



Full Length Article

Pediatric issues in thrombosis and hemostasis: The how and why of venous thromboembolism risk stratification in hospitalized children



Brian R. Branchford^{a,b,c,*}, Marisol Betensky^{d,f,g,h}, Neil A. Goldenberg^{d,e,f,g,h}

^a Division of Hematology/Oncology/Bone Marrow Transplant, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

^b Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, USA

^c Center for Cancer and Blood Disorders, Children's Hospital Colorado, Aurora, CO, USA

^d Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^e Department of Medicine, Divisions of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^f Johns Hopkins All Children's Cancer and Blood Disorder Institute, St. Petersburg, FL, USA

^g Johns Hopkins Medicine Pediatric Thrombosis Program, Johns Hopkins' All Children's Hospital, St. Petersburg, FL, USA

^h Johns Hopkins Children's Center, Baltimore, MD, USA

ARTICLE INFO

Keywords:

Pediatrics
Hospital-acquired venous thromboembolism
Thromboprophylaxis
Risk stratification
Prevention

ABSTRACT

Multiple observational studies have identified risk factors for venous thromboembolism (VTE) in hospitalized children, but very few interventional studies have assessed the safety and efficacy of thromboprophylaxis in this population. In recent years, however, evidence in pediatric VTE risk stratification has grown considerably. This has led to the conception of a pediatric subpopulation-specific risk-based paradigm for mechanical and pharmacological thromboprophylaxis in hospitalized children. More research is required to validate and further refine pediatric subpopulation-specific risk models and to subsequently investigate risk-stratified thromboprophylaxis strategies for hospitalized children.

1. Introduction

The incidence of hospital-acquired venous thromboembolism (VTE) in children is increasing [1], and there is growing awareness of the acute and chronic morbidities associated with this condition [2]. Acute VTE sequelae include pain, recurrent VTE, central nervous system complications including pseudotumor cerebri and/or cerebral hemorrhage (cerebral sinovenous thrombosis [CSVT]), hepato- and/or splenomegaly (portal vein thrombosis), compartment syndrome (extremity VTE), and pulmonary hypertension (pulmonary embolism). Chronic sequelae include pulmonary hypertension (pulmonary embolism), renal atrophy (renal vein thrombosis), neurologic deficits (CSVT), incomplete thrombus resolution, the post-thrombotic syndrome, and recurrent thrombosis, among others [3]. The development of adverse VTE outcomes are associated with a high physical and psychological burden in affected children, highlighting the need for developing risk-stratified approaches to prevent pediatric VTE. However, while high-quality evidence-based guidelines from randomized controlled clinical trials (RCTs) of the safety and efficacy of thromboprophylaxis drive intervention strategies in adults, [4] a paucity of data has slowed the development of a pediatric equivalent.

In general, the approach to pharmacologic VTE prophylaxis in children is not likely to be as universally appropriate for children as it is in most hospitalized adults, given the lower incidence of VTE in the general pediatric hospitalized population compared to hospitalized adults. Hence, a more highly risk-stratified approach to pediatric hospital acquired (HA)-VTE prevention is warranted. This review aims to summarize evidence on risk models for HA-VTE in children, and to highlight several areas of focus for research aimed at advancing knowledge on risk score and risk-stratified thromboprophylaxis in hospitalized children.

2. Risk factors and risk models

A few published pediatric HA-VTE risk models have been derived from single-institution studies. In 2014, the International Society for Thrombosis and Hemostasis (ISTH) Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee of the Scientific and Standardization Committee (SSC) convened a Working Group to develop and publish recommendations for standardization and future research priorities regarding pediatric VTE risk assessment models [5]. To inform that effort, this group conducted a meta-analysis, identifying intensive care

* Correspondence to: B. Branchford, Pediatric Hematology/Oncology/Bone Marrow Transplant, Research Laboratories, University of Colorado Anschutz Medical Campus, Research Complex 1, North Tower | 12800 E. 19th Ave. | Mail Stop, 8302 | Room P18-4102, Aurora, CO 80045, USA.

E-mail address: brian.branchford@childrenscolorado.org (B.R. Branchford).

