



### PEDIATRIC HEMATOLOGY

# Hemostatic and thrombotic disorders in the pediatric patient

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**This review focuses on significant advances in the field of pediatric hemostasis and thrombosis, with a focus on published studies within the past decade. The evaluation and management of patients with excessive bleeding remain cornerstones of consultative hematology. We will describe the development of validated bleeding assessment tools relevant to pediatric practice, laboratory advances in the evaluation of von Willebrand disease, and a shift in clinical practice regarding the interpretation of normal coagulation studies in patients with significant bleeding phenotypes. There have also been critical advances in the management of hemostatic disorders. This review highlights new treatment paradigms in hemophilia and the rise of multidisciplinary medical homes for women living with bleeding disorders. Given the continued increase in the incidence of thrombosis,**

**particularly in the hospital setting, a full call to arms against pediatric venous thromboembolism is now essential. We will describe recently completed clinical trials of direct oral anticoagulants in children and adolescents and ongoing work to elucidate the appropriate duration of therapy for children with provoked thrombosis. Recent work regarding the prevention of pediatric venous thromboembolism is highlighted, including studies of thromboprophylaxis and the development of risk prediction models for hospital-acquired thrombosis. Finally, we review advances in our understanding of thrombotic sequelae and the need for continued refinement of our evaluation tools. Despite the significant advances in pediatric hemostasis and thrombosis over the past decade, many unanswered questions remain for the next generation of investigators.**

## Introduction

This review focuses on significant advances in the field of pediatric hemostasis and thrombosis, including updates in diagnosis, management, and prevention of disease. We focus on published studies within the past decade and end with our hopes for future directions in this rapidly evolving subspecialty.

## Pediatric hemostatic disorders

### Use of bleeding assessment tools in children and adolescents

The assessment of bleeding symptoms in children has always presented its own unique set of challenges. The ability to quantify bleeding symptoms precisely and objectively through the use of validated bleeding assessment tools (BATs) has been an active area of investigation over the past 2 decades, and in recent years, pediatric-specific data have become available. The Pediatric Bleeding Questionnaire (PBQ) was derived from the Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (VWD) Bleeding Questionnaire with the addition of pediatric-specific symptoms such as umbilical stump bleeding and cephalohematoma.<sup>1</sup> The inclusion of healthy controls allowed for the determination of the

normal PBQ score, which is  $\leq 2$ . The PBQ has a high negative predictive value in children undergoing investigation for VWD and can clearly distinguish disease severity in children with different subtypes of VWD.<sup>2</sup> Pediatric hematologists can also use the International Society of Thrombosis and Haemostasis (ISTH) BAT, published in 2010, to provide a standardized method of reporting bleeding symptoms in adults and children. Like the PBQ, the normal range of ISTH-BAT is 0 to 2 in patients  $<18$  years of age.<sup>3</sup> Recently, attention has focused on self-administered BATs, which allow more seamless incorporation into busy clinical settings. A "Self-ISTH-BAT" and a "Self-PBQ" have both been validated.<sup>3,4</sup> These instruments demonstrate strong agreement with expert-administered versions and strong negative predictive values for VWD. A modified Self-PBQ has been developed that can be completed by 8- to 12-year-old children, with or without adult assistance.<sup>5</sup>

More work is needed to determine the normal bleeding score for adolescent females, who have typically experienced menarche but not yet experienced childbirth or the more frequent surgical challenges of adulthood. PBQ scores in children affected with VWD increase with age, from a median score of 4 in patients 0 to 3 years of age to 12 in patients 16 to 18 years of age.<sup>2</sup> One recent study demonstrated that in adolescents

presenting to a multidisciplinary hematology clinic with heavy menstrual bleeding (HMB), an ISTH-BAT score of >4 instead of the established cutoff of >2 in children was highly specific in predicting an underlying bleeding disorder.<sup>6</sup>

### Advances in the laboratory evaluation of VWD

In recent years, new assays have become available that enhance the ability to evaluate both children and adults with suspected VWD.<sup>7</sup> Traditionally, von Willebrand factor (VWF) activity has been measured by ristocetin-based assays, which unfortunately has several limitations and is prone to both false-positive and false-negative results. The VWF:GPIIbM assay introduces gain-of-function mutations into the platelet glycoprotein GPIIb $\alpha$ , allowing it to bind VWF spontaneously *in vitro* without requiring ristocetin.<sup>8</sup> The VWF:GPIIbM allows higher precision, with a reported lower limit of detection of 2 IU/dL and a coefficient of variation of 5.6%.<sup>9</sup> The availability of this assay is still limited in the United States and other regions. Hopefully, the availability of this assay will continue to increase, allowing for more diagnostic precision in VWD.

VWF also binds to exposed collagen at sites of injury, which requires specific testing. Collagen binding assays, a new addition to VWD testing algorithms, provide insight into a different function of VWF than the traditional activity tests that assess platelet binding. For example, in type 2M subjects, the mean bleeding score is higher in subjects with a platelet- and a collagen-binding defect compared with subjects with only a platelet-binding defect.<sup>10</sup> Finally, because of the increased availability and lower costs, genetic testing has become more widely used in the evaluation of VWD.<sup>7</sup> At this time, testing is most helpful in cases where a type 2 variant is suspected. A high percentage of patients with type 1 VWD do not have a specific VWF genetic variant; more work is needed to determine which identified novel variants in type 1 are actually pathogenic. Several genes outside the VWF locus have also been implicated in altering VWF levels, because of their effects on VWF clearance and endothelial cell exocytosis. ABO blood group has been the most well characterized of these modifier genes, but others that have been well studied include *CLEC4M*, *STXBPS*, and *STAB2*.<sup>11</sup>

The well-known variability in VWD test results caused by processing problems,<sup>12</sup> patient's stress, illness, or estrogen exposure has led to the clinical adage that tests should be performed 3 times before the diagnosis is formally ruled out. Although this practice may be even more relevant in pediatric patients, because of the high levels of stress surrounding venipuncture, for the same reason, it can be more burdensome and impractical for young children to undergo repeated testing. A large retrospective series by Doshi et al has finally provided evidence to inform this long-held clinical teaching.<sup>13</sup> In >800 pediatric patients evaluated for a suspected bleeding disorder, 22% were diagnosed with VWD, with ~70% diagnosed on the first test. A cutoff of 100 IU/dL for VWF antigen or activity on the first test yielded negative predictive values >95%. Based on these findings, providers can be confident that patients with initial VWF levels >100 IU/dL and a negative family history of VWD likely do not need repeated tests to rule out the diagnosis of VWD. However, additional bleeding diagnoses may have to be explored depending on the patient's bleeding phenotype.

