How We Manage Pediatric Deep Venous Thrombosis

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Abstract

Keywords

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Over the past two decades, the incidence and recognition of venous thromboembolism (VTE) in children has significantly increased, likely as a result of improvements in the medical care of critically ill patients and increased awareness of thrombotic complications among medical providers. Current recommendations for the management of VTE in children are largely based on data from pediatric registries and observational studies, or extrapolated from adult data. The scarcity of high-quality evidence-based recommendations has resulted in marked variations in the management of pediatric VTE among providers. The purpose of this article is to summarize our institutional approach for the management of VTE in children based on available evidence, guidelines, and clinical practice considerations. Therapeutic strategies reviewed in this article include the use of conventional anticoagulants, parenteral targeted anticoagulants, new direct oral anticoagulants, thrombolysis, and mechanical approaches for the management of pediatric VTE.

Objectives: Upon completion of this article, the reader will be able to (1) describe the management of venous thromboembolism (VTE) in the pediatric population; (2) identify the differences between pediatric and adult therapy recommendations; (3) and discuss the role of systemic and catheter-directed thrombolytic therapies in pediatric VTE.

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Over the past two decades, venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), has become an increasingly recognized problem in children. The incidence of pediatric VTE is estimated to be 0.07 per 10,000 children per year; however, much higher rates are observed among hospitalized children in whom VTE is estimated to occur in 1 of 200 children.^{1–3} The increase in pediatric thrombotic events is likely the result of improvements in the care of critically ill children and a heightened awareness of thrombotic complications among medical providers. Pediatric VTE has a bimodal distribution,

with a first peak occurring in children younger than 1 year followed by a second peak in adolescents.⁴ Unlike VTE in adults, pediatric VTE is rarely spontaneous or unprovoked. More than 90% of pediatric thrombotic events are associated with the presence of an underlying prothrombotic risk factor, including systemic infections, complex medical conditions such as cardiac or renal disease, inherited or acquired thrombophilias, and the presence of a central venous catheter (CVC).^{1,4-6} Of these, the presence of a CVC is the most common risk factor for pediatric DVT, with more than 50% of cases in children and nearly 90% of cases in newborns occurring in association with a CVC.^{1,7}

Pediatric VTE has a significant impact on the health outcomes of affected patients. Short-term complications include bleeding associated with anticoagulation therapy or the thrombotic event itself, early recurrent VTE, development of PE, limb ischemia, and most significantly, an estimated mortality rate secondary to large vein thrombosis of 1 to 4% and an estimated two- to sixfold increased risk of in-hospital mortality.^{1,8-10} The most significant long-term complications are recurrent thrombosis and the development of postthrombotic syndrome (PTS), a condition characterized by chronic limb pain, edema, ulceration, and limitation of activity, which significantly impacts the quality of life of affected patients.^{11,12}

Despite the increased frequency of pediatric VTE, published data on the management of pediatric thrombosis are limited, and the majority of current recommendations are largely based on pediatric registries and observational studies, or otherwise extrapolated from adult VTE data.¹³⁻¹⁵ The use of adult data to dictate the management of VTE in children is suboptimal, as there are significant differences in the physiology of the hemostatic system in children compared with adults, and these differences likely affect the pathophysiology of thrombosis formation and the response to anticoagulation agents in the pediatric population.^{16,17} Given the lack of high-quality evidence, there is marked clinical practice variation among physicians as well as uncertainty regarding the optimal management of VTE in children.

This article aims to summarize our institutional approach for the management of VTE in children based on available evidence, guidelines, and clinical practice considerations. Therapeutic strategies reviewed in this article include conventional anticoagulants, parenteral targeted anticoagulants (direct thrombin inhibitors or DTIs), direct oral anticoagulants (DOACs), thrombolysis, and mechanical approaches.

Clinical Presentation

The clinical presentation of VTE in children depends on several factors, including the patient's age, anatomic location of the thrombosis, affected organ system(s), characteristics of the thrombus (occlusive vs. nonocclusive), and chronicity. Common symptoms of an acute extremity DVT include unilateral limb pain, swelling, and redness of the involved extremity. In the upper extremity, in specific, DVT extension and occlusion of the superior vena cava (SVC) can result in SVC syndrome characterized by swelling of the neck and face; dilatation of the superficial collateral venous circulation of

the arms, neck, and chest; bilateral periorbital edema; and headaches. In the case of CVC-associated DVTs, the initial presenting symptom is often dysfunction of the CVC. In neonates, acute DVTs may present with new-onset thrombocytopenia. Chronic DVTs, as in the case of adults, can present with signs of chronic venous obstruction or PTS including edema, venous stasis dermatitis, limb pain, and skin ulceration. Renal vein thrombosis classically presents with thrombocytopenia and hematuria and, if bilateral, can lead to renal insufficiency. In the neonatal period, it can also manifest with a palpable flank mass on examination, while in older children it is often associated with nephrotic syndrome and presents with peripheral and periorbital edema.¹⁸ Thrombocytopenia can also be one of the presenting symptoms in intracardiac thrombosis and portal vein thrombosis with the latter also resulting in upper gastrointestinal bleeding in children. Due to their excellent cardiopulmonary reserve compared with adults, pediatric patients may present with nonspecific (i.e., cough, crackles/rales, tachycardia, and persistent tachypnea) or mild symptoms in the setting of a PE, especially when the PE is limited to the segmental branches of the pulmonary arteries.¹⁹ Adolescents most frequently present with pleuritic chest pain, dyspnea, cough, and hemoptysis.²⁰ Patients suffering from large proximal PEs, especially saddle emboli, can present with hypoxemia, cyanosis, and sudden collapse.

Diagnostic Evaluation

Radiologic Imaging

Radiologic imaging is used to confirm the diagnosis of VTE and to define the characteristics of the thrombosis including its extent and degree of occlusion. The most common radiologic modalities used in pediatric VTE include compression ultrasound with Doppler (CUS), venography, computed tomography (CT), and magnetic resonance venography (MRV).^{4,13,21} There is no single best imaging technique and the choice of a specific modality depends on the anatomic location of the thrombosis as well as on the patient's clinical characteristics (i.e., ability to be sedated or to receive intravenous contrast). While venography was historically the gold standard modality for the diagnosis of VTE, in recent years, it has largely been replaced by the use of minimally invasive imaging techniques. Currently, CUS is the most commonly used diagnostic technique for DVT.¹⁴ CUS is an inexpensive, noninvasive modality that is readily available and has good sensitivity for the diagnosis of DVT, especially in the lower extremity.¹⁴ It is the first-line imaging technique used for DVT of the upper and lower extremity, SVC, and inferior vena cava (IVC). It is also the modality of choice for the diagnosis of DVT of the jugular venous system.²² Limitations of this technique include limb thrombosis that extends into the deep pelvic or abdominal veins, or into the central vasculature of the upper extremities (i.e., subclavian, innominate, SVC, or right atrial thrombosis) in which the use of CT, MRV, and/or echocardiography is often required.⁴ Particularly in small children, CUS can be limited when bandages or dressings overly the area of concern, obscuring the underlying

