Thrombosis in Children


ABSTRACT

Thrombosis in children is becoming more prevalent due to increased awareness of these issues in the pediatric population and advances in medicine. Management of affected children are challenging due to differences in their hemostatic system compared with adults. Prospective, controlled trials for management/treatment of children with thrombosis are lacking. Many of the available guidelines for treatment of thrombosis in children are extrapolated from adult data and do not account for the uniqueness of the pediatric hemostatic system, although more research and data are becoming available. This review will focus on children over 1 year of age, including adolescents, looking at the etiology of thrombosis, diagnosis, management options, and any associated complications in this pediatric population.

KEYWORDS: Thrombosis, pediatrics, anticoagulation

Thrombosis in children has become more prevalent, or perhaps increasingly detected, as medical advances have increased intensity of treatment that children undergo in hospital. Often treatment recommendations are based on data from the adult population although there is increasingly more data available for children. There is a need for separate guidance for children due to several differences in etiology, the reasons for thrombosis, and the advances in management options. Neonates have the highest incidence of venous thrombosis in the pediatric population, but this review will focus predominantly on thrombosis in children over 1 year of age, including adolescents.

In the pediatric population, the developing hemostatic system results in variations in levels of coagulation factors in the blood with age, which affects the incidence of thromboembolism in children and differences in response to anticoagulant therapy. The etiology of thrombosis in a child with thromboembolism often varies from the underlying causes in adults. The gold standard investigations for thrombosis in adults may be more difficult to perform, as some will require the use of general anesthesia for young children. Obtaining venous access both for delivery of anticoagulant treatment and blood sampling for monitoring is more challenging in small veins. Most of the dosing guidelines are derived from adult data and do not always take into account differences in diet such as breast and formula milks which contain different quantities of vitamin K. Compliance often relies on parental input and in adolescents this may become a difficult issue.

This review article aims to look at the reasons why children may have thrombosis, diagnosis, management options, and potential complications.
PATHOGENESIS
Causes of pediatric thromboembolism can be considered under the triad of venous stasis, hypercoagulable states and thrombophilia, or endothelial cell wall injury, better known as Virchow triad. Overall, the incidence is lower than in adults and may be attributed to an intact vascular endothelium and physiological differences in clotting factors with age with lower capacity of thrombin generation and elevated levels of α-2-macroglobulin.

Endothelial cell wall injury occurs at times of infection, trauma, and surgery. Tissue factor can be exposed and triggers the clotting cascade to form thrombin, hence leading to increased risk of thrombosis.

When there is venous stasis or altered blood flow, such as turbulence within the vessel caused by the presence of central venous lines (CVLs), increased formation of thrombus can occur. Genetic factors such as inherited thrombophilia can play a role, resulting in alterations in natural anticoagulants, leading to an imbalance in rate of thrombus formation.

INCIDENCE AND EPIDEMIOLOGY
The incidence of thromboembolism is rare in children in comparison to the adult population. The annual incidence in a Canadian childhood registry was 0.07 to 0.14 per 10,000 children, with a higher incidence in hospitalized children at 5.3 per 10,000 referrals.

Most thrombosis in children occur in the neonatal period with a further peak in early adolescence, more marked in females. In the neonatal period, physiological differences in coagulation factor levels play an important role leading to increased risk of thrombosis (particularly in sick preterm infants often requiring CVL insertions), surgical interventions, or development of sepsis. In adolescents, hormonal changes around puberty are likely to contribute to the increased risk of thromboembolism as well as use of oral contraceptives, smoking, and pregnancy.

Thrombosis in children in 95% of cases is related to underlying conditions such as cancer, congenital heart disease, trauma, surgery, nephrotic syndrome, inflammatory bowel disease, and systemic lupus erythematosus. This is in contrast to adults, in whom spontaneous events would be more commonly seen.

DIAGNOSIS/INVESTIGATIONS
Thromboembolism may be symptomatic, presenting with symptoms of limb swelling and pain. Other cases may be asymptomatic and detected by radiological imaging, sometimes as an incidental finding. The method of imaging of suspected thrombosis depends on the site.

The PARKAA study was designed primarily to assess the use of antithrombin replacement in children with acute lymphoblastic leukemia (ALL) and CVLs to prevent thrombosis. The study also assessed the rate of asymptomatic upper venous system CVL-related thrombosis. Venography was shown to be the most effective investigation to detect central veins, such as subclavian vein thrombosis, and color Doppler ultrasound was more likely to detect thrombosis in the internal jugular and axillary veins, which are compressible with the ultrasound probe.