<https://doi.org/10.1016/j.thromres.2018.02.010>

Received 26 January 2018; Received in revised form 6 February 2018; Accepted 13 February 2018

Available online 17 February 2018

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Table 1
Clinical characteristics associated with increased VTE risk in hospitalized children.

(Listed alphabetically due to current lack of expert consensus or robust data regarding relative risk contribution)

- Anticipated hospitalization > 72 h^{a,b}
- Cancer (Active, not in remission)^b
- Central venous catheter presence^{a,b}
- Estrogen therapy started within last 1 month
- Inflammatory disease (newly diagnosed, poorly controlled, or flaring)
- Intensive Care Unit admission^a
- Mechanical Ventilation^a
- Mobility decreased from baseline (Braden Q score < 2)^b
- Obesity (BMI > 99th %ile for age)^b
- Post-pubertal age
- Severe dehydration, requiring intervention^b
- Surgery > 90 min within last 14 days^b
- Systemic or severe local infection (positive sputum/blood culture or viral test, or empiric antibiotics)^b
- Trauma as admitting diagnosis

Abbreviations: VTE, venous thromboembolism; BMI, body mass index.
^a Risk factors identified by a recent meta-analysis of the pediatric HA-VTE literature [3].
^b Risk factors defined in a recent review of pediatric HA-VTE [17].

unit (ICU) admission, central venous catheter (CVC) presence, mechanical ventilation, and prolonged admission as independent risk factors for HA-VTE, when considering the overall hospitalized pediatric population [6]. Table 1 lists relevant risk factors, many of which (CVC, infection, length of stay, etc.) are described further in the position paper from the aforementioned Working Group [5] and the associated meta-analysis of the literature on HA-VTE risk factors [3]. While adolescence/postpubertal age is a well-established risk factor for VTE in general, the influence of age on VTE risk among hospitalized children is less well-defined, and likely weaker than among children in an outpatient setting. Since 2013, research work has begun to differentiate risk profiles among specific clinical settings/subpopulations, such as non-critically ill hospitalized children [7], or those admitted to pediatric [8], cardiac [9], or neonatal [10] ICUs.

Recently, a multi-institutional registry, the Children's Hospital-Acquired Thrombosis (CHAT) registry, was developed with a primary aim of deriving and validating pediatric HA-VTE risk prediction tools.

Table 2
Recommended anticoagulant regimens for thromboprophylaxis in children by risk factor [25].

Risk factor	Neonates	Recommendation by age group	Children
Central Venous Catheter	UFH continuous infusion (0.5 U/kg/h) (Grade 1A)	Flushing with normal saline, UFH, or intermittent recombinant urokinase to maintain patency (Grade 2C)	
Cardiac Surgery	Modified Blalock-Taussig shunts: Interoperative UFH followed by ASA or no antithrombotic therapy as compared with prolonged LMWH or VKAs (Grade 2C)	VKAs for CVC with long-term TPN (Grade 2C) Modified Blalock-Taussig shunts: Interoperative UFH followed by ASA or no antithrombotic therapy as compared with prolonged LMWH or VKAs (Grade 2C) Endovascular stent insertion: postoperative UFH (Grade 2C) Bilateral cavopulmonary shunt: postoperative UFH (Grade 2C)	
Medical Condition	N/A	Cardiomyopathy: VKAs no later than activation on cardiac transplant waiting list (Grade 2C) Primary pulmonary hypertension: VKAs started at same time as other medical therapies (Grade 2C) Biologic or mechanical prosthetic heart valves: Follow adult guidelines VADs: UFH 8 and 48 h following implantation, followed by ASA within 72 h. Once clinically stable, switch from UFH to LMWH or VKA until transplanted or weaned from VAD (Grade 2C) Hemodialysis via an AV fistula: VKAs or LMWH as fistula thromboprophylaxis; UFH or LMWH during hemodialysis independent of type of vascular access (Grade 2C) Kawasaki Disease: High-dose ASA (80–100 mg/kg/day) in acute phase, then low-dose (1–5 mg/kg/day) for 6–8 weeks (Grade 1B). Moderate or giant coronary aneurysms: VKAs and low-dose ASA as primary thromboprophylaxis. Thrombolysis or acute surgical intervention for acute coronary artery thrombosis (Grade 2C)	

Abbreviations: ASA, acetylsalicylic acid (aspirin); CVC, central venous catheter; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VAD, ventricular assist device; VKA, vitamin K antagonist.