vasculature. Additionally, evaluation of acute DVTs occurring in areas of anatomic abnormalities of the venous system (i.e., May–Thurner anomaly) requires more sensitive imaging methods such as CT venography (CTV) or MRV.^{4,23} MRV is a noninvasive technique with high rate of sensitivity and specificity that is helpful in the evaluation of the proximal extent of lower and upper extremity thrombosis, including thrombosis extending into the proximal subclavian veins and SVC.²³ Unlike CTV, MRV requires no radiation exposure. However, it is more expensive than CT; typically requires the use of sedation in young, developmentally delayed or anxious patients; and may not be readily available at all centers.⁴ CT angiography has replaced the ventilation-perfusion (V/Q) scan as the first-line modality for the diagnosis of PE in children. V/Q scans are now typically reserved for patients with contraindications for intravenous contrast or when CT angiography is not available (►Fig. 1).²⁴

Laboratory Testing

The laboratory evaluation in *acute* VTE is aimed at assessing potential laboratory-based contraindications/precautions to anticoagulant therapy, as well as thrombophilia states that may impact management decisions. The former testing should include a complete blood count (including platelet count), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level. Additional laboratory tests depend on the clinical situation.

Although some studies have suggested to limit the evaluation of genetic and acquired prothrombotic traits (i.e., proteins C and S activity, antithrombin III (ATIII) level, antiphospholipid antibodies [APAs], factor VIII level, and homocysteine level) to those patients presenting with idiopathic or unprovoked VTE, it is our practice to perform these tests in all

patients at the time of diagnosis of young-onset VTE.^{25,26} While not supported by evidence, this practice is supported by our experience. It is recognized that a small but important proportion of children with acute VTE experience VTE progression despite “therapeutic” doses of anticoagulation, and in our experience these patients often have multiple positive APAs (e.g., can evolve into thrombotic storm) or deficiencies of the native anticoagulants protein C, protein S, or antithrombin (whether acquired or inherited). In patients with extensive VTE, we supplement protein C or antithrombin in the acute setting, when either is deficient. In patients with acute VTE with multiple positive (especially high-titer) APAs, we target the maximum of the therapeutic range of the administered anticoagulant.

Similarly, our experience is that, in the setting of absence of pediatric evidence to support the adult-derived recommended anticoagulant duration of 3 months for a first provoked VTE and 6 months or greater for unprovoked VTE, an assessment of acute versus convalescent-acquired thrombophilias can help inform physician–parent/patient discussions on whether these recommended durations seem appropriate to the given child’s circumstance. For example, when the D-dimer and/or factor VIII have been elevated in the pediatric acute VTE setting, and are negative at 3 months, this can reassure the patient and family from a laboratory perspective that coagulation activation has subsided, and prognostic markers are favorable,²⁷ in support of the adult-derived recommendation of discontinuing anticoagulation at 3 months for a first-provoked VTE.

Lastly, an assessment of inherited thrombophilias or persistence of APAs is helpful to us in counseling families regarding the risk of DVT recurrence and/or progression. For example, evidence suggests that patients with inherited

Fig. 1 Right arm venogram prior to treatment (a) shows complete occlusion of the subclavian vein. Numerous collaterals are present, which ultimately drain into the superior vena cava. After catheter-directed pharmacomechanical thrombolysis (b), there is complete lysis of the thrombus. There is residual stenosis due to extrinsic compression at the costoclavicular junction, for which partial first ribectomy was subsequently performed.

anticoagulant deficiencies,²⁸ homozygosity (or compound heterozygosity) for the factor V Leiden and factor II G20210A variants,²⁹ or two or more thrombophilia traits³⁰ are at increased risk for VTE recurrence. Hence, laboratory assessment for thrombophilias in our practice often informs physician–parent/patient discussions regarding any plans for episodic secondary VTE prevention with anticoagulation during times of heightened prothrombotic risk—again, in the absence of evidence supporting such a secondary prevention approach, but in the context of a dramatically rising incidence of VTE in pediatrics.

Although difficult to demonstrate cause and effect, with the aforementioned approaches to modulating consensus-based management guidelines with individualized findings of thrombophilia assessment, we have had low rates of recurrent VTE in most pediatric VTE subpopulations in our clinical practice.

Pharmacological Management of VTE

The goals of anticoagulation therapy in pediatric VTE are to limit thrombosis extension, reduce the risk of embolization, prevent VTE recurrence, and, in the long-term, improve vascular outcomes and decrease the incidence of complications such as PTS.³¹ The decision to initiate anticoagulation therapy in neonates and children should be made on an individualized basis, weighing the potential for morbidity and mortality related to the thrombotic event against the risk of bleeding associated with anticoagulation therapy. Management strategies for selecting the optimal agent and duration of VTE therapy should take into consideration patient-specific and thrombus-specific characteristics that influence the risk for unfavorable thrombosis outcomes.¹³ Risk factors associated with adverse thrombotic outcomes include homozygous anticoagulant deficiencies, presence of multiple thrombophilia traits, radiologic findings of complete venous occlusion at the time of diagnosis, and persistently elevated plasma FVIII levels (>150 U/dL) and D-dimer levels (>500 ng/mL).^{9,27,30}

First-Line Agents and Duration of Anticoagulation Therapy

The first-line agents for the management of pediatric VTE are known as conventional anticoagulants and include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKAs; ▶Table 1). We reserve the use of UFH for acute VTE management, as long-term use of this agent should be avoided due to the risk of osteoporosis.^{15,32,33} It is our practice also to avoid the use of VKAs in children younger than 5 years due to the unique challenges of managing VKAs in young patients.³⁴

The duration of anticoagulation therapy in children can be divided in three phases: acute (0 to ~7 days postthrombosis); subacute or long-term (~7 days to 3 months postthrombosis); and extended or chronic (3 months to indefinite).¹⁵ The American College of Chest Physician (ACCP) guidelines recommend anticoagulation therapy for at least 3 months in children presenting with a provoked VTE (presence of at least one risk factor) which should be extended to 12 months to

lifelong if the underlying risk factor persists. Children presenting with unprovoked VTE or with recurrent VTE should receive 6 to 12 months of anticoagulation therapy, assuming that the VTE recurrence is associated with the presence of an underlying reversible risk factor. Patients with VTE recurrence associated with a chronic risk factor or with idiopathic VTE recurrence should receive 12 months to lifelong anticoagulation therapy (▶Table 2).¹⁵ It is our institutional practice to treat VTE in neonates with the same therapeutic approach used in infants and older children.

