REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Pediatric venous thromboembolism in relation to adults

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Objective: **This review was performed to analyze the current knowledge and controversies in the pathophysiology, diagnosis, treatment, and outcomes of pediatric venous thromboembolism (VTE) compared with adults.**

Methods: **Searches of the MEDLINE database and manual searches of the references of selected articles were performed to select reports for their relevance and quality of information on the similarities and differences in pathophysiology, diagnosis, and treatment of VTE in children and adults.**

Results: **Symptomatic VTE incidence is reported at a rate of 0.07 in every 10,000 children, which is significantly lower than the rate in adults. Pulmonary emboli in adolescents are rarely fatal, unlike in adults. VTE recurrence is also much lower in children. Young age has been shown to be protective of VTE, whereas central venous catheters are very important in pediatric venous thrombosis. The incidence of postthrombotic syndrome varies from 20% to 65%, with mild symptoms in most children. Cerebral and visceral vein thrombosis may lead to severe morbidity and death. Some factors of thrombophilia have a significant effect in the pediatric population; however, its overall significance is controversial. Most data on VTE treatment are extrapolated from studies in adults. Children with acute VTE should be treated with anticoagulation therapy. Treatment duration depends on the nature of the thrombosis and previous VTE events.**

Conclusions: **There is a paucity of prospective randomized studies with data determining not only the effect of VTE but also the treatment options in children. Thrombophilia is a risk factor for pediatric VTE, but its significance has not been thoroughly investigated. Guidelines specific to children for antithrombotic therapy, prophylaxis, and optimal duration need re-evaluation and support by strong evidence. (J Vasc Surg 2012;55:1785-93.)**

Venous thromboembolism (VTE) is an important and relatively frequent cause of morbidity and death in adult patients. Historically, venous thrombosis in children is a rare condition. The incidence of VTE has increased over the years because of the survival of children with historically fatal conditions and advances in pediatric care. A recent retrospective study in the United States covering a 7-year span showed the rate of VTE ranged from 34 to 58 cases/10,000 hospital admissions ($P < .001$), even suggesting that this may be the new epidemic in pediatric tertiary care hospitals.[1] The goal of our study was to review and compare diagnosis, treatment, and outcomes of VTE in pediatric patients compared with adults.

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The estimated incidence of symptomatic VTE in children from the Canadian Childhood Thrombophilia registry in 1994 was 0.07/10,000 children, which is lower than the 5.6 to 16 cases/10,000 adults per year.[2-4] Later studies have reported higher pediatric VTE incidences, ranging from 4.9 to 21.9/10,000 hospital admissions, indicating a need for closer investigation[5-8] or possibly under-representation of this patient population. VTE incidence varies amongst different childhood age groups, with the highest numbers in infants aged 1 to 23 months and in teenagers, particularly teenaged girls.[7,9] This latter observation can be explained by pregnancy-related deep vein thrombosis (DVT), which also accounts for the 2.1-times higher rate of DVT in women vs men (95% confidence interval [CI], 2.02-2.13).[7]

Unlike in adults, pulmonary emboli (PE) in adolescents are rarely fatal and are seen twice as often in teenaged girls than boys.[9,10] The nonfatal outcome of PE in pediatric patients can be explained by the near absence of chronic lung disease, fewer cardiopulmonary comorbidities, and their greater pulmonary reserve. Surgery, especially orthopedic procedures, thrombophilia, and oral contraception are significantly associated with PE ($P < .5$).[9] Much of the data on incidence in pediatric VTE come from three main registries in Canada, Germany, and the Netherlands.[2,11,12]

The incidence of idiopathic VTE is only 5% in children and <1% in neonates compared with 40% in adults.[2,4,13] Although the neonatal period spans only 4 weeks, 12% of all pediatric thrombi occur in neonates.[4] Recurrent VTE is reported to occur in approximately 3% of neonates and 8% in older children.[2,4,12,14]

METHODS

A MEDLINE search of articles published from 1966 to 2011 was performed to select reports on the diagnosis, treatment, and prevention of first-time and recurrent VTE. The primary terms used were children and pediatrics, combined with deep vein thrombosis, pulmonary embolism, and venous thromboembolism. Secondary terms were central venous line, sinovenous thrombosis, postthrombotic syndrome, prevention, treatment, anticoagulation, thrombolysis, compression, mortality, morbidity, recurrence, portal vein, renal vein, and hepatic vein. A manual search was also performed from the references of the selected articles to identify any important reports that had been missed.

