Venous Thromboembolism in Pediatrics

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PRACTICE GAP

The increasing rates of venous thromboembolism (VTE) in children mandate a need for pediatricians, especially those who are hospital based, to be fully aware of the common signs and symptoms of VTE, the current management guidelines for VTE acute treatment and prophylaxis, and the role of emerging oral anticoagulant therapies.

OBJECTIVES   *After completing this article, readers should be able to:*

1. Describe the pathophysiology of pediatric venous thromboembolism (VTE).

2. Identify patients at risk for VTE.

3. Identify the clinical signs and symptoms associated with acute VTE.

4. Understand the indications for radiologic and laboratory testing for diagnosing and treating an acute VTE.

5. Describe the clinical management using standardized VTE anticoagulant therapies.

6. Become familiar with the emerging direct oral anticoagulant therapies.

ABBREVIATIONS

aPC	activated protein C
aPTT	activated partial thromboplastin time
ATIII	antithrombin III
CVC	central-access vascular catheter
DOAC	direct oral anticoagulant
DTI	direct thrombin inhibitor
DUS	Doppler ultrasonography
DVT	deep venous thrombosis
FDA	Food and Drug Administration
FVL	factor V Leiden
FXa	activated coagulation factor Xa
HIT	heparin-induced thrombocytopenia
LMWH	low-molecular-weight heparin
MRV	magnetic resonance venography
MTHFR	methylenetetrahydrofolate reductase
PE	pulmonary embolism
PF4	platelet factor 4
VKA	vitamin K antagonist
VTE	venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), which encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE), has become an increasingly recognized condition in pediatrics. There is now an overall awareness by pediatricians of the reality that VTE is no longer considered to be a medical problem exclusive to the adult population. (1)

Unfortunately, there is a paucity of strong clinical data to guide the management of VTE in children. To date there are 2 expert opinion VTE treatment guidelines developed for pediatric patients. (2)(3) Current VTE treatment recommendations rely on observational experience and extrapolated data from adult practice. (4)(5) Ongoing multicenter clinical trials are currently seeking answers to improve VTE management strategies in children. (6)

EPIDEMIOLOGY

The cause of the rising prevalence of diagnosed VTE in children is multifactorial. This is related to an increased presence of VTE-predisposing risk factors in pediatric patients, improved survival rates in infants and children with chronic medical

conditions, and improved diagnostic tools used by providers. Pediatric VTE occurs in a bimodal distribution, most commonly encountered in neonates and adolescents. (4)

Although VTE in the outpatient pediatric setting remains uncommon, hospital-acquired VTE is estimated to occur in 1 of 200 pediatric hospital admissions per year. (7)(8) Different cohort analyses have reported a dramatic increase in the incidence of pediatric VTE. Depending on the study, this increase ranges from 70% to 102%. (9)(10)

The presence of VTE is estimated to increase in-hospital mortality between twofold and sixfold. (4)(11) Hospital-acquired VTE has been shown to significantly increase the cost of admission and to extend length of stay by more than a week. (12)

An international VTE registry that included 137 consecutive patients reported a mortality rate directly related to VTE of 2.2%. (13) Potential complications of VTE include limb ischemia, anticoagulation-associated bleeding, VTE recurrence, and postthrombotic syndrome. (14)

VTE PATHOGENESIS

Unlike in the adult population, VTEs in children are almost always provoked. Risk factors that contribute to the development of a VTE are those that disrupt 1 or more of the Virchow triad's components: blood flow stasis, endothelial injury, and/or a hypercoagulable state. (8) Most children present multiple and simultaneous risk factors at the time of VTE diagnosis, including acquired (central line use, trauma, surgery, immobility, critical illness) and genetic thrombophilic conditions. (15)

The most common predisposing VTE risk factor in children is the presence of a central-access vascular catheter (CVC), either venous or arterial. (11) Presence of a CVC is associated with more than 90% of diagnosed VTEs in neonates and more than 60% in older children. (13) The introduction of a catheter into a blood vessel causes thrombosis by injuring the endothelial wall and disrupting the blood flow. When the catheter is used to deliver foreign substances, such as total parenteral nutrition, chemotherapy, or antibiotics, further damage and disruption occurs. Studies have shown that more than half of upper extremity VTEs in children and almost 80% in neonates are associated with a CVC. (16) When a thrombosis is identified in association with a CVC, it is generally recommended to administer anticoagulation through the central line until it can be removed. Removal of the central line should occur within 3 to 5 days of initiating anticoagulation, unless the catheter is necessary to use and if the catheter continues to appropriately function. Once a VTE is identified, serial radiologic imaging is necessary to assess for potential extension of the clot. (2)

Localized or systemic infections such as mastoiditis, sinusitis, and osteomyelitis, as well as inflammatory disorders (eg, systemic lupus erythematous, juvenile rheumatoid arthritis, and active cancer), are clinical conditions also associated with a higher risk of VTE development.