Conventional Anticoagulants

Conventional anticoagulants act by decreasing the hypercoagulable state of patients while relying on intrinsic fibrinolytic mechanisms to dissolve the thrombus over time.⁴ The most common agents used in children include heparins and VKAs.³⁵ The decision to choose a specific agent is largely guided by the patient's age, clinical status, bleeding risks, renal function, and, to maximize therapy compliance in the outpatient setting, patient's preferences.

Unfractionated Heparin

UFH exerts its anticoagulant effect by reversely binding to ATIII and potentiating its inhibitory effects over thrombin and factor Xa.³⁶ There is extensive clinical experience of the use of UFH in the pediatric population. Due to its short half-life (30 minutes), UFH is the drug of choice for the management of acute VTE in critically ill children who may be at an increased risk of bleeding or may require rapid extinction of anticoagulation activity after discontinuation of the drug. It is also the anticoagulant of choice for maintaining the patency of extracorporeal circuits and venous and arterial catheters.^{15,37} UFH's advantages include the availability of an antidote (protamine sulfate) that can completely reverse its effects, and due to its minimal renal excretion, the possibility to be used in patients with significantly impaired renal function. However, UFH has several limitations, including poor pharmacokinetics (PK) and high degree of inter- and inpatient dose response variability, which leads to difficulty achieving therapeutic levels and to a prolonged interval from therapy initiation to achievement of full anticoagulation effect.^{37–39} Further, due to its variability in dose response, maintaining levels within the therapeutic window can be challenging, potentially resulting in worsening thrombosis or bleeding complications and in the need of frequent therapeutic drug monitoring.³⁹

UFH doses for the management of acute pediatric VTE are shown in ▶Table 1. Neonates and young children require higher doses because of their lower ATIII plasma concentrations, increased clearance, and larger volume of distribution compared with adults.^{38,40} The aPTT and the anti-Xa activity level (calibrated to UFH) are used to monitor therapy. Notably, while the aPTT has been used for decades, it can be a suboptimal assay in pediatric patients, as factors commonly found in this population such as transient APAs, elevated FVIII levels (>250%), elevated fibrinogen, or systemic inflammation can alter its value.³⁸ Given these limitations, the anti-Xa activity assay is the preferred method to monitor UFH when available.^{41,42}

Table 1 Anticoagulation agents used in pediatric VTE

Agent	Mechanism of action	Route of administration	Metabolism and half-life	Initial dosing	Monitoring	Antidote
Conventional anticoagulants						
UFH	Potentiates inhibitory effects of ATIII over FXa and thrombin	IV	Hepatic and RES 30 min	Bolus: 75 unit/kg over 10 min Continuous infusion: age <1 year: 28 unit/kg/h Age ≥1 y: 20 unit/kg/h Adults: 18 unit/kg/h	aPTT 1.5–2.5 times upper limit of normal anti-Xa 0.3–0.7 U/mL 4 h after bolus and dose changes	Protamine Sulfate (complete reversal)
Enoxaparin	Potentiates inhibitory effects of ATIII over FXa and thrombin Greater activity over FXa than thrombin	SC	Renal 4.5–7 h	Age <3 months: 1.5–1.7 mg/kg every 12 h Age ≥3 mo to <2 y: 1–1.2 mg/kg every 12 h Age ≥2 y: 1 mg/kg SC every 12 h	anti-Xa 0.5–1 U/mL First value 4–6 h after second dose	Protamine Sulfate (partial reversal)
Warfarin	Inhibition of vitamin K-dependent carboxylation of factors II, VII, IX, and X, and anticoagulant proteins C and S	PO	Hepatic 35–40 h	Age 2–12 y: 0.09 mg/kg Age ≥12 y: 0.08 mg/kg	INR 2–3 INR 2.5–3.5 for patients with valvular heart disease or APS First level 3–5 d after therapy initiation, then daily until therapeutic	Vitamin K (IV or PO) Fresh-frozen plasma four-factor prothrombin complex concentrate
Direct thrombin inhibitor						
Bivalirudin	Direct inhibition of thrombin independently from ATIII	IV	Intravascular proteolysis and 20% renal 25 min	Bolus dose 0.125 mg/kg Continuous infusion: 0.125 mg/kg/h	aPTT 1.5–2.5 times upper limit of normal First value 3–4 h after initiation of therapy	None
Argatroban	Direct inhibition of thrombin independently from ATIII	IV	Hepatic 45 min	Bolus dose: none Continuous infusion: 0.75–1 µg/kg/min	aPTT 1.5–2.5 times upper limit of normal First value 2 h after initiation of therapy	None
Factor Xa inhibitor						
Fondaparinux	Selective inhibition of factor Xa in an ATIII-dependent manner	SC	Renal 17 h	0.1 mg/kg every 24 h	anti-Xa 0.5–1 U/mL First value 3 h after first dose	None

Abbreviations: APS, antiphospholipid syndrome; aPTT, activated prothrombin time; INR, international normalized ratio; IV, intravenous; PO, oral; RES, reticuloendothelial system; SC, subcutaneous; UFH, unfractionated heparin.

Table 2 Recommended duration of anticoagulation for pediatric VTE

Indication	Duration of anticoagulation	Agent	
		Acute therapy	Subacute and chronic therapy
Provoked VTE ^a			
Reversible risk factor	3 mo	UFH, LMWH	LMWH, warfarin
Chronic risk factor	12 mo to lifelong	UFH, LMWH	LMWH, warfarin
Idiopathic VTE	6–12 mo	UFH, LMWH	LMWH, warfarin
Recurrent VTE			
Reversible risk factor	6–12 mo	UFH, LMWH	LMWH, warfarin
Chronic risk factor	12 mo to lifelong	UFH, LMWH	LMWH, warfarin

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

Notes: Reversible risk factors include central venous catheters, infections, transient antiphospholipid antibodies, surgery. Chronic risk factors include genetic and acquired thrombophilias, malignancy, inflammatory diseases, and prosthetic cardiac valves.

^aACCP 2012 guidelines suggest consideration of a 6-week total duration of anticoagulation in certain circumstances of provoked VTE.

