISS medians; all other variables were compared with two sample *t* test

ED GCS Glascow Coma Score in trauma bay, *LOS* length of stay, *CVC* central venous catheter, *ISS* injury severity score

Table 2 Demographics and Characteristics of 1860 ICU Status Pediatric Trauma Patients ($n=1860$)

Variable	VTE patients ($n=19$)	Non- VTE patients ($n=1841$)	p
ICU duration (days)	15.79	4.2	<0.001
Length of overall stay (days)	22.58	9.49	<0.001
Require intubation (%)	100	44	0.003
Intubation time(days)	7.24	4.46	0.09
ISS (median)	19	19	0.42
ISS > 15 (%)	66	4	0.02
CVC placed (%)	94	18	<0.001

Mann–Whitney *U* test perform on ISS medians; all other variables were compared with two sample *t* test

CVC central venous catheter, *ISS* injury severity score

days, $p=0.09$) for the ICU patients developing a VTE and those that did not. Patients who developed a VTE, however, were more likely to be intubated (100% vs 44%, $p=0.003$) and have an ISS > 15 (66% vs.40%, $p=0.02$). Patients who developed a VTE also had longer overall hospital stays (22.58 days vs 9.49 days, $p<0.001$) as well as longer stays in the ICU (15.79 days vs 4.2 days, $p<0.001$). This may not only be a factor in the development of the VTE, but also be a part of sequelae due to monitoring and treatment of the VTE itself. The most significant risk factor for developing a VTE in this population was the presence of a CVC, which was associated with an odds ratio of 36.93 (CI 8.49–160.59, $p<0.0001$).

Analysis by age initially compares teenagers 13 and up with the younger patients (Table 3). Other papers had noted a difference with older patients (3, 4), however, our Chi-square test did not show any statistical difference between the two groups (0.003 vs 0.004 $p=0.47$). When evaluating patients with CVC placement, the incidence rates increased, but no statistical differentiation was seen between the teenagers and the younger cohort (0.031 vs.051 $p=0.435$). The younger cohort was divided to compare those patients less than 2 years old to the rest of the population as 45% of the total 20 VTE's were found in patients less than 24 months old. Stratification by age revealed two sub groups with higher incidence rates of VTE development during admission than the cohort's average; patients less than 2 years old (0.007) and our teenage population 13 years and up (0.004). These rates are seen in Table 4. Chi-square test analysis showed statistical differences between the various groups for VTE incidence as well as with the incidence in those children who had received a CVC; this last analysis used a Fisher's exact test ($p<0.05$). A logistic regression model was applied to control for age as the other variables. This is seen in Table 5, which shows that CVC alone has an OR of 84.078 (CI 24.45–289.10, $p<0.001$). This regression also compares the youngest and oldest children to the middle cohort. Odds ratios, respectively, are 4.10 (CI 1.34–12.53 $p<0.05$) and 2.49 (CI 0.74–8.30 $p=0.139$).

Our adjusted catheter rates are seen in Table 6. Overall, the cohort of 1243 patients likely to receive a PICC had an incidence rate of 0.12 central venous catheters. Dividing this sub-cohort into our age subgroups, those less than two had an incidence of 0.09, the middle children an incidence of 0.128, and the oldest with incidence 0.125. These rates suggest there were an extra 17.37 PICCs in our youngest age group, 87.94 in the middle age group and 44.75 in our oldest

Table 3 Rate of VTE and CVC in Teenage Trauma Patients ($n=6190$)

Variable	Patients under 13 years old ($n=1435$)	Patients 13–15 years old ($n=4755$)	Chi-square	p value
Rate of VTE	0.003	0.004	0.523	0.47
Rate of CVC	0.058	0.067	1.455	0.228
Rate of VTE with CVC	0.051	0.031	0.61	0.435

VTE Venous thromboembolism, *CVC* central venous catheter

Table 4 VTE and CVC Incidence in Pediatric Trauma Patients Stratified by Age (n = 6.190)

	All admitted patients ($n=6,190$)	<2 years old ($n=1176$)	2–12 years old ($n=3,977$)	13–15 years old ($n=1435$)	Chi-square	p value
Overall VTE Incidence	0.003	0.007	0.001	0.004	13.06	0.0015
Overall CVC Incidence	0.057	0.078	0.052	0.067	12.61	0.0018
*Incidence of VTE + CVC	0.046	0.098	0.024	0.031	8.821	0.0368

Chi-square test performed for overall VTE and CVC incidence

Fisher's exact test performed for VTE and CVC due to low values in sub-group

VTE Venous thromboembolism, *CVC* central venous catheter

Table 5 Logistic regression and Odds ratio of VTE occurrence comparing CVC placement and Age groups