Regardless of whether traditional or novel assays are being used to evaluate VWD, it remains essential to use assays that allow for onsite processing when possible. A recent study of adolescent and adult women confirmed the long-held clinical suspicion that VWD testing at off-site, non-hospital-based laboratories may lead to false-positive results. These investigators found that higher proportions of patients demonstrated low VWF:Ag, VWF:RCo, and FVIII levels with offsite processing compared with levels demonstrated onsite.<sup>12</sup>

### A shift in interpretation of "normal" laboratory test results in pediatric patients with a bleeding phenotype

Another recent shift in clinical practice has been in the interpretation of normal results of routine hemostatic assays in patients with positive bleeding phenotypes. Traditionally, such patients were discharged from care by hematologists because of an unremarkable laboratory evaluation, but today's approach has become more nuanced. In particular, 3 disease states are increasingly included in the population of patients living with bleeding disorders and/or phenotypes: (1) women with hemophilia, (2) patients with bleeding tendency related to generalized joint hypermobility, and (3) patients with bleeding of unknown cause.

There are an estimated 1.5 female carriers for every male with hemophilia. Approximately one-third of women with hemophilia have low factor (F) levels, generally in the range of men with mild hemophilia.<sup>14</sup> In recent years, it has come to light that women and girls with hemophilia, even those with normal FVIII or FIX levels, have increased bleeding scores compared with the general female population.<sup>15</sup> However, the severity of bleeding correlates only weakly with factor levels. Hemarthroses affects 4% to 19% of carriers, and subclinical joint bleeding can also occur.<sup>16-20</sup> The My Life, Our Future initiative, which provided genetic testing to thousands of patients and potential carriers,<sup>21</sup> and increasing clinical genetic testing availability, has helped increase the number of identified girls and women with hemophilia. However, much remains to be learned regarding natural history and optimal management for these patients.

Another population receiving increasing attention are those with bleeding tendencies due to joint hypermobility spectrum disorders (JHSDs). Patients with JHSD may bleed for various reasons, including mechanical weakness of blood vessel walls, defective subendothelial connective tissue supporting these blood vessels, and impaired interactions between platelets, VWF, and collagen.<sup>22</sup> Hematologists should have basic familiarity with the updated 2017 diagnostic criteria for hypermobile Ehlers-Danlos syndrome and other hypermobility spectrum disorders to improve JHSD's recognition in the evaluation of easy bruising and bleeding.<sup>23</sup> Although patients with JHSD may have platelet function defects or prolonged bleeding times, these findings are not consistent, and many have normal results in a hemostatic evaluation. Recent case series in pediatrics have (1) highlighted the complexity of managing heavy menses in adolescents with hypermobility<sup>24</sup> and (2) suggested that coexistent hypermobility among children and adults with VWD increases the severity of bleeding.<sup>25</sup>

Finally, there is increasing use in the hematology community of bleeding of unknown cause as a diagnosis for patients with unusual bleeding phenotypes and elevated BAT scores but a lack of abnormalities in clinically available laboratory assays. Such patients encompass a substantial percentage of patients with mild-to-moderate bleeding tendencies.<sup>26</sup> Studies in which such patients undergo extensive specialized testing suggest various causes for their bleeding, including increased fibrinolytic activity, decreased thrombin generation, and impaired plasma clot formation or lysis.<sup>26,27</sup>

### Therapeutic considerations for inherited bleeding disorders in pediatric patients

Treatment advances in the field of hemophilia have been truly astounding in the past decade, with the advent of long-acting factor products and new bypass products for adults and children and the first studies of gene therapy (limited to adults at this time). Methods used to create extended half-life factor products include PEGylation, fusion with protein conjugates, and protein structure or sequence modifications.<sup>28</sup> In previously treated adult and pediatric populations, phase 3 clinical trials have demonstrated a decrease in the necessary infusion frequency compared with standard half-life products. However, the half-life extension has been much more impressive in the FIX products.<sup>29</sup> Initial results of PUPs A-LONG, the first study of the extended half-life recombinant FVIII Fc fusion protein in previously untreated males <6 years old, demonstrated safety, efficacy, and a prevalence of inhibitor development within the expected range.<sup>30</sup>

Although extended half-life products have improved the treatment landscape for hemophilia, the development of emicizumab has significantly impacted the experience of children and adolescents living with hemophilia. This humanized bispecific monoclonal antibody offers subcutaneous administration advantages and a long half-life (~30 days).<sup>28</sup> HAVEN2, a phase 3 study of emicizumab in children <12 years of age with severe hemophilia and inhibitors, demonstrated a 99% reduction in annualized bleeding rates compared with prior bypassing agent prophylaxis.<sup>31</sup> A recently published study examined long-term outcomes of emicizumab prophylaxis for hemophilia A, with and without inhibitors from the HAVEN 1-4 studies, in which 32.9% of the 401 participants were <18 years of age.<sup>32</sup> Across a median efficacy time frame of 120 weeks, low annual bleeding rates were maintained, bleeding into target joints decreased substantially, and no new target joints formed. The risk of inhibitor development is also much lower with emicizumab, although recent reports of inhibitor formation have emerged.<sup>33</sup> Unanswered questions remain regarding these emerging therapies in hemophilia, including (1) risk of inhibitor development in previously untreated patients in whom emicizumab vs factor replacement is initiated as the primary prophylaxis; (2) long-term risk of thrombosis with use of emicizumab, especially during combination therapy for breakthrough bleeding; and (3) whether emicizumab can be combined safely with immune tolerance induction.<sup>34</sup>

The first recombinant VWF product was also introduced in the past decade, providing a new treatment option for adults with VWD. A pediatric study of the efficacy, safety, and pharmacokinetics of recombinant VWF, which allows providers to

administer doses of VWF and FVIII independently, is currently enrolling participants.