With the exception of a few technical reports that were important for determining the ability and quality of diagnosis, the rest of the articles were selected for their quality. Owing to a lack of prospective randomized studies, most of the larger cohorts giving an answer or at least an insight to clinical problems were selected for this review. Limits for the number of patients in each study were not used, with the exception of case reports and small case series. We selected most relevant articles from retrospective, cross-sectional studies, randomized clinical trials, clinical registries, or prospective studies with acceptable follow-up according to their subject.

Studies of VTE in children predominantly started after the Canadian Registry of VTE in 1994, although there were few isolated prior studies. A systematic review and meta-analysis were not performed because this article covers a complex subject with a multitude of factors. Therefore, pooling of data and separate analyses were not done. Age ranges were not clearly identified in all the reports, and thus definitions were omitted. However, most reports included patients aged <18 years.

RESULTS

Pathophysiology. The incidence of VTE is significantly lower in children compared with adults. Young age has a protective role on developing thrombosis and could be explained by the reduced capacity to generate thrombin,[15,16] increased capacity of α_2 macroglobulin to inhibit thrombin,[17] presence of a circulating anticoagulant at birth,[18-20] and enhanced antithrombotic potential by the vessel wall.[21,22] In addition, the vascular endothelium of children has not accumulated damage from diseases such as hypertension, diabetes, or hypercholesterolemia and therefore maintains its anticoagulant properties. In contrast to adults, children may have not been exposed to acquired thrombotic predictors, such as smoking or antiphospholipid antibodies, but when present, the cumulative effect of these predictors is much less.

VTE is divided into "provoked" and "unprovoked" etiologies. Provoked etiologies include trauma, catheter insertion, and surgery. Unprovoked factors include thrombophilia, idiopathy, and malignancy, although malignancy may also be considered a provoking factor. Most VTE events in children are secondary to conditions such as cancer, trauma/surgery, congenital heart disease, nephrotic syndrome, and systemic lupus erythematosus.[2,13,23-25] The most commonly thrombosed segments in children are the femoropopliteal veins.[5,26,27]

One study demonstrated that children with the highest risk for DVT before their admission were aged >11 years.[5] In hospitalized children, DVT most often is found in those aged <1 and >11years.[2,5] The information in the literature is limited for the bimodal pattern of DVT in hospitalized children. One explanation is that infants <1 year with DVT have more serious conditions, and those children who are aged >11 years are similar to the prehospitalized group.

The presence of a central venous line (CVL) in the pediatric population is one of the most important risk factors in the development of venous thrombosis.[5,26,28] The introduction of a catheter in a vessel can cause thrombosis by directly damaging the vessel wall,[29] disrupting blood flow, and subsequently occluding the vessel, introducing substances like total parenteral nutrition (TPN) that damage endothelial cells,[30] and by the thrombogenic nature of the catheter material.[31] The incidence of CVL-related thrombosis increases more in children with cancer than in adults.[5,32,33] Although CVLs are important for intensive or supportive care of children who require TPN, chemotherapy, or antibiotic administration, more than half of the DVT cases in children and >80% of newborn cases occur in the upper extremity veins secondary to CVLs.[2,11,13,28] Catheterization of the umbilical vessels is a unique predictor of thrombosis in neonates, with an incidence of approximately 13%.[34] In a prospective cohort of 76 children with CVLs placed for 48 hours in an intensive care unit (ICU), CVL-related DVT developed in 18%.[35] More impressively, the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) study[36] reported a DVT incidence of 37% by venography in children with acute lymphoblastic leukemia treated with asparaginase therapy.[33]

Cancer and sepsis are well-known risk factors for venous thrombosis, and recent literature supports the roles that they may play in VTE development in children[37] or adults.[38-40] Alterations in the coagulation pathway were reported in children with meningococcal infections and osteomyelitis associated with VTE in two small studies.[41,42] With respect to cancer, in adult patients who presented with VTE, malignancy was diagnosed in 1.2% to 4%.[43-45] This rate is not clearly reported in children, but most likely should be lower than in adults. This suggests other risks factors, such as mechanical obstruction, chemotherapy, and CVL, are significantly involved in the development of VTE in this population.

