

Antithrombotic therapy in children with venous thromboembolism

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Summary

Antithrombotic therapy has recently become more frequent for the treatment of venous thromboembolism (VTE) in the paediatric population. This can be explained by the increased awareness of morbidities and mortalities of VTE in children, as well as the improved survival rate of children with various kinds of serious illnesses. Considering the large number of years a child is expected to survive, associated morbidities such as postthrombotic syndrome and risk of recurrence can significantly impact on the quality of life in children. Therefore, timely diagnosis, evidence-based treatment and prophylaxis strategies are critical to avoid such complications.

This review summarizes the current literature about the antithrombotic treatment for VTE in infants and children. It guides the paediatric medical care provider for making a logical and justifiable decision.

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With the advances in paediatric medicine and the increasing awareness of venous thromboembolism (VTE) in children, the use of antithrombotic therapies have become much more popular compared to decades ago. Nevertheless, VTEs in children are still relatively infrequent compared to adults (1–6), which make clinical trials of different antithrombotic therapies difficult. There are several recently published, evidence-based guidelines for paediatric anticoagulant treatment for paediatric thromboembolism, including the American College of Chest Physicians (ACCP) guidelines (7), the United Kingdom paediatric stroke guidelines (8), and the American Heart Association guidelines for paediatric stroke (9).

Most of the current paediatric recommendations are extrapolated from published adult trials or studies, although there is in-

creasing body of literature, including prospective cohort studies, retrospective studies from multicentre registries and case reports. VTE in adults are more commonly associated with prolonged immobilization (10), surgery (11), cancer (12), pregnancy (13), use of oral contraceptives (14), hormone replacement therapy (15), and hereditary prothrombotic disorders (16, 17). In children, central venous catheters (CVCs) were present in 33% of children with DVT in the Canadian registry, which is much more common than adults (1). Other important risk factors include septicaemia, perinatal hypoxia, dehydration, cancer, congenital heart disease (CHD), factors that are unique to the paediatric age group.

Also, the haemostatic system is considered to be a dynamic, evolving system that eventually matures in the late adolescent stage, which may partly explain the relatively low incidence of VTE in children compared to adults (18–21). Other specific considerations in paediatrics include

- poor venous access,
- concurrent underlying illnesses,
- dietary differences that affect the efficacy of oral anticoagulants, and
- compliance issues.

Therefore, direct extrapolation of adult recommendations to paediatric patients is not helpful for making treatment decisions.

VTE in children

According to the first analysis of the Canadian registry, the incidence of VTE was 0.07 per 10 000 children and 5.3 per 10 000 hospital admissions. The VTE-associated mortality rate is 2.2% (1). The annual rate of VTE in children in the United States calculated from the National Discharge Survey

was 4.9 per 100 000 children per year (22). The incidence was highest in children <2 years of age (10.5/100 000 children per year) and >15 years of age (11.4/100 000 children per year) and the lowest incidence of VTE was found in children between 2 to 14 years of age (2.4/100 000 children per year). The study from the Netherlands estimated the incidence of VTE in children to be 0.14 per 10 000 children (4). In both the Canadian and Netherlands studies, VTE was related to the presence of CVCs in one-third of the affected children. Moreover, both registries confirmed a bimodal age distribution, signifying the high incidence in neonatal and early infancy period, and the other peak in the late adolescent age group, corresponding to the maturation and loss of protective factors in the haemostatic system from early childhood.

The most important cause of VTE in neonates is the presence of CVCs, a subset of which is umbilical vein catheters (UVC) that can lead to portal vein thrombosis (PVT), but other perinatal events can also cause VTE in neonates, such as renal vein thrombosis (RVT) which can be diagnosed before time of birth, and cerebral sinovenous thrombosis (CSVT) which can be related to birth trauma. Other factors underlying neonatal VTE are infection, perinatal hypoxia and dehydration.

In older children, the causes of VTE, apart from the use of catheter, include childhood cancer and chemotherapy that alter their haemostatic composition, protein losing state (such as nephrotic syndrome or gut failure syndromes), parenteral nutrition and congenital heart defects after surgeries.

Based on the difference in aetiologies, and the difference in pharmacokinetics of antithrombotic therapies in neonates and children with VTE, it is recommended to always consider them separately in making decision for management.