Complications from the use of UFH include bleeding and the development of heparin-induced thrombocytopenia (HIT).⁴³ HIT results from the formation of antibodies against the heparin-PF4 complex on the surface of platelets. It is characterized by the onset of thrombocytopenia, classically occurring 5 to 10 days post-heparin exposure, and the development of catastrophic arterial and venous thrombosis. It has a reported incidence in the pediatric population of 0 to 2.3%.^{44,45} When HIT is suspected, administration of all heparin, including heparin-containing flushes and catheters, should be discontinued immediately, and anticoagulation therapy should be re-initiated with a nonheparin anticoagulant such as a DTIs.⁴⁶

Low-Molecular-Weight Heparin

LMWHs are agents derived from UFH that act by binding and potentiating the inhibitory effects of ATIII. Compared with UFH, LMWHs have a greater inhibitory activity on factor Xa than on thrombin.⁴⁷ These agents are administered via subcutaneous (SC) injection and renally cleared. Over the past decade, LMWHs have replaced UFH as the drug of choice for the prophylaxis and treatment of acute VTE in noncritically ill children, and are commonly used for the subacute and chronic management of pediatric VTE.^{3,15} In the vanguard phase of the Kids-DOTT trial, an ongoing multicenter randomized controlled trial (RCT) assessing the duration of anticoagulation therapy in patients younger than 21 years with provoked VTE, more than 90% of enrolled patients received LMWH for the subacute management of VTE.⁴⁸ LMWHs offer several advantages over UFH, including more reliable PK and more predictable dose response leading to fewer dose adjustments and decreased frequency of blood monitoring.⁴⁶ Additionally, they have a longer half-life allowing for outpatient use, lack drug or diet interactions, and have a lower risk for HIT and osteoporosis compared with UFH.^{23,31,35,43}

Enoxaparin is the most studied and frequently used LMWH in the United States.³ Similar to UFH, neonates and younger children require higher weight-based doses to achieve therapeutic target.⁴⁹ Initial age-dependent doses can be seen in **Table 1**. Enoxaparin reaches its peak anticoagulant effect

at 4 to 6 hours after SQ administration, and has a half-life of 4.5 to 7 hours.³ Although once-daily dosing has been approved in adults, PK studies in children suggest that this dose schedule is not appropriate for pediatric VTE management.⁵⁰ Thus, it is our current practice to use twice-daily dosing for the treatment of pediatric VTE. Unlike therapy in adults, we recommend monitoring of anti-Xa levels (calibrated to LMWH) in children until therapeutic levels have been achieved.¹⁵ Due to its renal excretion, enoxaparin should be avoided in patients with moderate to severe renal insufficiency and doses may need to be adjusted in patients with mild renal function impairment. The major safety concern of enoxaparin is bleeding. Unlike UFH, enoxaparin can only be partially reversed with protamine sulfate. Due to its longer half-life, enoxaparin should be held for 24 hours (longer in patients with renal impairment) prior to any interventional procedure to minimize the risk of bleeding.^{3,31} Although the risk of osteoporosis is lower in enoxaparin compared with UFH, we recommend routine bone density screening (every 1–2 years) in patients receiving long-term (>6 months) enoxaparin therapy, particularly among children predisposed to osteopenia (e.g., nutritional deficiencies, chronic disease).

Vitamin K Antagonist

VKAs are oral anticoagulants that act by inhibiting the vitamin K-dependent carboxylation of clotting factors II, VII, IX, and X, and anticoagulant proteins C and S. Warfarin is the most common VKA used in children. It is rapidly absorbed and metabolized by CYP2C9 in the liver. It has a long half-life (35–40 hours) and long duration of action (2–5 days) allowing for once-daily dosing.⁵¹ Due to its oral administration and long half-life, warfarin has been the anticoagulant of choice of many providers for the subacute and chronic management of pediatric VTE.^{15,52} Despite its frequent use, warfarin therapy can pose significant challenges in the neonate and young pediatric population in whom physiologic levels of vitamin K-dependent factors change rapidly over time, and who have inconsistent dietary intake of vitamin K. Additionally, warfarin is available only as a tablet and cannot easily be

compounded into a liquid formulation, making it difficult to administer to young children. Further, warfarin levels can be affected by several other factors, including numerous drug interactions, genetic polymorphisms of CYP2C9 and VKORC1, and the development of intercurrent illnesses, leading to the need of frequent blood monitoring to ensure safety and efficacy.³⁵ Most importantly, due to its very narrow therapeutic window, warfarin possesses a high risk for serious bleeding complications.⁵²

Pediatric warfarin dosing depends on patient's age, diet, and use of other medications. Age seems to be the most significant factor in determining dosing in children.⁵³ Unlike adults, in whom genetic polymorphisms of CYP2C9 and VKORC1 seem to have a significant impact, the contribution of these genetic factors on warfarin dosing in children is less clear and genotyping is not currently recommended for this population. The international normalized ratio (INR) is the standard assay used to monitor and dose-adjust warfarin therapy. Prior to initiation of warfarin therapy, patients with an acute thrombosis should first receive anticoagulation with UFH or LMWH due to warfarin's transient procoagulant effects and risk of warfarin-skin necrosis.⁴⁶ Warfarin must be discontinued at least 5 days prior to any invasive procedures and we recommend obtaining an INR prior to any surgical intervention. Additionally, an INR should always be obtained in the setting of bleeding symptoms, with significant changes in the patient's medications or diet, with illnesses that affect gastrointestinal absorption (vomiting, diarrhea) and with changes in liver function.⁴⁶ The most significant safety concern with warfarin is its narrow therapeutic window and multiple drug and diet interactions that can lead to supratherapeutic levels of the drug and increase the risk of bleeding. Vitamin K administration is the first-line therapy for bleeding complications in patients receiving VKAs. Additionally, fresh frozen plasma (FFP) and prothrombin complex concentrate can be administered in the setting of bleeding associated with markedly supratherapeutic INR levels.¹⁵

Parenteral Targeted Anticoagulants

Direct Thrombin Inhibitors

DTIs act by directly inhibiting thrombin in a mechanism that is independent from ATIII.⁵⁴ The use of DTIs in children has been limited to two parenteral agents that require continuous infusion, argatroban and bivalirudin.^{55–58} DTIs have been most commonly used in critically ill children, who are in need for a short-acting anticoagulant as an alternative to heparin due to development of HIT, evidence of heparin resistance (inability to achieve anticoagulation goals with heparin doses >70 unit/kg/h), heparin allergy, or failure of heparin therapy.^{55–58} DTIs offer several advantages over conventional anticoagulants, including a more predictable PK that allows for a more consistent and effective anticoagulation effect, and a lower risk for bleeding complications compared with UFH.