### Rapid expansion of multidisciplinary care for young women with bleeding disorders

Although there have not been groundbreaking therapeutic developments in the management of reproductive bleeding, there has been a substantial shift in the evaluation and care of women with suspected or diagnosed bleeding disorders, with pediatric hematologists leading the charge. Multidisciplinary clinics with expertise in hematology, adolescent medicine, and gynecology allow for more rapid diagnoses of bleeding diatheses and treatment of HMB.<sup>35</sup> In 2013, the Foundation for Women and Girls with Blood Disorders established a formal network of clinics devoted to the care of women and girls with bleeding disorders, which has now grown to 61 institutions in the United States, Canada, and the Netherlands.<sup>36</sup>

The establishment of this new career niche within hematology is also leading to collaborative research efforts. A recent multicenter observational cohort study included adolescents ( $n = 113$ ) with HMB (Pictorial Blood Assessment Chart score >100) and low VWF (2 values of VWF activity 30-50 IU/dL). A large majority (94%) of participants had an abnormal BAT and a high percentage of HMB complications (60% iron deficiency, 21% anemia, 12% transfusion, and 10% hospitalization).<sup>37</sup> Ongoing genotypic analysis in this same cohort reveals that approximately one-third of these young women have VWF gene variants. Gene variants in hemostasis, platelet biology, and vascular integrity may also contribute to the variation in bleeding severity.<sup>38</sup> An ongoing multicenter crossover clinical trial of adolescent and adult females with mild-to-moderate VWD and HMB will compare menstrual blood loss with recombinant VWF compared with tranexamic acid (registered on <https://clinicaltrials.gov> as NCT02606045).

### Thrombotic disorders

Venous thromboembolism (VTE) has emerged as a significant medical event in tertiary care pediatric hospitals. The rarity and heterogeneity of pediatric VTE lend to difficulties in designing and managing randomized controlled clinical trials in this setting.<sup>39</sup> As a result, pediatric VTE research has lagged; however, the phase 3 anticoagulant (AC) era in VTE treatment and prevention has now begun<sup>40</sup> (Table 1).

#### VTE treatment

Pharmacological treatment with ACs remains the standard-of-care for acute VTE, along with the removal of the underlying provoking risk factor.<sup>41</sup> The current standard comprises unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), followed by LMWH or vitamin K antagonists. LMWH is by far the most commonly reported off-label AC for pediatric VTE.<sup>42</sup> The use of LMWH for treatment and thromboprophylaxis in children was primarily driven by earlier experience reported from Canada, an important milestone in pediatric VTE management, but the evidence to support AC in children is indirect at best. The "epidemic of thrombosis" in pediatric hospitals prompted the recent completion of international, collaborative phase 3 AC trials of direct oral ACs (DOACs). DOACs selectively target thrombin (eg, dabigatran) or coagulation FXa (eg,

**Table 1. Active pediatric phase 2 and 3 trials for thrombotic disorders**

ClinicalTrials.gov identifier	Name	Study design	Condition	n (age)	Intervention	Primary outcome(s)	Study start date
<b>Treatment</b>							
NCT00687882	Kids-DOTT	Phase 3, RCT	Duration of therapy in pediatric VTE	608 (birth to <21 y)	Shortened (6 wk) duration of AC	Symptomatic recurrent VTE Major plus CRNM bleeding	March 2008
NCT02464969	—	Phase 3, RCT	VTE	250 (0 to <18 y)	Apixaban	Composite of major and CRNM bleeding Composite of asymptomatic and VTE-related mortality	November 2015
NCT02981472	SAXOPHONE	Phase 2	Congenital or acquired heart disease	200 (28 d to <18 y)	Apixaban	Incidence of bleeding events	January 2017
NCT02798471	Hokusai Study	Phase 3, RCT	VTE	274 (0 to <18 y)	Edoxaban	Composite of symptomatic recurrence, VTE-related death, and thrombotic burden	March 2017
<b>Prevention</b>							
NCT02369653	PREVAPIX-ALL	Phase 3, RCT	Malignancy	500 (<18 y)	Apixaban	Composite of VTE and VTE-related deaths	April 2015
NCT02846532	UNI..VERSE	Phase 3, RCT	Single ventricle physiology	112 (2-8 y)	Rivaroxaban	Major bleeding Major Venous and arterial thromboses	November 2016
NCT04354155	COVAC-TP	Phase 2	SARS-CoV-2 infection	38 (birth to <18 y)	Twice-daily low dose enoxaparin thromboprophylaxis	Safety of in-hospital thromboprophylaxis	June 2020

CRNM, clinically relevant, nonmajor bleeding.

apixaban, betrixaban, edoxaban, and rivaroxaban) and are designed to be given in fixed doses without routine monitoring.