INHERITED THROMBOPHILIAS

A thrombophilia is defined as an inherited coagulation disorder associated with an increased risk of thrombosis. There are 2 main categories of inherited thrombophilias: genetic conditions associated with deficiencies of natural anticoagulants (antithrombin, protein C, and protein S) (Fig 1) and gain-of-function mutations in procoagulant factors (factor V Leiden [FVL] and prothrombin G20210A mutation) (Table 1).

A complete thrombophilia panel includes protein C and S activity levels, antithrombin III (ATIII) antigen and activity levels, antiphospholipid antibody levels, FVL mutation analysis, and prothrombin G20210A gene mutation analysis. Some centers might consider performing the activated protein C (aPC) resistance assay before sending the FVL mutation analysis.

The prevalence of at least 1 inherited thrombophilic condition in children with a newly diagnosed VTE ranges from 13% to 79%. (20) Thrombophilias are most commonly found in adolescents presenting with unprovoked thrombosis or children with a family history of VTE. However, most patients with VTEs who are found to have an inherited thrombophilia present in the context of an additional thrombosis risk factor, suggesting that the inherited trait by itself may not be sufficient to cause a VTE. (17)

Recommendations for testing for inherited thrombophilia conditions in children are not well established. There is debate among hematologists as to who should be tested for inherited thrombophilias. In 2002, the International Society of Thrombosis and Hemostasis recommended that all children with new VTEs should be tested for the presence of a thrombophilia. However, as more data become available, this guideline has come into question.

Most centers suggest testing for these conditions in children with idiopathic or unprovoked VTEs.

FVL mutation is the most common inherited thrombophilia. The prevalence of the heterozygous mutation ranges from 1% to 9% in the general population. FVL is more common in European populations and is rare in African and Asian populations. FVL results from a mutation in the factor V protein at the site of aPC cleavage, causing resistance of activated factor Va to the cleaving effect of aPC, thereby creating a hypercoagulable state. (17) When FVL is suspected, an aPC resistance assay may be sent. A positive result should
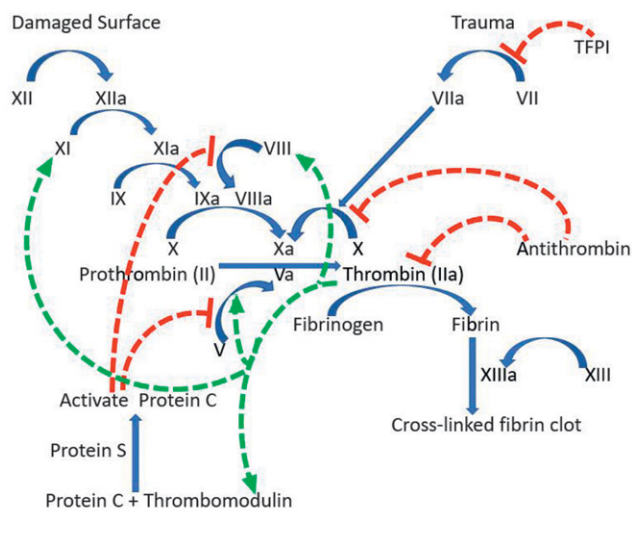
Figure. Coagulation cascade.

lead to more direct molecular testing for factor V mutation analysis. (21)

Other thrombophilias, such as ATIII deficiency, prothrombin G20210A mutation, and protein C and S deficiencies are less common. Diagnosis of these deficiencies is difficult in pediatrics because the levels of some of these natural anticoagulants are physiologically lower in children and neonates than in adults. For example, protein S activity and antithrombin do not reach adult levels until age 6 months, and protein C activity levels may remain low until adolescence. (17) Furthermore, even in the mature coagulation system, these proteins may be physiologically low in the setting of an acute thrombosis. As a result, establishing the diagnosis of a thrombophilia requires confirmation via a second sample performed 3 to 6 months after the initial one. (20)

Methylenetetrahydrofolate reductase (MTHFR) mutation variants and high plasma levels of homocysteine have been suggested as risk factors for VTE. The utility of testing for MTHFR mutation variants is debated because its prognostic value has not been proven. MTHFR C677T heterozygous and homozygous mutations are relatively common, especially in North American and European populations. The mutation results in an MTHFR protein that is less active than the wild type and had been linked to abnormally high levels of plasma homocysteine in homozygotes. Elevated homocysteine levels are hypothesized to pose an increased risk of thrombosis, either by inhibiting natural anticoagulants or promoting the coagulation cascade. However, even among those with abnormal fasting homocysteine levels, there has been no correlation with an increased risk of thromboembolism. (22) The presence of an isolated MTHFR mutation is not an absolute indication for DVT prophylaxis. Positive results may lead to unnecessary patient concern and referrals to a pediatric hematologist.

Thrombophilia testing rarely influences the acute management of VTEs. However, results may be useful in providing anticipatory guidance to patients regarding their risk of recurrent thrombosis as well as the potential risk of thrombosis in family members. Patients with inherited thrombophilias may be advised against the use of prothrombotic agents such as estrogen-based oral contraceptives and to avoid prolonged immobility. Adolescent females with a history of VTE, a family history of VTE, or a family history of inherited thrombophilia should be referred to a pediatric hematologist before starting oral contraceptives. These adolescents may be tested for thrombophilia depending on individual characteristics. (20) Those with inherited thrombophilia may also be considered for thromboprophylaxis during high-risk situations, such as orthopedic procedures or prolonged hospitalizations. (17)

There are not enough data to determine whether the presence of an isolated inherited thrombophilia should guide the duration of anticoagulation treatment. It is used in combination with other clinical, laboratory, and imaging modalities. (20) The decision of who to test should be made on an individual basis and with appropriate counseling by a pediatric hematologist.