Antithrombotic therapy for VTE in neonates and children

The purpose of administration of antithrombotic therapy in children to treat VTE in the early stage is to prevent thrombus propagation, embolization and achieve clot resolution, whereas the aim for secondary prophylaxis is to prevent recurrence and to decrease long-term morbidities of VTE. Management decision of VTE in children must always balance the risk (bleeding, agent-specific complications) and benefits (resolution of clot) of anticoagulant use. Antithrombotic therapies in the paediatric population include anticoagulant agents such as

- unfractionated heparin (UFH),
- low molecular weight heparin (LMWH),
- vitamin K antagonists (VKAs).

Thrombolytic agents such as urokinase and recombinant tissue-plasminogen activator will not be discussed. Specific dosing and duration are discussed in later sections.

UFH

Heparin is a glycosaminoglycan that catalyzes the reaction of antithrombin to inhibit procoagulant serine proteases, mainly thrombin and activated factor X (FXa), in the coagulation cascade. It is commonly administered in the paediatric setting and activated partial thromboplastin time (aPTT) is used to measure the therapeutic range of UFH for the treatment of VTE in children. The data is extrapolated from calculations using adult plasma. This is not ideal since recent research have suggested that baseline aPTT in children, especially in neonates, is normally elevated compared to adult references. This indicates that the relative increase into the therapeutic range is reduced in the pediatric population compared to adults (23). Furthermore, it has been shown that aPTT does not correlate with anti-FXa level (24), which is a measure of the anticoagulation effect of heparin. Before more evidence is available, aPTT and anti-FXa activities should be used in monitoring of UFH if the tests are available. Presently, due to lack of evidence-based information,

extrapolation from adult data is necessary to determine the therapeutic range for UFH use in children.

One complication secondary to UFH use is bleeding, which can usually be controlled by cessation of infusion. Due to the rapid clearance of UFH (half-life of 1 to 2 hours), termination of infusion will usually be adequate. If bleeding is life-threatening, immediate reversal of heparin activity can be achieved by administration of intravenous protamine sulfate. The dose of protamine sulfate is based upon the amount of heparin administered in the previous two hours (1 mg of protamine sulfate can neutralize 100 U of UFH).

Osteoporosis is another complication associated with the long-term use of UFH that has been shown in adults (25). Although osteoporosis is a rare complication in children, the prolonged use of UFH should be avoided. Heparin-induced thrombocytopenia (HIT) is caused by antibodies against complexes of platelet factor 4 (PF4) and heparin (or called the heparin-platelet complex). It usually begins 5 to 15 days (median 10 days) after commencement of therapy, and typically recovers within 4 days after heparin is discontinued. Although it is uncommon among pediatric patients (26–28), it should be considered when all other causes of thrombocytopenia have been ruled out. UFH should be terminated immediately when HIT is present and other antithrombotic agents, direct thrombin inhibitors or heparinoids should be used (e.g. danaparoid, lepirudin, argatroban) (29, 30).

UFH therapy in neonates

ACCP guidelines suggest a UFH bolus of 75 to 100 U/kg for neonates to achieve therapeutic range of 60 to 85 seconds as measured by aPTT, reflecting 0.2 to 0.4 U/ml by protamine titration or 0.35 to 0.7 U/ml by anti-FXa assays. Maintenance doses are calculated at an average of 28 U/kg/h for neonates, a higher requirement than children over one year of age (20 U/kg/h), likely reflecting the faster clearance of UFH in neonates due to a larger volume of distribution (31, 32). Definitive guidelines for optimal prophylactic doses

for UFH in pediatric patients are lacking but clinicians commonly use a dose of 10 U/kg/h as continuous infusion (33). The lack of correlation between anti-FXa and aPTT in a select subset of pediatric patient group, children <1 year old or those in the pediatric ICUs, have led clinicians to preferentially use anti-FXa values when adjusting dosage requirement in this patient subset, although there are no published data to support this practice.

UFH therapy in children

Administration of UFH, as recommended by the ACCP guidelines, is similar to neonates at 75 to 100 U/kg bolus but the maintenance dose is lower than for neonates at 20 U/kg/h. For older children, the dose of UFH required is 18 U/kg/h, similar to the weight-adjusted requirements in adults (34). Data for optimal prophylactic dose for this age group is lacking but clinicians commonly use a dose of 10 U/kg/h as continuous infusion (33).