**New therapeutic agents** Recently, the EINSTEIN-Jr, a multicenter, randomized study compared rivaroxaban to standard ACs (heparin or a vitamin K antagonist) in 500 children to treat acute VTE of any type.<sup>43</sup> After establishing age-appropriate dose regimens targeting adult exposures,<sup>44</sup> rivaroxaban was shown to be similarly effective and without increased bleeding, as compared with standard ACs. Symptomatic recurrent VTE occurred in 4 (1.2%) of 335 children receiving rivaroxaban and 5 (3%) of 165 receiving standard AC (HR, 0.40; 95% CI, 0.11-1.41). Nonmajor bleeding occurred in 10 (3%) of children receiving rivaroxaban and major and nonmajor bleeding in 3 (2%) of children on standard AC. The study was not powered to independently show noninferiority for the efficacy of rivaroxaban compared with standard AC; thus, interpretation of the results relied in part on partial extrapolation of data from adults. Children <24 months and with catheter-associated VTE comprised only 10% and 25% of the cohort. Despite these limitations, the study provides critical initial evidence to inform rivaroxaban's practical use as standard of care in children on a broad scale. Pediatric providers who take care of young adults between the ages of 18 to 25 years should consider using the adult approach to rivaroxaban dosage: 15 mg twice a day for 21 days, followed by 20 mg daily.<sup>45</sup>

The DIVERSITY trial, a randomized, controlled, noninferiority phase 2b/3 trial, compared standard AC with age- and weight-adjusted oral dabigatran in 267 children with VTE randomly assigned to the study groups in a 1:2 ratio (standard of care: dabigatran).<sup>46</sup> In children completing 3 months of VTE treatment, dabigatran was noninferior to standard of care in efficacy, with similar pharmacokinetics-pharmacodynamic relationships as in adults. Similar proportions of children treated with standard of care and dabigatran met the primary composite efficacy end point of complete thrombus resolution, freedom from recurrent VTE, and VTE-related mortality: 38 (42%) of 90 vs 81 (46%) of 177. The trial allowed only 1 dabigatran dose modification (up or down titration) according to the nomogram. Therefore, if a trough plasma dabigatran concentration of 50 to less than 250 ng/mL was not achieved after 1 dose adjustment, dabigatran treatment was discontinued, and the patient was treated with the standard of care AC. Seventeen (9.7%) children prematurely discontinued treatment because they did not obtain the target dabigatran plasma concentration, and 62 (35%) of 177 patients assigned to dabigatran had a dose adjustment (3% were dose reductions). Although these findings question whether dabigatran can be used without monitoring, the DIVERSITY Investigators have recently shown, using an updated population PK model enriched with data from phase 2b/3 studies of dabigatran, that the final dosage algorithms are appropriate for all dabigatran formulations (oral solution, pellets, or capsules), and no dose titration is needed.<sup>47</sup> This, together with the efficacy and safety of dabigatran in the pediatric VTE setting, validates and supports the use of dabigatran for the treatment of VTE in children.

We point out that both EINSTEIN-Jr and DIVERSITY evaluated the use of a DOAC after at least 5 days of parenteral anticoagulation. Thus, there are no data to support DOACs as initial therapy immediately after VTE diagnosis in children.

**Duration of treatment** Efficacy estimates in children of standard-of-care AC vs placebo or no treatment of acute symptomatic pediatric VTE are unknown. The pediatric community largely accepts evidence from adults demonstrating that AC protects against VTE progression, embolization, and recurrence. However, well-designed, rigorous studies are needed to provide evidence where the disease pathophysiology is different, and a proof of concept is not available. One such area is the optimal duration of AC. Pediatric VTE typically occurs as a secondary complication of hospitalization or underlying diseases and their treatment. Within each provoked VTE type, the pathophysiology and risk-benefit ratio of therapy, especially duration, varies. The American College of Chest Physicians guidelines<sup>48</sup> and, more recently, the 2018 American Society of Hematology pediatric VTE guidelines address these aspects but are limited by low certainty in the evidence.<sup>41</sup> The lack of evidence has now been addressed by the recently completed Kids-DOTT trial, a National Heart, Lung, and Blood Institute-sponsored multinational, randomized controlled trial investigating the duration of anticoagulation therapy following the first episode of provoked VTE.<sup>49,50</sup>

### VTE treatment in special circumstances

**Catheter-related VTE** Anticoagulant treatment of pediatric central venous catheter-related VTE (CVC-VTE) has not been specifically evaluated. The EINSTEIN-Jr CVC-VTE, a predefined substudy of EINSTEIN-Jr, investigated the VTE risk factor profile of 126 pediatric patients with symptomatic or asymptomatic CVC-VTE who received either rivaroxaban (n = 90) or standard AC (n = 36).<sup>51</sup> Anticoagulant therapy with either rivaroxaban or standard AC in children after initial heparin therapy was efficacious (no recurrence), safe (no major bleeding), and associated with complete or partial vein recanalization in more than 90% of the 103 evaluable children. Results were similar for symptomatic and asymptomatic patients and applicable to children with symptomatic or asymptomatic CVC-VTE.

**Asymptomatic VTE** The management of asymptomatic thrombosis in a patient with a CVC has always been more controversial and variable than symptomatic thrombosis.<sup>52</sup> Fear of thrombus extension or embolization and concerns regarding CVC function and future vascular access are factors that result in anticoagulation in patients with asymptomatic CVC-VTE. Jones and colleagues recruited children admitted to the intensive care unit and requiring a CVC and performed an ultrasound of the extremity in which the CVC was placed.<sup>53</sup> The study design's unique and key strength was that the clinical team was blinded to the presence or absence of asymptomatic thrombosis, so patients did not receive anticoagulation. Two years later, participants underwent follow-up ultrasonography and a clinical assessment for postthrombotic syndrome (PTS) with validated instruments. The researchers found that ~1 in 5 patients developed CVC-related thrombosis despite prophylactic UFH (mean dose, 10.4 U/kg per hour; standard deviation, 3.8 U/kg per hour) in most patients. Of the 73% retained until the exit visit, clinically significant PTS was reported in only 2 children, and none of the children experienced VTE progression. Although the study supports the practice of observation alone in younger children with incidentally discovered CVC-VTE, the results are applicable only to patients with congenital heart disease (>75% of the cohort) and nontunneled, short-term CVCs. These findings have been corroborated by another recent systematic review of clinically unsuspected VTE in children predominantly

diagnosed with CVC-VTE, which suggested that most asymptomatic VTE, with or without anticoagulation, have a benign clinical course with few immediate or long-term complications.<sup>54</sup>

## VTE prevention

Preventing primary or secondary VTE in children poses a challenge for clinicians because of the evolving hemostatic system in children,<sup>55</sup> the pharmacokinetics and responses to ACs, and limitations of the current standard-of-care AC.<sup>56</sup> Some of these limitations can be overcome by DOACs for children with persistent VTE risk factors, as shown by recently completed studies.

