Diagnosis and Management of Pediatric Venous Thromboembolism

New Therapies on the Horizon

Bhavya S. Doshi, MD† and Angela M. Ellison, MD, MSc*‡*

Abstract: The incidence of venous thromboembolism (VTE) is increasing in pediatric patients. Prompt recognition and evaluation of VTE in young patients could prevent significant morbidity or mortality. In contrast to VTE in adults, current treatment guidelines are largely based on expert opinion as limited randomized controlled trial data exist about the appropriate management in pediatric patients with traditional anticoagulants. However, recently approved direct-acting oral anticoagulants in adults are also being investigated in pediatric VTE and these data could inform future evidence-based treatment principles. Thus, healthcare providers must be well informed about the management of pediatric VTE and the data from these trials to date. This continuing medical education article will provide a summary of management of pediatric VTE with particular emphasis on emerging direct-acting oral anticoagulants.

Key Words: venous thromboembolism, anticoagulation

(*Pediatr Emer Care* 2021;37: 273–281)

TARGET AUDIENCE

This CME activity is intended for health care providers who care for children with thromboembolic disease, including pediatric and general emergency medicine physicians, nurses, nurse practitioners, and pharmacists.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Describe the epidemiology, risk factors, and pathogenesis of venous thromboembolism in children
2. Diagnose and evaluate pediatric patients with venous thromboembolism
3. Explain the mechanisms of action, limitations, and indications for traditional and upcoming anticoagulant regimens

OVERVIEW

Venous thromboembolism (VTE) is an increasingly recognized entity in pediatric patients. Recent epidemiologic studies estimate an incidence of 0.07 to 1 in 10,000 per year and a prevalence of 5.3 to 9.7 per 10,000 admissions in hospitalized children.[1–3] Moreover, the incidence in hospitalized patients has been increasing dramatically over time with a bimodal peak wherein thromboembolism occurs most commonly in neonates and adolescents.[4]

Management of thromboembolism in children requires a systematic approach to identify risk factors and comorbidities, which may then guide therapeutic options including thrombolysis (with systemic or catheter-based approaches) and anticoagulation. Thrombolysis is generally reserved for life or limb-threatening thrombosis. Therefore, the majority of pediatric patients are either managed with anticoagulation or with observation and close monitoring in patients considered at high risk for adverse outcomes with drug therapy. Younger patients are generally anticoagulated with intravenous unfractionated (UFH) or subcutaneously administered low molecular weight heparin (LMWH) while oral vitamin K antagonists (VKA) are reserved for older patients who are able to swallow tablets. However, new direct-acting oral anticoagulants (DOACs) targeting activated factor X (FXa) or thrombin, which are approved in adults[5–10] and have promising initial results in pediatric trials, could provide a new avenue for pharmacologic therapy going forward. Here, we briefly review the pathogenesis and risk factors for pediatric VTE and discuss both the established and upcoming anticoagulation options.

PATHOGENESIS AND RISK FACTORS

Rudolf Virchow proposed the triad of stasis, inflammation and hypercoagulability as responsible for the development of venous thrombosis. Altered blood flow is thought to contribute to thrombosis by mediating fibrinolytic resistance of a thrombus.[11] Endothelial injury caused by inflammatory cytokines leads to a localized procoagulant state via (1) depletion of surface thrombomodulin; (2) increase in tissue factor expression; (3) increase in cell-surface adhesion molecules; and (4) release of von Willebrand factor from endothelial cells, which then binds platelets.[12–14] Thrombus formation at these sites can be triggered by either the extrinsic (factor XIIa) or intrinsic (tissue factor/factor VIIa) pathways (Fig. 1) as both have been implicated in animal models. Further, excess of prothrombotic factors (eg, the prothrombin c.97G>A mutation[15] or the activated protein-C resistant factor V Leiden variant[16,17]) or deficiencies of antithrombotic factors[18] (eg, protein C, protein S, and antithrombin) can propagate pathologic thrombosis.

Although congenital thrombophilias may underlie the development of spontaneous VTE in children, the vast majority of children with VTE have underlying comorbidities leading to an acquired prothrombotic state (Table 1). These risk factors include central venous catheters, cardiac disease, malignancy, infections, certain drugs, hematologic disorders, and conditions that result in prolonged immobility, protein loss, or inflammation. The single most important risk factor in pediatric VTE is the presence of a central venous catheter. Catheter-associated thrombi represent ~85% of VTEs in neonates and over half of the VTEs in older children.[19,20] In neonates, perinatal and maternal factors should also be considered including maternal diabetes, hypertension, or

From the *Instructor and Associate Professor, Department of Pediatrics, Perelman School of Medicine at The University of Pennsylvania; †Division of Hematology, and ‡Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.

The authors, faculty, and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations relevant to this educational activity.

Reprints: Bhavya Doshi, MD, 3501 Civic Center Blvd, CTRB 5024, Philadelphia, PA 19104 (e-mail: doshibs@email.chop.edu).