VTE DIAGNOSIS

To diagnose a VTE, providers must properly identify patients at risk for VTE development. They should also be able to recognize common VTE-associated signs and symptoms.

Table 1 Inherited Thrombophilias (17)(18)(19)

THROMBOPHILIA	PROCOAGULANT MECHANISM	ESTIMATED PREVALENCE IN PEDIATRIC POPULATION, %	ESTIMATED PREVALENCE IN PATIENTS WITH FIRST VTE, %[a]	RELATIVE RISK FOR FIRST VTE[a]	RELATIVE RISK FOR RECURRENT VTE[a]
Factor V Leiden	Resistance of both factors V and Va to the cleaving effect of aPC	3–7	15.7	3–5	1.4
Antithrombin deficiency	Decreased inactivation of factors IIa, Xa, IXa, XIa, and XIIa	0.02–0.04	2.0	5–10	1.9–2.6
Prothrombin G20210A mutation	Increased levels and activation of prothrombin (factor II)	0.7–4.0	3.8	2–3	1.4
Protein C deficiency	Decreased inactivation of factors Va and VIIIa	0.2–0.5	5.2	4–6.5	1.4–1.8
Protein S deficiency	Decreased inactivation of factors Va and VIIIa	0.03–0.13	3.3	1–10	1–1.4

aPC=activated protein C; CI=confidence interval; OR=odds ratio; VTE=venous thromboembolism.
[a]Prevalence and relative risks are based on meta-analysis studies.

Clinical presentation of a VTE reflects the location and chronicity of the thrombus and the degree of vessel occlusion. An acute DVT typically presents with unilateral pain, swelling, and/or erythema of the involved extremity. In neonates, acute DVTs may also result in new-onset and otherwise unexplained thrombocytopenia by way of local platelet consumption. If a DVT is associated with a CVC, it may present as catheter dysfunction. In the upper extremities, extensive DVTs may cause superior vena cava syndrome, characterized by swelling of the face and upper extremities, shortness of breath, and cough. (4) Cerebral sinovenous thrombosis can present with severe headaches, vomiting, papilledema, focal neurologic deficits, seizures, or changes in mental status. (23) PE usually presents with cough, crackles, and acute-onset tachypnea and tachycardia. (4) Large PEs can present as severe and acute respiratory or cardiac decompensation. (12) Unlike in adult populations, PEs in pediatrics are rarely fatal. (16)

Other less common DVT locations include thrombosis of the renal and portal veins. Patients with renal vein thrombosis present with acute-onset hematuria, and, in cases of bilateral renal thromboses, children may develop severe renal insufficiency and/or nephrotic syndrome. Portal vein thrombosis can result in acute upper gastrointestinal bleeding. (16)

When there is a high index of clinical suspicion, a VTE should be confirmed radiologically. Selection of the imaging modality will depend on the site of the suspected thrombosis. Currently, the most common imaging technique used for DVT diagnostic purposes is Doppler ultrasonography (DUS). DUS is a noninvasive, readily available, and sensitive diagnostic

tool. (24) This technique is useful in identifying the location, characteristics, and degree of thrombus occlusion. Once a VTE is identified, subsequent DUS will help assess potential extension of the blood clot. (2) DUS can also be used to identify the presence of collateral vessels, which will suggest a chronic rather an acute thrombosis.

DUS is limited in the detection of thrombosis in deep abdominal or pelvic veins and in upper extremity central veins. In these cases, other imaging modalities, such as computed tomography with intravenous contrast or magnetic resonance venography (MRV), are preferred. MRV has high rates of sensitivity and specificity for thrombosis and, unlike computed tomography venography, does not expose the patient to radiation. MRV is also the preferred imaging modality in patients presenting with cerebral sinovenous thrombosis. However, MRV is expensive, requires sedation in young children, and is not readily available at all centers. Computed tomography angiography is the first-line technique for diagnosis of PE in children. (4)

Laboratory testing in the acute setting is useful to determine potential contraindications to starting anticoagulation and to establish a baseline to guide future therapeutic decisions. Initial evaluation should include a complete blood cell count, prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen level. A basic metabolic panel is useful because many anticoagulants are excreted through the kidneys. Anticoagulation is usually contraindicated if the platelet count is less than 75,000/mm³. If a coagulation factor deficiency is suspected, based on a prolonged prothrombin time or aPTT, it needs to be corrected before starting anticoagulation.

Other testing, such as factor VIII activity level and quantitative D-dimer level, are used to establish a baseline for comparison when considering duration of therapy. (11) D-dimer testing has not been fully validated in pediatrics for diagnostic purposes. Certain clinical scenarios may warrant evaluation for genetic and acquired prothrombotic states.

