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Current and future management of pediatric venous thromboembolism

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Abstract

Venous thromboembolism (VTE) is an increasingly common complication encountered in tertiary care pediatric settings. The purpose of this review is to summarize the epidemiology, current and emerging pharmacotherapeutic options, and management of this disease. Over 70% of VTE occur in children with chronic diseases. Although they are seen in children of all ages, adolescents are at greatest risk. Pediatric VTE is associated with an increased risk of in-hospital mortality; recurrent VTE and post-thrombotic syndrome are commonly seen in survivors. In recent years, anticoagulation with low molecular weight heparin has emerged as the mainstay of therapy, but compliance is limited by its onerous subcutaneous administration route. New anticoagulants either already approved for use in adults or in the pipeline offer the possibility of improved dose stability and oral routes of administration. Current recommended anticoagulation course durations are derived from very limited case series and cohort data, or extrapolations from adult literature. However, the pathophysiologic underpinnings of pediatric VTE are dissimilar from those seen in adults and are often variable within groups of pediatric patients. Clinical studies and trials in pediatric VTE are underway which will hopefully improve the quality of evidence from which therapeutic guidelines are derived.

Introduction

Over the last 2 decades pediatric venous thromboembolism (VTE) has become an increasingly important endemic complication in pediatric tertiary care settings. Epidemiologic analysis of both the Kids' Inpatient Database (KID) and the Pediatric Health Information System (PHIS) demonstrate that pediatric VTE is an increasingly common complication amongst hospitalized children, now occurring in 42–58/10,000 admissions [1,2]; representing roughly a 10-fold increase over the original Canadian estimates from the early 1990s [3]. Further analysis of the KID has demonstrated that the majority of VTE occur in the tertiary care, children's hospital setting (40.2/10,000 admissions vs. 7.9/10,000 community hospital admissions; $P < 0.00001$) [4]. The population prevalence of VTE amongst children in the US has recently been estimated at 0.6–1.1 per 10,000 [5]. General population data from Denmark reveals that the population incidence is relatively stable

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(statistically, but with an upward trend) over the 1994–2006 time frame [6]. Thus, the dramatic rise in incidence appears to be isolated to children hospitalized in the tertiary care setting; bolstering the postulate amongst pediatric VTE experts that the increasing incidence is related to advances in tertiary healthcare, which result in improved survival of critically ill children at the cost of VTE [7,8]. There are at least three possible explanations for the dramatic rise in the incidence of VTE in tertiary care pediatrics [2,8]. First, in previous eras, these children may have died from their underlying medical condition before developing VTE. Second, they may be developing VTE as a direct consequence of more intense medical interventions that in some way disrupt their vascular and/or hemostatic health (e.g., central venous access devices). Alternatively, the increase could be secondary to increased awareness and recognition. A combination of these possibilities should not be disregarded. Environmental influences, such as obesity, are less likely to be responsible since the population incidence appears to be stable.

Pediatric VTE has a significant impact on both acute and chronic health outcomes. Acutely, VTE is associated with an estimated 2–6 fold increased risk of in-hospital death [2–4]. Chronically, there are two major consequences of VTE: recurrence and post-thrombotic syndrome (PTS). The risk for recurrent VTE in children is estimated at 5–10% but may be higher for those children with one or more ongoing VTE risk factors (e.g., central venous access devices, chronic disease, thrombophilia, etc.) [9–11]. PTS is the manifestation of chronic venous insufficiency resulting from venous damage due to VTE. Symptoms may include varicosity, chronic edema, pain, and venous ulcers and may range from minor cosmetic problems to major symptoms that limit activities of daily living. The incidence of clinically significant childhood PTS is estimated at about 10% [10]. The adjusted mean expenditures related to the care for these children has recently been estimated to range from $87,000 to $105,000 in 2009 US dollars [5]. Costs for care of secondary VTE (those associated with a chronic illness), were nearly five times higher (mean: $95,120) than were the costs associated with an idiopathic VTE (mean: $20,238). However, much of the expenditure associated with secondary VTE may be attributable to care for the underlying condition. Thus, the estimated healthcare costs directly attributable to a pediatric VTE episode are around $20,000. In the 2006 KID, over 4,500 episodes of pediatric VTE occurred in a 38 state sample of US pediatric hospital discharges [4], we can therefore conservatively estimate that the annual healthcare costs of pediatric VTE in the US are over $90 million.