ISSN: 0749-5161

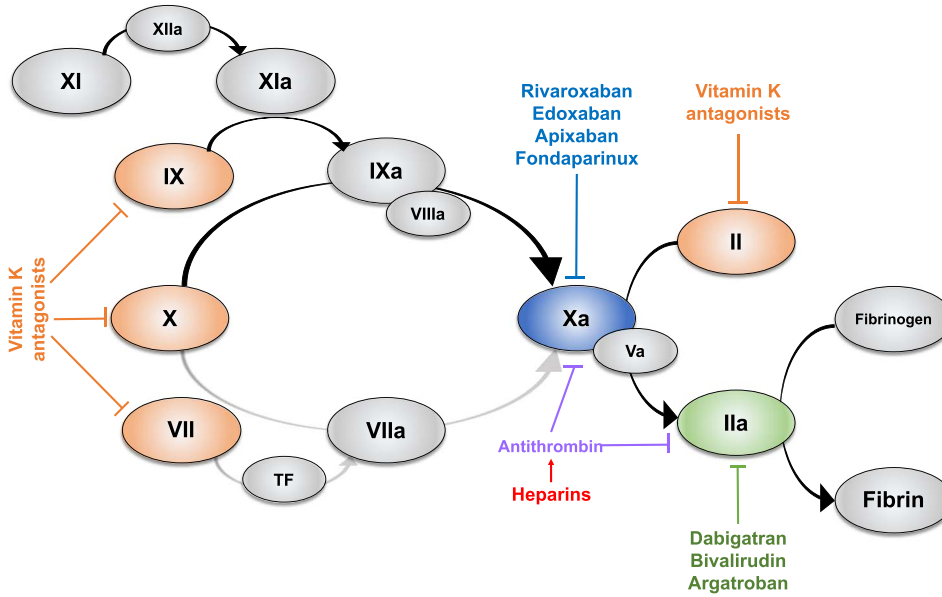

FIGURE 1. Mechanism of action of anticoagulants. Coagulation is initiated via the extrinsic pathway via tissue factor (TF) mediated activation of factor VII to generate activated factor X (FXa) and a small thrombin (IIa) burst. This thrombin feeds back to propagate the intrinsic pathway where activated factors IX and VIII assemble into the Xase complex to generate more FXa which then pairs with factor Va in the prothrombinase complex to generate thrombin from prothrombin (II). Thrombin then generates fibrin which is subsequently cross-linked by factor XIII. The heparins potentiate the action of antithrombin, the natural inhibitor for FXa and thrombin whereby the vitamin K antagonists decrease generation of functional factors II, VII, IX and X. New oral anticoagulants directly inhibit FXa (rivaroxaban, edoxaban, apixaban) or thrombin (dabigatran).

antiphospholipid syndrome and perinatal asphyxia, sepsis, polycythemia or heart disease, respectively.

PRESENTATION AND DIAGNOSIS

The symptoms of a deep venous thrombus depend on the location but generally include swelling, pain, and discoloration for extremity thromboses. Patients may also have superior vena cava syndrome or chylothoraces in the upper extremities, whereas in the lower extremities, they may present with abdominal or inguinal pain or abdominal swelling. Patients with pulmonary embolism may present with chest pain, cough, hemoptysis, dyspnea, or in severe cases in shock. Pediatric patients with neurovascular events, such as stroke or sinus venous thrombosis, may present with focal neurologic deficits, seizures, headache, or vomiting. Imaging modalities used for diagnosis include compression Doppler ultrasonography for extremity thrombi, CT with contrast for pulmonary emboli, sinus venous thrombosis, and abdominopelvic thrombi, and MRI with venography for intracranial clots. Echocardiography is the imaging modality of choice for suspected intracardiac clots. In contrast to adults, the Wells score has not been shown to be predictive in children[21] and D-dimers

TABLE 1. Risk Factors for Pediatric Venous Thromboembolism

Thrombophilia Type	Stasis	Inflammation	Hypercoagulability
Congenital/Inherited	Paget-Schroetter May-Thurner	Primary APS	Factor V Leiden Prothrombin mutations Protein C deficiency Protein S deficiency Antithrombin deficiency
Acquired	Hyperleukocytosis Hyperviscosity Polycythemia vera Essential thrombocythemia Hemoglobinopathies Sickle cell disease Thalassemia Surgery/trauma Neurologic diseases Cardiac diseases Congenital heart disease Heart failure	Secondary APS Cancer Hemoglobinopathies Sickle cell disease Thalassemia Infections Autoimmune disorders Vasculitis Inflammatory bowel disease Cardiac diseases Shunt/stent/valve ECMO	Drugs Asparaginase Steroids Hormonal therapy Paroxysmal nocturnal hemoglobinuria Nephrotic syndrome Protein-losing enteropathies Cardiac diseases Shunt/stent/valve Chylothorax

ECMO indicates extracorporeal membrane oxygenation.

have not been evaluated in prospective studies.[22,23] Thus, clinical suspicion integrating patient's symptoms and risk factors should drive the decision to obtain diagnostic imaging. The decision to pursue thrombophilia testing should be individualized to the patient's presentation and risk factors. Baseline laboratory analyses should include a complete blood count, renal and hepatic function, and coagulation studies including a prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and D-dimer as these will help identify any potential etiologies as well as guide anticoagulation management.