LMWH

LMWHs are derived from heparins that have been chemically modified by several processes to yield heparin fragments. LMWH still mediate antithrombotic activity via catalysis of antithrombin but have a higher specific activity against FXa than thrombin (35). Therefore, monitoring of LMWH therapy is by anti-FXa assays instead of aPTT values. Use of LMWH is favored in the pediatric population to treat VTE due to its superior bioavailability, longer half-life and dose-dependent clearance resulting in a more predictable anticoagulant response (36). Also, LMWHs can be subcutaneously administered with minimal monitoring required, an advantage for those with poor or non-existent venous access. Therapeutic doses of LMWH are generally extrapolated from adult guidelines. However, dosing guidelines are available for enoxaparin, dalteparin, reviparin and tinzaparin (37–40).

Adverse effects of LMWH include major bleeding but the incidence ranges from 0 to 10.8% (37, 41, 42) and likely to be around

5%. Currently, no data is available on the frequency of osteoporosis or HIT in children on LMWH therapy. LMWH anticoagulant activity can partially be neutralized by protamine sulfate given intravenously, based upon the LMWH dose administered in the last 3 to 4 hours (one intravenous dose of protamine sulfate can neutralize approximately 75% of the anti-FXa activity (43)). Repeated doses of protamine sulfate may be required for subcutaneous administration of LMWH (44). Anticoagulation with LMWH in children with severe renal insufficiency is contraindicated.

LMWH therapy in neonates

Dosages of LMWHs are titrated with the target therapeutic anti-FXa levels between 0.5 and 1.0 U/ml. The blood samples need to be taken 4 hours after the last subcutaneous injection. It has been recommended by ACCP guidelines that enoxaparin be administered at 1.5 mg/kg/dose BID for neonates. However, newborns usually need a higher dose per body weight compared to older children possibly because of their larger volume of distribution, different pharmacokinetics (37), and low plasma antithrombin levels in younger children. A review by Malowany et al. suggested a higher starting dose of enoxaparin at 1.7 mg/kg q12 h for term neonates and 2.0 mg/kg q12 h for pre-term neonates (45), postulating that therapeutic range of anti-FXa levels may be attained more rapidly with a decrease in the number of dose changes. This recommendation for a higher dose in neonates was published after the publication of the ACCP guidelines but in the event that the patient faces considerable bleeding risk, the original recommendation of 1.5 mg/kg q12 h may be considered.

LMWH therapy in children

The ACCP guideline currently recommends 1.0 mg/kg q12 h with therapeutic anti-FXa levels to be 0.5 to 1 U/ml for enoxaparin. Dose adjustments should be done according to nomogram. Recommended dosing guidelines are available for enoxaparin, dalteparin, reviparin and tinzaparin (37–40).

VKAs

Oral anticoagulants like VKAs (such as warfarin) inhibit the synthesis of biologically active vitamin K-dependent coagulation proteins (factors II, VII, IX and X). It is monitored using prothrombin time (PT) and is reported in a standardized format as international normalized ratio (INR). Therapeutic ranges for children are extrapolated from adult data. The use of VKAs can be complicated in children due to the need for frequent monitoring and dose adjustments, mainly due to diet with low vitamin K sources (breast milk) that can increase anticoagulant sensitivity or diets supplemented with vitamin K (total parenteral nutrition, nutrient formula) that can induce resistance to the anticoagulant (46, 47). Also, treatment for underlying diseases or intercurrent illness in these children can affect the absorption from the intestines or modify the metabolic clearance of VKAs (46). There is difficulty in monitoring VKA therapy in children and requires close supervision with frequent need for dose adjustments but 10–20% can be safely monitored monthly (48). Point-of-care monitoring in neonates and children can be considered with two monitors evaluated in the pediatric population which can decrease the trauma of venipunctures and minimize interruption of school and work as testing can be done at home.