Efforts through this registry are underway to retrospectively develop, then prospectively validate, a pediatric-specific HA-VTE risk score to identify high-risk children. It is planned that such children would then be the subject of future risk-stratified RCTs evaluating the efficacy and safety of thromboprophylaxis strategies. An additional benefit of this work through the CHAT group may be a decreased real-world use of thromboprophylaxis in patients defined to be at low risk of HA-VTE, thus reducing potential harm.

Ongoing studies of clinical subgroups may help determine the particular VTE risk associated with specific clinical conditions or risk factors. One example is the multi-institutional prospective observational Clot Incidence Rate in Central Line (CIRCLE) study [11] that has reported preliminary data from almost 1100 children with CVCs, ultimately planning to include approximately 2000 children. The cumulative incidence of symptomatic CVC-related VTE rate in this study was 5.7%, 85% of which occurred in children with peripherally-inserted central catheter (PICC) lines.

3. Thromboprophylaxis

3.1. Modalities and approach

Thromboprophylaxis strategies that have been well-studied in adult populations include mechanical prophylaxis with pneumatic sequential compression devices and pharmacological prophylaxis with anticoagulation. As noted previously in this review, however, pediatric HA-VTE risk is generally markedly lower than adult HA-VTE risk, although in specific pediatric subpopulations/settings HA-VTE risk may more closely approximate that in adults. Hence, thromboprophylaxis considerations in individual clinical scenarios in hospitalized children should consider available evidence on associated HA-VTE risk. Table 2 provides recommended anticoagulant regimens for thromboprophylaxis in specific subgroups of children with certain risk factors and/or co-morbidities, as summarized from the American College of Chest Physicians 9th guideline on antithrombotic therapy [12]. In addition, Table 3 provides a suggested general framework for considering risk-based thromboprophylaxis in hospitalized children. Specific risk categories in Table 3 are deliberately undefined, given the relative immaturity of the evidence (a small number of studies, each of which are single-institutional, as discussed above) to support specific risk-

Table 3
Suggested thromboprophylactic interventions by VTE risk category.

	VTE Low (0–1 RFs) ^a	VTE Med (2 RFs) ^a	VTE High (> / = 3 RFs) ^a
Bleed Low (Unlikely to bleed)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical Pharmacologic
Bleed Med (Moderate bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical ± Pharmacologic
Bleed High (Current bleeding or high bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical

Mechanical prophylaxis – Sequential compression device (preferred) and/or graduated compression stockings.

Pharmacologic prophylaxis – Low dose unfractionated heparin or low molecular weight heparin.

Abbreviations: RF, risk factors; VTE, venous thromboembolism.

^a Defined by number of risk factors from Table 1.

definitions in hospitalized children. Indeed, patient subgroups based on hospital location (ICU vs. general inpatient ward) or underlying disease type are relevant components of such a risk-based thromboprophylaxis strategy. For example, given the thresholds of $\geq 2\%$ and $1 - < 2\%$ modeled in medically-ill hospitalized adults to guide pharmacological and mechanical thromboprophylaxis, respectively [13], various risk score thresholds have been suggested to trigger either pharmacologic thromboprophylaxis (low-dose anticoagulation), mechanical prophylaxis (pneumatic compression devices in children of appropriate size), or observation without specific prophylactic intervention, depending on subgroup-specific risk factors in such groups as non-critically-ill children, [7] critically-ill children not undergoing cardiothoracic surgery, [8] or critically-ill children following cardiothoracic surgery or therapeutic cardiac catheterization [14].