Currently, recommended therapeutic regimens for pediatric VTE are largely based upon case series and cohort studies, and are otherwise extrapolated from adult VTE data [8,12,13]. Adequately powered interventional trials for pediatric VTE have been hampered by the rarity of both the disease and its complications, which make large, multicenter studies a necessity; as well as the prolonged follow-up period required to measure the outcomes of interest (PTS and recurrence). These issues are compounded by the multifactorial nature of pediatric VTE. Pediatric VTE is associated with a number of chronic, underlying disorders which may each be associated with unique prothrombotic physiology [4]. Thus, even when interventional trials are undertaken a large number of potential confounding variables will need to be considered and generalizability will remain limited.

This review will examine currently available pharmacotherapeutic options and new anticoagulant agents in various stages of pediatric clinical development. Appropriate duration of therapy for common pediatric VTE scenarios will also be discussed. As part of the American College of Chest Physicians task force on anticoagulant therapy, an expert panel on pediatric thrombosis is convened every few years to review the literature and update pediatric guidelines for antithrombotic therapy [13]. This review is intended as an interim update to those guidelines, including a summary of ongoing research in the field.

Pediatric VTE Pharmacotherapeutic Agents

The mainstays of anticoagulant therapy for children are unfractionated heparin, low molecular weight heparin, and warfarin. Each of these agents comes with advantages and disadvantages which dictate the choice of regimen. Several new compounds in the pipeline may overcome some of these issues providing improved safety and efficacy (Table I).

Unfractionated heparin

Unfractionated heparin (UFH) is, perhaps, the most widely utilized anticoagulant in children; ~15% of hospitalized children are exposed to UFH [14]. However, low molecular weight heparin is likely the most commonly used agent for treatment of VTE [1]. UFH has a short half-life and is readily reversible with protamine sulfate [13], making it the anticoagulant of choice for those children with VTE who are at high risk for bleeding complications or who may need urgent procedural intervention. The pharmacokinetics of UFH varies with age, due to developmental changes in coagulation factor activities, volume of distribution, and clearance rates [13,15]. Infants have a prolonged activated partial thromboplastin time (aPTT) at baseline due to developmental hemostatic differences from adults and older children [15,16]. Therefore, aPTT therapeutic ranges developed using adult normal pooled plasma are not relevant to pediatric anticoagulant therapy. Doses should be adjusted to reach therapeutic antifactor Xa levels, which can then be correlated with an aPTT range, if desired [13]. Disadvantages of UFH use in children include frequent therapeutic drug monitoring contributing to iatrogenic blood loss, the need for ongoing intravenous access, as well as a prolongation of the interval from starting therapy to achieving therapeutic levels and less time spent in the therapeutic window compared with low molecular weight heparin [17,18]. Although rare in pediatrics, heparin-induced thrombocytopenia/thrombosis (HIT/T) is more likely with UFH than with low molecular weight heparin [14,19,20].

Low molecular weight heparins

Enoxaparin is probably the most commonly utilized low molecular weight heparin (LMWH) compound in the US. Other LMWH compounds reported in the pediatric literature include reviparin (not available in the US), dalteparin, and tinzaparin. For inpatient pediatric VTE, enoxaparin use has increased over the past several years in-parallel to the increasing incidence of VTE [1]. Although the pharmacokinetics of enoxaparin is more predictable than UFH, they are not as predictable as in adults [13,21]. Thus, therapeutic drug monitoring is recommended in pediatrics utilizing the antifactor Xa assay [13]. The initial dose should be adjusted for age, neonates and infants may require doses as high as 3 mg/kg/dose while older children are generally therapeutic at 1 mg/kg/dose [21]. Other LMWH advantages include less frequent monitoring and a lower risk of osteoporosis compared with UFH [22,23]. HIT/T complicating LMWH therapy in children has been reported [24]. Subcutaneous administration can be both an advantage and disadvantage: while the lack of need for intravenous access can ease outpatient administration [15], the twice daily dosing regimens may interfere with adequate compliance and decrease quality of life, especially amongst younger children [25].