An adverse event associated with oral anticoagulants is major bleeding. The anticoagulant effect can be reversed by intravenous vitamin K and/or transfusion with fresh frozen plasma (FFP), prothrombin complex concentrates, or recombinant human factor VIIa if life threatening bleeds occur. Rare non-haemorrhagic complications have been reported including tracheal calcification (49) and hair loss. Reduced bone density was also reported in two uncontrolled studies in children on warfarin for more than one year, but it is unclear what the contribution of the underlying disorders are to the reduced bone density (50, 51).

VKA therapy in neonates and children

There is very little information available on the safety and efficacy of the use of VKAs in neonates, and is usually not recommended.

Due to a lack of clinical trials to determine the optimal INR range for children, therapeutic INR range is basically extrapolated from adult data, with INR between 2.0 and 3.0 for treatment of VTE and low dose prophylactic target INR range of 1.5 to 1.9. The general recommended loading dose is 0.2 mg/kg to a maximum of 5 mg for pediatric patients with normal liver function and dosing can be adjusted according to nomogram thereafter.

Specific indications for antithrombotic therapy

Neonatal VTE

Approximately two-thirds of VTE in children are associated with the use of CVCs (1, 4). However, CVCs are important devices for the overall management of pediatric patients with severe diseases (e. g. administration of drugs, nutrition, blood products). There are no published data on the effectiveness of different treatment modalities or outcomes for neonatal VTE.

Before the initiation of antithrombotic therapy, baseline testing of aPTT, PT/INR, plasma fibrinogen levels and platelet counts should be performed. Intracranial bleeding should be excluded, especially in premature infants, by performing a cranial ultrasound examination. Recommendations for VTE treatment in neonates suggest that CVCs or UVCs associated with thrombosis be removed, if possible, after 3 to 5 days of anticoagulation. Treatment can be with initial anticoagulation or supportive care with radiologic monitoring. If there is extension of thrombosis during supportive care, anticoagulation should be initiated with LMWH (twice daily; therapeutic anti-FXa levels of 0.5 to 1.0 U/ml) or UFH (3 to 5 days; therapeutic anti-FXa levels of 0.35 to 0.7 U/ml) followed by LMWH for a total duration of anticoagulation course of between 6 weeks and 3 months. If the CVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH can be administered until CVC removal. Thrombolytic therapy is not recommended for neonatal VTE unless major thrombus occlusion is organ- or limb-threatening (7).

Neonatal RVT

RVT can occur as an extension of inferior vena cava (IVC) thrombosis but can also occur in neonates with various underlying risk factors. RVT occurs primarily in the neonatal period, but may initially develop in utero (52, 53) and is the most common non-CVL-related thrombosis (54). Epidemiologic data on the incidence of RVT is lacking but an international registry has reported an incidence of 0.5 per 1000 admission to NICUs (2). Another German study reported an incidence of 2.2 per 100 000 live births (55). A recent retrospective review of neonatal RVT identified 271 patients from 13 case series, reported that 70% of patients had unilateral RVT that was more prevalent on the left side (63.6%) and was male-predominant (67.2%) (56). In this study, different treatment modalities were reported (UFH, 21.6%; LMWH, 20.7%; fibrinolytics, 11.2%; antithrombin, 1.7%; warfarin, 0.9%, surgical intervention, 0.3%) but 70.6% of the kidneys involved became atrophic, thus antithrombotic therapy may not improve long-term outcomes of neonatal RVT when compared to supportive care alone. Mortality rate was 3.3% with non-RVT-related thrombosis. Bilateral RVT comprises approximately 25% of RVT cases with 52–60% reported to have evidence of extension into the IVC (6, 52).

Optimal antithrombotic treatment regimens for RVT is lacking and current options include supportive care, anticoagulation and thrombolytic therapy. Evidence on RVT management comes from small case series and individual case reports. For unilateral RVT in the absence of renal impairment or extension into the IVC, supportive care with monitoring of RVT for extension or anticoagulation therapy with UFH or LMWH or LMWH in therapeutic doses (suggest continuation for 3 months) is recommended. Personal clinical experience of the authors prefers initiation of anticoagulant treatment upon clot detection. As for unilateral RVT that extends into the IVC, anticoagulation with UFH/LMWH or LMWH at therapeutic levels for duration of 3 months is suggested. For bilateral RVT with various degrees of renal failure, aggressive therapy with anticoagulation with

UFH and initial thrombolytic therapy with t-PA is suggested, followed by anticoagulation with UFH/LMWH.