It is worthy of note that, as shown in Table 3, mechanical prophylaxis may be instituted in most hospitalized children assessed to be at either moderate or high risk of VTE (Table 2); hence, this modality of thromboprophylaxis warrants a few additional discussion points here. With specific relevance to lower extremity thrombosis, data from adult studies suggest that sequential compression devices are preferred over compression stockings [15,16] with the exception of presence of a known thrombus, when only the latter may still be used. Additional risks (pressure ulcer or other skin irritation) and contraindications (acute VTE, fracture, burns, wound, post-operative site, peripheral IV access, or inappropriate fit) exist and must be considered. With the exception of some potential beneficial effect by increasing systemic fibrinolysis [17], the utility of mechanical prophylaxis has not been well established for upper and central venous system VTE, particularly if CVC-associated.

3.2. Ongoing trials

Three prior RCTs have evaluated the use of pharmacological prophylaxis for the prevention of VTE in children with CVCs [Massicotte P. 2003; Ruud E. 2006, and Schroeder A.R. 2010]. Pharmacologic interventions assessed in these trials included warfarin, low molecular weight heparin and unfractionated heparin. The three trials were underpowered and unable to detect a difference in the incidence of VTE between the comparison arms.

Currently, there are two ongoing trials investigating the efficacy and safety of direct oral anticoagulants (DOACs) for VTE prevention in children. The PREVAPIX-ALL (A Study of the Safety and Effectiveness of Apixaban in Preventing Blood Clots in Children With Leukemia Who Have a Central Venous Catheter and Are Treated With Pegylated (PEG)

L-Asparaginase, ACCL1333, www.clinicaltrials.gov NCT02369653) trial through the Children's Oncology Group [18] is a phase 3 RCT on the efficacy and safety of apixaban for VTE prevention during induction chemotherapy in children with leukemia and a CVC who are receiving L-Asparaginase.

A second thromboprophylaxis trial in preparation, the ENNOBLE (Edoxaban for Prevention of Blood Vessels Being Blocked by Clots (Thrombolytic Events) in Children at Risk Because of Cardiac Disease, www.clinicaltrials.gov NCT03395639), is an RCT of edoxaban versus standard-of-care anticoagulation in children with cardiac disease who are deemed to require anticoagulation as primary (e.g., severe heart failure or Kawasaki disease) or secondary (e.g., history of shunt thrombosis with shunt still in place; status-post Fontan with history of thromboembolism) prophylaxis.

The PREVAPIX-ALL and ENNOBLE are expected to be completed in 2020 and 2021 respectively. Despite the progress represented by the launch of these two RCTs on pediatric thromboprophylaxis in the era of the DOACs, further trials are needed. Once risk models are validated and further refined pertaining to additional patient subpopulations in hospitalized children, collaborative interventional studies (ultimately, RCTs, if warranted by initial non-randomized interventional studies) should address these expanded pediatric populations, and should be designed to address the inherent tradeoff between the increased bleeding risk of pharmacological thromboprophylaxis (safety) and reduced VTE risk (efficacy). This inherent trade-off (i.e. net clinical benefit) can be modeled as a bivariate endpoint, as recently described and applied to recent DOAC RCTs in adults as well as the Kids-DOTT (Evaluation of the Duration of Therapy for Thrombosis in Children, www.clinicaltrials.gov NCT00687882) study, a randomized controlled clinical trial whose primary objective is to evaluate non-inferiority of shortened-duration (6 weeks) versus conventional-duration (3 months) anticoagulation therapy in children with first-episode acute VTE provoked by an identifiable temporary clinical risk factor.

3.3. Limitations and special considerations

Several limitations of the present literature, and special considerations based on patient scenarios and characteristics, are important to note in the context of pediatric HA-VTE thromboprophylaxis. Firstly, it is generally held that patients over age 18 years, even if hospitalized in a pediatric institution, should be subject to available standard adult VTE prevention guidelines [19–21]. However, it must be recognized that the young adult has been poorly represented in the adult evidence that has informed current adult guidelines. Furthermore, with approximately 80–85% of HA-VTE in patients under 18 years of age at pediatric institutions occurring in patients with CVCs [22,23], it is likely that CVCs are more prevalent among the young adults hospitalized at pediatric institutions than adult hospitals. This notion is made more challenging by the fact that previous studies of thromboprophylaxis for CVC-VTE have not demonstrated clear benefit, as recently reviewed by Vidal et al. [24] Identification of the characteristics most highly associated with CVC-related VTE (e.g.: type of CVC, CVC material, site of insertion, tip location, ultrasound guidance) may greatly inform future risk stratification and mitigation strategies.

