Management of thrombosis in children and neonates: practical use of anticoagulants in children

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Venous thrombosis (VTE) in children and neonates presents numerous management challenges. Although increasing in frequency, VTE in children and neonates is still uncommon compared with adults. The epidemiology of VTE is vastly different in neonates vs children vs adolescents vs adults. In reality, pediatric thrombosis should be viewed as a multitude of rare diseases (eg, renal vein thrombosis, spontaneous thrombosis, catheter-related thrombosis, cerebral sinovenous thrombosis), all requiring different approaches to diagnosis and with different short- and long-term consequences, but linked by the use of common therapeutic agents. Further, children have fundamentally different physiology in terms of blood flow, developmental hemostasis, and, likely, endothelial function. *The American Society of Hematology 2017 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric VTE* provides up-to-date evidence-based guidelines related to treatment. Therefore, this article will focus on the practical use of therapeutic agents in the management of pediatric VTE, especially unfractionated heparin, low-molecular-weight heparin, and oral vitamin K antagonists, as the most common anticoagulants used in children. Direct oral anticoagulants (DOACs) remain in clinical trials in children and should not be used outside of formal trials for the foreseeable future.

Learning Objectives

- Understand the basic epidemiology of VTE in children and neonates
- Understand the extent of extrapolation from adult data related to use of anticoagulants, including into the design for current trials of DOACs in children
- Understand the evidence supporting the currently recommended use of unfractionated heparin, low-molecular-weight heparin, and warfarin in children

Introduction

Pediatric venous thromboembolism (VTE) is considered a severe problem because of the potential for associated mortality and significant complications, including pulmonary embolism, cerebrovascular events, and postthrombotic syndrome (PTS).[1,2] VTE occurs when ≥1 component of Virchow's triad is activated: stasis of blood flow, injury to the endothelial lining, and hypercoagulability of blood components. This is the most useful pathophysiological construct for thinking about thromboembolism in children.[3]

The incidence of VTE in children at a population level is very low, reported to be 0.07 to 0.14 per 10 000 children.[4-6] However, in hospitalized children, the rate is increased 100- to 1000-fold, to ≥58 per 10 000 admissions.[7] Thus, despite some exceptions, VTE should be considered a disease of sick children. The most common age groups for VTE are neonates and teenagers, and this reflects the pattern of associated underlying diseases and interventions. More than 90% of pediatric patients with VTE have >1 risk factor, with central venous access devices (CVADs) being the most common single risk factor, accounting for >90% of neonatal VTE and >50% of pediatric VTE.[4,8] Although rare, spontaneous thrombosis in previously well children can often present the most challenging treatment dilemmas, especially in terms of determining optimal treatment duration.

Pediatric VTE includes a wide range of VTE with differing underlying pathophysiology, requiring different diagnostic imaging modalities and with potential for differing acute and chronic complications, based on anatomic location. For example, neonatal renal vein thrombosis, the most common spontaneous thrombosis in neonates, has a specific pathophysiology and specific acute and chronic complications that are totally different from that of cerebral sinovenous thrombosis, which, in turn, are totally different from CVAD-related VTE or pulmonary embolus. Even CVAD-related VTE has different short- and long-term consequences, depending on the presence or absence of right-to-left shunting in the child and the underlying cardiac anatomy. Thus, although VTE in neonates and children is often spoken about as a single entity, perhaps a better construct would be to consider each anatomical site of VTE as an individual "rare disease" (which is borne out by considering the numbers published related to each individual entity) that is merely linked by the use of common therapies in its treatment. However, the reality is that the

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Off-label drug use: UFH, LMWH, and VKA are off label in children.

risk-benefit ratio of the common treatment (ie, anticoagulation) also varies according to the site and type of VTE.