MANAGEMENT

There are limited primary trial data in pediatrics about the recommended therapy for VTE. However, consensus expert guidelines for the management of pediatric VTE are available from the American College of Chest Physicians[24] and more recently the American Society of Hematology.[25] The goals of therapy are to limit extension and/or embolization of the thrombus, prevent recurrence, and decrease the risk of postthrombotic syndrome. The decision to treat a thrombus should be carefully weighed against the risk of hemorrhage for each patient. Consensus guidelines suggest treatment of all symptomatic VTE in children with either heparins or vitamin K antagonists unless thrombolysis is indicated by the presence of hemodynamic compromise or limb-threatening thrombi. If bleeding risk is low, duration of therapy should be 3 months or less in patients with provoked VTE and 6 to 12 months for unprovoked VTE. Although adult data suggest benefit in treatment of asymptomatic VTE, the differences in epidemiology and pathophysiology between these 2 populations limits the applicability of these data to asymptomatic pediatric VTE. Thus, the American Society of Hematology guidelines leave treatment of asymptomatic VTE to patient and provider discretion. The anticoagulants exert their effects at different points in the coagulation cascade (Fig. 1). Each of these agents has its own risks, benefits, and data to support their use as reviewed below and summarized in Table 2.

Conventional Anticoagulants

Heparins

The heparins (UFH or LMWH) exert their inhibition on FXa and thrombin via potentiation of antithrombin to block the generation of cross-linked fibrin from fibrinogen (Fig. 1). The choice of which version to use depends on the clinical situation and bleeding risk of the patient. Unfractionated heparin is generally the drug of choice in a critically ill patient with high risk of hemorrhage or for short-term prophylaxis (eg, surgery) because of its reversibility and short half-life. It is infused via continuous intravenous infusion or can be used subcutaneously. Unfractionated heparin has disappointing pharmacokinetic predictability because of both poor correlation between dose and measures of effect (aPTT or anti-Xa level) and patient aspects including systemic inflammation and/or the properties intrinsic to developmental hemostasis that can limit efficacy at the same dose in patients of different ages.[28–31] The anticoagulant effect is monitored and dose adjustments made to fall within a desired range (aPTT 2–3 fold increased from baseline or anti-Xa of 0.3–0.7 IU/mL). Thus, UFH generally requires more dose adjustments than other anticoagulants; nevertheless, weight-based dosing of UFH has been clinically effective with a decent safety profile in pediatric VTE.[28,31]

Although intravenous use[32–34] has been reported, LMWH is generally administered subcutaneously and, despite its lack of approval by the Food and Drug Administration (FDA) in pediatric patients, has a decades-long history of use in pediatric VTE. Massicotte et al[35] initially found the need for age and weight-based dosing to target adult anti-Xa levels and this was confirmed in subsequent studies to establish the current guidelines of higher dosing for neonates (1.5–1.8 mg/kg) than older children (1 mg/kg). In contrast to adult populations, doses are typically adjusted to maintain the anti-Xa level within a goal range (typically 0.5–1 IU/mL). However, as with UFH, there are limited data supporting a rigorous relationship between anti-Xa level and efficacy[36–38] and differences in assay reagents may alter dosing requirements in the same patient.[39] Enoxaparin is primarily metabolized by the kidneys and the use in patients with renal

TABLE 2. Anticoagulant options for the management of pediatric VTE

Agent	VTE Treatment Dose	Half-Life (h)	Metabolism	Monitoring	Reversal Agent(s)	Enzymatic Interactions
UFH	75 u/kg bolus then 18–28 U/kg/hr	0.5	Hepatic	aPTT Anti-Xa Anti-IIa ACT	Protamine	
Enoxaparin	Infants: 1.2–1.8 mg/kg BID Children: 1 mg/kg BID	4.5–7	Renal	Anti-Xa	Protamine (partial)	
Warfarin	0.2 mg/kg loading dose	40	Hepatic	INR	Vitamin K FFP PCC	CYP3A4, vitamin K
Dabigatran	>32 kg and >12 y: 1.71 mg/kg[26]	14–17	Renal	DTT	Idarucizumab	P-glycoprotein, PPIs
Rivaroxaban	<12 kg – nomogram[27] 12–30 kg: 5 mg BID 30–50 kg: 15 mg QD > 50 kg: 20 mg QD	5–13	Renal and hepatic	Anti-Xa	Andexanet alfa	CYP3A4 and P-glycoprotein
Edoxaban	Not available	10–14	Hepatic and renal	Anti-Xa	Andexanet alfa	P-glycoprotein
Apixaban	Varies by trial	9–14	Hepatic and renal	Anti-Xa	Andexanet alfa	CYP3A4 and P-glycoprotein

BID indicates twice daily; QD, daily.

dysfunction can be complicated by drug accumulation. Measuring trough anti-Xa levels can help with the monitoring of enoxaparin accumulation. Enoxaparin should generally be avoided in patients with a glomerular filtration rate less than 30 mL/min.