Bivalirudin's half-life is approximately 25 minutes. Most of its clearance is performed by proteolytic cleavage in the blood with only 20% of the drug cleared by the kidneys. Two

prospective safety and dose-finding studies assessed the use of bivalirudin in pediatric VTE, demonstrating an acceptable safety profile and allowing the establishment of pediatric dosing.^{57,59} The aPTT is the most common assay used for therapeutic monitoring with ranges extrapolated from UFH. However, prior studies have demonstrated that this assay correlates poorly with plasma bivalirudin concentrations; thus, we recommend confirmation of any unexpected values and interpretation of these results within the clinical scenario, prior to performing any significant dose adjustments.

Compared with bivalirudin, argatroban has a slightly longer half-life (45 minutes) and is metabolized by the liver; thus, it should be avoided in children with significant hepatic dysfunction. The safety, efficacy, and dosing guidelines were established in a single prospective study evaluating its use in children with suspected or documented HIT.^{58,60} Based on these findings, argatroban currently is the only parenteral DTI that is FDA-approved for use in children with HIT.⁵⁸

There is no reversal agent for the DTIs but given their short half-life, management of bleeding complications can be done by cessation of the drug and supportive measures. Of note, both argatroban and bivalirudin increase INR's levels. Thus, when transitioning a patient from a DTI to warfarin therapy for outpatient management, we recommend overlapping both medications for at least 5 days while targeting a higher-than-goal INR level before discontinuation of the DTI.⁴⁶

Direct Factor Xa inhibitor

Fondaparinux is a synthetic anticoagulant that selectively inhibits factor Xa in an ATIII-dependent manner. It has a longer half-life (~17 hours) than LMWH allowing for once-daily dosing in children. It is administered SQ and renally cleared. Two pediatric studies demonstrated an excellent safety profile and supported the once-daily dosing schedule in children.^{61,62} The initial dosing recommendation can be seen in ▶Table 1. As with LMWHs, fondaparinux is monitored in children using a fondaparinux-based anti-Xa assay.^{61,62} Besides its once-daily dosing schedule, other advantages of this agent include lower risk of osteoporosis compared with UFH and LMWH, and no risk for the development of HIT, making this agent an excellent alternative to LMWH. Fondaparinux should be held for at least 24 hours prior to any interventional procedure to prevent bleeding complications. There is no reversal agent in the case of bleeding.

Direct Oral Anticoagulants

The two classes of DOACs currently approved by FDA in adults for various anticoagulation indications include factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and a DTI (dabigatran).^{63–65} Advantages of these agents over conventional anticoagulants include their oral administration, more predictable anticoagulant effect, minimal food and drug interactions, and the theoretically benefit of improved compliance, as these agents allow for once-daily dosing without the need of frequent laboratory monitoring.^{63–65} Although none of the DOACs has been FDA-approved for use in children, there are few reports of their off-label use in this population.^{66–68} Most published pediatric data have been limited to

the use of rivaroxaban and dabigatran. The limited data from these reports suggest that DOACs may have an age-dependent response, highlighting the need for clinical trials investigating appropriate age-specific doses of these agents. Currently, there are several ongoing studies assessing the safety and efficacy of DOACs in the management of pediatric VTE. Of these, a Canadian phase 1, open-label safety and tolerability trial of dabigatran was the first completed study of the use of a DOAC in children.⁶⁹ In this trial, dabigatran was given to adolescents (12–17 years old) at the end of standard anticoagulation. Overall, dabigatran was well tolerated and there were no major or minor bleeding events reported within 30 days from therapy. Three phase II trials assessing the PK, safety, and tolerability of dabigatran in liquid formulation are underway.^{70–72} Additionally, two open phase III trials are investigating the safety and efficacy of dabigatran for the management and secondary prophylaxis of VTE in children.^{73,74}

To date, the use of rivaroxaban in pediatric VTE has been assessed in two studies. A phase I trial studying the PK/PD and safety/efficacy of oral rivaroxaban for secondary prevention of VTE in pediatric patients was recently completed and results are awaiting publication.⁷⁵ Additionally, the EINSTEIN-Junior is an ongoing study recruiting patients for two phase II and one phase III randomized studies, investigating the PK/PD and safety/efficacy of rivaroxaban compared with conventional anticoagulation in children.^{76–78}

One of the disadvantages of the use of DOACs has been the limited availability of reversal agents in the case of a major bleeding complications or overdose. Recently, Idarucizumab was FDA-approved for the reversal of dabigatran in adults.⁷⁹ In addition, two other agents, andexanate alfa and ciraparantag, are in development.⁸⁰ Both of these agents reverse the effects of oral factor Xa inhibitors, with the latter also acting as a reversal of oral thrombin inhibitors. The FDA gave both of these agents fast track status to facilitate their rapid approval for use in adults. The safety and efficacy of these reversal agents will need to be further studied in the pediatric population. Current strategies for the management of bleeding complications with DOACs include the use of prothrombin complex concentrates, recombinant factor VIIa, and transfusions.⁸¹

Until the safety and efficacy of DOACs for pediatric VTE is demonstrated, we recommend exercising caution when considering the use of these agents as an alternative anticoagulation therapy in children. The current lack of information on their safety, efficacy, and appropriate dosing in pediatric patients, along with limited data on reversal agents, limits the ability to provide best clinical care for children with VTE.

Thrombolytic Therapy in VTE

Unlike conventional anticoagulation, which attenuates hypercoagulability, thrombolytic therapy catalyzes the conversion of plasminogen into plasmin, promoting fibrinolysis and resulting in rapid clot resolution.⁴ The goals of thrombolytic therapy in the acute management of DVT are to reduce thrombus burden, restore venous patency, and reduce venous congestion.¹⁵ In the short term, thrombolysis has the poten-

tial of saving a limb or organ in the setting of limb- or organ-threatening DVT, of allowing faster resolution of thrombosis symptoms, and of decreasing the potential risk of PE. The most significant long-term benefit is the prevention of late venous complications, including venous valvular reflux and venous obstruction, which are key contributors to the development of PTS.