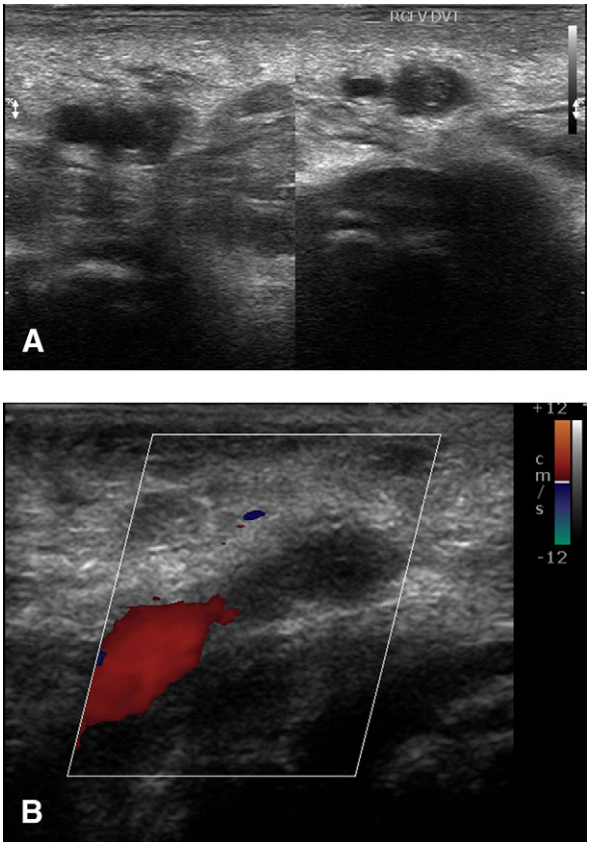

Fig 1. Acute thrombosis of the common femoral vein in 2-year-old boy is demonstrated by cross-sectional imaging of the femoral vessels. **A,** The *left panel* shows a dilated common femoral vein with echolucent luminal material. The *right panel* shows that the common femoral vein is not compressible, despite the use pressure that reduced the common femoral artery diameter by half. **B,** The common femoral vein from the same patient is viewed with color imaging. The vein is dilated, contains echolucent material, and has absence of flow in contrast to normal flow in the adjacent common femoral artery.

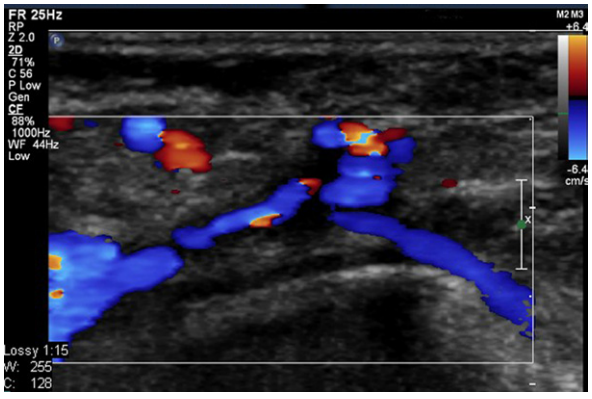

Fig 2. Chronic thrombosis of the common femoral vein is seen a year after it was diagnosed in a 4-month-old girl. Echogenic material is seen in the lumen of the partially recanalized vein. Irregular flow channels are seen through the old thrombus in the common femoral vein.