Vitamin K antagonists

Warfarin is the only vitamin K antagonist (VKA) available for clinical use in the US, and is thus the most commonly utilized VKA for pediatric VTE. Children are subject to the same dose instability issues as adults when treated with VKAs; however, the impact of pharmacogenomics (e.g., *CYP2C9*, *VKORC1*) on pediatric dose requirements has not been fully elucidated [26,27]. Two recent cohort studies have revealed conflicting information with one suggesting that genomics play a very minor role in dose variation [27], while the

other suggests that a large proportion of dose variability is explained [26]. The utility of pharmacogenomic warfarin dosing in the pediatric population is the subject of an ongoing NICHD-sponsored project [28]. Warfarin management is particularly complicated in infants due to dietary considerations (breast milk is low in vitamin K, whereas commercial formulas and pediatric parenteral nutrition are typically vitamin K fortified) [29]. As with adults, frequent medication changes and dose adjustments alter the p450 metabolism of warfarin. Frequent intercurrent illnesses may further impair dose stability. Therefore, most pediatric experts recommend against the use of VKA in children less than 1 year of age [30]. Although, VKA likely carry a lesser risk of osteoporosis, there is some data suggesting that bone density may be impaired with long-term VKA use [31]. Oral administration is an obvious advantage, but is somewhat diminished by the need for frequent therapeutic drug monitoring. Children often reside at a distance from their tertiary care treatment facility and, although effective [32], obtaining insurance approval for point-of-care testing is arduous and usually denied.

Recombinant tissue-type plasminogen activator

Recently, retrospective and prospective data from two small cohorts suggests that aggressive treatment with thrombolysis of carefully selected “high risk” pediatric VTE patients may decrease the incidence of subsequent PTS [33,34]. Whether thrombolysis or other novel therapeutic approaches will demonstrate improvement in PTS, recurrent VTE, or mortality after large, prospective randomized controlled trials are conducted remains to be determined. Thus, thrombolytic therapy is currently only recommended for life or limb-threatening VTE, with the goal of rapid thrombus resolution to enhance the probability of survival or limb-salvage [13]. However, actual practice varies widely and appears to correlate with institutional experience [35]. These goals must be balanced against the risks of life-threatening bleeding caused by the use of thrombolytic agents, and thus, should be administered under the supervision of a hematologist experienced with their use. Recombinant tissue-type plasminogen activator has emerged as the thrombolytic agent of choice for pediatric patients [35].

New anticoagulant agents

Pentasaccharides

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa in an antithrombin dependent manner [36]. A recent study has demonstrated that once daily dosing is feasible for children [37], a significant advantage over the twice daily dosing required with the LMWH compounds [25,38,39]. Additionally, there are data suggesting that fondaparinux may cause less or even no osteoporosis [22,40,41]. Pediatric dosages have not been added to the US labeling.

Direct thrombin inhibitors

Argatroban is a small molecule direct (antithrombin independent) inhibitor of thrombin that binds reversibly to the enzymatically active site. Recently, detailed pharmacokinetic (PK) and pharmacodynamic (PD) data has been generated for children resulting in pediatric dosage information being added to the Food and Drug Administration approved labeling, the first anticoagulant to gain pediatric specific labeling in the US [42,43]. Children with hepatic impairment had approximately 80% lower clearance, which requires adjustment of the starting dose [42,44].

Bivalirudin is a synthetic oligopeptide analog of the naturally occurring leech venom component, hirudin [45]. Similar to argatroban, bivalirudin is a selective, reversible direct thrombin inhibitor. Recent pediatric investigations have begun to define the dose and safety

profile of bivalirudin for neonatal VTE [46] as well as its efficacy in pediatric interventional cardiology [47]. An additional Phase I study investigating the safety and efficacy of bivalirudin in children up to age 18 has recently completed accrual [48]. Both argatroban and bivalirudin require intravenous continuous infusions, similar to standard heparin, with intensive therapeutic monitoring. Pediatric specific dosing has not yet been added to the bivalirudin labeling in the US.

Dabigatran etexilate is an orally available direct thrombin inhibitor recently approved in the US for nonvalvular atrial fibrillation. In Canada it is also labeled for postarthroplasty thromboprophylaxis. The manufacturer currently has two pediatric Phase II trials open to study the safety and PK/PD of the capsule in adolescents and an oral solution in children <12 years old [49,50], neither study is open at a US site.