The use of thrombolytic therapy in children is rapidly increasing; however, well-established indications for the use of this modality are still lacking. The ACCP guidelines recommend thrombolysis for pediatric VTE only for life- or limb-threatening thrombosis, while the American Heart Association suggests consideration of thrombolytic therapy in young patients in whom the “benefit may outweigh risk.”^{15,82} The decision to use thrombolytic therapy for the management of acute pediatric DVT should be highly individualized to select those patients who are most likely to benefit from this therapeutic approach. Factors to take into consideration include⁸³ (1) *potential risk of bleeding*: factors that may increase the risk of bleeding include, but are not limited to, recent major surgery, invasive procedure or trauma, intracranial lesions, and refractory thrombocytopenia, among others. A low threshold should be used to exclude those patients with bleeding concerns unless they have a clear indication for urgent thrombolytic therapy as in the case of life-, limb-, or organ-threatening thrombosis; (2) *clinical severity of DVT*: urgent thrombolysis is indicated for the treatment of life-, limb-, or organ-threatening DVT. Non-urgent thrombolysis can be considered in patients who have failed initial anticoagulation therapy, including patients with significant DVT progression or increase in DVT symptoms severity while on anticoagulation; (3) *anatomic extent of DVT*: patients who are at high risk for the development of PTS and/or recurrent VTE are most likely to benefit from thrombolytic therapy. This group includes those presenting within 14 days of symptom onset with large DVTs involving the iliofemoral or axillary/subclavian veins. Currently, thrombolytic therapy is not recommended for patients with asymptomatic or isolated calf DVT, or in patients presenting with DVT symptoms for ≥ 4 weeks, as thrombolytic agents are unlikely to be effective in dissolving an organized thrombus; and (4) *comorbidities and life-expectancy*: patients in whom the risks of thrombolytic therapy may outweigh its potential benefits include those with very short-life expectancy and those who are non-ambulatory.⁸⁴ Contraindications for the use thrombolytic therapy in children are listed in ►Table 3.

There is no consensus recommendation regarding the best thrombolytic agent for pediatric VTE. Tissue plasminogen activator (tPA) is the most frequently and preferred fibrinolytic used in children. It offers the advantages of rapid hepatic clearance, a very short half-life (~5 minutes), and lower immunogenicity compared with streptokinase and urokinase.¹⁵ In vitro studies have also suggested an improved clot lysis effect compared with urokinase, but this finding has not been validated in vivo.^{85,86} Unless the bleeding risk is deemed too high, adjuvant administration of low-dose UFH during thrombolysis is recommended. This recommendation is based on data showing improved outcomes and decreased mortality/development of PE in adult

Table 3 Published relative contraindications for thrombolysis in pediatric VTE^{80,87}

Relative contraindications
Major surgery or invasive procedure within 7–14 d
Active severe bleeding
Central nervous system surgery, trauma, or hemorrhage within 60 d
Severe asphyxia within 7 d of therapy
Sepsis
Serum creatinine >2 mg/dL
Seizures within 48 h
Uncontrolled or uncorrectable coagulopathy with inability to maintain:
Platelet count >75,000/ μ L
Fibrinogen >100 mg/dL
Uncontrolled hypertension
Contrast allergy

patients with acute iliofemoral DVT who receive concomitant UFH therapy, despite an increased incidence of bleeding complications in this population, as well as on pediatric data demonstrating both improvement of thrombosis and no increase in bleeding complications in children.^{10,87,88} Doses for thrombolytic agents and adjuvant anticoagulant therapy are shown in **Table 4**.

We recommend that patients receiving thrombolytic therapy be closely monitored in an intensive care unit. While receiving fibrinolytic agents, fibrinogen levels should be maintained at >100 mg/dL and the platelet count should remain >75,000 $\times 10^9$ /L to minimize the risk of bleeding. Plasminogen levels can be monitored and replaced with FFP when they fall below 50% of baseline, as low levels can limit the efficacy of thrombolytic therapy.⁸⁵ A complete blood count should be obtained at least every 6 to 12 hours to monitor for the development of bleeding complications.⁸⁴ To

evaluate the efficacy of thrombolysis as well as the need of any dose adjustments, follow-up imaging with Doppler ultrasound should be obtained every 24 hours, while D-dimer levels can be monitored more frequently as a surrogate marker of therapy response.^{13,85,86}

Thrombolytic agents can be administered systemically or by local infusion (catheter-directed thrombolysis [CDT]). Although there are no randomized trials comparing each modality in pediatric patients, results from case series suggest improved efficacy and safety with CDT compared with systemic thrombolysis.⁸² CDT has the advantages of delivering a higher intrathrombus drug concentration which allows for the use of lower fibrinolytic doses and a shorter treatment time, potentially reducing the risk of bleeding.¹⁰ However, this modality can lead to worsening endothelial damage due to vessel manipulation, particularly in neonates and small children; and its use may be limited by the availability of qualified interventional radiologists with expertise on this technique.⁸⁵ CDT methods can be categorized into three groups: (1) drug-only CDT, (2) device-only percutaneous mechanical thrombectomy (PMT), and (3) drug plus device pharmacomechanical CDT (PCDT). PCDT is a combination of site-directed fibrinolytic infusion with mechanical thrombectomy. Retrospective and observational studies have shown that this method has similar efficacy and safety compared with drug-only CDT with the advantages of reducing the total drug dose and treatment time compared with drug-only CDT.^{89,90} A single-institution prospective study of PCDT in adolescents demonstrated the feasibility and safety of this approach in children.⁹¹ However, PCDT was associated with a high rate of early, postprocedural DVT recurrence in these studies (up to 40%), likely as a result of the endothelial activation/disruption associated with this procedure.⁹¹ Given this finding, until further prospective studies assessing the outcomes of PCDT in the management of pediatric DVT are published, we suggest the use of drug-only CDT as the preferred modality for local thrombolysis in young children to minimize endothelial damage and potentially reduce the risk of early rethrombosis. We suggest that PCDT should be reserved for certain adolescents at a high risk of PTS (i.e.,

Table 4 Thrombolytic and adjuvant anticoagulation dosing in pediatric VTE

Agent	Dose	Duration	Comments
tPA			
Low dose	Infants and children: 0.03–0.1 mg/kg/h (max 2 mg/h) Neonates: 0.06–0.1 mg/kg/h	24–96 h	Preferred method for venous thrombosis
High dose	0.5–0.6 mg/kg/h	6 h	Assess thrombosis 6 h after therapy initiation. If no resolution, second 6-h course may be given 24 h later
Adjuvant anticoagulation			
UFH	Bolus: none Infusion: 5–15 U/kg	12–96 h	Transition to LMWH for subacute/chronic management

Abbreviations: LMWH, low-molecular-weight heparin; tPA, tissue plasminogen activator; UFH, unfractionated heparin; VTE, venous thromboembolism.

extensive complete veno-occlusive proximal lower extremity DVT with adverse prognostic biomarkers) and for refractory cases that have failed initial drug-only CDT.

Systemic thrombolysis should be considered for the management of patients with massive PE who are hemodynamically unstable, or those with submassive PE who have evidence of right ventricular dysfunction.⁸⁴ We do not recommend the use of systemic thrombolysis for the management of acute DVT due to significant increase in major bleeding complications compared with conventional anticoagulation alone.⁹²

The main complication of thrombolytic therapy is bleeding. Major bleeding complications are defined as any bleeding requiring surgical intervention and/or resulting in a ≥ 2 g/dL drop in hemoglobin in a 24-hour period, as well as any central nervous system hemorrhage or retroperitoneal bleeding. The reported incidence of bleeding complications following thrombolysis therapy in the pediatric population ranges from 0 to 68%.¹⁵ Prolonged duration of thrombolytic therapy is associated with an increase in bleeding. Bleeding complications should be managed with discontinuation of the fibrinolytic infusion and transfusion of blood products, including cryoprecipitate, as needed based on the severity of bleeding.