VTE TREATMENT IN CHILDREN

The mainstay of VTE treatment is anticoagulation. Anticoagulation does not hasten the resolution of an identified clot. Rather, it is primarily used to avoid extension or embolization of an acute thrombus, to prevent thrombosis recurrence, and to mitigate long-term complications. (12)

There are no anticoagulant drugs officially approved for use in the treatment of children with VTE because very little research on anticoagulation has been specifically tailored to the pediatric population. (3) Currently, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKAs) are first-line therapy for VTE treatment in pediatrics (Table 2). (11)

In pediatrics, therapeutic anticoagulation is most frequently initiated after identification of a VTE. However, the risks and benefits of anticoagulation need to be assessed on an individual basis because the class and duration of anticoagulation will vary depending on the characteristics of the patient and the thrombosis.

Table 2 Standard Anticoagulants Used in Children (4)(25)

ANTICOAGULANT	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	DOSING FOR ACUTE VTE	TARGET THERAPEUTIC RANGE	REVERSAL AGENT	METABOLISM
UFH	Potentiates inhibitory effects of ATIII over activated factors X and II	Intravenous	Bolus: 75–100 U/kg over 10 min Continuous infusion: <1 y: 28 U/kg per hour >1 y: 20 U/kg per hour	aPTT 1.5–2.5 times upper limit of normal Anti-Xa 0.3–0.7 U/mL	Protamine sulfate	Hepatic and RES
LMWH	Similar to UFH but with more specificity toward activated factor X	Subcutaneous	<2 mo of age: 1.5 mg/kg per dose, every 12 h ≥2 mo of age: 1 mg/kg per dose, every 12 h Prophylactic dosing: <2 mo of age: 1.5 mg/kg per dose daily ≥2 mo of age: 1 mg/kg per dose daily or 0.5 mg/kg per dose twice daily	Anti-Xa 0.5–1 U/mL[a] Not necessary to monitor level	Protamine sulfate (partial reversal only)	Renal
Warfarin (VKA)	Inhibits the carboxylation of vitamin K–dependent factors (II, VII, IX, X)	Oral	2–12 y of age: 0.09 mg/kg per dose daily ≥12 y of age: 0.08 mg/kg per dose daily	INR 2–3[b] INR 2.5–3.5 (for patients with valvular heart disease or APS)	Vitamin K, fresh frozen plasma	Hepatic
Argatroban (DTI)	Direct inhibition of thrombin (independently from ATIII)	Intravenous	Continuous infusion: 0.75 μg/kg per minute (no bolus required)	aPTT 1.5–2.5 times upper limit of normal[c]	None	Hepatic

APS=antiphospholipid syndrome; aPTT=activated partial thromboplastin time; ATIII=antithrombin III; DTI=direct thrombin inhibitor; INR=international normalized ratio; RES=reticuloendothelial system; LMWH=low-molecular-weight heparin; UFH=unfractionated heparin; VKA=vitamin K antagonist.

[a]Anti-Xa level should be measured 4 to 6 hours after the second LMWH dose.
[b]First INR level should be measured 3 to 5 days after therapy initiation, then daily until therapeutic.
[c]First value 2 hours after initiation of therapy.

UFH exerts its anticoagulant effect by reversibly binding to ATIII, causing a conformational change that potentiates its inhibitory effect on both activated coagulation factor II/thrombin and coagulation factor Xa (FXa). (26) UFH is administered intravenously as a continuous infusion. The recommended loading dose is 75 to 100 U/kg over 10 minutes followed by a maintenance dose of 28 U/kg per hour for infants younger than 1 year and 20 U/kg per hour for children older than 1 year. (3) The initial bolus should be omitted if there is a significant risk of bleeding in the patient and when treating neonates (<28 days of age), especially those who are premature. (3)

The UFH maintenance dose is titrated to maintain therapeutic levels. The target goal for therapeutic UFH anticoagulation is an anti-Xa level of 0.35 to 0.7 U/mL, which is assumed to be equivalent to an aPTT of 60 to 80 seconds. The therapeutic effect of UFH can be monitored using either the aPTT or anti-Xa level. Anti-Xa level is preferred due to multiple contaminant factors that can influence the aPTT results. An anti-Xa level should be measured 4 to 6 hours after administering the UFH bolus and every 4 to 6 hours thereafter until the therapeutic range is achieved. (15)

UFH has a very short half-life of approximately 30 minutes. It is the preferred anticoagulant in cases that require rapid anticoagulation reversal, such as in patients who may need urgent surgery. The reversal agent of UFH is protamine sulfate, which binds to heparin and neutralizes its effect. UFH is also preferred for patients with renal failure because UFH is primarily metabolized by the reticuloendothelial system and the liver. The primary disadvantages of UFH are its unpredictable pharmacokinetics and difficulty obtaining stable therapeutic levels. This is especially true in younger children and neonates who have physiologically lower levels of ATIII, a larger volume of distribution, and increased heparin metabolism. Long-term use of UFH also increases the risk of osteoporosis. (27)