Neonatal PVT

Umbilical vein catheterization in the neonate is associated with an increased risk of PVT (57, 58) but it is crucial to the care of critically ill infants. A prospective study of 100 neonates with UVC using ultrasonography reported clinically silent PVT in 43% of their patients with over half of the thrombi undergoing spontaneous resolution without any treatment (59). In this study, it was recommended that the catheters be removed upon detection of a thrombus since the significant risk factor for PVT was prolonged catheter use (>6 days) and transfusion. A retrospective study estimated the incidence of PVT to be 3.6 per 1000 admissions, as detected by abdominal ultrasonography (58). Of 133 infants identified with PVT, 97 had UVC and of these, 36 had poor outcomes resulting in either hepatic lobar atrophy (30 infants) or portal hypertension (6 infants). Anticoagulant treatment was given to 59 infants but this did not significantly affect the outcome. No specific recommendations are made regarding neonatal PVT in the ACCP guidelines. However, if there are no contraindications to the use of anticoagulants, therapy can be initiated up to a maximum of three months, or earlier if the clot resolves, and monitoring for clot extension.

Neonatal CSVT

The incidence of CSVT in neonates is estimated to be 2.6 per 100 000 (60) but this may be underestimated since clinical manifestations of CSVT in neonates are seizures (61) and lethargy (62) as opposed to focal neurologic signs usually seen in older children or adults (60, 63). Venous infarcts, the majority being hemorrhagic, are present in > 50% neonatal CSVT (62, 64). Intraventricular haemorrhage (IVH) is common (31%) in term neonates with CSVT (65). Risk factors for neonatal CSVT are numerous from maternal complications to neonatal complications including genetic thrombophilias, meningitis, dehydration,

and CHD. Multiple risk factors are present in over half of neonates with CSVT (65). Generally, early outcomes of neonatal CSVT are good with 77% having no neurologic sequelae after one year (62) but long-term outcomes are unclear and can include epilepsy, developmental delay, recurrent thrombosis, cognitive and speech impairments and death.

Anticoagulation for neonatal CSVT is usually with LMWH in the absence of hemorrhage but optimal dose and duration of therapy are not known. Of note, neonates recanalize at a faster rate than older children (66), hence assessment for recanalization can be done at 6 weeks and if recanalization is complete, anticoagulation therapy can be stopped. If not, therapy can continue for an additional six weeks (three months of anticoagulation) and then stop. There are no randomized controlled studies but some safety data on anticoagulation for treatment of neonatal CSVT are available (60, 62, 64). The current recommendation from ACCP guidelines for treatment of neonatal CSVT without significant hemorrhage is to initiate anticoagulation with UFH or LMWH followed by LMWH or VKA for a minimum of six weeks up to a maximum of three months. When significant haemorrhage is present, radiologic monitoring of the thrombosis at 5 to 7 days is suggested and anticoagulation if thrombus propagation is noted.

VTE in children

The incidence of symptomatic VTE in children is significantly less than in adults, reported at 5.3 per 10 000 hospital admissions. The majority of VTE in children are secondary complications to serious illnesses such as cancer, trauma, surgeries, congenital heart disease, and systemic lupus erythematosus (1, 4, 42, 67). The most common risk factor is the presence of CVC and the incidence of recurrent VTE is estimated to be 7.5% in children (1, 4, 5). One multicentre, randomized trial of anticoagulation for VTE in children (REVIVE) (42) had to close early due to slow recruitment, thus the study was underpowered for the determination of primary outcome. There are many case series, retrospective and prospective cohort studies and data from registries

from which recommendations can be based in the anticoagulant treatment of VTE in children (7).