Mechanical Approaches in VTE

Inferior Vena Cava Filters

The purpose of an IVC filter is to prevent the development of life-threatening PE. IVC filters are placed through a femoral or jugular approach as either permanent or retrievable devices. Retrievable devices can remain in place for up to 3 months and are preferred over permanent devices in children, as they offer the advantage of removal once the risk of PE has subsided, mitigating the potential for long-term complications including filter migration, filter fracture, subsequent IVC thrombosis, and IVC wall penetration.^{93,94} There are no specific guidelines regarding the indication for placement, retrieval, and follow-up of IVC filters in children; and the risk-benefit of this intervention should be carefully considered in a case-by-case basis. In general, IVC filters are considered in pediatric VTE patients who have a contraindication to anticoagulation therapy or who have recurrent or progressive VTE despite adequate anticoagulation therapy.^{15,93} Other frequent indications include free-floating IVC thrombus and pre-thrombolysis PE prophylaxis. In addition, the Society of Interventional Radiology supports the prophylactic use IVC filters in certain high-risk situations, such as severe trauma.⁹⁵

A recent multicenter study on the use of IVC filters in children across tertiary care centers in the United States found that the placement of filters remains a relatively uncommon intervention in pediatric VTE (mean yearly incidence of 6 per 100,000 admissions).⁹⁵ This study found that, unlike adult patients in whom the majority of filters are placed for prophylactic indications (i.e., after severe trauma, malignancy, or orthopedic surgery), only a small proportion of IVC filters (~24%) are placed prophylactically in children. The majority of IVC filters in the pediatric population were used in adolescent patients with either a lower extremity DVT or PE and contraindications for anticoagulation.⁹⁵

IVC filters should be placed and removed by an experienced interventional radiologists trained in the use of these devices. Acute complications related to filter placement include bleeding at the insertion site, infection, pneumothorax, IVC injury, and failure of filter deployment. Once an IVC filter is placed, it is recommended to initiate anticoagulation therapy as soon as it is deemed safe. We recommend that patients remain on anticoagulation therapy until the device is removed, as thrombotic complications are the most common adverse event associated with retained IVC filters. Removal of the device should occur as soon as possible to minimize the risk of long-term complications.^{95,96}

Elastic Compression Stockings

Elastic compression stockings (ECSs) reduce edema and venous hypertension resulting from a DVT.⁹⁷ The use of ECS for the prevention and management of PTS has been studied mostly in adult patients with conflicting data regarding their efficacy.^{97,98} Although an early meta-analysis of randomized controlled trials concluded that ECSs were effective in reducing the incidence of PTS; a more recent large, multicenter, randomized placebo-controlled trial showed no evidence of benefit in the prevention of PTS.^{97,98} Based on these findings, the current ACCP guidelines recommend the use of ECS for the management of acute or chronic DVT/PTS symptoms but recommends against the routine use of ECS for the prevention of PTS.¹⁵ Although there is no available evidence on the benefit of ECS in pediatric patient, we recommend following adult guidelines. It is important to note that the use of ECS in pediatric patients has unique challenges, including difficulty obtaining appropriately fit garments in young children, need for frequent replacements due to growth of the child, and lack of compliance in older children and adolescents due to concerns with appearance, making the use of ECS in pediatric patients challenging.

Special Considerations: Anatomic Predisposition Syndromes

Venous Thoracic Outlet Syndrome/Paget-Schroetter Syndrome

Venous thoracic outlet obstruction (VTOS), also known as Paget-Schroetter syndrome, results from the anatomic compression of the subclavian vein at the level of the thoracic outlet leading to venous thrombosis.⁹⁹ The subclavian vein enters the anterior thoracic outlet at the level of the costoclavicular junction, anterior to the scalene muscle. Anatomic compression can occur by the presence of a cervical rib, by the costoclavicular ligament, or by a hypertrophied scalene or subclavian muscle.¹⁰⁰ VTOS typically affects adolescents and young adults (mean age at presentation is early to mid-30s) and rarely presents during the first decade of life.^{101,102} It is predominantly seen in male patients and most frequently involves the dominant limb. Between 60 and 80% of cases are associated with vigorous exercise or repetitive activities involving hyperabduction or external rotation of the shoulder joint.^{103,104} Symptoms are exacerbated by either exercise or arm elevation and include upper extremity swelling, limb

heaviness, skin discoloration (cyanosis or erythema), and prominent collateral veins over the shoulder region.⁹⁹ vTOS can result in significant acute and long-term complications. In the acute setting, the risk of symptomatic PE following vTOS is estimated at 10%.¹⁰⁵ This risk decreases to 2% when multimodality therapy (anticoagulation, thrombolysis, and surgical decompression) is used to treat patients.¹⁰⁶ In the long term, the most significant complication is the development of PTS. Although the risk of PTS in children with vTOS is not well studied, a recent retrospective Canadian study of 23 children with primary upper extremity DVT found that 87% of patients had mild to moderate PTS symptoms at a median follow-up of 1.6 years.¹⁰⁷ Additionally, 13% of patients in this study experience a recurrent DVT during the follow-up period.¹⁰⁷

The current consensus for the management of vTOS in adults is to perform a multimodal approach that includes the use of anticoagulation, thrombolysis, and surgical thoracic outlet decompression.^{104,105} There is no consensus regarding the management of pediatric patients, with vTOS and only a few studies, most of them retrospective in nature, have evaluated the outcomes of endovascular and/or surgical interventions in this population.^{101,102,108–111} In a retrospective single-institution cohort of six adolescents with vTOS who received conventional anticoagulation therapy alone (LMWH followed by warfarin), five out of the six patients reported persistent symptoms 3 months postdiagnosis, and all patients who were followed up for more than 12 months ($n = 3$) had moderate to severe PTS symptoms.¹¹⁰ Two of these patients experienced an early DVT recurrence, suggesting that the use of anticoagulation alone in pediatric patients with vTOS results in poor outcomes.¹¹⁰ In an adult retrospective series of patients with vTOS who received anticoagulation followed by thrombolysis with no surgical intervention, 23% developed a recurrent thrombosis at a mean follow-up time of 13 months after thrombolysis.¹¹² In contrast with these findings, a retrospective series reviewing the outcomes of six adolescent patients with vTOS managed with a combination of thrombolysis, anticoagulation, and surgical decompression reported complete resolution of symptoms in all patients receiving this treatment approach.¹¹¹ Most recently, results from a retrospective cohort of 21 adolescents with vTOS treated by a multidisciplinary team confirmed the safety and efficacy of endovascular and surgical approaches in the management of pediatric vTOS.¹⁰⁹ In this study, patients were treated with thrombolysis (CDT or PMCDT) and conventional anticoagulation (LMWH or warfarin), followed by surgical thoracic outlet decompression (first rib resection, anterior scalenectomy, and venolysis) 3 to 4 weeks postthrombolysis. Postsurgery, patients were continued on conventional anticoagulation therapy and completed a median of 4.5 months of therapy. Following this treatment strategy, 90% of patients had complete resolution of symptoms at a mean follow-up of 12 months.¹⁰⁹ Only one patient, a heterozygous carrier of factor V Leiden, experienced a recurrent DVT 3 days after surgery and three patients experienced a postsurgical complication (two pneumothorax and one hemothorax).¹⁰⁹