Bleeding represents the primary safety concern with both UFH and LMWH. The short half-life and ability to use protamine for reversal of UFH effect has made it more desirable in high-risk situations, whereas the stability and subcutaneous administration of LMWH makes it more desirable for the duration of therapy typical for acute VTE. Low molecular weight heparin can be reversed partially by protamine administration with the dose of protamine dependent on anti-Xa level and time of last LMWH exposure. Heparin-induced thrombocytopenia is more common with UFH than LMWH but, in general, is far less common in pediatric patients than adults.[40–42] The most common adverse events with subcutaneous LMWH are bruising or hematoma at the site of injection. There are a few case reports of osteopenia with subcutaneous heparin use in pregnant women whereas long-term use of LMWH has clearly been associated with osteopenia.

Vitamin K Antagonists

Warfarin is the primary vitamin K antagonist used in children. It works by preventing the action of vitamin K epoxide reductase, which is critical to gamma carboxylation of factors II, VII, IX, and X and the anticoagulant proteins C and S. The uncarboxylated forms cannot bind to phospholipid membranes or calcium to function in coagulation. Warfarin initiation is typically accomplished with a heparin bridge as depletion of anticoagulant proteins occurs before depletion of clotting factors rendering a procoagulant state initially. Anticoagulation is generally achieved approximately 5 to 7 days into therapy after factors II, IX, and X are depleted (FVII depletion occurs earlier owing to its short half-life). At therapeutic dosing, warfarin prolongs the PT which is reported after normalization with an international reference (international normalized ratio [INR]). Warfarin is typically initiated with a loading dose of 0.2 mg/kg with subsequent doses based on INR levels. As warfarin is absorbed in the stomach and metabolized by the liver, this dosage may change based upon a patient's nutritional status (which affects vitamin K intake) and other medications. Genotypic variations that affect warfarin metabolism or inter-current viral illnesses that affect absorption may affect INR values. Patients require regular monitoring of INR given the narrow therapeutic window to prevent recurrent thrombosis and bleeding. Because of the number of variables that can lead to potentiation or reduction of the anticoagulant effect, there can be poor control of warfarin levels. In addition, it carries a teratogenic risk and may adversely affect bone health with long-term use. In cases of supratherapeutic INR with bleeding, warfarin can be reversed quickly with vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) infusion.

DOACs

Several novel anticoagulants targeting either thrombin (bivalirudin, argatroban, dabigatran) or FXa (rivaroxaban, apixaban, edoxaban, and fondaparinux) have been approved for stroke prevention in the setting of nonvalvar atrial fibrillation and treatment or prevention of VTE in adults. Here, we will focus the discussion on the oral formulations of these drugs. In pooled analysis of the adult studies, the DOACs showed lower rates of major bleeding compared with warfarin with similar efficacy,[43,44] however, there is a slightly increased signal of gastrointestinal bleeding.[45] In pediatrics, argatroban is the only currently approved direct anticoagulant for use in patients with known or suspected heparin-induced thrombocytopenia. Several pediatric clinical trials are either ongoing or have been completed and presumably DOACs will become available for use in pediatric patients in the near future. Thus, knowledge of these drugs in terms of dosing, pharmacokinetics, monitoring, side effects, and reversibility will be of critical importance to emergency care personnel who often make initial contact with these patients.

Important considerations before prescribing these medications when they become available for pediatric use include: (1) dose reductions for moderate to severe renal disease; (2) lack of data regarding safety in patients with platelet counts <50,000/μL; (3) inability to use these agents in patients with hepatic disease and coagulopathy; (4) limited clinical data to guide use of these drugs in patient with a body mass index greater than 40 or weight greater than 120 kg[46]; and (5) evidence to suggest increased risk of recurrent thrombosis when used in patients with antiphospholipid syndrome.[47] Furthermore, several drugs can interact with medications that are inducers and/or inhibitors of the cytochrome p450 or p-glycoprotein enzymes and careful review of patient medications should be completed when considering prescribing a DOAC.