For first VTE in children (both CVC- and non-CVC-related), initial treatment with UFH or LMWH for at least 5 to 10 days is recommended. If VKAs are subsequently prescribed for the patient, oral anticoagulation therapy is recommended as early as day 1 and discontinuing UFH/LMWH on day 6 or later if the INR has not exceeded 2.0. After the initial 5 to 10 days treatment period, LMWH is preferred over VKA therapy if therapeutic levels are difficult to maintain or VKA therapy is challenging for the child or family. As for CVC-related thrombosis in children, it is recommended that the CVC be removed if it is no longer required or it is non-functioning. It is recommended that anticoagulation therapy be initiated 3 to 5 days prior to catheter removal. If CVC is required and still functioning, the recommendation is to leave the CVC in place and start anticoagulation therapy for the patient. As for first CVC-related thrombosis, it is recommended that after the three months of initial anticoagulant therapy, prophylactic doses of VKA (INR range 1.5 to 1.9) or LMWH (anti-FXa level range 0.1 to 0.3 U/mL) be given until the removal of the CVC. Should recurrent thrombosis occur during prophylactic therapy, continuation of therapeutic doses of anticoagulants is recommended until the removal of CVC but therapy should be for a minimum of three months.

For idiopathic VTE in children, anti-coagulant therapy should be for at least six months, using VKAs to achieve target INR of 2.5 (INR range 2.0 to 3.0) or alternatively use LMWH (target anti-FXa range of 0.5 to 1.0 U/ml). A study showed that the rate of recurrence in children (neonates to 18 years; n = 301) was 21.3% with a median time of 3.5 years (range 7 weeks to 15 years) after anticoagulation withdrawal (68). At least one prothrombotic risk factor was present in 58.5% of the subjects and cumulative thrombosis-free survival was significantly shorter in children with more than one risk factor. This recommendation for six months to one year duration over life-long anticoagulation in treating idiopathic VTE in children imparts more importance on the

avoidance of the inconvenience and bleeding risk associated with anticoagulation therapy and places relatively low value on unknown risk of recurrence in the absence of an ongoing risk factor. A clinical, randomized controlled trial in adults with extended anticoagulation therapy for first episode of idiopathic VTE showing that risk of recurrent VTE was decreased by 95% in the group assigned to receive further warfarin therapy past the standard three months with 3/79 subjects on warfarin having nonfatal major bleeding complications (69).

Symptomatic VTE can be a secondary complication of chemotherapy treatment in children with acute lymphoblastic leukaemia (ALL), with incidence as high as 12% (70, 71). For children with secondary thrombosis, in whom the risk factor has resolved, anticoagulation therapy for at least three months with VKA or LMWH is recommended. However, for children with potentially reversible risk factor such as nephrotic syndrome or ongoing L-asparaginase therapy, the recommendation is to continue anticoagulation treatment in either therapeutic or prophylactic doses until the risk factor is resolved.

For recurrent idiopathic VTE, the current recommendation is indefinite treatment with VKAs to achieve a target INR of 2.5 (INR range 2.0 to 3.0). Long-term LMWH may be preferable for some patients but minimal data is available on the safety of long-term LMWH use in children.

For children with recurrent secondary VTE with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the risk factor but for a minimum of three months therapy duration.

CSVT in children

The incidence of children with CSVT is 0.67 cases per 100 000 children per year, with neonates most commonly affected (62). This may be an underestimation as clinical signs of CSVT in children are non-specific and may develop very gradually over days or weeks. Clinical outcomes for pediatric CSVT assessed in the Canadian Pediatric Stroke Registry reported an increase in severity of neurological deficits in 25% of affected children and that 13% of

children with CSVT had recurrent cerebral or systemic thrombosis (62). In the same study, over half of the children were given antithrombotics but neurological deficits were present in 38% of the children and 8% died. The mainstay of treatment is general medical and neurologic supportive care. Although there are no randomized clinical trials in children with CSVT, anticoagulant therapy is routinely provided in many centres. Supporting data on the use of anticoagulants come from literature analysis, nonrandomized studies, and safety studies. Most suggest that anticoagulation in the setting of CSVT may improve outcome (72–75).

Current recommendations for treatment of CSVT in children without significant intracranial hemorrhage (ICH) favor anticoagulation treatment over no anticoagulation. Anticoagulation should be initially with UFH or LMWH, and subsequently with LMWH or VKAs for a minimum of three months. If after the initial three months of therapy and there is incomplete recanalization or ongoing symptoms, anticoagulation therapy should be continued for another three months. For children with CSVT with significant ICH, radiographic monitoring of the thrombosis at 5 to 7 days is suggested, followed by anticoagulation if thrombus propagation is noted at that time. Prophylactic anticoagulation is recommended for children with CSVT who have potentially recurrent risk factor (e. g. nephrotic syndrome, asparaginase treatment) and should be initiated at time of risk factor recurrence.