Thrombin is a multifunctional enzyme that has important signaling properties in a variety of cell types through protease activated – G-protein coupled receptors [51,52]. Recent evidence suggests that thrombin inhibition may paradoxically increase total thrombin production via interruption of the thrombomodulin-protein C negative feedback loop [53,54]. Thus, although these compounds may be potent anticoagulants, they may eventually prove to have undesirable consequences. For example, rebound thrombin generation has been reported after discontinuation of the lessfactor Xa specific heparin compounds [55] and slight increases in the incidence of cardiovascular events were seen on-therapy in both the dabigatran trials [54,56,57]. The potential consequences of increased thrombin signaling in the pediatric population are not known.

Direct factor Xa inhibitors

In contrast to thrombin inhibitors, factor Xa inhibitors reduce total thrombin generated, thus factor Xa may be a more desirable anticoagulant target [55]. Rivaroxaban is the first to market (in US), orally available, small molecule inhibitor of factor Xa [58]. It binds reversibly to both free factor Xa and factor Xa that is incorporated in to the prothrombinase complex. It is approved in the US for postarthroplasty thrombophrophylaxis and for nonvalvular atrial fibrillation. The manufacturer currently is investigating pediatric PK/PD in a Phase I study [59]. Similar to rivaroxaban, apixaban is an orally available direct factor Xa inhibitor, approved in the European market for postarthroplasty thromboprophylaxis. In the US, adult trials are recently completed or enrolling patients and a Phase I PK/PD trial for children with central venous catheters is currently enrolling patients [60–62].

One major concern regarding these new agents is the lack of validated monitoring assays [63]. This is of particular relevance to the pediatric community because, as discussed above, developmental differences in coagulation factor levels and/or hepatic or renal clearance rates may vary in children, necessitating dose adjustment based upon age or developmental stage [13,15]. Similarly, the development of effective antidotes for these compounds is lagging behind clinical development of the agents [64]. The latter is of significant concern to the treatment of the acutely bleeding, overdosed patient or the patient who requires emergent surgical intervention while fully anticoagulated.

Although pediatric VTE is an increasingly common occurrence in tertiary care children's hospitals, it remains a relatively rare disease, confounding efforts to perform prospective studies and randomized, controlled therapeutic trials (RCT) [65]. Thus, only one RCT has been conducted (REVIVE; REVIparin in Venous ThromboEmbolism), but was closed early due to slow recruitment [66]. This study randomized pediatric VTE patients to either LMWH or UFH followed by VKA therapy for a total treatment course of 3 months on either arm. The study was underpowered, but did reveal trends toward reduced VTE recurrence and fewer bleeding complications for the LMWH group. Consequently, the majority of

pediatric VTE therapy recommendations are extrapolated from adult RCT data and from limited numbers of pediatric case series and cohort studies [13]. However, the results from this one underpowered pediatric RCT may be contributing to the increased use of LMWH and slight decrease in VKA use seen in the PHIS analysis [1].

Pediatric VTE Treatment Duration

Similarly to choice of anticoagulant agents, RCT investigating varying durations of therapy for specific clinical scenarios are limited or nonexistent. Current treatment course recommendations are derived from case series and otherwise extrapolated from adult data (Table II) [13].

Central venous access device related VTE vs. other VTE

Central venous access devices (CVAD) are the most common risk factor for VTE in children, being associated with over 50% of thrombi [7,67]. Unfortunately, although CVAD are an iatrogenic risk factor for VTE, they are a necessary evil for the management of children with acute, critical illness and for the administration of dialysis, chemotherapy, long-term antibiotic therapy, or parenteral nutrition. CVAD-associated VTE is often heralded by catheter dysfunction and/or infection, but may often be clinically silent. Current recommendations for CVAD-associated VTE include initial anticoagulation with UFH or LMWH [13]. If the catheter is no longer required and/or nonfunctional, removal may be considered, but many experts recommend delaying removal until after 3–5 days of anticoagulation to guard against paradoxical embolism [13,68]. Anticoagulation may then be continued with LMWH or VKA for 3 months, followed by thromboprophylactic doses for children with continued CVAD requirement [13]. The relative importance of detecting and treating occult, subclinical CVAD-related VTE in children with cancer is the subject of an ongoing NHLBI-sponsored clinical trial [69–71], retrospective data suggest that clinically significant PTS can result from these asymptomatic VTE [72].