**New therapeutic agents** Brandão et al conducted an open-label, single-arm, phase 3 trial of dabigatran for extended secondary thromboprophylaxis in children with a history of VTE.<sup>57</sup> Dabigatran showed a favorable safety profile for secondary VTE prevention in children aged >3 months to <18 years with persistent prothrombotic risk factor(s). The median duration of dabigatran administration was ~8 months. Primary end points included VTE recurrence, bleeding events, and mortality at 6 and 12 months. Clinically relevant bleeding occurred in 2.5% of patients and recurrence in 1% with no on-treatment deaths. Twenty-six percent of patients had a dose adjustment (increase or decrease of dose), but in light of recent pharmacokinetic simulations and the low frequency of clinically relevant bleeding, dabigatran is safe for extended VTE treatment in children, and it is appropriate to follow an age- and weight-adjusted dosage algorithm without routine laboratory monitoring for this indication.<sup>47</sup>

## Thromboprophylaxis in special circumstances

**Malignancy** The first randomized trial in this field, PARKAA, assessed primary thromboprophylaxis using antithrombin replacement in children with acute lymphoblastic leukemia and CVC during induction chemotherapy. However, PARKAA was a feasibility study with limited power.<sup>58</sup> THROMBOTECT, an RCT performed by the Berlin-Frankfurt-Munster cooperative group, assessed the efficacy and safety of primary thromboprophylaxis during induction chemotherapy, including asparaginase for leukemia in children, most of whom had a CVC.<sup>59,60</sup> Nine hundred forty-nine patients were randomly assigned to 3 arms: antithrombin substitution, prophylactic-dose LMWH, or low-dose UFH. The low UFH dose was intended to prevent CVC occlusion and did not achieve a systemic antithrombotic effect, so it could be considered a placebo arm. The primary efficacy (symptomatic VTE) and safety (bleeding) outcomes were assessed during both induction and consolidation chemotherapy. The study showed a significant reduction in VTE incidence with the use of antithrombin (1.9%) and LMWH (3.5%) compared with UFH (8.0%). Because a large proportion of children assigned to LMWH crossed over to other arms, an as-treated analysis demonstrated approximately equal reductions in VTE risk for antithrombin and LMWH, compared with UFH. The incidence of bleeding was low (0.9%) and similar between the 3 arms. The THROMBOTECT study is the first adequately powered RCT of primary thromboprophylaxis in pediatric patients and showed that thromboprophylaxis with antithrombin or LMWH effectively prevents VTE without increasing the risk of bleeding. Despite these results, there remain challenges with these choices for thromboprophylaxis. Of the patients assigned to LMWH, 33% refused the intervention after randomization because of the subcutaneous injections. One notable and unexpected finding was an

increased rate of relapse in patients receiving antithrombin. Though this association was not consistent throughout the analyses, a biologic effect of antithrombin substitution cannot be completely ruled out, and antithrombin cannot be recommended until more evidence is available.

## VTE risk prediction

The incidence of hospital-acquired VTE (HA-VTE), defined as a VTE that develops in a patient while hospitalized, has increased in children by 70% to 200%.<sup>61,62</sup> A first critical step to prevent HA-VTE is to identify the risk of HA-VTE using risk assessment at hospital admission to help guide future trials of thromboprophylaxis in high-risk patients. One ongoing multicenter effort, the Children's Hospital-Acquired Thrombosis (CHAT) registry, has developed a pediatric HA-VTE risk assessment model.<sup>63</sup> The CHAT study used weighted modeling to describe 11 VTE risk factors at or within a day of admission, using data from more than 700 cases of symptomatic HA-VTE. The risk factors included age <1 year or adolescent/young adult; cancer, congenital heart disease, or other identified high-risk diseases; recent hospitalization or surgery; steroid treatment; immobility; presence of a CVC; an elevated platelet count; or mechanical ventilation. Once externally validated, the CHAT model can define populations for whom the benefit of thromboprophylaxis outweighs the risks.

## VTE outcomes

Pediatric patients who survive a VTE should be continuously monitored or treated. Two VTE outcomes, PTS and post-PE syndrome, have gained recent increased attention,<sup>64</sup> because of their impact on the quality of life.<sup>65,66</sup> A systematic review of the frequency of pediatric PTS after lower or upper extremity deep vein thrombosis (DVT) reported an overall frequency of 26% and a frequency of 17% when only considering prospective studies.<sup>64</sup> In a recent systematic review of 12 studies involving 1076 patients, CVC-associated DVT, complete veno-occlusion, and incomplete DVT resolution were deemed as statistically significant prognostic factors for the development of pediatric PTS.<sup>67</sup> There are several instruments to measure PTS and no accepted gold standard.<sup>68</sup> The Modified Villalta Scale and the Manco-Johnson Instrument are the current reference instruments proposed by the ISTH for the "definition and outcome measurement" of PTS in children,<sup>69</sup> but only the Manco-Johnson Instrument has undergone both reliability and validity testing.<sup>70</sup> Their use for the definition and outcome assessment of upper extremity PTS was acknowledged but not explicitly endorsed by the ISTH.<sup>71</sup> One study compared 2 pediatric PTS instruments (the Modified Villalta Scale and Manco-Johnson Instrument) to each other, as well as to the validated, widely accepted adult Villalta scale in a group of older children and young adolescents with DVT and showed significant discordance between the prevalence of PTS.<sup>68</sup> These instruments represent a step toward a more consistent definition of pediatric PTS but do not capture the full clinical impact of PTS and overdiagnose mild PTS. The CAPTSure (Clinical Assessment of Post-thrombotic Syndrome) is the newest pediatric PTS available for diagnosis and severity rating of pediatric PTS in the upper and lower extremities.<sup>72</sup> CAPTSure has good reliability and small measurement error in assessing PTS for both upper and lower extremities; the investigators also determined the minimal detectable change in the total score, which indicates the smallest amount of change deemed clinically important beyond

measurement error. CAPTSure also evaluates impaired endurance to better understand the functional impact of PTS.<sup>72-74</sup> Further studies are needed to confirm whether CAPTSure is an adequate instrument to detect and follow PTS over time across different studies and patient populations.