Direct Thrombin Inhibitors

The only available oral direct thrombin inhibitor is dabigatran. In adults, dabigatran was the first DOAC approved by the FDA and is currently licensed for both the treatment of VTE and the prevention of VTE in the setting of orthopedic surgery or atrial fibrillation. In adults, it is initiated after a period of 5 to 7 days of heparin therapy. Dabigatran binds free and fibrin-bound thrombin with a high affinity preventing fibrinogen from being converted to fibrin (Fig. 1). In adult studies, dabigatran showed similar efficacy with a slightly lower bleeding risk than warfarin.[9,10] Phase 1 and 2 studies of dabigatran in children have been completed and demonstrated a linear relationship between plasma concentration of dabigatran and dilute thrombin time (DTT).[26,48,49] Dabigatran was given via weight adjusted doses in these studies to attain the pharmacokinetic profiles seen in adult patients and accounting for better renal function in children as compared with adults. As these studies were done with single doses of drug, efficacy evaluation is not yet possible. However, as in adults, adolescents given dabigatran twice daily as part of a phase II study did experience mild gastrointestinal complaints.[26] These complaints may be mitigated with proton pump inhibitors (PPIs) but concurrent use of PPIs with dabigatran may lower drug concentration. Current pediatric phase 3 trials are evaluating dabigatran versus standard of care for VTE treatment (NCT01895777) and secondary VTE prevention (NCT02197416) but results are not yet available.

FXa Inhibitors

The oral FXa inhibitors include edoxaban, apixaban, and rivaroxaban. All are under investigation via pediatric investigation plans with phase 3 trials ongoing for edoxaban (NCT02798471 and NCT 03395639) and apixaban (NCT01707394) and recently published for rivaroxaban.[50] These drugs work by binding to the factor X active site to prevent its activation and participation in the prothrombinase complex (Fig. 1). The major differences are in bioavailability, pharmacokinetics, and clearance. The adult dosing for edoxaban is once daily from the outset compared with rivaroxaban (15 mg twice daily for 21 days followed by 20 mg daily) and apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily). Similar to dabigatran, pediatric investigations of the FXa inhibitors are using weight-based dosing that accounts for renal function and bioavailability of suspension forms compared with tablets. Edoxaban trials are evaluating pharmacokinetics (NCT02303431) and efficacy compared with standard of care for DVT and VTE (NCT02798471, NCT03395639) in the

pediatric population. Apixaban seems to have a safer bleeding profile in adult studies and is being studied extensively at all phases of clinical trials for pharmacokinetics (phase 1 NCT01707394), safety (phase 2 in heart disease NCT02981472 and for secondary VTE prophylaxis NCT04041843), and efficacy (NCT02464969, also being studied in pediatric cancer via NCT02464969). Dosing nomograms for these studies are based on the earlier phase trials of single-dose administrations.

The phase 3 trial for rivaroxaban was recently published and showed noninferiority to warfarin or LMWH in patients aged 0 to 18 years.[50] In this study, pediatric patients with newly diagnosed VTE were randomized 2:1 adjusting for site of thrombosis and presence of thrombophilia risk factors to weight-adjusted rivaroxaban tablets or suspension versus standard of care after 5 to 9 days of heparin or fondaparinux therapy. The primary efficacy outcome was symptomatic recurrent VTE and secondary outcome was resolution of thrombus as documented by repeat imaging when feasible; safety was assessed as major and nonmajor bleeding. The dosing for this study was based upon pharmacokinetic data from the phase 2[27] trial and is summarized in Table 2. A total of 500 patients were included in the study and results showed that rivaroxaban had a similar low incidence of recurrent thrombosis (hazard ratio [HR], 0.40 with 95% confidence interval [CI], 0.11–1.41) and risk of bleeding (HR, 1.58; 95% CI, 0.51–6.27) compared with standard of care. Two clear differences exist between this study and its adult counterparts: first, there was a period of initial heparin therapy in these patients and second, there was not a requirement for a higher dose of rivaroxaban for the initial 3 weeks. Of note, there were 37 and 47 patients treated with rivaroxaban in the 0 to 23 months and 2 to 5 years age groups, respectively, providing limited data in this subset of patients. Further, in addition to the exclusion criteria listed above for all DOACs, children younger than 6 months were excluded from the rivaroxaban study if they were born before 37 weeks gestation, weighed less than 2.6 kg, or had not been fed orally for at least 10 days. Thus, care must be used in extending the results of this study to the excluded population. Rivaroxaban is also currently under investigation for thromboprophylaxis in comparison to aspirin in children who have undergone a Fontan procedure (NCT02846532).

Emergency Department Considerations

Clinicians should be aware of the effects of DOAC on clinical monitoring parameters both in routine and emergency situations. Both the PT and aPTT may be prolonged in the setting of these new anticoagulants and the degree depends on the reagents used to conduct the assay and the drug (eg, rivaroxaban prolongs the PT more than edoxaban or apixaban).[51] In the setting of bleeding, specific factor assays, including fibrinogen, may also be affected by the presence of DOACs. Testing for thrombophilias, such as antithrombin deficiency, protein C/S deficiencies, activated protein C resistance, dilute Russell viper venom test, and factor assays, should thus occur either before starting these agents or at the trough concentration of these drugs.