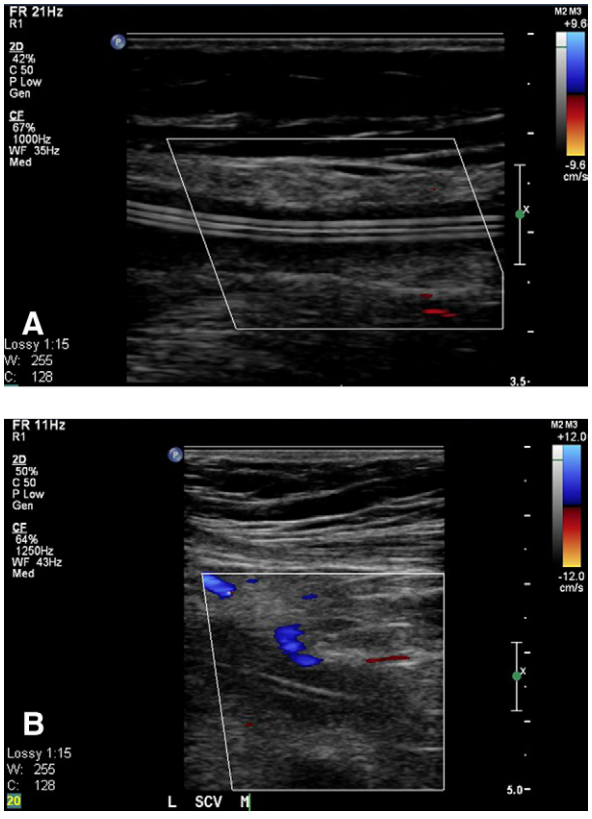

Fig 3. Ultrasound imaging shows catheter-induced thrombosis in the left arm of a 13-year-old girl. **A,** Acute thrombosis of the basilic vein is seen around the catheter. No flow is seen in the dilated lumen, with the catheter being very bright in the center and the thrombus being echolucent around it. **B,** Acute thrombosis of the subclavian vein is seen in the same patient. The catheter is seen in the lumen with absence of flow in the vein.

Diagnosis. Duplex ultrasound (DUS) imaging, venography, computed tomography (CT), and magnetic resonance imaging (MRI) can be used to diagnose venous thrombosis in pediatric patients.[2,13,32] Venography is considered the gold standard for the diagnosis of DVT, but it is rarely used today[33,46] because it is painful, invasive, and peripheral venous access is difficult to obtain in children.

DUS imaging is the first modality that should be used because it is safe, painless, inexpensive, portable, and readily available. It is able to distinguish acute vs chronic thrombus (Figs 1, *A* and *B*, and 2). Factors unique to the pediatric population that may interfere with ultrasound imaging include small diameter vessels, low pulse pressure, and the presence of a CVL at the site of a thrombus (Fig 3, *A* and *B*), which make the vein difficult to compress and subsequently hard to interpret.[47] If the clinical suspicion for venous thrombosis is high and DUS imaging is negative or

equivocal, then CT scan or MRI can be performed to confirm the results. Unlike in children, Prandoni et al[48] published a study in adults with suspected upper extremity DVT that demonstrated a sensitivity of 100% and specificity of 94% for compression ultrasound and color Doppler ultrasound imaging for DVT.

It is critical to detect CVL-related thromboses in children with objective imaging for many reasons. Evidence shows that CVL-related thrombosis may lead to CVL-related sepsis. In a meta-analysis, prophylactic unfractionated heparin therapy reduced CVL-related VTE (relative risk [RR], 0.43; 95% confidence interval [CI], 0.23-0.78) and decreased bacterial colonization (RR, 0.18; 95% CI, 0.06-0.60).[49] CVL-related thrombosis is one of the most common sources for PE in children, which may be fatal.[4,32,50] Recurrent CVL-related thrombosis may result in the loss of venous access that may be required for life-saving interventions such as organ transplant.[4,12,51] Finally, children may have persistent right-to-left intracardiac shunts where thrombus could embolize to the brain and cause a stroke.[4,32]

The diagnosis of DVT in the subclavian, innominate, or superior vena cava with DUS interrogation yields lower sensitivity, and therefore, CT scan or MRI is used. Older studies[52] recommend venogram for detecting thrombi in those locations, but today venograms are discouraged because of the invasiveness and the difficulty of access in children. Pulmonary angiography is the gold standard for diagnosing pulmonary embolus in adults, but in children it can be difficult to get access or interpret the result, and it can be dangerous because of its deleterious effects on renal function. The ventilation/perfusion scan historically has been the preferred method of documenting PE in pediatrics,[46] but because this modality still requires intravenous access and contrast, CT angiography is preferred. CT scan is more frequently used because it is less invasive, relatively quicker, and more accurate, although CT has not been validated in children.[53]

Thrombophilia. The role of thrombophilic disorders in childhood VTE still remains controversial. A recent meta-analysis investigating the role of thrombophilia considered thrombophilia as an additional prothrombotic risk factor in pediatric populations where thrombosis was associated with underlying diseases.[14] The combination of the thrombophilia traits of antithrombin, protein C, and protein S produced the highest odds ratio (OR) and showed a significant association with the first onset of pediatric VTE, as well as recurrence. A similar correlation is seen in adult studies, where patients with deficiencies in protein C, protein S, and antithrombin are considered to be at higher risk for recurrent VTE.[54] Current evidence supports that the association of multiple prothrombotic defects, or the combination of prothrombotic risk factors with acquired ones, increases the risk of thrombosis not only in adults but also in infants and children.[55-61]

However, other studies investigating the deficiencies of antithrombin, protein C, and protein S, in addition to the factor V Leiden and prothrombin gene mutations, found negligible rates of thrombosis in children.[62] A study of an unselected cohort of children with VTE suggested that inherited prothrombotic coagulation proteins do not contribute significantly to the occurrence of pediatric VTE, except in older children with spontaneous VTE.[63] Another study showed that children with VTE had a significantly higher rate of combined genetic risk factors than their parents,[55] posing the question whether screening for genetic risk factors in symptomatic patients is necessary.