In addition, it should be emphasized that, since evidence on risk-stratification and risk-stratified pediatric HA-VTE prevention is still evolving, there are not yet clear distinctions between approaches for medical vs. surgical patients (and certainly limited based upon which to tailor such approaches for orthopedic vs. non-orthopedic surgery), which is in stark contrast to the current state of the thromboprophylaxis field in adults. Future perioperative strategies in children may involve a truncated risk assessment (focused on post-pubertal age, obesity, and underlying inflammatory disease in addition to personal or family history of thrombosis or thrombophilia) and primarily consist of the use of intraoperative ± transient post-operative mechanical prophylaxis while inpatient, until mobility/ambulation is restored.

Lastly, and perhaps most importantly, given the challenges regarding assessment of bleeding risk as well as HA-VTE risk, clinical decision-making on pediatric HA-VTE prophylaxis (particularly when outside of institutional guidelines) should involve input from a pediatric hematologist with expertise in anticoagulation, and should involve frequent reassessment in the context of an often-changing clinical status of the hospitalized child.

References

- [1] L. Raffini, Y.S. Huang, C. Witmer, C. Feudtner, Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007, *Pediatrics* 124 (2009) 1001–1008.
- [2] B.L. Biss, Kahr W.H. TT, A.K. Chan, S. Williams, Clinical features and outcome of pulmonary embolism in children, *Br. J. Haematol.* 142 (2008) 808–818.
- [3] N.A. Goldenberg, Long-term outcomes of venous thrombosis in children, *Curr. Opin. Hematol.* 12 (2005) 370–376.
- [4] G. Guyatt, D. Gutterman, M. Baumann, D. Addrizzo-Harris, E. Hylek, B. Phillips, G. Raskob, S. Zelman Lewis, et al., Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force, *Chest* 129 (2006) 174–181.
- [5] B.R. Branchford, A. Mahajerin, L. Raffini, E. Chalmers, C.H. van Ommen, A.K.C. Chan, N.A. Goldenberg, S.p.N. Hemostasis, Recommendations for standardized risk factor definitions in pediatric hospital-acquired venous thromboembolism to inform future prevention trials: communication from the SSC of the ISTH, *J. Thromb. Haemost.* 15 (2017) 2274–2278.
- [6] A. Mahajerin, B.R. Branchford, E.K. Amankwah, L. Raffini, E. Chalmers, C.H. van Ommen, N.A. Goldenberg, Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models, *Haematologica* 100 (2015) 1045–1050.
- [7] C.M. Atchison, S. Arlikar, E. Amankwah, I. Ayala, L. Barrett, B.R. Branchford, M. Streiff, C. Takemoto, N.A. Goldenberg, Development of a new risk score for hospital-associated venous thromboembolism in noncritically ill children: findings from a large single-institutional case-control study, *J. Pediatr.* 165 (2014) 793–798.
- [8] S.J. Arlikar, C.M. Atchison, E.K. Amankwah, I.A. Ayala, L.A. Barrett, B.R. Branchford, M.B. Streiff, C.M. Takemoto, N.A. Goldenberg, Development of a new risk score for hospital-associated venous thromboembolism in critically-ill children not undergoing cardiothoracic surgery, *Thromb. Res.* 136 (2015) 717–722.
- [9] C.M. Atchison, E. Amankwah, J. Wilhelm, S. Arlikar, B.R. Branchford, A. Stock, M. Streiff, C. Takemoto, I. Ayala, A. Everett, G. Stapleton, J. Jacobs, N.A. Goldenberg, *Cardiol in Young* (in press), (2017).
- [10] E.K. Amankwah, C.M. Atchison, S. Arlikar, I. Ayala, L. Barrett, B.R. Branchford, M. Streiff, C. Takemoto, N.A. Goldenberg, Risk factors for hospital-associated venous thromboembolism in the neonatal intensive care unit, *Thromb. Res.* 134 (2014) 305–309.