Magnetic resonance venography (MRV) has been used in the diagnosis of thrombosis in adult patients, but there is less experience in children. Advantages include high rates of sensitivity and specificity, noninvasiveness of the technique, and avoidance of radiation exposure. However, sedation may be necessary for young children.

In the lower extremity, compression Doppler ultrasound has been shown to be effective in diagnosis of venous thrombosis. MRV may be helpful in assessing the proximal extent of lower limb thrombosis. In the case of a blocked CVL, a linogram will detect occlusion at the tip of the line and flow abnormalities suggestive of a fibrin sheath. Lineography has been shown to underestimate the extent of thrombosis, as it underestimates any proximal thrombosis. Therefore, ultrasound or venography should be performed if large vessel thrombosis is suspected as a cause of line blockage. In the same study, ultrasound underestimated the number and extent of thrombosis in the subclavian vein in comparison to MRV. Echocardiogram can be used to detect intracardiac thrombosis.

In conclusion, a combination of jugular vein ultrasonography and bilateral upper limb venography (subclavian and central veins) is recommended. MRV is a good alternative depending on local availability and expertise in scanning children. For lower limb thrombosis, ultrasonography should be a reasonable method of detection. For more proximal veins, venography or MRV should be considered.

PULMONARY EMBOLISM (PE)
PE is uncommon in children with an incidence of 0.86 to 5.7 per 10,000 hospital admissions. Most cases of PE in children are secondary to an underlying identifiable risk factor with less than 5% of cases idiopathic. This study also identified the most common risk factors as immobility, presence of a CVL, and recent surgery. On testing, 35% patients were found to have an underlying thrombophilic abnormality. Around half the children also had evidence of deep vein thrombosis (DVT) in the extremities. The incidence is greatest in infancy and adolescence.

PE is most commonly seen in children with underlying medical problems and in particular malignancy, congenital heart abnormalities, nephrotic syndrome, and
those in intensive care units. Central venous catheters increase the risk most significantly.\(^6\)

Ventilation perfusion scanning is the first-line investigation for children with suspected PE. Pulmonary angiography is the gold standard when available but computed tomography angiography is being used increasingly in children although there are no published studies on sensitivity or specificity.

There is a significant mortality rate associated with PE in children leading to death in around 9 to 10% of patients\(^5\) and a recurrence rate of 12.5%\(^5\) indicating the need for careful consideration of ongoing risk factors in these children and the benefits of long-term anticoagulation.

**RISK FACTORS FOR THROMBOSIS IN CHILDREN**

**CVL**
The majority of thromboses in children are related to CVL. These lines are often inserted into children requiring more intensive treatments such as chemotherapy, total parenteral nutrition, long-term antibiotics, and chronic transfusion. Most lines are inserted percutaneously into the upper venous system through the jugular or subclavian vein. Infection also contributes to the increased risk of CVL-related thrombosis. The incidence of CVL-related thrombosis varies widely, with the incidence of asymptomatic thrombosis much greater than symptomatic thrombosis.

Several factors make these patients more prone to developing thrombosis. First, the nature of the underlying condition the line has been inserted for, such as malignancy or sepsis, increases the risk of thrombosis.\(^7\) The catheter disrupts normal blood flow and in addition to the thrombogenic nature of the catheter material, both act to increase the risk of thrombosis.

**Childhood Cancer**
Thromboembolism is a well-recognized complication of cancer in children. There are several factors which contribute including the presence of central venous catheters, the underlying malignancy with the highest incidence in those with ALL due to prothrombotic agents such as L-asparaginase and steroid therapy, and an increased risk of dehydration and infection.

**Thrombosis and the Antiphospholipid Syndrome**
Primary and secondary antiphospholipid syndrome results in an increased risk of DVT, acute ischemic stroke, and transient ischemic attack.\(^8\) In children, there is a long-term risk of recurrence following thrombosis, without long-term anticoagulation.

**HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)**
HIT type 2 is rare in children. HIT is an immune-mediated reaction to heparin, more commonly seen with unfractionated heparin (UFH). It is characterized by a drop in the platelet count following exposure to heparin, to less than 50% of baseline. Laboratory confirmation can be made using an enzyme-linked immunosorbent assay, although the serotonin-release assay is more specific.