Screening for thrombophilia is generally not recommended because this knowledge does not aid in decision making about primary prophylaxis of VTE, and may result in needless concerns for the parents and unnecessary treatment. Specific subsets of patients may benefit from screening, including neonates with catheter-related thrombosis, children with leukemia, and adolescents with unprovoked thrombosis.[14] More important than screening seems to be education of the family to avoid behavioral prothrombotic risk factors such as immobility, dehydration, sedentary lifestyle, overweight/obesity, and smoking.[64] The term "family history of thrombosis" is not a well-defined variable, and how to use this information in assessing children for risk of thrombophilia is not established. If the clinician and family decide to pursue thrombophilia testing because of a positive family history, consideration should be given to testing the affected family members before testing the child.

Treatment. Pediatric studies are challenging to perform, and as a result, antithrombotic therapy recommendations are largely extrapolated from adult studies. Similarly, most of the recommendations for treatment and prophylaxis are derived from generalization of the evidence from remote pediatric and adult clinical trials. In 1995, the American College of Chest Physicians first proposed recommendations for the treatment and management of pediatric DVT, and revisions followed.[65] Anticoagulant therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) should be performed in children with first episode of VTE, with the duration depending on the nature of the thrombosis.[65] The use of routine systemic thromboprophylaxis for children with CVLs was not advised.

Hospitalized children at greatest risk for DVT are considered to be those admitted with severe respiratory, oncologic, or infectious diseases, those receiving TPN, and those who require a prolonged ICU and hospital stay with CVL placement. These children may benefit from thromboprophylaxis.[66] The American College of Chest Physicians guidelines for antithrombotic therapy in children do not include the presence of inherited thrombophilia to guide the duration of anticoagulant therapy,[65] and there are no evidence-based guidelines for thromboprophylaxis in children with inherited thrombophilia.

Unlike in adult trauma patients where the incidence of DVT is as high as 21% without prophylaxis,[67] prophylaxis while an inpatient may not be necessary in pediatric trauma patients aged <13 years old without serious systemic disease.[68] One study found the incidence of clinically significant VTE after trauma in all pediatric patients was 0.06%,[68]

and in a previous study, the incidence of PE was 0.000069% in the same population and 1.85% in children with spinal cord injuries.[28] Therefore, routine prophylaxis in all pediatric patients should not be implemented unless all risk factors are accounted for.

A randomized controlled trial reporting thromboprophylaxis for CVL-related DVT was the Prophylaxis of Thromboembolism in Kids Trial, which attempted to answer the question of whether LMWH may prevent CVL-related DVT.[69] Although this study did not achieve sufficient power to recommend routine thromboprophylaxis for children with CVL in situ, it did show that LMWH is safe to use in children.[69] A randomized controlled trial comparing an LMWH (reviparin sodium) with unfractionated heparin or oral anticoagulation for the treatment of VTE during childhood showed that LMWH was safe and effective for the treatment of VTE in children.[70] The study was underpowered, but it demonstrated that symptomatic recurrent thrombosis occurred after the treatment was stopped and provided information for future studies on the issues associated with therapy for VTE in children.

Thrombolytic regimens have been associated with markedly decreased odds of postthrombotic syndrome (PTS) at 18 to 24 months compared with standard anticoagulation alone (OR, 0.018; 95% CI <0.001-0.483; P = .02), suggesting that systemic or catheter-directed thrombolysis may safely and substantially reduce the risk of PTS in children with occlusive lower extremity acute DVT.[71] When a life-threatening or limb-threatening VTE is present, thrombectomy is recommended. An aggressive treatment of VTE with thrombolysis or surgical thrombectomy is also recommended in children with severe sinovenous thrombosis (SVT) who do not improve with initial anticoagulation therapy. Tissue plasminogen activator has shown efficacy in thrombolysis in venous thrombosis in pediatric patients, but there are no clear indications for venous thrombolysis in children. The only clear recommendations mentioned by the Scientific Subcommittee on Perinatal and Pediatric Thrombosis is that when concomitant heparin is used with thrombolytics, heparin should be administered in prophylactic doses.[72]

Besides thrombolytic therapy, the use of inferior vena cava filters has been described in children. The threshold of placing an IVC filter in children is much higher because there are concerns with IVC size and child growth, as well as long-term complications. IVC filters are used in children with venous thrombosis and contraindications to anticoagulation, such as active bleeding,[73,74] or failed anticoagulation.[74,75] IVC filter placement is restricted to children who weigh >10 kg due to the size of the IVC and the available filter sizes.