The natural history of VTE in children remains unclear in many circumstances. The reported direct VTE mortality from registry data is ~3%, in the context of ~16% of children with VTE instead dying from their underlying illness.[4] The recurrence risk is reported to be up to 10% to 15%. Reports of PTS vary from 10% to 60%, depending on the tools used for its assessment, and there remains great controversy about the clinical implications of PTS in many children.[9]

There are no anticoagulant drugs approved for use in children, with very little specific research in children. Much of the evidence for treatment is inferred from adult practice, despite the major differences between adults and children in the epidemiology and pathophysiology of thrombosis, the physiology of the coagulation system, and the impact of this on the pharmacology of antithrombotic agents.[10]

In fact, the current multitude of industry-sponsored phase 3 studies of direct oral anticoagulants (DOACs) extrapolate efficacy from adult data (rivaroxaban NCT02234843, apixaban NCT02464969, dabigatran NCT02197416). This is for a variety of reasons. First, good efficacy estimates in this population of standard of care anticoagulation vs placebo or even no treatment are unknown, because no such trials have been performed. Second, the heterogeneity of the population and the clinical entities involved makes estimation of baseline data from observational studies extremely difficult. Third, a properly powered study would likely require several thousands of children, which seems impossible because of the low incidence of venous thrombosis in childhood. We must remember that no completed randomized controlled trial (RCT) of an anticoagulant treatment in children has ever enrolled >200 children, and all completed trials closed early due to slow recruitment.[11] The Kids-DOTT study comparing duration of anticoagulation in children is ongoing and has enrolled >300 children, but it has been running for >10 years.[12] To allow extrapolation of efficacy and safety data from adults, the studies are designed such that the plasma exposure/concentration in the children matches the plasma exposure/concentration of the drug achieved in the adult trails. This assumes that children require the same exposure for effective therapy. The studies assume that the clinical course (ie, incidences of symptomatic recurrent VTE, major bleeding, and mortality) of VTE is similar in children and adults, which may or may not be true given the heterogeneity of the disease in children. Finally, the studies assume that the response to the therapy compared with standard-of-care anticoagulation should be similar in children and adults. This method of designing trials in children, which extrapolate efficacy based on these conditions, is frequently supported by regulators, such as the US Food and Drug Administration.[13] Although the DOAC studies will undoubtedly give us much useful information (arguably more information than exists for the currently used anticoagulants), we must remember the assumptions on which they are based.

The American Society of Hematology 2017 Guidelines for Management of Venous Thromboembolism: Treatment of Pediatric VTE[14] provides up-to-date evidence-based guidelines related to treatment. There are 3 main anticoagulant drugs used in neonates and children, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and oral vitamin K antagonists (VKAs), and they each have advantages and disadvantages.[15] Fondaparinux is used in some centers, but its use is not widespread internationally. This article will summarize the current literature related to these 3 most common pharmacological agents used in the management of VTE in neonates and children, highlighting what we know and where further research is required.

UFH

UFH remains a commonly used anticoagulant in pediatric patients. UFH has the advantage of a short half-life and rapid onset and offset of action, making it ideal for cardiopulmonary bypass, circuit prophylaxis, procedural prophylaxis (eg, cardiac catheterization), and for maintaining vascular access patency. In tertiary pediatric hospitals, ~15% of in-patients are exposed to UFH each day.[10] Indeed, much of our clinical experience with UFH comes from these other indications, rather than being specific to VTE management. However, the features of rapid onset/offset and reversibility make it an ideal agent for managing VTE in patients with perceived high bleeding risk, such as postoperative patients or patients in whom other interventions, such as surgery or even thrombolysis, are potentially required over the coming days. Heparin-induced thrombocytopenia, for reasons that remain unclear, seems to occur rarely in children, making heparin a very useful agent in hospitalized children.[10]

Despite this, a search of Embase, Medline, and PubMed from 2007 to 2017 (limited to English, but including cohort, cross-sectional, longitudinal, retrospective, or prospective studies, as well as RCT and systematic reviews, in neonates to adolescents) revealed only 14 original studies and 1 systematic review specifically describing UFH use in children. The only RCT was in cardiac angiography.[16]

There are a number of specific factors that may alter the effect of UFH in children compared with adults (Table 1). The clinical implications of these changes on dosing, monitoring, and the effectiveness:safety profile of UFH in children remain uncertain.