	Odds ratio	*p*	Confidence interval 95%
CVC placement compared to non-CVC	84.078	< 0.001	24.45–289.10
< 2 years old compared to 2–12 years old	4.10	0.013	1.34–12.53
13–15 years old compared to 2–12 years old	2.49	0.139	0.744–8.30

CVC central venous catheter

Table 6 VTE and Estimated Total Catheter Incidence in Pediatric Trauma Patients Stratified by Age ($n = 6.190$)

	All admitted patients ($n = 6190$)	< 2 years old ($n = 1176$)	2–12 years old ($n = 3977$)	13–15 years old ($n = 1435$)	Chi-square	*p* value
Overall VTE incidence	0.003	0.007	0.001	0.004	13.06	0.0015
Overall CVC incidence	0.088	0.090	0.074	0.098	9.474	0.0088
*Incidence of VTE + CVC	0.031	0.083	0.017	0.021	11.96	0.0054

Chi-square test performed for overall VTE and CVC incidence

Fisher's exact test performed for VTE and CVC due to low values in sub-group

VTE Venous thromboembolism, *CVC* central venous catheter

age group. These were rounded to 17, 88 and 45 respectively. These adjustments led to an increase in in CVC incidence and a decrease in the rates of VTE associated with CVC. However, due to the differences in the use of PICCs for each age group, the Chi square and *p* value were more significant when examining the association of VTE and CVC ($p < 0.01$).

Reviewing the treatment of the 20 VTE patients, 11 patients did not receive any form of anticoagulation because their DVT's were resolving on repeat ultrasound evaluation. Three patients were started on anticoagulation prior to the detection of a DVT secondary to other injuries or procedures. One patient was started on anticoagulation after no appreciable decrease in size of the DVT on repeat duplex ultrasound. Three patients were anticoagulated because their femoral vein DVT was found to extend proximally to iliac veins on ultrasound. Our study included two patients who had developed a PE. Both were 15 years old and both presented after being discharged from their initial admission and neither had a CVC during their initial admission. The first patient with a PE was readmitted 1 month after discharge after presenting to the emergency department with chest pain and shortness of breath. This patient did not have a previous central venous catheter, but did have an orthopedic procedure for a long bone fracture during their index admission and had continued compromised mobility despite physical therapy. The other patient with a VTE event was diagnosed with both a DVT and a PE, and was readmitted with chest pain and shortness of breath 8 days after the index admission. Reviewing the records there was concern for thrombophlebitis at a peripheral intravenous site in the vicinity of the DVT, but no other injury to the area. Both patients with diagnosed pulmonary emboli were anticoagulated and sustained no clinically significant sequelae from the VTE or treatment. No cases of post-thrombotic syndrome in the twenty VTE cases were noted in follow-up either.

Discussion

This cohort demonstrates that the relationship between age and VTE may not be as linear as previously thought especially in young children with large bore and PICC lines. It also adds to the pool of data suggesting that in children, CVC's are very common in children who develop a VTE. While other risk factors were identified such as higher ISS, lower GCS scores on presentation, and longer LOS their influence was negligible apart from CVC use. In every child less than 13 years of age who developed a VTE, a CVC was placed at some point during their index admission. The association of VTE with CVC is highlighted in the logistic regression model with an odds ratios over 20 times when controlling for age, the next strongest risk factor identified. Of the 17 patients who developed a VTE with a CVC placed, 15 of these VTEs were in the same extremity or on the catheter itself; in addition, of all patients under the age of two, the VTE exclusively occurred in the same location as the CVC placed. The highlight of this study is that very young children might be a particularly apt to developing VTE when a large catheter is placed. It has been suggested that catheter-related thrombi develop from a fibrin sleeve that deposits on the catheter and leads to flow occlusion and cellular adhesion between the catheter and vein wall [14]. It is possible that this pathway is either more easily initiated or the pathway reaches the end more frequently in these small vessels.

One of the limitations in this study is determining a "true" VTE incidence. Different institutions implement

different screening strategies. As stated before, the patients who were diagnosed were symptomatic, which prompted further screening usually with radiologic tests. The overall VTE rate is likely higher than what we are reporting as smaller thrombi would likely not be symptomatic, and therefore, would not prompt screening and detection. The review by Mahajerin et al. discussed the need for universal screening in pediatric trauma patients with ultrasound and they deemed the potential risks of anticoagulation to not warrant the potential benefits of treating small thrombi [13]. As discussed several patients did require anticoagulation therapy, but these decisions were made on a case by case basis often with pediatric hematologists. At this time due to rarity of these events our institution has not adopted a universal screening policy for traumatic pediatric patients.