The placement and removal of retrievable IVC filters is technically feasible and safe in children.[76,77] Because of the long-term complications associated with filter use, which are similar in adults, retrievable filters should be removed as soon as the risk of PE has resolved.[76] The same study showed that the most common reason for failure of retrieval of an IVC filter was endothelialization of the filter hook or struts.[76] A retrospective review from a trauma database demonstrated that children with filters in place had more severe injuries, as assessed by the Glasgow coma scale, than those without a filter.[73]

Complications. The clinical sequelae of thrombosis depend on the location of the VTE. Specific complications include swelling, chylothorax, portal hypertension (which leads to splenomegaly and varices), PE or pulmonary hypertension, or both, renal vein thrombosis, cerebral vein thrombosis, and superior vena cava syndrome.[78-84] Paradoxical emboli may occur in children with congenital shunts.

Postthrombotic syndrome. PTS is a well-known complication of DVT that occurrs in 20% to 50% of adult patients.[85-88] PTS is defined as swelling, skin pigmentation, pain, and ulceration of the limb secondary to DVT. At present, there are no properly validated outcome measurements for PTS in children because there are very few studies with proper criteria and adequate follow-up. Although previously underestimated,[4,89] PTS occurs in up to 65% of children after venous thrombosis.[51,90,91] Unlike in adults, where the predictors of PTS are well described,[86,92,93] risk factors in children are limited due to lack of resolution of the DVT by radiographic assessment (OR, 3.96; 95% CI, 1.68-9.30), the number of vessels involved in the initial DVT (OR, 2.05; 95% CI, 1.52-2.77), and length of follow-up (OR, 1.22; 95% CI, 1.08-1.39).[51] One of the higher PTS incidences of 63% was given by a cross-sectional study of 153 children at a median follow-up of 16 months.[51] It is important to note that the PTS was mild in 83% and moderate in 17%, with no one developing severe signs and symptoms. Severe PTS is described in 9.3% of adults at 5 years.[85] However, long-term prospective data in children are absent. PTS in the upper extremity is seen less frequently because there are more collaterals, almost nonexistent reflux, and a shorter hydrostatic column compared with the lower extremities for both adults and children.

The low rate of recurrent VTE in children may imply that risk factors for pediatric DVT, such as CVL or underlying primary disorders, are transient in most cases. In addition, the higher rate of PTS described in children may indicate a lack of sufficient knowledge for treating DVT in children. Although controversial, the presence of acquired or congenital prothrombotic markers in children was not a significant risk factor for development of PTS,[51] as seen in adults.

The established therapy for PTS includes the use of compression stockings, limb elevation, avoidance of prolonged standing, and early ambulation. Weight loss and mild exercise have recently been investigated as therapy for PTS.[94,95] As seen in adults, compliance with compression stockings is problematic in children because they dislike displaying visible signs of a disability that make them vulnerable to criticism from their peers. In addition, the difficulty in obtaining appropriately fitted garments in young children and the need for resizing stockings due to the growth of the child makes compliance even harder.

Venous thrombosis in other locations. Pediatric renal vein thrombosis is seen more often in newborns than in older children. Most renal thrombi are unilateral and present within the first 2 days of life, with hematuria, proteinuria, thrombocytopenia, and a palpable abdominal mass.[96,97] Renal vein thrombosis in children is a multifactorial disease, and predisposing factors include dehydration, sepsis, birth asphyxia, maternal diabetes, traumatic delivery, congenital renal vein defects, and umbilical catheterization. Recent surveys suggest the importance of underlying prothrombotic conditions in renal vein thrombosis, such as antithrombin, protein C and S deficiency, and point mutations/substitutions in other coagulation factors, with the factor V Leiden being the most important.[98-101] A recent retrospective trial showed that larger perinatal kidneys had reduced long-term function, suggesting more aggressive treatment should be implemented.[101]