There are no pediatric data available on post-PE limitations. Its frequency and the underlying mechanisms of exertional dyspnea and exercise intolerance after pulmonary embolism are the aims of an ongoing, National Heart, Lung, and Blood Institute-funded prospective study (registered on <https://clinicaltrials.gov> as NCT04583878).

## Future directions

Despite the significant advances in pediatric hemostasis and thrombosis over the past decade, many unanswered questions remain in our field. In the coming years, we hope to see further advances in laboratory testing that will allow us to more easily identify patients with rare bleeding disorders and those whom we currently recognize as patients with bleeding of unknown cause. We expect to see continued treatment advances in hemophilia and VWD, specifically completion of ongoing pediatric studies of recombinant VWF and the initiation of gene therapy trials for children with hemophilia. Across the span of hemostatic disorders, we hope to see increased inclusion of women and reproductive bleeding outcomes, particularly in industry-funded studies. Of utmost importance in our field is improving access to hemophilia therapy. At the time of this review, most patients with hemophilia worldwide are still without access to factor replacement.

Given the continued increase in the incidence of thrombosis, a full call to arms against pediatric VTE is now essential. Future studies must address population demographics and lifestyle factors contributing to the rise in VTE and associated morbidity. Additional areas in need of investigation include the role of DOACs in inherited and acquired thrombophilia, in primary thromboprophylaxis among hospitalized children at risk for VTE, and the safety and optimal dosages of reversal agents in DOAC-associated bleeding. Inhibitors of contact activation,

particularly FXI and FXII, show promise for preventing thrombotic disease, including safe prevention of artificial surface-induced thrombosis, and represent future therapeutic targets for CVC-VTE.<sup>75</sup> The true incidence and clinical impact of pediatric PTS remain to be elucidated. Two major priorities for the refinement and development of assessments of pediatric thrombotic sequelae should be consistent definitions of postthrombotic venous disease severity and improvement in measuring the functional impact of such complications in children.<sup>71,76</sup>

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## Authorship

Contribution: S.H.O. and A.Z. conceptualized the outline and drafted and edited the manuscript.

Conflict-of interest disclosure: S.H.O. serves as study chair for a clinical trial by the Children's Oncology Group (COG) of apixaban, a direct oral anticoagulant. For this work, S.H.O.'s institution has received salary support from COG, and S.H.O. has received travel reimbursement from COG and advisory board honoraria from Bristol Myers Squibb. A.Z. has received honoraria from Takeda in an advisory capacity.

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## Footnote

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## REFERENCES

1. Bowman M, Riddell J, Rand ML, Tosetto A, Silva M, James PD. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. *J Thromb Haemost.* 2009;7(8):1418-1421.
2. Biss TT, Blanchette VS, Clark DS, et al. Quantitation of bleeding symptoms in children with von Willebrand disease: use of a standardized pediatric bleeding questionnaire. *J Thromb Haemost.* 2010; 8(5):950-956.
3. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. *Haemophilia.* 2015;21(5): e384-e388.
4. Casey LJ, Tuttle A, Grabell J, et al. Generation and optimization of the self-administered pediatric bleeding questionnaire and its validation as a screening tool for von Willebrand disease. *Pediatr Blood Cancer.* 2017;64(10):e26588.
5. Bui J, Martyres D, James PD, et al. Validation of the school age self-administered pediatric bleeding questionnaire (Self-PBQ) in children aged 8-12 years. *Pediatr Blood Cancer.* 2019;66(6):e27709.
6. Jain S, Zhang S, Acosta M, Malone K, Kouides P, Zia A. Prospective evaluation of ISTH-BAT as a predictor of bleeding disorder in adolescents presenting with heavy menstrual bleeding in a multidisciplinary hematology clinic. *J Thromb Haemost.* 2020; 18(10):2542-2550.
7. Sharma R, Flood VH. Advances in the diagnosis and treatment of Von Willebrand disease. *Blood.* 2017;130(22):2386-2391.
8. Patzke J, Budde U, Huber A, et al. Performance evaluation and multicentre study of a von Willebrand factor activity assay based on GPIb binding in the absence of ristocetin. *Blood Coagul Fibrinolysis.* 2014;25(8):860-870.
9. Graf L, Moffat KA, Carlino SA, et al. Evaluation of an automated method for measuring von Willebrand factor activity in clinical samples without ristocetin. *Int J Lab Hematol.* 2014;36(3):341-351.
10. Flood VH, Schlauderaff AC, Haberichter SL, et al; Zimmerman Program Investigators. Crucial role for the VWF A1 domain in binding to type IV collagen. *Blood.* 2015; 125(14):2297-2304.
11. Flood VH, Garcia J, Haberichter SL. The role of genetics in the pathogenesis and diagnosis of type 1 Von Willebrand disease. *Curr Opin Hematol.* 2019;26(5):331-335.
12. Jaffray J, Staber JM, Malvar J, et al. Laboratory misdiagnosis of von Willebrand disease in post-menarchal females: a multi-center study. *Am J Hematol.* 2020;95(9):1022-1029.
13. Doshi BS, Rogers RS, Whitworth HB, et al. Utility of repeat testing in the evaluation for von Willebrand disease in pediatric patients. *J Thromb Haemost.* 2019;17(11): 1838-1847.
14. Kasper CK, Lin JC. How many carriers are there? *Haemophilia.* 2010;16(5):842.