There have been no reported clinical outcome studies to determine the target therapeutic range (TTR) for UFH in neonates or children, so the TTR for all indications is inferred from those used in VTE therapy in adults. This equates to an activated partial thromboplastin time (APTT) that reflects a heparin level by protamine titration of 0.2 to 0.4 U/mL or an anti-factor Xa level of 0.35 to 0.7 U/mL. There are multiple reasons why this extrapolation might be invalid; however, the safety and efficacy of this approach, in experienced hands, seem reasonable.

Bolus doses of 75 to 100 U/kg result in therapeutic APTT values in 90% of children at 4 to 6 hours postbolus. However, boluses of 75 to 100 U/kg in children have recently been shown to result in excessive prolongation of APTT for >100 minutes, implying that the

Table 1. Factors in children that affect the action of UFH

UFH factor	Age-related difference
UFH acts via antithrombin-mediated catabolism of thrombin and factor Xa	Reduced levels of antithrombin and prothrombin
	Reduced capacity to generate thrombin
	Age related difference in anti–factor Xa/anti–factor IIa activity of UFH
UFH is bound to plasma proteins, which limits free active UFH	Alterations in plasma binding
Endothelial release of TFPI	Age-related differences in amount of TFPI release for same amount of UFH

Table 2. Nomogram for managing heparin infusion according to monitoring of APTT or anti–factor Xa levels

APTT (s)	Anti–factor Xa level (IU/mL)*	Bolus (U/kg)	Hold (min)	Rate change (%)
<50	<0.1	50	—	↑ 20
50-59	0.1-0.34	—	—	↑ 10
60-85	0.35-0.70	—	—	No change
86-95	0.71-0.89	—	—	↓ 10
96-120	0.9-1.2	—	30	↓ 10
>120	>1.2	—	60	↓ 15

*This assumes that the APTT range of 60 to 85 seconds correlates with an anti–factor Xa level of 0.35 to 0.70 IU/mL. This will depend on the reagent and analyzer used in the laboratory.[21]

—, not applicable.

recommendations may need to be reexamined. Maintenance UFH doses are age dependent, with infants (up to 2 months) having the highest requirements (average 28 U/kg per hour) and children older than 1 year of age having lower requirements (average 20 U/kg per hour). The doses of UFH required for older children are similar to the weight-adjusted requirements in adults (18 U/kg per hour). In many cases, especially in which the bleeding risk is higher, therapy should be commenced with an infusion only (no boluses). Reduced doses are usually required in renal insufficiency.

Monitoring of UFH therapy is standard practice, but the optimal assay remains unknown.[17] The anti–factor Xa/anti–factor IIa ratio of UFH effect changes with age.[18] Patient age and the concentration of UFH impact UFH-mediated thrombin inhibition. Use of APTT vs anti-Xa results in different rates of TTR achievement. The plasma concentration of UFH (protamine titration) does not correlate well with measures of UFH effect (anti–factor Xa, APTT, thrombin clot time, or anti–factor IIa).[17,19] UFH measures of effect do not correlate with UFH dose, and measures of effect do not match clinical outcomes.[20] There are no published studies in children that establish the ideal frequency of UFH monitoring, and vascular access is a frequent limiting factor. Contamination of results when blood is taken from the same limb in which infusion is being given or from a CVAD is often a major issue. A typical nomogram for manipulating UFH doses in children is shown in Table 2. Such nomograms are based on the original study by Andrew et al in 1994, which considered frequency of blood tests and time to therapeutic target range but measured no clinical outcomes.[21] Many experienced clinicians use small incremental changes and no boluses to feel comfortable about monitoring on a once-daily basis, which is often more practical. Given that there are no data to support the clinical advantage of a defined therapeutic range, and if one takes into account the rationale for treating, as well as the clinical progress of the patient into decision making, then this seems a reasonable approach.