Anticoagulation and lytic therapy have both been suggested for renal vein thrombosis in small studies, but treatment recommendations still remain uncertain. A retrospective case review of 10 years showed duration of anticoagulation ranging from 6 to 14 days for intravenous heparin and from 14 days to 3 months for enoxaparin.[102]

Another form of thrombosis in pediatric patients is portal vein thrombosis. The incidence of neonatal portal vein thrombosis is controversial, ranging from 1% to 43%, which may be explained by its silent nature and the extensive use of umbilical venous catheters.[103-105] Portal vein thrombosis leads to portal hypertension,[80] which may manifest years later as splenomegaly without liver disease, reversal of portal vein flow, and gastric and esophageal varices.[79] Portal vein thrombosis is also associated with umbilical sepsis. Major bleeding related to the varices may become life-threatening.[4,11]

Stroke in neonates from SVT has been well described[47,106] and occurs more often than in adults.[107] The most frequently involved sinuses in neonatal SVT are the superior sagittal and lateral sinuses, the major components of the superficial venous system. Although the overall incidence of SVT in childhood is 0.67/100,000, the incidence in newborns is 41/100,000.[106] The most common presentations of neonatal stroke are seizures and lethargy. Nonneonates with SVT present frequently with focal neurologic deficits or hemiparesis, whereas neonates show signs only up to 25% of the time, explained by the immaturity of the nervous system in the early days of life.[47,106,108] Illnesses in neonates that predispose to SVT include dehydration, sepsis, and head and neck disorders, including meningitis.[47] Neonatal mortality from SVT is estimated at 12%, whereas <5% of neonates will have recurrent SVT.[106]

Mortality. Death after childhood stroke from SVT occurs in 9% to 20%[106,108] of children of all ages, representing all-cause mortality in children that includes cancer, cardiac diseases, and sickle cell anemia. Prospective studies of neonatal thrombosis report 5% to 18% all-cause mortality, with ~50% of deaths due to thrombus formation.[11,13] A registry of noncentral nervous system VTE reported all-cause mortality of 15% to 17%, but DVT/PE related mortality of only 2%.[4]

Limitations. There is limited published information on the recurrence rates of VTE in neonates and on the incidence of PTS. In contrast to adults, where they can verbalize pain, heaviness, swelling, cramps, and itching, these symptoms are more complicated to assess in younger children because they have difficulty in conceptualizing. Children also have difficulties in verbalizing relative pain severity or location; therefore, pain may be underestimated in most of the studies.

Some studies indicate that thrombophilia serves as a risk factor for thrombosis. However, the effect of each type of thrombophilia alone on the outcome and recurrent risk of thrombosis needs to be further investigated. Although we have information on the epidemiology and risk factors of pediatric renal vein thrombosis, evidence about optimal therapy is very limited, suggesting that future trials are required. Until today, few clinical trials have been conducted in pediatric VTE, in contrast to adults, resulting in major gaps in pediatric evidence-based care. Nearly 80% of all drugs approved in the United States have not been labeled for pediatric use, emphasizing the need for more studies to improve medical management in pediatric patients. Another barrier that must be overcome is the reluctance to fund pediatric trials because they present complex ethical and practical issues that reduce feasibility and increase costs compared with adult trials.

FUTURE PERSPECTIVES

Prospective studies are needed to provide validated guidelines for antithrombotic therapy and prophylaxis in neonates and children. The Wells criteria cannot be applied in pediatrics as the only method for diagnosis of VTE, which makes D-dimer testing a possible tool to improve accuracy. The incidence of PTS in children, the relationship to various predictors, and the natural history of VTE need to be delineated in the different age groups. The optimal duration and dose of anticoagulation, the identity of prothrombotic laboratory markers that predispose children to thrombosis, and the effect of thrombolysis have not been investigated adequately, which demands more research. The role of thrombophilia in the development of pediatric VTE, isolated from secondary causes, has not been investigated adequately. The biologic evaluation of genetic predisposition for vascular events in children still remains unclear, and future trials are also urgently needed.

AUTHOR CONTRIBUTIONS

Conception and design: NL, GS
Analysis and interpretation: NL, GS
Data collection: NL, GS
Writing the article: NL, GS
Critical revision of the article: NL, GS, RS, TL
Final approval of the article: NL, GS, RS, TL
Statistical analysis: NL, GS
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