VTE and cancer in children

Children with cancer are at an increased risk for VTE, similar to that in adults. The Canadian Pediatric Thrombophilia Registry reports that 20% of patients with VTE had cancer (76). The incidence of cancer and VTE in children is dependent upon study design and cancer type. With respect to VTE, childhood acute lymphoblastic leukaemia is one of the most studied paediatric cancers and have identified the use of asparaginase and corticosteroid as the main risk factors for VTE in this group of patients (70). One clinical trial (PARKKA) using

antithrombin concentrate in paediatric ALL patients showed a trend toward a decrease in the incidence of thrombosis but the study was underpowered (77). Other case series using LMWH in patients with cancer have been promising but none had the sample size to address the efficacy of LMWH use in the paediatric population (78,79).

Routine antithrombotic prophylaxis is not recommended in paediatric patients with cancer due to the lack of evidence of efficacy and potential for increased bleeding risk. However, for management of VTE in children with cancer, it is recommended that LMWH be used for a minimum of three months until the risk factor is resolved such as cessation of asparaginase therapy.

Cardiac procedures and VTE in children

Children with CHD who need some form of palliative surgery will need anticoagulation during and after the procedure to prevent thrombotic complications. Many of the procedures relate to alteration of flow and some involve the introduction of foreign materials in contact with blood and hence is a risk factor for thrombosis. The Blalock-Taussig shunts (subclavian to pulmonary artery shunt), which uses the MBTS plastic tube graft, enhances pulmonary artery blood flow in patients with severe or progressive cyanosis. For pediatric patients undergoing MBTS, intraoperative therapy with UFH followed by either aspirin (1 to 5 mg/kg/d) or no further antithrombotic therapy is favored over prolonged LMWH or VKAs. The Norwood procedure is commonly performed as initial surgery for children with hypoplastic left heart, and who will subsequently undergo the Fontan procedure, therefore, thrombotic complications can hinder further surgery. For patients who have had the Norwood procedure done, UFH therapy is recommended immediately after the procedure, with or without ongoing antiplatelet therapy.

The Glenn or Bilateral Cavopulmonary Shunts is frequently performed as an intermediate step in patients with single ventricles prior to definitive Fontan surgery. Thromboprophylaxis is recommended with UFH therapy postoperatively. This can be followed by no anticoagulation or followed with antiplatelet therapy or anticoagulation

with VKAs (target INR of 2.5, range 2.0 to 3.0) until Fontan surgery. Currently, there is no evidence-based guideline. Fontan surgery, or a modified version, is a palliative surgical procedure used in children with complex CHD. The surgery diverts the venous blood from the right atrium to the pulmonary arteries by passive flow, and bypasses the usually underdeveloped hypoplastic right ventricle. VTE (and right atrial thrombosis) remains a prime risk factor post-surgery and may occur anytime after the Fontan procedure but often present months to years later. There are few reports on treatment options and thromboprophylaxis after Fontan procedures (80–83).

The current recommendation from the ACCP guidelines for children after Fontan surgery is to use aspirin (1 to 5 mg/kg/d) or therapeutic UFH followed by VKAs to achieve a target INR of 2.5 (INR range, 2.0 to 3.0). It is noted that optimal duration of anticoagulation therapy is unknown at this time.

Conclusions

There are many randomized controlled trials and evidence-based guidelines for anticoagulant treatment in adults but for the pediatric patient group, there is little information available upon which to base recommendations for proper treatment. For instance, *Chest* Supplement guideline on anticoagulation therapy was first published in 1986, but only in the 1995 edition was a paediatric chapter added. Many of the recommendations, then and now, for antithrombotic management the pediatric population are Grade 2C, indicating that the risk and benefits of the recommended course of treatment is unclear and most of the data are based on observational studies. This highlights the need for international or multi-centre randomized controlled trials in the paediatric population for treatment and prophylaxis of VTE in neonates and children so that evidence-based guidelines can be specified. Until then, the best data comes from extrapolation from adult data, case series reports and observational studies that can be modified based on first principles and clinical

experience for the benefit of the individual patient.

Conflict of Interest

The authors declare no conflict of interest.

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