Drug Level Monitoring

Although no routine monitoring of these drugs is recommended, situations may arise where knowing the drug level is necessary. In these scenarios, drug-specific tests with fairly rapid turnaround times have been developed but are not widely available. The direct thrombin inhibitors can be measured via the DTT assay calibrated to dabigatran concentrations.[52] The FXa inhibitors can be measured via chromogenic anti-Xa assays calibrated to the drug of interest but may be inaccurate in the setting of concurrent heparin exposure.[53] As these assays are not routinely available, conventional coagulation tests may be used as surrogates to assess for DOAC presence. A normal thrombin time excludes dabigatran presence and a heparin-calibrated anti-Xa chromogenic assay can be used to rule out presence of clinically relevant FXa inhibitors, although it is a less sensitive assay.

Drug Reversal and Management of Bleeding

Although the DOACs have a lower risk of bleeding in adult studies compared with heparin or VKA therapy, there is still a risk of major bleeding in these patients. Further, although routine surgeries can be performed by holding the drug for 1 to 3 days, patients may need urgent interventions that require quick reversal of drug effect. Dabigatran may be partially removed by dialysis and activated charcoal reduces the absorption of the FXa inhibitors if administered within 2 hours of ingestion. Plasma drug cutoff thresholds for use of reversal agents have not been established in prospective studies as of yet although extrapolation of bleeding risk from adult phase 2/3 studies have been published for edoxaban[54] and dabigatran[55] and guidance from the FDA is available for apixaban[56] and rivaroxaban.[57] The International Society on Thrombosis and Hemostasis (ISTH) recommends considering reversal in patients with serious bleeding and drug levels greater than 50 ng/mL or greater than 30 ng/mL in those needing invasive procedures.[58] To this end, more specific reversal agents for dabigatran (idarucizumab) and the FXa inhibitors (andexanet alfa) have been developed.

Idarucizumab is a humanized monoclonal antibody that complexes with both thrombin-bound and free dabigatran to target the complex for elimination by the kidneys. The drug is given as 2 infusions separated by 15 minutes and was studied in adult patients treated with dabigatran who presented with uncontrolled bleeding (group A) or need for urgent procedures (group B). Idarucizumab administration led to normalization of the DTT within 4 hours, cessation of bleeding within ~2.5 hours in group A, and normal surgical hemostasis in ~94% of patients in group B.[59] However, there was an observed prolongation of clotting time around 12 hours after drug administration and mortality rates of ~18% were noted with recurrent thrombosis found in ~5% of patients within 30 days of idarucizumab administration.

Andexanet alfa is a modified, inactive, recombinant FXa designed to bind and sequester the Xa inhibitors to restore FXa activity.[60] The drug is administered as a bolus followed by a 2-hour infusion with the exact dosage determined based upon last FXa inhibitor administration. The ANNEXA-4 study[61] was a single-arm study designed to assess the safety and efficacy of andexanet in adult patients presenting with major acute bleeding while taking rivaroxaban, edoxaban, apixaban, or enoxaparin. Of the 352 patients enrolled, the vast majority were on apixaban (55%) followed by rivaroxaban (36%), and bleeding sites were primarily intracranial (64%) or gastrointestinal (26%). Andexanet alfa reduced median anti-FXa activity by ~92% for apixaban and rivaroxaban and 75% for enoxaparin by the end of the infusion. However, this effect waned to ~30% to 40% by the 4-hour mark. Hemostatic efficacy at 12 hours postadministration was achieved in 82% of patients but there was no relationship between reduction in anti-Xa activity and hemostatic efficacy in the total patient population, albeit some correlation was seen in the subset of patients with intracranial hemorrhage. Ten percent of patients developed a thrombotic event (myocardial infarction, stroke, DVT or PE) in the 30-day follow-up period. A randomized clinical trial of andexanet alfa is planned (NCT03661528) to address the limitations of this study and better answer the question of clinical benefit with andexanet use.

The ISTH recommends using these agents in the setting of life threatening bleeding, bleeding in enclosed spaces or critical organs, persistent major bleeding despite local measures, or need for urgent/emergent procedures with high risk of bleeding. Importantly, ISTH recommends against use of these agents for elective or nonurgent surgeries, gastrointestinal bleeding that responds to supportive measures, and high drug levels without bleeding. The safety of these drugs in the pediatric population is unknown at this time, although the phase 3 study of idarucizumab in pediatric patients has completed recruitment (NCT02815670). As these reversal agents are quite expensive and are not prohemostatic per se, management of serious bleeding may require adjunctive therapy in the form of fresh frozen plasma, antifibrinolytics, PCCs, recombinant factor VIIa or factor VIII inhibitor bypassing agent.[62–65] These agents have been tried for hemostasis in the setting of DOAC use, but they are not FDA approved for this indication.