Children in the pediatric intensive care unit (PICU) are most at risk, and the incidence of HIT-associated thrombosis in a retrospective study of children who received more than 5 days of UFH was 2.3%.\(^9\)

In suspected cases, all forms of heparin should be discontinued. There is limited experience with heparin alternatives in children, but if anticoagulant therapy is to be continued, alternatives include danaparoid, lepirudin, and argatroban.\(^10,11\)

**HEREDITARY PROTHROMBOTIC FACTORS**
The role of inherited thrombophilia in children is not as well known as in the adult population, partly due to lack of studies. Routine testing in asymptomatic children and those with only one episode of venous thromboembolism (VTE), especially those associated with CVL, remains controversial. In children with thrombosis and clear etiological factors such as CVL-related thrombosis, testing for congenital prothrombotic states is unlikely to change the management, and the reasons for not testing should be explained to parents. In children without apparent etiological factors, a study of congenital prothrombotic state will be recommended. Exceptions to testing are children who present in the neonatal period with purpura fulminans, which would suggest underlying inherited severe protein C or protein S deficiency. Antithrombin deficiency may also present early in childhood with thrombosis and it may be worth considering testing those with a known family history.

One study has shown that the most significant predictor of thrombosis was a positive family history.\(^12\) Inherited risk factors such as Factor V Leiden (FVL), prothrombin G20210A variant, TT677 methylenetetrahydrofolate reductase (MTHFR) genotype, protein C and protein S, antithrombin, and lipoprotein(a) vary widely in children with VTE.\(^13\)

In a second study, an underlying medical condition was the most likely predictive factor for thrombosis, occurring in 91% with the presence of a central line accounting for thrombosis in 77%. An inherited prothrombotic disorder accounted for 13%. In children with
a spontaneous VTE, 60% had an inherited prothrombotic defect compared with 10% with an underlying medical condition. One study demonstrated a 2.6% risk of combined inherited thrombophilic abnormalities.

Prothrombin Gene Mutation
Heterozygosity for the prothrombin (Factor II) mutation 20210G/A is found at a prevalence of 2.7% in the normal Caucasian population and 7.1% of those with thrombosis. In two other studies of children with previous thrombosis, inherited prothrombin mutations were present in 2.3% and 3%, respectively.

FVL
FVL results from a mutation Arg506 to Gln506 on the FV gene, resulting in resistance against cleavage by the activated protein C complex. It is the most common genetic risk factor found in those with thrombotic episodes. The incidence is highest in a Northern European population, found in around 5% of the population. In pediatric studies the incidence can vary widely with two studies showing an incidence of between 4.7 and 13% of children with thrombosis. The relative thrombotic risk factor for heterozygotes is six- to eightfold, increasing to 80-fold in homozygotes. In children with thrombosis, FVL was found in up to 30%. The presence of FVL does not appear to increase the risk of recurrent thrombosis.

MTHFR
MTHFR is an enzyme involved in folate and homocysteine metabolism. The MTHFR polymorphism c.677C>T in the homozygous form may lead to mild elevations in blood homocysteine levels. As far as we are aware there are no data to suggest that the mutation is an independent risk factor for VTE in children, but it may be associated with ischemic stroke.

Lipoprotein(a)
Lipoprotein(a) increases the risk of venous and arterial thrombosis in children, in particular arterial stroke.

FVIII
Elevated FVIII activity may be secondary to acute phase activity due to the high incidence of proinflammatory conditions in pediatric thrombosis. Persistence of elevated FVIII after VTE may predict an unfavorable prognosis. Normal hemostasis is regulated by several natural anticoagulants. The most important are tissue factor pathway inhibitor, the protein C system, antithrombin, and the von Willebrand factor cleaving protease ADAMTS 13. ADAMTS 13 deficiency is extremely rare but can result in thrombotic thrombocytopenic purpura.

Protein C
The protein C pathway comprises protein C, and the cofactors protein S, FVIII and FV. Protein C is activated by thrombin. The activated protein C cleaves and inactivates FVa and FVIIIa, therefore regulating the formation of thrombin. Homozygous deficiency of protein C or protein S can present as purpura fulminans in the neonatal period. Incidence in pediatric thrombosis was 0.6 and 1% in two respective studies.