The incidence of VTE amongst critically ill neonates (<28 days old) is estimated to be 22–60 per 10,000 admissions [1,4,73]. Similar to the overall pediatric population, the incidence of VTE in this age group appears to be on the rise [1]. Furthermore, 89–94% of neonatal VTE are CVAD-associated events [73,74]. Therefore, the considerations for management of neonatal VTE are similar to those above, with the added special considerations for neonatal specific bleeding risks (e.g., intraventricular hemorrhage, necrotizing etc.) [13]. However, an abbreviated anticoagulation course of only 6 weeks may suffice in this age group, especially if the CVAD can be removed [13].

Secondary VTE vs. idiopathic VTE

Over 70% of children with VTE have an underlying chronic medical condition [1,4]. Many of the remaining children have transient illness-related VTE risk factors such as infection, trauma, or surgery [4]. For children with a transient underlying illness, anticoagulation for a 3-month period is often adequate [13]; however, for the majority of children who have a chronic underlying disease process with ongoing thrombotic risk, continued thromboprophylaxis may be beneficial until such time as the disease process is controlled or resolved [13]. In comparison, true idiopathic VTE in the pediatric age group is relatively rare. A recent large epidemiologic analysis estimated that only 12.6% of pediatric VTE are idiopathic [4], but this is probably an overestimate because medication data were not available for the cohort and thus, contraceptive-related VTE were included in the idiopathic category [75]. Nonetheless, because these children are more likely to have a genetic or anatomic predisposition to thrombosis, longer courses of anticoagulation (up to 6 months) are recommended for idiopathic VTE [13].

Recurrent VTE

Recent data from the PHIS study suggest that ~14% of children develop recurrent VTE, with the likelihood of recurrence being greatest in adolescents (~19%) [1]. Children with recurrent disease were also more likely to have a chronic underlying health condition—further justifying the recommendation that long-term thromboprophylaxis be considered for children with secondary VTE who have an ongoing chronic disease process [1,13]. How ever, for those who have had a second or subsequent VTE event, indefinite duration anticoagulation at full therapeutic dose levels is currently recommended [13]. Because of the lesser likelihood of osteoporosis associated with long-term warfarin therapy and the unknown consequences of longterm LMWH use, VKA are currently preferred for indefinite duration therapeutic anticoagulation [13], for those children who will tolerate VKA and are able to be compliant.

Antiphospholipid syndrome associated VTE

Nonpathologic lupus anticoagulants are not uncommon in children [76,77]. However, pathologic antiphospholipid antibodies can contribute to pediatric VTE [78]. Thus, children with VTE should be carefully evaluated prior to making a diagnosis of antiphospholipid syndrome (APS), ensuring that they meet accepted diagnostic criteria [79]. Unfortunately restricting pediatric VTE patients to the subpopulation with APS further prohibits clinical study feasibility, thus it is not surprising that no pediatric trials have been conducted for this disease. Therefore, current consensus guidelines are to treat these patients similarly to non-APS pediatric VTE (above), with the recognition that adult guidelines for indefinite duration anticoagulation may be appropriate for adolescents [13,80,81]. It is not clear whether pediatric APS patients would benefit from long-term, indefinite anticoagulation as is recommended for adult APS patients. We also do not know whether continuation of anticoagulation after antibody titers have reverted to undetectable levels is necessary in either population.

Other considerations

Several other features should be considered when tailoring anticoagulant regimens for pediatric VTE. Although universal thrombophilia screening of all pediatric VTE patients remains controversial [82], there is emerging evidence that children with multitrait thrombophilia have an increased likelihood of recurrent VTE [9,11]. Recurrent VTE is associated with the same morbidity and mortality risks associated with first VTE with the added risk for development of chronic thromboembolic pulmonary hypertension [83,84]. There is no prospective clinical trial data demonstrating that chronic anticoagulation for children with multitrait thrombophilia would be clinically beneficial.