Further studies are required to accurately determine the frequency of UFH-induced bleeding in optimally treated children, which is probably <1%, depending on patient selection and experience of the managing team. Probably the most common cause of fatal bleeding secondary to UFH relates to accidental overdose, especially in neonates.[22] Although rarely reported in the medical literature, the number of deaths reported in the popular press appears to be increasing. This often occurs in children who are receiving low-dose UFH flushing of vascular access devices, intended for example to be 50 U/5 mL UFH. Errors in vial selection and failure of bedside checking procedures result in 5000 U/5 mL UFH being injected; this results in a massive and unexpected overdose of UFH in small infants. Units should actively manage the choices of UFH preparations available to their staff to minimize the risk for confusion. Staff should be educated about the dangers of UFH and encouraged to be vigilant at all times when administering a drug that consistently ranks on hospital lists of the drugs most commonly involved in medication errors.[23,24] Rapid reversal of UFH can be achieved with protamine titration although, in many instances, simple cessation of UFH infusion is adequate.

Other than bleeding, potential side effects of UFH include anaphylaxis and osteoporosis. Clinicians would be prudent to avoid long-term (weeks to months) use of UFH in children.

LMWH

LMWH has become the anticoagulant of choice in many pediatric patients for a variety of reasons. However, the predictability of the anticoagulant affect with weight-adjusted doses is less than in adults, presumably due to differences in binding to plasma proteins. The most commonly reported LMWH used in pediatric patients is enoxaparin, although initial doses have been reported for a number of LMWHs (Table 3).[10]

A search of EMBASE, Medline, and PubMed from 2007 to 2017 (limited to English, but including cohort, cross-sectional, longitudinal, retrospective, or prospective studies, as well as RCT and systematic reviews, in neonates to adolescents) revealed 21 original studies specifically of LMWH in children. Subcutaneous dosing (predominantly twice daily compared with once daily) was most frequent (n = 18), but intravenous LMWH (n = 2) was reported. One pharmacokinetic study comparing 12-hourly vs 24-hourly dosing reported no difference in recurrence rates, and 50% of patients had trough level > 0.1 U/mL. There was high interindividual variation.[25] Reduced doses are required in renal insufficiency.

TTRs for LMWH are inferred from results in adults and are based on anti-Xa levels, with the guideline for subcutaneous administration twice daily being 0.50 to 1.0 anti–factor Xa U/mL at 2-6 hours following injection.[10] Most studies in children have used this therapeutic range, although 1 study used a lower maximal level (0.8 U/mL) with good efficacy and safety outcomes.[24] Rates of TTR achievement at first monitoring test ranged from 14% to 64% (reduced rates in infancy) (n = 7).[26,27] Dose escalation of starting dose was required in 10% to 50% (increased rates in infancy) (n = 7).[28] The mean number of dose increases was 1 to 3.5 (increased in

Table 3. Therapeutic and prophylactic subcutaneous dosing of enoxaparin, tinzaparin, and dalteparin according to age

	Therapeutic dose	Prophylactic dose
Enoxaparin		
≤2 mo of age	1.5 mg/kg, twice daily	1.5 mg/kg, once daily
>2 mo of age	1 mg/kg, twice daily	1 mg/kg, once daily
Tinzaparin		
≤2 mo of age	275 U/kg, once daily	75 U/kg, once daily
2-12 mo of age	250 U/kg, once daily	75 U/kg, once daily
1-5 y	240 U/kg, once daily	75 U/kg, once daily
5-10 y	200 U/kg, once daily	75 U/kg, once daily
10-16 y	175 U/kg, once daily	50 U/kg, once daily
Dalteparin		
≤2 mo of age	150 U/kg, twice daily	150 U/kg, once daily
>2 mo of age	100 U/kg, twice daily	100 U/kg, once daily