Antithrombin
Antithrombin inhibits thrombin formation but also FXla, FIXa, and FXa. Deficiency of antithrombin increases the risk of thrombosis. Its action on thrombin is increased 100-fold by heparin, therefore deficiency results in resistance to heparin therapy in the treatment of thrombosis. Incidence in children with thrombosis is 1%.

CONGENITAL VENOUS ABNORMALITIES

May-Thurner Syndrome
The left common iliac is longer than the right and passes behind the right common iliac artery. May-Thurner syndrome is an anatomical anomaly resulting in left-sided iliac vein outflow obstruction caused by compression of the left common iliac vein by the right common iliac artery. There is intimal hypertrophy of the intima of the left common iliac vein resulting in partial obstruction. This in turn leads to an increased risk of VTE.

MANAGEMENT
Anticoagulation in children may be administered prophylactically to prevent thrombosis in high-risk individuals, or in therapeutic doses in those with confirmed thrombosis. The most comprehensive guidelines published are those of the American College of Chest Physicians; a new edition is expected to be published by the end of 2011. The decision to anticoagulate will depend on each individual situation, weighing up the benefits against risks of bleeding. Anticoagulation therapy is administered for prevention of clot extension or embolization, to reduce the risk of recurrence, prevention of long-term complications of vascular compromise such as postthrombotic syndrome (PTS), and to maintain blood vessel patency for long-term venous access.
**Vitamin K Antagonists**

Coumarin agents include warfarin and phenindione and result in anticoagulation by inhibition of γ-carboxylation of vitamin K-dependent proteins. This in turn reduces the plasma concentrations of the vitamin K-dependent clotting factors (FII, FVII, FIX, and FX). Its use has been long established in adult and children when medium- to long-term anticoagulation is required.

However, several challenges apply to its use in children. A combination of a physiologically changing hemostatic system, low vitamin K levels in breast milk, and vitamin K supplements in formula milk, results in a need to monitor warfarin effect frequently in infants. Changes in nutrition, medications such as steroid therapy, intercurrent illness, and the use of alcohol or recreational drugs in older children may cause fluctuations in anticoagulant levels.

The initial recommended starting dose of warfarin is 0.2 mg/kg. Doses are adjusted thereafter according to nomograms for loading doses on days 2 to 4 and maintenance doses thereafter. Warfarin is monitored using the international normalized ration (INR) level with a therapeutic target in most cases of 2.5 with a range of 2 to 3. In low dose prophylaxis, the target INR is 1.7 with a range of 1.5 to 1.9. To facilitate easier monitoring of the INR, a whole blood capillary method, such as the CoaguChek systems (Roche Diagnostics, Mannheim, Germany), can be used and are appropriate for outpatient and home monitoring by parents after formal training. This avoids the need for repeated venous access, but it is necessary to ensure the machines are correctly calibrated in consultation with the local coagulation laboratory. Nomogram for adjustment of warfarin dose is widely published and can be found online (http://www.tigc.org/clinical-guides/Warfarin-in-Children.aspx).

Bleeding complications can be serious and life-threatening and treatment depends on the INR and degree of bleeding at presentation. The risk of bleeding in children on warfarin is 0.5%. Bleeding can be managed by withholding further doses, administration of intravenous vitamin K of 30 μg/kg and depending on severity may require immediate reversal with clotting factors such as fresh frozen plasma, prothrombin complex concentrate, or recombinant FVIIa.

**UFH**

There is much experience in using UFH in children and despite many newer agents being available, it has some advantages. In children who may require surgical intervention, UFH can be fairly rapidly reversed by stopping the infusion due to its short half-life. Complete and rapid reversal can be obtained with protamine.

There are disadvantages to the use of UFH in children, which has been partly overcome by newer heparin agents. Difficulties with UFH include the need for venous access, frequent monitoring, laboratory issues with activated partial thromboplastin time (APTT) analysis, obtaining therapeutic levels, age-dependent factors in the pharmacokinetics, along with the potential increased risk of HIT.