The most severe complication of UFH therapy is the development of heparin-induced thrombocytopenia (HIT). (27) HIT is characterized by the development of multiple acute and severe arterial and/or venous thromboses and thrombocytopenia (defined as a drop in platelet count >50% from baseline) that occurs after at least 4 days of heparin exposure. The pathophysiology of HIT is due to the development of IgG antibodies that bind to the heparin–platelet factor 4 (PF4) complex causing massive platelet activation and subsequent thromboses. Thrombocytopenia occurs both through platelet consumption and early clearance of antibody-coated platelets. (27) Prompt diagnosis and treatment of HIT can be lifesaving and/or limb saving. HIT can be diagnosed by specific immunoassays such as the enzyme-linked immunosorbent assay for anti-PF4/heparin antibodies and the C-serotonin release assay. Although both of these tests are highly sensitive for HIT, the anti-PF4/heparin test has very low specificity and the C-serotonin release assay is not widely available. Patients should be immediately treated for HIT as soon as the clinical suspicion arises. Treatment consists of discontinuation of all heparin-containing products and the start of an anticoagulation regimen with heparin alternatives such as direct thrombin inhibitors (DTIs). (28)

DTIs act by directly inhibiting thrombin. Two parenteral DTIs have been reported to be used in pediatrics, argatroban, and bivalirudin. Argatroban is currently the only agent that is Food and Drug Administration (FDA) approved for the treatment of HIT in children. Parenteral DTIs do not have a reversal agent. Because they have a very short half-life, bleeding complications are managed by immediately discontinuing the DTI infusion. (4) DTIs should also be considered in patients with heparin resistance or allergy.

LMWHs are derived from depolymerization of UFH. Despite the availability of several different LMWHs, enoxaparin is the most commonly used LMWH in pediatrics. The LMWH mechanism of action is similar to that of UFH; however, LMWH inhibits FXa in a more selective way relative to thrombin. (29) LMWH has a longer half-life than UFH, approximately 3 to 6 hours, and it is administered subcutaneously with nearly 100% bioavailability. In pediatrics, twice daily dosing is recommended when managing an acute thrombosis. Initial dosing is age dependent, and the dosing regimen is titrated based on anti-FXa activity level results. Younger patients typically require higher doses per kilogram than older patients; infants may require up to 50% increased dosing. (30)

LMWH has more reliable pharmacokinetics than UFH. The recommended LMWH starting therapeutic dose regimen for infants younger than 2 months with acute DVT is 1.5 mg/kg per dose twice daily, and for children older than 2 months the starting dose is 1 mg/kg per dose twice daily. Premature infants' doses may reach up to 2 mg/kg per dose before achieving the therapeutic range. (31) The therapeutic range for acute DVT treatment with LMWH is an anti-Xa level between 0.50 and 1.0 U/mL. This sample should be taken 4 to 6 hours after a dose, when its peak effect is expected. (2) The initial anti-Xa level should be measured after the second or third dose. (31) Anti-Xa levels are monitored until therapeutic levels are achieved. When used for prophylaxis, the dosage of LMWH in children older than 2 months is 1 mg/kg per dose daily or 0.5 mg/kg per dose twice daily, and in infants younger than 2 months the dose is 1.5 mg/kg per dose daily. For patients undergoing or in need

of long-term prophylactic anticoagulation, LMWH is given daily, with a target anti-Xa level of 0.1 to 0.3 U/mL. (2) However, it is not necessary to routinely monitor this level during prophylaxis.

LMWH should be held 24 hours before and after any surgical or invasive procedure (including lumbar punctures) to minimize the risk of bleeding. Unlike UFH, LMWH is only partially reversed by protamine sulfate. (4)(24) LMWH is excreted by the kidneys and must be dose-adjusted in patients with renal failure.

LMWH has become the drug of choice for both short- and long-term treatment of an acute DVT and for DVT prophylaxis in children. Patients treated with LMWH have more predictable anti-Xa levels and require less frequent monitoring. There is a lower incidence of HIT and a decreased risk of osteoporosis. Compared with VKAs, LMWH has very few dietary and drug-drug interactions, making it a more viable option for children.

VKAs, such as warfarin, are oral anticoagulants that work by inhibiting the vitamin K–dependent carboxylation of clotting factors in the liver (factors II, VII, IX, and X). These agents have a longer half-life of 35 to 40 hours and a longer duration of action of 2 to 5 days compared with UFH and LMWH. The therapeutic range for VKAs is titrated to target an international normalized ratio of 2.0 to 3.0, except when used for prosthetic cardiac valves wherein adult recommendations are used with a target of 2.5 to 3.5 depending on the type of valve. (2)(32) VKAs have a very narrow therapeutic window and require frequent monitoring. Vitamin K and fresh frozen plasma are the reversal agents for VKA. Fresh frozen plasma is the agent of choice for VKA-related severe bleeding. (4)

Theoretical advantages of VKA include a once-daily dosing regimen and oral administration. However, these agents are challenging to use in pediatrics because of physiologically variable levels of vitamin K–dependent clotting factors during development (developmental hemostasis). VKAs also have multiple food and drug interactions and are unable to be compounded into a liquid formulation. VKAs also carry an increased risk of serious and sometimes fatal bleeding.