Another limitation of our paper is how institutions decide who an adult and pediatric trauma patient is. This makes it difficult to compare the relationship between VTE and age between different studies. Our institution's cutoff is at 16 years of age, where patients 16 and older are admitted to the adult trauma service and are given VTE prophylaxis per our adult trauma guidelines. As mentioned the oldest patients in our cohort had a higher incidence compared to everyone under 13, but again the youngest children in our cohort actually had the highest incidence rate. These older children also have a lower rate of CVC's, and the association between VTE and CVC was less in this group compared to the rest of the cohort.

A retrospective study will suffer from limitations not seen in a prospective or active surveillance study for diagnosing rare events. This study is subject to accurate record keeping, coding and billing. These issues are amplified with a single institution study as to the generalizability of our findings. That all these inputs are accurately reflected in the center's database cannot be assumed to be 100%. This further complicates comparisons to other databases and studies. This can be seen in the issue with PICC lines. As described in our methods they are not actively counted as a CVC in the TRACS database. This paper tried to mitigate that flaw by trying to find their incidence in the institution. However, this is an initial estimate and it's unclear how other studies deal with these additional lines. This is of particular importance as most of the literature highlights CVC use with VTE and it's possible that the relationship may be more significant than thought if other VTEs were associated with a PICC and were not registered as being associated with a CVC.

Conclusion

As new guidelines are being implemented, pediatric trauma and critical care practitioners continue to evaluate and identify risk factors to stratify high-risk children in an effort to tilt clinical risk–benefit decisions in the patient's favor. This study reiterates that CVC use is the most significant risk factor for VTE formation in pediatric trauma patients and the use of chemical prophylaxis might be more dependent on the presence of such catheters especially in younger children. This study suggests that the infant and young toddler population has a higher risk of VTE development than previously thought when requiring central access; and that diligent monitoring of the extremities with use of these catheters is required. At this time it is not clear that age has a direct linear correlation with VTE development, and that further investigation is warranted as guidelines for screening and prophylaxis are implemented in the pediatric trauma population.

Acknowledgements Jeffrey Tomasek and the Center for Translational Research (CeTIR) for their assistance in compiling and maintaining this database that this study was based on.

Funding No funding was provided for this study.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived after review by IRB due to retrospective, anonymous and minimal risk nature of this study.

References

1. Raffini L, Huang YS, Witmer C, Feudtner C (2009) Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 124(4):1001–1008
2. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D et al (1994) Venous thromboembolic complications (VTE) in children: first analyses of the Canadian registry of VTE. Blood 83(5):1251–1257
3. Takemoto CM, Sohi S, Desai K, Bharaj R, Khanna A, McFarland S et al (2014) Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. J Pediatr 164(2):332–338
4. van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M (2001) Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 139(5):676–681
5. Kerlin BA (2012) Current and future management of pediatric venous thromboembolism. Am J Hematol 87(Suppl 1):S68–S74
6. Goudie A, Dynan L, Brady PW, Fieldston E, Brilli RJ, Walsh KE (2015) Costs of venous thromboembolism, catheter-associated urinary tract infection, and pressure ulcer. Pediatrics 136(3):432–439
7. Malec L, Young G (2017) treatment of venous thromboembolism in pediatric patients. Front Pediatr 5:26

8. Van Arendonk KJ, Schneider EB, Haider AH, Colombani PM, Stewart FD, Haut ER (2013) Venous thromboembolism after trauma: when do children become adults? JAMA Surg 148(12):1123–1130
9. Allen CJ, Murray CR, Meizoso JP, Ray JJ, Neville HL, Schulman CI et al (2016) Risk factors for venous thromboembolism after pediatric trauma. J Pediatr Surg 51(1):168–171
10. Yen J, Van Arendonk KJ, Streiff MB, McNamara L, Stewart FD, Conner KG et al (2016) Risk factors for venous thromboembolism in pediatric trauma patients and validation of a novel scoring system: the risk of clots in kids with trauma score. Pediatr Crit Care Med 17(5):391–399
11. Vavilala MS, Nathens AB, Jurkovich GJ, Mackenzie E, Rivara FP (2002) Risk factors for venous thromboembolism in pediatric trauma. J Trauma 52(5):922–927
12. Hanson SJ, Punzalan RC, Arca MJ, Simpson P, Christensen MA, Hanson SK et al (2012) Effectiveness of clinical guidelines for deep vein thrombosis prophylaxis in reducing the incidence of venous thromboembolism in critically ill children after trauma. J Trauma Acute Care Surg 72(5):1292–1297
13. Mahajerin A, Petty JK, Hanson SJ, Thompson AJ, O'Brien SH, Streck CJ et al (2017) Prophylaxis against venous thromboembolism in pediatric trauma: a practice management guideline from the eastern association for the surgery of trauma and the pediatric trauma society. J Trauma Acute Care Surg 82(3):627–636
14. Geerts W (2014) Central venous catheter-related thrombosis. Hematol Am Soc Hematol Educ Program 2014(1):306–311