Monitoring of therapeutic range of heparin can be based on APTT or the anti-FXa level of 0.35 to 0.7 U/mL. The APTT-based assay is based on adult plasma levels and varies widely with age. In children, the APTT can be affected in younger children by an immature hemostatic system or the presence of a lupus anticoagulant. It is also important to keep in mind the local laboratory differences in APPT reagent used. The anti-FXa level also depends on the commercial kit used. The target range is a heparin level by protamine titration of 0.2 to 0.4 U/mL. The APTT has been shown to be less predictive of the anti-FXa effect in children under 2 years of age. Anti-FXa results are also affected by the antithrombin added during testing; younger children physiologically have lower levels. Therefore, the current strategy of monitoring the dosing of UFH has much limitation. One should use the nomogram for adjustment of dose (http://www.tigc.org/clinical-guides/Heparin-and-LMWH-in-Children.aspx) as a practical guide with many limitations as cited above.

A bolus dose of 75 to 100 U/mL achieves therapeutic anticoagulation in the majority of children at 4 to 6 hours. A continuous infusion should be administered after the initial bolus starting at 20 U/kg/h for children over the age of 1 year. Older children require less and should be started on an infusion at 18 U/kg/h, a dose more similar to that required in adults. A suggested dose for prophylactic anticoagulation is 10 U/kg/h. UFH in adult studies has identified an association with osteoporosis; therefore long-term treatment should be avoided in children. The bleeding rate is reported at 1.5% in one study and as high as 24% in another study performed in PICU. HIT is uncommon in children with a reported incidence of up to 2.3%.

One advantage to the use of heparin is the ability to completely reverse the effect with protamine. Protamine is contraindicated if there is an allergy to fish and may lead to hypersensitivity in those previously exposed to protamine containing insulin.

**Low Molecular Weight Heparin (LMWH)**

There is now a reasonable amount of experience with LMWH in the pediatric population. It has become the anticoagulant of choice in many cases, usually due to practical advantages in administration and monitoring. Administration is subcutaneous once or twice daily depending on the preparation, with less frequent monitoring required once therapeutic values are obtained and fewer interactions with other medications. A subcuta-
neous catheter (Insuflon™ [Maersk Medical, Roskilde, Denmark]) can be inserted to reduce the amount of needling but can be associated with bruising and localized skin reactions. We recommend avoiding the use of Insuflon in patients with little subcutaneous tissue.

The therapeutic range for LMWH is a target anti-FXa assay range of 0.5 to 1 U/mL with a level taken at 4 hours from the last dose. Prophylactic LMWH can be administered and suggested target range for prophylaxis is an anti-FXa of 0.1 to 0.3 U/mL. This therapeutic range has not been validated. Complications such as HIT and osteoporosis are likely less common than with UFH.

One disadvantage to the use of LMWH is the difficulty in reversal in the case of bleeding. Protamine can be used at a dose of 1 mg for every milligram of enoxaparin, but is unlikely to totally reverse the effect due to incomplete reversal of the anti-FXa activity.29 LMWH has a longer half-life than UFH and therefore doses will need to be omitted before invasive procedures. In thrombosis at high risk of progression without anticoagulation, consideration will need to be given to bridging UFH. LMWH is supplied in prefilled syringes or multidose vials designed for adults. Care should be taken when calculating small volume doses for young children.

The most commonly used LMWHs in pediatric practice are enoxaparin, dalteparin, nadroparin, and tinzaparin. Several studies have published data on dosing in children. There is most experience with enoxaparin, with a recommended starting dose of 1 mg/kg twice daily. However, neonates require higher doses and although 1.5 mg/kg has been recommended, more recent studies have indicated that term neonates require 1.7 mg/kg and preterm infants 2 mg/kg to achieve therapeutic levels.30 There is some debate over dosing frequency. In adult patients, enoxaparin is administered once daily but pharmacokinetic studies in children suggest that drug clearance is faster in children with subtherapeutic levels after 12 hours,31 therefore twice daily administration is recommended in children.

Monitoring the therapeutic effect of LMWH is with anti-FXa levels. Although in adults dosing is based on weight with little indication for monitoring anti-FXa levels except in pregnancy and renal impairment, guidelines for treating children have suggested routine monitoring.32 This reflects age-related variation in levels of clotting factors and faster clearance of heparin in younger children.33 This applies especially to neonates. The peak anti-FXa level is achieved at ~4 hours after subcutaneous administration of LMWH.34 This varies slightly with age and preparation of LMWH, but in general, it is recommended that levels are checked by a peripheral venous sample where possible to prevent heparin contamination. Anticoagulant prophylaxis does not generally require monitoring of levels. Nomogram for adjustment of dosing can also be found online (http://www.tigc.org/clinical-guides/Heparin-and-LMWH-in-Children.aspx).