15. D'Oiron R, O'Brien S, James AH. Women and girls with haemophilia: lessons learned. *Haemophilia*. 2021;27(suppl 1):75-81.
16. James PD, Mahlangu J, Bidlingmaier C, et al; Global Emerging Hemostasis Experts Panel (GEHEP). Evaluation of the utility of the ISTH-BAT in haemophilia carriers: a multinational study. *Haemophilia*. 2016;22(6):912-918.
17. Raso S, Lambert C, Boban A, Napolitano M, Siragusa S, Hermans C. Can we compare haemophilia carriers with clotting factor deficiency to male patients with mild haemophilia? *Haemophilia*. 2020;26(1):117-121.
18. Paroskie A, Gailani D, DeBaun MR, Sidonio RF Jr. A cross-sectional study of bleeding phenotype in haemophilia A carriers. *Br J Haematol*. 2015;170(2):223-228.
19. Plug I, Mauser-Bunschoten EP, Bröcker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood*. 2006;108(1):52-56.
20. Sidonio RF, Mili FD, Li T, et al; Hemophilia Treatment Centers Network. Females with FVIII and FIX deficiency have reduced joint range of motion. *Am J Hematol*. 2014;89(8):831-836.
21. Konkle BA, Johnsen JM, Wheeler M, Watson C, Skinner M, Pierce GF; My Life Our Future programme. Genotypes, phenotypes and whole genome sequence: approaches from the My Life Our Future haemophilia project. *Haemophilia*. 2018;24(suppl 6):87-94.
22. Jesudas R, Chaudhury A, Laukaitis CM. An update on the new classification of Ehlers-Danlos syndrome and review of the causes of bleeding in this population. *Haemophilia*. 2019;25(4):558-566.
23. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):8-26.
24. Kendel NE, Haamid FW, Christian-Rancy M, O'Brien SH. Characterizing adolescents with heavy menstrual bleeding and generalized joint hypermobility. *Pediatr Blood Cancer*. 2019;66(6):e27675.
25. Hall SA, Meier ER, Gupta S, et al. Clinical features of children, adolescents, and adults with coexisting hypermobility syndromes and von Willebrand disease. *Pediatr Blood Cancer*. 2018;65(12):e27370.
26. Gebhart J, Hofer S, Panzer S, et al. High proportion of patients with bleeding of unknown cause in persons with a mild-to-moderate bleeding tendency: results from the Vienna Bleeding Biobank (VIBB). *Haemophilia*. 2018;24(3):405-413.
27. Hofer S, Ay C, Rejtö J, et al. Thrombin-generating potential, plasma clot formation, and clot lysis are impaired in patients with bleeding of unknown cause. *J Thromb Haemost*. 2019;17(9):1478-1488.
28. Sankar AD, Weyand AC, Pipe SW. The evolution of recombinant factor replacement for hemophilia. *Transfus Apheresis Sci*. 2019;58(5):596-600.
29. Mancuso ME, Santagostino E. Outcome of clinical trials with new extended half-life FVIII/IX concentrates. *J Clin Med*. 2017;6(4):E39.
30. Königs C, Dunn A, Kulkarni R, et al. Final Results of PUPs A-LONG Study: Evaluating Safety and Efficacy of rFVIIIc in Previously Untreated Patients with Haemophilia A [abstract]. Presented in abstract form at the ISTH 2020 Virtual Congress. 12-14 July 2020.
31. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
32. Callaghan MU, Negrier CG, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with/without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137(16):2231-2242.
33. Harkins Druzgal C, Kizilocak H, Brown J, Sennett M, Young G. Neutralizing antidrug antibody to emicizumab in a patient with severe hemophilia A with inhibitors: new case with detailed laboratory evaluation. *J Thromb Haemost*. 2020;18(9):2205-2208.
34. Arruda VR, Doshi BS, Samelson-Jones BJ. Emerging therapies for hemophilia: controversies and unanswered questions. *F1000 Res*. 2018;7:489.
35. Zia A, Lau M, Journeycake J, et al. Developing a multidisciplinary Young Women's Blood Disorders Program: a single-centre approach with guidance for other centres. *Haemophilia*. 2016;22(2):199-207.
36. The Women and Girls Bleeding Disorder Learning Action Network. Welcome to the Foundation's Learning Action Networks (LANs)! 2021 Available at: <https://www.fwgbd.org/learning-action-networks/>. Accessed 13 January 2022.
37. Srivaths L, Minard CG, O'Brien SH, et al. The spectrum and severity of bleeding in adolescents with low von Willebrand factor-associated heavy menstrual bleeding. *Blood Adv*. 2020;4(13):3209-3216.
38. Sadler B, Minard CG, Haller G, et al. Whole-exome analysis of adolescents with low VWF and heavy menstrual bleeding identifies novel genetic associations. *Blood Adv*. 2022;6(2):420-428.
39. Massicotte MP, Sofronas M, deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. *Thromb Res*. 2006;118(1):153-163.
40. Goldenberg NA, Branchford BR. The phase 3 pediatric anticoagulant era. *Blood*. 2020;135(7):459-460.
41. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292-3316.
42. Chan AK, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? *Hematology Am Soc Hematol Educ Program*. 2012;2012:439-443.
43. Male C, Lensing AWA, Palumbo JS, et al; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol*. 2020;7(1):e18-e27.
44. Young G, Lensing AWA, Monagle P, et al; EINSTEIN-Jr. Phase 3 Investigators. Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. *J Thromb Haemost*. 2020;18(7):1672-1685.
45. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.
46. Halton J, Brandão LR, Luciani M, et al; DIVERSITY Trial Investigators. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomized, controlled, open-label, phase 2b/3, non-inferiority trial. *Lancet Haematol*. 2021;8(1):e22-e33.
47. Röshammar D, Huang F, Albisetti M, et al. Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism. *J Thromb Haemost*. 2021;19(5):1259-1270.
48. Monagle P, Chan AKC, Goldenberg NA, et al. 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*. 2012;141(2 suppl):e737S-e801S.
49. Goldenberg NA, Kittelson JM, Abshire TC, et al. Effect of anticoagulant therapy for 6 weeks vs 3 months on recurrence and bleeding events in patients younger than 21 years of age with provoked venous thromboembolism: the Kids-DOTT Randomized Clinical Trial. *JAMA*. 2022;327(2):129-1137.
50. Goldenberg NA, Abshire T, Blatchford PJ, et al; Kids-DOTT Trial Investigators. Multicenter randomized controlled trial on Duration of Therapy for Thrombosis in Children and Young Adults (the Kids-DOTT trial): pilot/feasibility phase findings. *J Thromb Haemost*. 2015;13(9):1597-1605.
51. Thom K, Lensing AWA, Nurmeev I, et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). *Blood Adv*. 2020;4(19):4632-4639.
52. Jones S, Monagle P, Newall F. Do asymptomatic clots in children matter? *Thromb Res*. 2020;189:24-34.
53. Jones S, Butt W, Monagle P, Cain T, Newall F. The natural history of asymptomatic central venous catheter-related thrombosis in critically ill children. *Blood*. 2019;133(8):857-866.
54. Sharathkumar AA, Biss T, Kulkarni K, et al; SSC Subcommittee on Pediatrics and