CONCLUSIONS

The incidence of VTE in pediatric patients and the complexity of these cases is ever increasing. Anticoagulant management of these patients with heparins or VKAs is cumbersome due to the need for injections and/or frequent monitoring. Direct-acting oral anticoagulants have properties that are more amenable in terms of quality of life and treatment burden including oral administration and lack of need for frequent monitoring. Further, the systematic and rigorous investigation of these drugs for pediatric VTE treatment and prevention is a distinct advantage over the traditional agents. However, clinicians should be aware of the challenges of DOACs in terms of interactions, monitoring, and excluded patient populations. Further, although there is a case report[66] of idarucizumab use in an adolescent who suffered dabigatran overdose, safety and efficacy data for the reversal agents are not yet available in the pediatric population. Finally, although the prospect of DOACs is promising, they are not yet licensed for pediatric use.

REFERENCES

1. Chan AK, Deveber G, Monagle P, et al. Venous thrombosis in children. *J Thromb Haemost*. 2003;1:1443–1455.
2. Kim SJ, Sabharwal S. Risk factors for venous thromboembolism in hospitalized children and adolescents: a systemic review and pooled analysis. *J Pediatr Orthop B*. 2014;23:389–393.
3. Parasuraman S, Goldhaber SZ. Venous thromboembolism in children. *Circulation*. 2006;113:e12–e16.
4. Raffini L, Huang YS, Witmer C, et al. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124:1001–1008.
5. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808.
6. Hokusai-VTE Investigators, Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415.
7. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510.
8. EINSTEIN–PE Investigators, Buller HR, Prins MH, Lensin AWA, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287–1297.
9. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772.
10. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352.
11. Byrnes JR, Wolberg AS. New findings on venous thrombogenesis. *Hamostaseologie*. 2017;37:25–35.
12. Furie B, Furie BC. Role of platelet p-selectin and microparticle psgl-1 in thrombus formation. *Trends Mol Med*. 2004;10:171–178.
13. Moore KL, Andreoli SP, Esmon NL, et al. Endotoxin enhances tissue factor and suppresses thrombomodulin expression of human vascular endothelium in vitro. *J Clin Invest*. 1987;79:124–130.
14. Pinsky DJ, Naka Y, Liao H, et al. Hypoxia-induced exocytosis of endothelial cell weibel-palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. *J Clin Invest*. 1996;97:493–500.
15. Poort SR, Rosendaal FR, Reitsma PH, et al. A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood*. 1996;88:3698–3703.
16. Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369:64–67.
17. Zoller B, Svensson PJ, He X, et al. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. *J Clin Invest*. 1994;94:2521–2524.
18. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur thrombose- und hamostaseforschung (gth) study group on natural inhibitors. *Arterioscler Thromb Vasc Biol*. 1996;16:742–748.
19. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (vte) in children: first analyses of the Canadian registry of VTE. *Blood*. 1994;83:1251–1257.
20. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics*. 1995;96:939–943.
21. Biss TT, Brandao LR, Kahr WH, et al. Clinical probability score and d-dimer estimation lack utility in the diagnosis of childhood pulmonary embolism. *J Thromb Haemost*. 2009;7:1633–1638.
22. Kanis J, Hall CL, Pike J, et al. Diagnostic accuracy of the d-dimer in children. *Arch Dis Child*. 2018;103:832–834.
23. Sharaf N, Sharaf VB, Mace SE, et al. D-dimer in adolescent pulmonary embolism. *Acad Emerg Med*. 2018;25:1235–1241.
24. Monagle P, Chan AK, 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:e737S–e801S.
25. 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;2:3292–3316.
26. Halton JM, Lehr T, Cronin L, et al. Safety, tolerability and clinical pharmacology of dabigatran etexilate in adolescents. An open-label phase iia study. *Thromb Haemost*. 2016;116:461–471.
27. Monagle P, Lensing AWA, Thelen K, et al. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (einstein-jr): results from three multicentre, single-arm, phase 2 studies. *Lancet Haematol*. 2019;6:e500–e509.
28. Al Obary EE, Al-Jazairi AS, Zaghloul IM, et al. Assessment of the standard pediatric unfractionated heparin dosing protocol. *Asian Cardiovasc Thorac Ann*. 2012;20:153–159.
29. Hanslik A, Kitzmuller E, Tran US, et al. Monitoring unfractionated heparin in children: a parallel-cohort randomized controlled trial comparing 2 dose protocols. *Blood*. 2015;126:2091–2097.
30. Kuhle S, Eulmesekian P, Kavanagh B, et al. Lack of correlation between heparin dose and standard clinical monitoring tests in treatment with

unfractionated heparin in critically ill children. *Haematologica*. 2007;92: 554–557.