Retrospective data from the Colorado cohort demonstrates that children with elevated Factor VIII or D-dimer at VTE presentation may be at elevated risk for persistent VTE, recurrent VTE, and PTS [85]. Evaluating whether children without these features, who are at “low-risk,” can be adequately treated with an abbreviated anticoagulation course of only 6 weeks is the subject of the NHLBI-sponsored Kids-DOTT trial, currently open at multiple US child ren's hospitals [86,87]. In this study, patients who lack elevated D-dimer, factor VIII, multitrait thrombophilia, or APS will be biologically randomized to the abbreviated course, while children with “high-risk” features or in whom recanalization does not occur at the end of the 6-week course will receive standard duration (3 month) therapy. Both groups will be followed for 2 years with serial evaluations for recurrent thrombosis and/or PTS symptoms.

An important emerging consideration for both the treatment and prevention of pediatric VTE comes from the recent breakthroughs in epidemiologic study of the disease. The development of large claims and healthcare utilization databases, such as KID, PHIS,

Medicaid databases, and private insurance claims data have allowed investigators to overcome the problem of limited access to large numbers of patients [1,4,5,88]. While these data give us a much needed “bird's eye” view of the pediatric VTE problem as a whole, they also demonstrate that pediatric VTE is better described as a complication than a disease in and of itself. As discussed above, the majority of children with VTE have an underlying chronic health condition. Furthermore, the hypercoagulopathic physiology of these diseases are not identical. For instance, the hemostatic derangements of single ventricle congenital heart disease are broad and may get worse following corrective surgical procedures [89], with continued VTE risk [90]. In contrast, the coagulopathy associated with asparaginase chemotherapy is less broad with the defects being primarily in fibrinogen and antithrombin deficiencies [91], both of which improve within days after completion of therapy [92]. Furthermore, the VTE risk in childhood cancer exists with other, asparaginase-insensitive, malignancies—most notably sarcomas [93,94], which may be related to tumor tissue factor expression [95,96]. Nephrotic syndrome is amongst the most common glomerular diseases in children, carries a substantial risk of VTE [97], and has very complex hemostatic derangements which are reversible when the disease is in remission [98], yet are different from the hemostatic derangements seen in single ventricle heart disease. Thus, it is naïve to assume that a “one size fits all” approach to pediatric VTE management will suffice. Chronic disease specific therapeutic trials may eventually be needed to determine the best-tailored treatment regimens. Unfortunately, this approach would further complicate the conduct of appropriately powered clinical trials [65]. For the time being, the clinical team needs to remain cognizant of the underlying disease pathophysiology and disease status, individualizing therapy after consultation with the appropriate subspecialist caring for the child's underlying disease process.

Pediatric VTE Clinical Trial Design

Because of the many limitations associated with the study of a rare pediatric disease process [65], innovative strategies are needed to enhance feasibility. The obvious methods of multicenter, collaborative efforts should always be employed whenever feasible to maximize enrollment. Novel study design and statistical techniques such as decision analysis [99], existing database integration [88], and propensity scoring [100,101], should be considered to reduce the necessary sample size, while maintaining statistical power. Currently, most pediatric VTE studies have been powered to detect recurrent VTE and/or PTS, the most common morbidities (see Introduction). Recently, the Perinatal and Paediatric Haemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommended the adaptation of composite primary end-points including recurrence and VTE-related mortality [102]. Secondary outcome variables include the individual components of the primary composite and PTS. Fortunately, mortality is too infrequent to adequately power a standard multivariate logistic regression analysis as a single outcome. Unfortunately (for study design), recurrent VTE and PTS require long-term post-treatment follow-up because they take time to develop, which requires added cost for additional study visits, assays, and procedures. Thus, novel outcome variables that are readily measured in the short-term should be considered. For CVAD-associated VTE, these may include CVAD-associated bacteremia, recurrent catheter dysfunction, or necessity for CVAD replacement [70]. Recent, retrospective data, suggest that CVAD-associated VTE that occurs in the intensive care unit (ICU) may be associated with fewer ICU-free and ventilator-free days [103]. If these variables are confirmed in prospective analysis, these would be useful, easy to measure, short-term outcome variables for children who develop VTE during an ICU admission.