- [11] J. Jaffray, C. Witmer, B. Vasquez, R. Diaz, J. Malvar, G. Young, Determining the incidence and risk factors for central venous catheter-related thrombosis in children, *Blood* 128 (2016) (Abstract 419).
- [12] C.A. Monagle P, N. Goldenberg, R. Ichord, J. Journeycake, U. Nowak-Gottl, S. Vesely, Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-based Clinical Practice Guidelines, *Chest* 141 (2012) e737S–e801S.
- [13] A.C. Spyropoulos, F.A. Anderson Jr., G. FitzGerald, H. Decousus, M. Pini, B.H. Chong, R.B. Zotz, J.F. Bergmann, V. Tapson, J.B. Froehlich, M. Monreal, G.J. Merli, R. Pavanello, A.G.G. Turpie, M. Nakamura, F. Piovella, A.K. Kakkar, F.A. Spencer, I. Investigators, Predictive and associative models to identify hospitalized medical patients at risk for VTE, *Chest* 140 (2011) 706–714.
- [14] C.M. Atchison, E. Amankwah, J. Wilhelm, S. Arlikar, B.R. Branchford, A. Stock, M. Streiff, C. Takemoto, I. Ayala, A. Everett, G. Stapleton, M.L. Jacobs, J.P. Jacobs, N.A. Goldenberg, Risk factors for hospital-associated venous thromboembolism in critically ill children following cardiothoracic surgery or therapeutic cardiac catheterisation, *Cardiol. Young* (2017) 1–9.
- [15] R.J. Morris, J.P. Woodcock, Intermittent pneumatic compression or graduated compression stockings for deep vein thrombosis prophylaxis? A systematic review of direct clinical comparisons, *Ann. Surg.* 251 (2010) 393–396.
- [16] K.M. Ho, J.A. Tan, Stratified meta-analysis of intermittent pneumatic compression of the lower limbs to prevent venous thromboembolism in hospitalized patients, *Circulation* 128 (2013) 1003–1020.
- [17] A.J. Comerota, V. Chouhan, R.N. Harada, L. Sun, J. Hosking, R. Veermansunemi, A.J. Comerota Jr., D. Schlappy, A.K. Rao, The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis, *Ann. Surg.* 226 (1997) 306–313 (discussion 313–4).
- [18] Bristol-Myers Squibb, PREVAPIX-ALL, *Trials* (2015) US National Institutes of Health. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/home). Available at: <https://clinicaltrials.gov/ct2/home> (accessed 01 September 2017).
- [19] F.C. Falck-Ytter Y, N. Johanson, C. Curley, O. Dahl, S. Schulman, T. Ortel, S. Pauker, C. Colwell, Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, *Chest* 141 (2012) 3278S–e3255.
- [20] M.K. Gould, D.A. Garcia, S.M. Wren, P.J. Karanicolas, J.I. Arcelus, J.A. Heit, C.M. Samama, P. American College of Chest, Prevention of vte in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, *Chest* 141 (2012) e227S–77S.
- [21] L.W. Kahn S, A. Dunn, M. Cushman, F. Dentali, E. Akl, D. Cook, A. Balekian, et al., Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, *Chest* 141 (2012) e195S–e226S.
- [22] J. Jaffray, A. Mahajerin, G. Young, N. Goldenberg, L. Ji, R. Sposto, A. Stillings, E. Krava, B. Branchford, A multi-institutional registry of pediatric hospital-acquired thrombosis cases: the Children's Hospital-Acquired Thrombosis (CHAT) project, *Thromb. Res.* 161 (2017) 67–72.
- [23] J. Jaffray, M. Bauman, P. Massicotte, The impact of central venous catheters on pediatric venous thromboembolism, *Front Pediatr* 5 (2017) 5.
- [24] E. Vidal, A. Sharathkumar, J. Glover, E.V. Faustino, Central venous catheter-related thrombosis and thromboprophylaxis in children: a systematic review and meta-analysis: reply, *J. Thromb. Haemost.* 13 (2015) 161–162.
- [25] P. Monagle, A.K. Chan, N.A. Goldenberg, R.N. Ichord, J.M. Journeycake, U. Nowak-Gottl, S.K. Vesely, P. American College of Chest, Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, *Chest* 141 (2012) e737S–801S.