infancy) (n = 8), and the mean days to TTR was 1 to 11 (increased in neonates/infants) (n = 6). In neonates, the mean dose to achieve TTR ranged from 1.62 to 2 mg/kg twice daily, whereas, in infants, the mean dose to achieve TTR ranged from 1.12 to 1.9 mg/kg twice daily. Both age groups needed more dose changes, monitoring tests, and days to achieve TTR compared with older children. Even after TTR is achieved, Malowany et al reported that 44% of subsequent anti–factor Xa assay results were subtherapeutic in their cohort of neonates.[29] Although numerous investigators suggest using higher initial doses to reduce time to TTR, none of these studies have used clinical outcome data as an end point.[30]

As stated, anti–factor Xa assays are used to monitor LMWH, and the assay must be calibrated to the specific LMWH; however, even with this calibration, significant assay variability has been reported.[31] Reagent additives, substrates, and exogenous factor Xa are implicated as potential causes for interassay variation. Again, there are no clinical outcome studies to suggest an optimal monitoring strategy. Although the interindividual variation in dose response suggests the need for monitoring, 6 original studies report no association between laboratory results and clinical outcomes. In all cases, resolution/recurrence rate was more positive than TTR achievement rate.[29,32-36] Further, there was no association between anti–factor Xa level and bleeding.

The optimal scheduling of anti–factor Xa assays in children receiving LMWH has received surprisingly little attention, with no article clearly outlining a preferred schedule.[29,32,34] It appears that many studies have performed monitoring of anti–factor Xa assays daily or twice daily until the LMWH is therapeutic and then weekly thereafter with reducing frequency if the patient remained therapeutic or stable and in the absence of renal impairment. The practicalities of being able to draw blood often further reduce the frequency of monitoring. There is considerable interest in whether neonates should be managed with unmonitored fixed-dose treatment, but pilot studies are yet to be completed.

Major bleeding rates with LMWH in children appear to be low in stable patients, and although reports of bleeding rates range from 0% to 19%, patient selection is critical; in many cases of bleeding, titratable and more readily reversible UFH would have been a better therapeutic option (eg, immediate postoperative patients).[37] LMWH is only partially reversed by protamine. There are no data on the frequency of osteoporosis (although case reports exist on the extended use of LMWH, especially in premature infants), heparin-induced thrombocytopenia, or other hypersensitivity reactions in children exposed to LMWH. Temporary hair loss is reported.

VKAs

Warfarin is the most commonly used and studied VKA worldwide. Acenocoumarol is administered with high frequency in some European and South American countries, and phenprocoumon is the preferred VKA in some parts of Europe. A search of EMBASE, Medline, and PubMed from 2007 to 2017 (limited to English, but including cohort, cross-sectional, longitudinal, retrospective, or prospective studies, as well as RCT and systematic reviews, in neonates to adolescents) revealed 25 original studies and 3 systematic reviews/meta-analyses specifically of warfarin in children.

The current therapeutic international normalized ratio (INR) ranges for children with VTE are inferred from recommendations for adult patients, because no clinical trials have assessed the optimal INR range for children. The therapeutic target INR is 2.5 (range, 2.0-3.0). Warfarin is usually commenced at 0.1 to 0.2 mg/kg and capped at 5 mg maximal starting dose.[10] Patients with liver impairment or post-Fontan surgery require lower doses. A typical nomogram for guiding dosing is shown in Table 4.[10] A number of studies examined the pharmacogenomics of warfarin and demonstrated that VKORC1 and CYP2C9 variants likely contribute to warfarin dose requirements. However, the contribution of genome variation to clinical outcomes remains inconclusive.[38]