Long-Term Follow-Up for Pediatric VTE

Because the major morbidities of concern, recurrent VTE and PTS, both require time to develop, continued close clinical follow-up after completion of planned anticoagulant therapy is important. All patients and their caregivers should be advised of the signs and symptoms of recurrent VTE and encouraged to contact the hematology clinic promptly when these develop. This allows for prompt diagnostic evaluation and institution of therapy, hopefully prior to the development of life-threatening thromboembolic complications. At follow-up visits the history and physical should focus on any past or present evidence of recurrent VTE. Clinical scoring systems for the diagnosis of PTS have recently been validated for use in children [34,104]. These should be administered at each follow-up visit and the patient and caregivers instructed as to the signs and symptoms of PTS. Adult PTS prevention data suggest that elastic compression stocking (ECS) use during the first 24 months following VTE may decrease the incidence and/or severity of PTS [105]. There are limited pediatric data regarding the effect of ECS on PTS [106]; however, ECS use comes without known adverse consequences, so their empiric use seems justifiable. In our clinic, we typically follow children with VTE for a minimum of two years following the completion of anticoagulation therapy.

Summary

Pediatric VTE is an increasingly common complication in tertiary care pediatrics and is associated with significant morbidity and mortality. Unfortunately, there is a paucity of strong scientific evidence to guide the management of this disease. Recent efforts have focused on improved understanding of pediatric VTE epidemiology utilizing secondary analysis of powerful large databases and designing multicenter, focused clinical trials that will, hopefully, set the stage for additional, broader trials. Much work is needed to better understand the prothrombotic physiology of the underlying diseases and thus, what the best treatment strategies and which hemostasis-specific therapeutic targets are most appropriate. New anticoagulant agents which may have more predictable and stable PK/PD and require less intensive monitoring need to be developed for use in children to improve compliance, efficacy, and safety.

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Table I

Properties of Current and Future Anticoagulants for Children

Compound	Route of Administration	Starting Dose	Monitoring	Half-life	Antidote	Pediatric Labeling (in US)
Currently utilized anticoagulants						
Unfractionated Heparin	Intravenous	Loading: 75–100 units/kg Maintenance: Neonates: 28 units/kg/hr Children: 18–20 units/kg/hr	Antifactor Xa activity: 0.3-0.6 units/mL aPTT: adjusted to 60–85 sec	~90 min*	Protamine Sulfate	No
Enoxaparin	Subcutaneous	1-3 mg/kg/dose every 12 hr	Antifactor Xa activity: 0.5-1 units/mL	~4.5 hr*	Protamine Sulfate(partial reversal)	No
Warfarin	Oral	Loading: 0.2 mg/kg Maintenance: ~0.1 mg/kg	INR: 2–3	20-60 hr*	Vitamin K; FFP	No
Pentasaccharide (antithrombin dependent factor Xa inhibitor)						
Fondaparinux	Subcutaneous	0.1 mg/kg daily	Antifactor Xa activity?: NE	17–21 hr*	NE	No
Direct thrombin inhibitors						
Argatroban	Intravenous	0.75 mcg/kg/min(adjust for hepatic impairment)	aPTT: 1.5-3 times baseline	39–51 min	NE	Yes
Bivalirudin	Intravenous	NE	NE	15-18 min*	NE	No
Dabigatran etexilate	Oral	NE	NE	12–17 hr*	NE	No
Direct factor Xa inhibitors						
Rivaroxaban	Oral	NE	NE	5–9 hr*	NE	No
Apixaban	Oral	NE	NE	9–14 hr*	NE	No

NE, not established.

*Based on data from adults.

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Table II

Recommended Duration of Anticoagulant Therapy for Common Pediatric VTE Scenarios

VTE scenario	Therapeutic anticoagulation	Convalescent
CVAD-associated VTE	LMWH or VKA: 3 months	Thromboprophylaxis until catheter removed
Secondary VTE	LMWH or VKA: 3 months	Thromboprophylaxis until primary illness resolved
Idiopathic VTE	LMWH or VKA: 6 months	–
Recurrent VTE	VKA: Indefinite	–
Antiphospholipid syndrome	LMWH or VKA: 3 months	Consider Indefinite Therapy