DIRECT ORAL ANTICOAGULANTS

The novel direct oral anticoagulants (DOACs) have been approved for the acute treatment and prevention of VTEs in adults but are not yet officially approved for use in pediatric patients younger than 18 years.

There are 2 main classes of DOACS: FXa inhibitors (rivaroxiban, apixaban, edoxaban, and betrixaban) and DTIs (dabigatran). These agents are administered orally and have a more consistent pharmacokinetic profile, allowing for less frequent laboratory monitoring compared with traditional anticoagulants. There are currently several ongoing clinical trials investigating the efficacy and safety of DOACs in pediatrics. (30) Dabigatran and rivaroxaban are the most studied DOACs in children (Table 3). A recently completed phase 3 trial showed efficacy and safety of rivaroxaban in treatment of pediatric VTE, similar to that of standard anticoagulation. Rivaroxaban treatment in children is bodyweight-adjusted and administered either once, twice, or three times daily for children with bodyweights of ≥30, 12 to <30, and <12 kg, respectively. (35)

The disadvantage of DOACs is the lack of experience with use in pediatrics compared with UFH and LMWH. There is also a limited number of reversal agents. Reversal agents for dabigatran, idarucizumab, and FXa inhibitors, such as andexanet alfa, have been approved in adults. (36) Other reversal agents for FXa inhibitors are under investigation. (37) DOACs offer a promising option to children who require long-term anticoagulation. However, further studies are needed to establish appropriate dosing and monitoring guidelines and to evaluate pediatric-specific comorbidities and outcomes. (30)

Table 3 Direct Oral Anticoagulants in Pediatrics (33)(34)

MECHANISM OF ACTION	MEDICATION	PEDIATRIC INDICATIONS UNDER INVESTIGATION IN CURRENT AND FUTURE CLINICAL TRIALS
Factor Xa inhibitors	Rivaroxaban	Arterial TE prevention after Fontan surgery (versus aspirin) Acute VTE treatment
	Apixaban	VTE prevention in acute leukemia with CVC (versus placebo) Arterial TE prevention in cardiac diseases (versus LMWH/VKA) Acute VTE treatment
	Edoxaban	Arterial TE prevention in various cardiac diseases Acute VTE treatment (versus LMWH/VKA)
	Betrixaban	VTE prevention in medical illness or surgery VTE prevention in neonates with umbilical CVC
Direct thrombin inhibitor	Dabigatran	Acute VTE treatment (versus LMWH/VKA) Extended secondary VTE prophylaxis

CVC=central-access vascular catheter; LMWH=low-molecular-weight heparin; TE=thromboembolism; VKA=vitamin K antagonist; VTE=venous thromboembolism.

Table 4 Guidelines for Therapeutic Anticoagulation Treatment Duration (2)(3)

INDICATION	RISK FACTOR	THERAPEUTIC ANTICOAGULATION TREATMENT DURATION
First VTE episode	Provoked, reversible	3 mo
	Provoked, chronic	3 mo, then continue anticoagulation with either therapeutic or prophylaxis regimens until the risk factor is resolved
	Idiopathic	6–12 mo
Recurrent VTE	Reversible	3 mo
	Chronic	If recurrence occurs while the patient was on prophylaxis regimen, after first VTE episode, restart therapeutic regimen until risk factor is resolved
	Idiopathic	Restart therapeutic regimen for at least 3 mo and then switch to lifelong VTE prophylaxis regimen

VTE=venous thromboembolism.

DURATION OF ANTICOAGULATION FOR ACUTE VTE

The duration of anticoagulation depends on both the clinical characteristics and the presence or absence of thrombosis risk factors. The American College of Chest Physicians and the American Society of Hematology have released guidelines for anticoagulation management in children in different clinical scenarios (Table 4). (2)(3)

According to the most recent guidelines, provoked acute VTEs secondary to a known and transient risk factor (CVC, infection) should be treated for at least 3 months. If the risk factor persists (nephrotic syndrome, ongoing asparaginase therapy), anticoagulation should be extended at either therapeutic or prophylactic doses until the risk factor resolves. A CVC-associated thrombosis should be treated for at least 3 months; if the CVC is required for clinical use and cannot be removed, prophylactic anticoagulation should be initiated after the acute anticoagulation regimen has been completed.

If there is thrombosis recurrence while the patient is receiving prophylactic therapy, therapeutic doses should be restarted for at least another 3 months or until the provoking factor has been eliminated.