- Neonatal T&H of the ISTH. Epidemiology and outcomes of clinically unsuspected venous thromboembolism in children: a systematic review. *J Thromb Haemost.* 2020; 18(5):1100-1112.
55. Ignjatovic V, Mertyn E, Monagle P. The coagulation system in children: developmental and pathophysiological considerations. *Semin Thromb Hemost.* 2011;37(7):723-729.
56. Young G. Anticoagulants in children and adolescents. *Hematology Am Soc Hematol Educ Program.* 2015;2015:111-116.
57. Brandão LR, Albigsetti M, Halton J, et al; DIVERSITY Study Investigators. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood.* 2020;135(7):491-504.
58. Mitchell L, Andrew M, Hanna K, et al. Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. *Thromb Haemost.* 2003; 90(2):235-244.
59. Greiner J, Schrappe M, Claviez A, et al; THROMBOTECT Study Investigators. THROMBOTECT – a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. *Haematologica.* 2019;104(4):756-765.
60. Male C, O'Brien SH, Mitchell L. THROMBOTECT takes the lead. *Haematologica.* 2019;104(4):644-645.
61. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics.* 2009;124(4):1001-1008.
62. Carpenter SL, Richardson T, Hall M. Increasing rate of pulmonary embolism diagnosed in hospitalized children in the United States from 2001 to 2014. *Blood Adv.* 2018;2(12):1403-1408.
63. Jaffray J, Branchford B, Goldenberg N, et al. Development of a risk model for pediatric hospital-acquired thrombosis: a report from the Children's Hospital-Acquired Thrombosis Consortium. *J Pediatr.* 2021;228:252-259.e1.
64. Goldenberg NA, Donadini MP, Kahn SR, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. *Haematologica.* 2010;95(11):1952-1959.
65. Kumar R, Rodriguez V, Matsumoto JM, et al. Health-related quality of life in children and young adults with post-thrombotic syndrome: results from a cross-sectional study. *Pediatr Blood Cancer.* 2014;61(3):546-551.
66. Manco-Johnson MJ. Postthrombotic syndrome in children. *Acta Haematol.* 2006; 115(3-4):207-213.
67. Engel ER, Nguyen ATH, Amankwah EK, et al. Predictors of postthrombotic syndrome in pediatric thrombosis: a systematic review and meta-analysis of the literature. *J Thromb Haemost.* 2020;18(10):2601-2612.
68. Raffini L, Davenport J, Bevilacqua L, Iosifescu S. Comparison of 3 postthrombotic syndrome assessment scales demonstrates significant variability in children and adolescents with deep vein thrombosis. *J Pediatr Hematol Oncol.* 2015;37(8):611-615.
69. Goldenberg NA, Brandão L, Journeycake J, et al; Perinatal and Paediatric Haemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome following lower extremity deep venous thrombosis and standardization of outcome measurement in pediatric clinical investigations. *J Thromb Haemost.* 2012; 10(3):477-480.
70. Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood.* 2007;110(1):45-53.
71. Revel-Vilk S, Brandão LR, Journeycake J, et al; Perinatal and Paediatric Haemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Standardization of post-thrombotic syndrome definition and outcome assessment following upper venous system thrombosis in pediatric practice. *J Thromb Haemost.* 2012;10(10):2182-2185.
72. Avila ML, Feldman BM, Pullenayegum E, et al. Post-thrombotic syndrome in children: measurement properties of CAPTSure, a new diagnostic tool. *Res Pract Thromb Haemost.* 2019;3(4):652-657.
73. Avila ML, Brandão LR, Williams S, et al. Development of CAPTSure™ – a new index for the assessment of pediatric postthrombotic syndrome. *J Thromb Haemost.* 2016;14(12):2376-2385.
74. Avila ML, Stinson J, Lumia C, et al. Characteristics of pain, other symptoms and function in pediatric post-thrombotic syndrome. *Res Pract Thromb Haemost.* 2018; 2(2):334-338.
75. Demoulin S, Godfroid E, Hermans C. Dual inhibition of factor Xlla and factor Xia as a therapeutic approach for safe thromboprotection. *J Thromb Haemost.* 2021;19(2):323-329.
76. Jones S, Newall F, Monagle P. Novel perspectives on diagnosis and clinical significance of the post-thrombotic syndrome in children. *Expert Rev Hematol.* 2016;9(10):965-975.

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