Monitoring oral anticoagulant therapy in children is difficult and requires close supervision, with frequent dose adjustments. During initiation of therapy, monitoring should be daily or every few days; however, even after stable long-term therapy is achieved, only 10% to 20% of children are safely monitored monthly.[39] Younger children usually require monitoring every 2 weeks, although the key is to be flexible and to base frequency of monitoring on the individual child's stability, taking into account intercurrent infections, other medication changes, and diet. Some children might require weekly monitoring during periods of instability. Rates of TTR achievement vary with age, and low rates of TTR achievement are frequently reported; however, they do not correlate with adverse event rates.[10,40]

Studies in children comparing point-of-care (POC) monitors with venipuncture INR confirm their accuracy and reliability, as well as improved quality of life. The major advantages of POC devices include reduced trauma of venipuncture, minimal interruption of school and work, ease of operation, and portability. However, all POC devices are operator dependent, considerable family education is required to ensure accurate use, and an ongoing quality-assurance program is recommended.[41] Home monitoring is often best introduced once the child is stable and used to its warfarin therapy, and funding models to support home monitoring vary widely across countries.

VKAs are often avoided in infants for VTE treatment, for several reasons, which is likely reasonable given that the treatment duration is usually 6 weeks to 3 months. First, the plasma levels of the vitamin K–dependent coagulation factors are physiologically decreased in comparison with adult levels. Second, infant formula is supplemented with vitamin K to prevent hemorrhagic disease, which makes formula-fed infants resistant to VKAs. Alternatively, breast milk has low

Table 4. Adjustment of VKA dose according to INR during initiation and maintenance phases of therapy

INR	Action
Initiation	
Day 1	
Baseline 1.0-1.3	Give 0.1-0.2 mg/kg orally (maximum 5 mg)
Days 2-4	
1.1-1.3	Repeat initial loading dose
1.4-1.9	50% of initial loading dose
2.0-3.0	50% of initial loading dose
3.1-3.5	25% of initial loading dose
>3.5	Hold until INR < 3.5 then restart at 50% of initial loading dose
Maintenance	
1.1-1.4	Increase dose by 20%
1.5-1.9	Increase dose by 10%
2.0-3.0	No change
3.1-3.5	Decrease dose by 10%
>3.5	Hold until INR < 3.5 then restart at 20% of dose

concentrations of vitamin K, making breast-fed infants sensitive to VKAs, which can be compensated for by feeding 30 to 60 mL of formula each day. Third, VKAs are available only in tablet form in most countries, thus being unsuitable for newborns even if suspended in water. Fourth, VKA requirements change rapidly across infancy because of rapidly changing physiological values of the vitamin dependent coagulation proteins and changes in diet. Finally, there is little efficacy or safety information specific to VKA use in neonates.

Bleeding is the main complication of VKA therapy; however, in experienced hands, the bleeding rates are reported to be <0.5% per patient year.[10] However, ~30% of teenage girls on VKAs will have menorrhagia; proactive management of menstrual bleeding, often involving gynecology services, and attention to iron status are critical. A high proportion of teenagers who start VKAs during their teenage years will develop clinical depression or anxiety (eg, related to the psychosocial challenges involved in lifestyle restrictions), and proactive psychological support of these patients is important.[42] Nonhemorrhagic complications of VKAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Reduced bone density in children on warfarin for >1 year has been reported in a number of studies, and many programs routinely monitor bone density in all children on long-term VKA. Patient and family education protocols are major factors in reducing bleeding events in children on VKA therapy.[43]

Conclusions

Management of VTE in children and neonates requires the use of anticoagulation, and there remains much to be learned, through well-designed research, about the currently used therapeutic agents, as well as DOACS. Despite this, the safety and efficacy of currently available antithrombotic agents can be excellent in experienced hands and with adequate infrastructure to support in-hospital and outpatient use of anticoagulants. Due to the low frequency of VTE in children, and hence the lack of experience for most pediatric physicians and surgeons in using anticoagulation, the development of dedicated pediatric anticoagulation services, with nurse-led models of care, is highly recommended.[43]

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