Children who develop idiopathic, or unprovoked, acute VTE should be treated for a minimum of 6 to 12 months. Guidelines for more detailed management and complex clinical scenarios should be managed in close consultation with a pediatric hematologist. (2)(3)

Currently, the Duration of Therapy for Thrombosis in Children and Young Adults Study is an ongoing multicenter randomized controlled trial investigating the duration of anticoagulation therapy in pediatric patients with a first provoked acute VTE. The aim of the study is to evaluate the safety and efficacy of shorter (6-week) anticoagulation therapy against the conventional regimen (3 months). The primary efficacy end point of the study is the development of recurrent and symptomatic VTE. (11)

Other clinical trials have evaluated the use of serological and imaging markers to help guide the decision to discontinue anticoagulation in patients with a recent VTE. These markers include radiologic evidence of return of blood flow to previously occluded areas in the vessel and serial measurements of quantitative D-dimer and factor VIII activity level at baseline and at the time of intended completion of anticoagulation. A study of 82 children with acute DVT found that the presence of elevated factor VIII activity and/or quantitative D-dimer levels, either at diagnosis or at the time of anticoagulation discontinuation, were predictors of poor clinical outcome and associated with higher risk of thrombosis recurrence. (38)

VTE PRIMARY PROPHYLAXIS

Primary thromboprophylaxis in pediatrics is highly debated. There are limited data as to who would benefit from primary VTE prophylaxis and in what clinical scenarios a prophylactic regimen should be considered.

In 2008, the Joint Commission implemented a national initiative to reduce the rates of hospital-acquired VTE in adolescents. Those guidelines were specifically directed toward an adolescent population, which represents only a small fraction of pediatric patients with VTE.

Patient age (adolescents) and prolonged immobility, defined as being bedridden for more than 72 hours, are considered to be the most important factors when determining the need for VTE prophylaxis. Despite the presence of CVCs being the most common risk factor for VTE in children, it is not universally considered an independent indicator for a DVT prophylactic regimen. Other VTE clinical risk factors include the use of exogenous estrogens, recent lower extremity trauma, obesity, history of VTEs, and the presence of a concomitant and poorly controlled chronic inflammatory disease such as systemic lupus erythematous or inflammatory bowel disease.

A recent publication reviewed and compared 5 published guidelines for VTE prevention in children. These guidelines

stratify patients as being at low, moderate, or high risk for hospital-acquired VTE depending on the presence of 1 or more of the previously mentioned clinical risk factors. The number of risk factors needed for each of these categories varies depending on the study. (7) Overall, for children in the low-risk category, early and frequent ambulation is the best recommended strategy for VTE prevention. For moderate-risk patients, the use of mechanical thromboprophylaxis with sequential compression devices is recommended. In high-risk groups, when there is no contraindication for anti-coagulation, pharmacologic prophylaxis, most commonly with LMWH, should be considered. (7) None of the current guidelines suggest universal VTE prophylaxis for all hospitalized pediatric patients.

The multi-institutional Children's Hospital-Acquired Thrombosis "CHAT registry" study has been recently developed to try to overcome limitations and differences in the establishment of VTE primary prophylaxis in children. The investigators' goal is to identify and provide information regarding the magnitude of the VTE risk factor attributable to different patients, diseases, and interventional factors. (39)

THROMBOLYSIS

As per the most recent American College of Chest Physicians guidelines, thrombolytic therapy is used only in the setting of a life- or limb-threatening thrombotic episode. (2) In pediatrics, thrombolysis is rarely used but has been increasingly recommended in children with complex congenital heart disease who develop abnormal hemodynamics due to venous insufficiency, surgical interventions, and lifelong-dependence on CVCs. Thrombolytic agents accelerate the breakdown of a catastrophic thrombi by catalyzing the conversion of plasminogen to plasmin, which promotes fibrinolysis. (2)

Several thrombolytic agents have been used in children, but tissue plasminogen activator is the most frequently used. Tissue plasminogen activator has a very short half-life of approximately 5 minutes and is cleared through the liver. Thrombolytic agents can be administered systemically or through a catheter-directed infusion directed toward the site of the thrombosis. Due to the associated high risk of bleeding, patients undergoing thrombolysis must be closely monitored in the ICU with frequent DUS imaging and laboratory studies in addition to close hematology follow-up. (40)

CONCLUSION

VTE has become a widely recognized problem in pediatrics, especially in the hospital setting and in children with chronic medical conditions. VTE can have both short- and long-term effects on health outcomes. Despite an increased awareness by clinicians and improvements in VTE diagnostic tools, many questions remain surrounding optimal treatment strategies and the need for thrombophilia testing in children. Current anticoagulation therapies are cumbersome for young patients and families because they require painful injections, close monitoring, medication, and diet restrictions and may pose a risk of bleeding. Although there have been numerous advancements in the field of pediatric VTE, more data and research are needed to establish universal anticoagulation management and prophylaxis guidelines and to determine the efficacy and safety of the novel DOAC agents.

Summary

- Based on multiple cohort analyses, venous thromboembolism (VTE), which encompasses both deep venous thrombosis (DVT) and pulmonary embolism, has become an increasingly recognized condition in pediatrics. (1)

- Based on several international registries, pediatric VTE occurs in a bimodal distribution, most commonly encountered in neonates and adolescents. (4)

- Based on retrospective cohort studies, the most common predisposing VTE risk factor in children is the presence of a central-access vascular catheter, either venous or arterial. (11)

- Diagnosing a VTE requires full awareness not only of potential VTE risk factors have but also of presenting signs and symptoms. (4)

- Based on observational data and clinical experience, acute DVT typically presents with unilateral pain, swelling, and/or erythema of the involved extremity. (4)

- Based on several randomized control trials, the most common imaging technique used for DVT diagnosis is Doppler ultrasonography. (15)