Based on these findings, it is our recommendation that pediatric vTOS be managed by an experienced multidisciplinary

team that includes a pediatric hematologist, an interventional radiologist, a pediatric surgeon, and a vascular surgeon. Pediatric patients should receive a multimodal treatment approach with the use of conventional anticoagulation therapy (LMWH) and prompt CDT or PMCDT (–Fig. 1), followed by surgical thoracic outlet decompression. Surgical correction should be performed approximately 4 weeks postthrombolysis to allow for resolution of the perivascular inflammation resulting from the thrombotic event and the endovascular procedure. Postsurgery, we recommend continuation of conventional anticoagulation to complete a total duration of 6 to 12 weeks of therapy. Repeat imaging assessing the subclavian vein patency should be performed prior to discontinuation of anticoagulation therapy. Longer duration of anticoagulation therapy should be considered based on individual risk factors, including the presence of a thrombophilia disorder or incomplete resolution of the initial thrombosis.

May–Thurner Syndrome

May–Thurner syndrome (MTS) results from the chronic, pathologic compression of the left common iliac vein (LCIV) by the right common iliac artery that leads to the formation of venous spurs and stenosis of the LCIV with subsequent thrombosis and obstruction of the deep left venous system.¹¹³ Although the true incidence is unknown, it is estimated that up to 50% of left sided iliofemoral DVTs in adults are associated with extrinsic compression of the iliac vein.^{114,115} MTS more frequently affects young and middle age women (mean age at presentation is 42 years).¹¹⁶ As in the case of PSS, most pediatric cases present during the second decade of life. Clinically, MTS is characterized by left lower extremity swelling; pain; claudication and, in chronic cases, ulceration; skin hyperpigmentation; and the development of varicose veins.¹¹⁷ There is no optimal imaging modality for the diagnosis of MTS. Noninvasive imaging techniques include transabdominal compression Doppler ultrasound, CTV, and MRV, all of which have significant limitations, including the inability to properly visualize the LCIV due to overlying bowel gas (Doppler ultrasound), difficulty of timing imaging sequences with the optimal contrast opacification of the target vein often resulting in nondiagnostic results (CTV), and limited imaging resolution for subtle intravenous lesions (CTV and MRV).¹¹⁸ Invasive imaging testing with catheter venography, and/or intravascular ultrasound, is often required to establish a definitive diagnosis.¹¹⁸ Since compression of the LCIV can be a normal anatomic variant and not necessarily a pathologic condition, the most confident diagnosis of LCIV DVT secondary to MTS should ideally include confirmation of persistent stenosis of the luminal diameter of the LCIV regardless of the patient's positioning, presence of venous collaterals and intraluminal spurs, and changes in hemodynamic flow, measured by venography, greater than 2 to 4 mm Hg across the stenotic region.^{118,119}

MTS is a severe, progressive disease that can lead to significant long-term morbidity due to the development of PTS. An aggressive treatment approach, directed at relieving the mechanical compression of the iliac vein, is often recommended. Treatment is aimed at re-establishing flow through

the affected vessel, preventing PE, recurrent DVT, and the development of PTS. It should consist of the use of anticoagulation therapy and endovascular approaches, including CDT, angioplasty, and stent placement.^{115,116,120} The efficacy of the use of anticoagulation, CDT, and iliac vein stent placement has been evaluated in a few RCTs of adult patients with iliofemoral DVT.^{121–123} Results from these trials confirmed that the implementation of a multimodal therapeutic approach leads to improved clinical outcomes, including a lower incidence of rethrombosis, PTS, and valvular reflux, compared with the use of anticoagulation alone.^{121–123} Although no RCTs have assessed the safety and efficacy of this approach in pediatric patients, published data from retrospective studies and case reports have shown that the use of conventional anticoagulation, CDT, and stent placement results in high rates of recanalization and long-term patency of the iliac vein, with significant improvement in symptoms while potentially decreasing the development of PTS.^{113,124,125} Surgical approaches, including thrombectomy of the iliofemoral veins with iliac venous reconstruction or placement of a cross-femoral venous bypass graft, are not recommended as first-line management, and are typically reserved for patients with significant contraindications to CDT, as they can result in high morbidity with variable rates of successful venous recanalization.^{114,116}

Conclusion

VTE has become an increasingly recognized problem in pediatrics that can significantly impact the health outcomes of affected children. Despite its increased frequency, high-quality data to guide the management of pediatric thrombosis are lacking and the majority of recommendations are extrapolated from adult guidelines. However, great advances have been made in understanding the underlying risk factors of pediatric thrombosis and on designing risk-stratified therapy strategies for children. Strides have also been made on optimizing the dosing of conventional anticoagulants for pediatric patients. When possible, pediatric thrombosis should be managed by a multidisciplinary team that includes a pediatric hematologist with expertise in thrombosis. Multidisciplinary expertise is particularly important in managing vTOS and MTS, which should be suspected in settings of unprovoked acute DVT of the upper extremities and left iliofemoral veins, respectively. The mainstay agents for anticoagulation therapy in pediatric VTE remain UFH, LMWH (enoxaparin in the United States), and VKA (warfarin), all of which have significant limitations in this population. Thrombolytic therapy represents a major treatment option for selected patients and has the potential of improving the long-term quality of life of children by reducing the risk of PTS. The recently approved DOACs for adult anticoagulation may provide significant advantages in the management of pediatric VTE due to their noninvasive administration and less frequent laboratory monitoring. Currently, DOACs have been extensively studied in pediatric VTE trials. Until results from these trials demonstrate their safety and efficacy in children, providers should exercise caution when considering

the use of these agents as an alternative anticoagulation therapy in children.

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