Newer Anticoagulant Agents
In adult practice, there are several new anticoagulant agents available. The direct thrombin inhibitors such as lepirudin, argatroban, and bivalirudin have been used as alternative anticoagulant therapy in HIT, more commonly in adults. Argatroban has been used in children with HIT11 as an alternative to UFH.

The indirect FXa inhibitor, fondaparinux, is licensed for prophylaxis in surgical and medical adult patients. A study is currently being done in children looking at the potential use for fondaparinux as an alternative to LMWH. Rivaroxaban and dabigatran have been used as prophylaxis in orthopedic surgery in adults.35

Thrombolytic Agents
Plasminogen levels are only 50% of adult levels at birth resulting in a slower generation of plasmin in neonates and therefore less effective thrombolysis with streptokinase, urokinase, and tissue plasminogen activator (tPA). Supplementation with plasma will increase the thrombolytic effect.

tPA is the recommended agent in children requiring thrombolysis, at a dose of 0.5 mg/kg/h initially for 6 hours. One study gave in addition, UFH at a dose of 10 U/kg/h and fresh frozen plasma at 10 mL/kg 30 minutes before the tPA infusion. The use of tPA may be useful in critical ischemia in a vessel, for example, causing limb- or organ-threatening arterial thrombosis.36 There is no direct test for monitoring although fibrinogen levels may drop during treatment and should therefore be maintained above 100 mg/dL. Administration may be local or systemic. Complications of bleeding are not uncommon and therefore children at particular risk are those with recent bleeding or surgery.

Bleeding complications should be managed by stopping the infusion of thrombolytic agent and administering cryoprecipitate at 5 to 10 mL/kg along with an antifibrinolytic agent. There is much controversy for the dosing of tPA37 and the suggestion reflects personal experience. Protocol for use of tPA can be found online (http://www.tigc.org/clinical-guides/Thrombolytic-Therapy-in-Children.aspx).

DURATION OF ANTICOAGULANT THERAPY
Anticoagulant therapy in children with idiopathic thrombosis should be continued for 6 months, while those with a secondary thrombosis may be treated for
3 months, if the risk factor is no longer present and the thrombosis has resolved. Longer duration of anticoagulant therapy should be considered in those with ongoing risk factors, such as active nephrotic syndrome. In recurrent DVT, long-term anticoagulant therapy should be considered.\(^\text{20}\)

**PREVENTION OF VTE**

In older children, graduated compression stockings for the lower limbs are used often in surgical patients to reduce the risk of VTE. There are little, if any, data on the use of graduated compression stockings in children for DVT prophylaxis. However, they may be of particular use when anticoagulant thromboprophylaxis is contraindicated.

Thromboprophylaxis is widely used in the prevention of VTE in adults. In children there is less evidence. Adolescents should be considered at higher risk of VTE, also taking into account risk factors such as prolonged immobility, presence of central venous catheters, sepsis, malignancy, congenital heart disease, and trauma. LMWH is the most commonly used form of thromboprophylaxis. Routine prophylaxis for children with CVLs is not recommended.\(^\text{20}\) In the absence of a clear guidance for the best use of thromboprophylaxis in children, each case should be individualized and those at high risk considered for prophylaxis.

Although monitoring of anti-FXa levels in anticoagulant prophylaxis therapy is not generally required, a suggested target range for anti-FXa is 0.1 to 0.3 U/mL.

**INFERIOR VENA CAVA (IVC) FILTERS**

IVC filters can be considered in children with VTE in the lower extremity with a contraindication to anticoagulation such as bleeding or extension of thrombosis despite anticoagulation therapy. There are limited published data on the use of filters in children and most evidence is extrapolated from adult data and publications or small case series in children.\(^\text{38}\)

Indications for use in children include pediatric trauma patients with DVT or PE,\(^\text{39}\) who due to hemorrhagic risk associated with for example, head injury, are not suitable for anticoagulation therapy. Children who have extension of thrombosis on anticoagulant therapy or those with infrarenal thrombi are also suitable candidates for IVC filters.