- Based on several randomized control trials, computed tomography angiography is the first-line technique for diagnosis of pulmonary embolism in children. (4)

- Based on retrospective and prospective registry reviews, the prevalence of at least 1 inherited

thrombophilia condition in children with a newly diagnosed VTE ranges from 13% to 79%. (20)

- Based on systematic review and meta-analysis, it is recommended that adolescent females with a history of VTE, a family history of VTE, or a family history of genetic thrombophilia who are interested in starting estrogen-based oral contraceptives be referred to a pediatric hematologist to be considered for thrombophilia testing before starting this therapy. (20)

- Based on observational studies, unfractionated heparin, low-molecular-weight heparin (LMWH), and vitamin K antagonists are first-line therapies for VTE treatment in pediatrics. (9)

- Based on case reports and observational data, the most serious complication of unfractionated heparin therapy is the development of heparin-induced thrombocytopenia. (27)

- Based on randomized control trials, LMWH has become the drug of choice for short- and long-term treatment of an acute DVT as well as for DVT prophylaxis in children. (2)(3)

- Direct oral anticoagulants have been approved for the acute treatment and prevention of VTEs in adults but are not yet officially approved for use in pediatric patients younger than 18 years. (27)

- Based on observational data and in accordance with ongoing randomized controlled trials, the duration of anticoagulation depends on both the clinical characteristics and the presence or absence of thrombosis risk factors. (2)(3)(30)

- Based on international registry review, patient age and prolonged immobility are considered the most important factors when determining the need for VTE prophylaxis. (7)

- Based on expert opinion, thrombolytic therapy is used only in the setting of a life- or limb-threatening thrombosis episode. (2)

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 2/78.

1. You are the chief quality officer for a relatively large pediatric health system that includes both inpatient and outpatient clinical services. You plan to conduct a quality improvement project to prevent venous thromboembolism (VTE) through the creation of clinical pathways, and order sets. You recommend aiming to improve VTE in the inpatient setting given its incidence. Which of the following best represents the incidence of hospital-acquired VTE in pediatrics?

    A. 25%.
    B. 10%.
    C. 1%.
    D. 0.5%.
    E. 0.01%.

2. A 13-year-old boy was brought to the emergency department by emergency medical services after being a victim of a motor vehicle accident involving a car versus a bike. The patient was riding his bike when he was struck by a car that ran a stop sign. The patient was wearing a helmet but experienced mild concussion and an opened femur fracture and significant blood loss. A central line was placed on admission. The patient received a blood transfusion in surgery. He is now admitted to the trauma unit. He is mildly sedated and receiving intravenous pain medication. Of the following factors that can potentially predispose this patient to VTE, which is the most commonly reported risk factor?

    A. Central venous catheter.
    B. Immobilization.
    C. Sedation.
    D. Surgery.
    E. Trauma.

3. A 14-year-old girl was seen in the adolescent medicine clinic 4 months earlier for dysfunctional uterine bleeding. She was started on oral contraceptive pills. Today she presents to the emergency department with a 1-day history of progressive shortness of breath. The patient reports that 24 hours earlier she started feeling tired and short of breath on walking a few steps. She also experienced chest pain with deep inspiration associated with cough. She denies any fever or upper respiratory tract infection symptoms. She has no history of asthma, but she feels difficulty in catching her breath. Family history is significant for an episode of deep venous thrombosis in her grandmother during her childbearing years. Lung examination showed decreased breath sounds diffusely. An evaluation was initiated, and she was diagnosed as having pulmonary embolus. Specific tests for thrombophilia are still pending. Which of the following is the most likely cause of inherited thrombophilia in this patient?

    A. Antithrombin III deficiency.
    B. Factor V Leiden mutation.
    C. Methylenetetrahydrofolate reductase mutation.
    D. Protein C or protein S deficiency.
    E. Prothrombin G20210A mutation.

4. You are the pediatrician for an adolescent girl with a personal and family history of lower extremity VTE. She presents to the clinic requesting a prescription for birth control pills. Which of the following is the most appropriate management plan to meet the family planning need in this patient?

    A. Avoid oral contraceptives and undergo evaluation by a gynecologist for placement of a progesterone-containing intrauterine device.
    B. Evaluation by a pediatric hematologist before starting oral contraceptives.
    C. Prescribe combination birth control pills as long as she does not play competitive sports.
    D. Prescribe enoxaparin prophylactically along with a combination oral contraceptive.
    E. Prescribe progesterone-only birth control pills.

5. A critically ill overweight 17-year-old girl was admitted 3 weeks ago to the ICU with severe respiratory failure due to complicated pneumonia. She has been intubated and mechanically ventilated since admission and is in the process of weaning slowly off the ventilator. The patient was diagnosed as having VTE. She is started on unfractionated heparin. You explain to the residents caring for the patient that compared with enoxaparin, unfractionated heparin has which of the following advantages?

    A. Easier to maintain target anti–factor Xa levels.
    B. Excreted by the kidneys.
    C. Has a smaller volume of distribution.
    D. Has a very short half-life.
    E. Less likely to provoke heparin-induced thrombocytopenia.

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