31. Schechter T, Finkelstein Y, Ali M, et al. Unfractionated heparin dosing in young infants: clinical outcomes in a cohort monitored with anti-factor xa levels. *J Thromb Haemost*. 2012;10:368–374.
32. Crary SE, Van Orden H, Journeycake JM. Experience with intravenous enoxaparin in critically ill infants and children. *Pediatr Crit Care Med*. 2008;9:647–649.
33. Diab YA, Ramakrishnan K, Ferrell B, et al. Iv versus subcutaneous enoxaparin in critically ill infants and children: comparison of dosing, anticoagulation quality, efficacy, and safety outcomes. *Pediatr Crit Care Med*. 2017;18:e207–e214.
34. Fiamoli V, Blatny J, Zapletal O, et al. Treatment of deep vein thrombosis with continuous iv infusion of lmwh: a retrospective study in 32 children. *Thrombosis*. 2011;2011:981497.
35. Massicotte P, Adams M, Marzinotto V, et al. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *J Pediatr*. 1996;128:313–318.
36. Chander A, Nagel K, Wiernikowski J, et al. Evaluation of the use of low-molecular-weight heparin in neonates: a retrospective, single-center study. *Clin Appl Thromb Hemost*. 2013;19:488–493.
37. Ignjatovic V, Najid S, Newall F, et al. Dosing and monitoring of enoxaparin (low molecular weight heparin) therapy in children. *Br J Haematol*. 2010; 149:734–738.
38. Malowany JI, Knoppert DC, Chan AK, et al. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. *Pharmacotherapy*. 2007;27:1263–1271.
39. Greene LA, Law C, Jung M, et al. Lack of anti-factor xa assay standardization results in significant low molecular weight heparin (enoxaparin) dose variation in neonates and children. *J Thromb Haemost*. 2014;12:1554–1557.
40. Avila ML, Shah V, Brandao LR. Systematic review on heparin-induced thrombocytopenia in children: a call to action. *J Thromb Haemost*. 2013; 11:660–669.
41. Severin T, Sutor AH. Heparin-induced thrombocytopenia in pediatrics. *Semin Thromb Hemost*. 2001;27:293–299.
42. Warkentin TE, Sheppard JA, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000; 96:1703–1708.
43. van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin k antagonists for acute venous thromboembolism: Evidence from phase 3 trials. *Blood*. 2014;124:1968–1975.
44. Makam R, Hoaglin D, McManus D, et al. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: systematic review and meta-analysis. *PLoS One*. 2018;13:e0197583.
45. Miller CS, Dorreen A, Martel M, et al. Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15:1674–1683.
46. Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: guidance from the ssc of the isth. *J Thromb Haemost*. 2016;14:1308–1313.
47. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132:1365–1371.
48. Halton JML, Albisetti M, Biss B, et al. Phase iia study of dabigatran etexilate in children with venous thrombosis: pharmacokinetics, safety, and tolerability. *J Thromb Haemost*. 2017;15:2147–2157.
49. Halton JML, Picard AC, Harper R, et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate oral liquid formulation in infants with venous thromboembolism. *Thromb Haemost*. 2017;117:2168–2175.
50. 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:e18–e27.
51. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost*. 2018;16:209–219.
52. Douxfils J, Dogne JM, Mullier F, et al. Comparison of calibrated dilute thrombin time and aptt tests with lc-ms/ms for the therapeutic monitoring of patients treated with dabigatran etexilate. *Thromb Haemost*. 2013; 110:543–549.
53. Douxfils J, Gosselin RC. Laboratory assessment of direct oral anticoagulants. *Semin Thromb Hemost*. 2017;43:277–290.
54. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-factor xa activity, and outcomes: an analysis of data from the randomised, double-blind engage af-timi 48 trial. *Lancet*. 2015;385:2288–2295.
55. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the re-ly trial (randomized evaluation of long-term anticoagulation therapy). *J Am Coll Cardiol*. 2014;63:321–328.
56. Food and Drug Administration. Clinical pharmacology/biopharmaceutics review: Apixaban. 2012.
57. Food and Drug Administration. Clinical pharmacology and biopharmaceutics review: Xarelto. 2010.
58. Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the ssc of the isth. *J Thromb Haemost*. 2016;14:623–627.
59. Pollack CV Jr., Reilly PA, Van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med*. 2017;377: 431–441.
60. Lu G, DeGuzman F, Hollenbach S, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor xa. *Nat Med*. 2013;19:446–451.
61. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor xa inhibitors. *N Engl J Med*. 2019;380:1326–1335.
62. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124:1573–1579.
63. Escolar G, Fernandez-Gallego V, Arellano-Rodrigo E, et al. Reversal of apixaban induced alterations in hemostasis by different coagulation factor concentrates: significance of studies in vitro with circulating human blood. *PLoS One*. 2013;8:e78696.
64. Fukuda T, Honda Y, Kamisato C, et al. Reversal of anticoagulant effects of edoxaban, an oral, direct factor xa inhibitor, with haemostatic agents. *Thromb Haemost*. 2012;107:253–259.
65. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost*. 2014;12:1428–1436.
66. Shapiro S, Bhatnagar N, Khan A, et al. Idarucizumab for dabigatran overdose in a child. *Br J Haematol*. 2018;180:457–459.