Filter use can be considered in children >10 kg and should be inserted by an experienced interventional radiologist. The filter is inserted into the femoral or jugular vein. Depending on the reason for insertion, the filter may be temporary (10 days to 3 months) or long term.\(^\text{20}\) IVC filters are not specifically designed for pediatric patients. There are various types available including the Gunther-Tulip IVC and Greenfield filter.\(^\text{40}\)

Anticoagulation therapy should be initiated as soon as any contraindications have been resolved.\(^\text{41}\) Complications of filter placement include filter migration or fracture, extension of existing thrombus as far as and occasionally into the filter or risk of PE during manipulation of the filter at insertion, perforation of the blood vessel,\(^\text{42}\) or perforation of adjacent structures as the child grows.\(^\text{43}\) Only temporary filters should be used in children.

**TREATMENT OF PROGRESSION OF CLOT DESPITE ANTICOAGULATION THERAPY**

In children on warfarin therapy who have progression of thrombosis despite a therapeutic target INR range of 2 to 3, heparin should be resumed and subsequently switched back to warfarin using a higher therapeutic INR of 3 to 4 or addition of aspirin to a warfarin therapy. For patient on LMWH, increasing the dose of LMWH to a higher targeted anti-FXa level can be considered. In children with extensive lower limb venous thrombosis with progression despite anticoagulation therapy, the use of an IVC filter could be considered. Use of newer anticoagulant can be considered if the above measures failed.\(^\text{13}\)

**LONG-TERM COMPLICATIONS OF THROMBOSIS**

**PTS**

PTS is a chronic complication of venous thrombosis and can vary widely in its severity. Typical symptoms are that of localized edema, pain, change in skin temperature, and discrepancy in limb circumference. On examination there may be varicose veins, trophic skin changes, and skin ulceration. The changes are felt to be secondary to venous hypertension.

The incidence in children is unknown. Lack of recognition and follow-up for PTS may contribute. In comparison to adults, limited studies have been performed in children to determine the risk factors and long-term outcome of PTS in children. There is a wide variation in reported incidence. Pediatric scoring systems have been employed to study the incidence, for example the Villalta PTS scoring system.\(^\text{44}\)

A meta-analysis reported 17% and 43% incidence for prospective and retrospective studies in children giving an overall rate of 26%.\(^\text{45}\) A Canadian follow-up registry suggests a lower incidence of ~10 to 12% clinically detected PTS in children.\(^\text{46}\) A pediatric PTS score demonstrated in one study that venous thrombosis in children was associated with a mild degree of PTS in 52% and moderate degree in 10%.\(^\text{47}\) In children who had undergone previous cardiac catheterization for
congenital heart disease, 50% had PTS 5 to 10 years later.  

**Risk of Recurrence**

The results of a meta-analysis reported an 11.4% risk of thrombosis recurrence in children following one episode of nonidiopathic thrombosis.13 In the same study, most cases of recurrence were in adolescents and in ~80%, occurred following discontinuation of anticoagulant therapy. There was an association of recurrence in those with protein C, protein S, and antithrombin deficiency and the prothrombin gene mutation. FVL and lipoprotein(a) did not appear to confer an increased risk of thrombosis. In one pediatric study, the presence of elevated D-Dimer and FVIII levels suggest an increased risk of thrombosis.49 In adults, these have been proposed as a method of determining the duration of anticoagulation.50 Lupus anticoagulant and anti-β2 glycoprotein-1 antibodies may suggest a need for long-term anticoagulation in children with spontaneous VTE.49

Residual thrombosis is a further risk factor for the recurrence of thrombosis. It is, therefore, advisable to perform imaging studies before discontinuing anticoagulation therapy and to reevaluate the duration of anticoagulant therapy to be used.

**CONCLUSION**

VTE in children continues to be a topic of growing interest and importance. In contrast to adults, most episodes of thrombosis in children are not spontaneous in nature and therefore pose less of a long-term risk for recurrence once the precipitating factor has been removed.

Several useful and regularly updated guidelines are now available specific to children, such as the American College of Chest Physicians guidelines, which lead to a more uniform international approach to treating children with VTE. Less is known about the use of thrombophilic markers in predicting outcome in children, and will no doubt be an area increasingly studied in the future. Novel anticoagulant agents should be introduced as part of pediatric clinical trials. Overall, the most important aim of management in a growing child is to limit the long-term complications of vascular occlusion due to venous thrombosis while limiting the risk of bleeding on anticoagulant therapy.

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