How I treat venous thrombosis in children

Marilyn J. Manco-Johnson

Introduction

Evidence-based medicine for pediatric thrombosis is in its infancy. As recently as 10 years ago, antithrombotic therapy for infants and children was largely based on individual empiric experience, small case series, or was extrapolation from adult recommendations.[1-4] Due to fear of bleeding complications associated with anticoagulation, clinicians were especially reluctant to treat neonates with thrombosis aggressively with antithrombotic therapy despite a high prevalence of short- and long-term sequelae in this age group.[5-7] Most published reports failed to describe therapeutic dosing or duration, and documentation of anticoagulant activity achieved was almost nonexistent. Many thrombi, particularly renal, central nervous system sinovenous thrombosis (CSVT), and catheter-related venous thrombosis, were treated "conservatively," which meant using supportive care with fluid, electrolyte, and blood pressure management.[8-10]

The prevalence and pathologic significance of central and proximal venous thrombi affecting the atrium and vena cava, as well as the subclavian, jugular, iliac, and femoral veins, was not appreciated widely until the ability to detect these clots in infants and children was enhanced by the development of noninvasive imaging techniques using color-flow and pulsed Doppler in addition to gray scale ultrasound (US), echocardiography, and computerized tomography and magnetic resonance with or without angiography (CT, CTA, MR, and MRA). In addition, it is clear that advances in intensive support of critically ill children have involved widespread use of indwelling central venous catheters and invasive procedures that have increased the incidence of deep venous thrombosis (DVT) in children.[11] The development of national and international registries helped to increase awareness of thrombosis in children and focus attention on the serious need for objective data regarding epidemiology, etiology, diagnosis, treatment, and outcome.[5,11-13]

The following discussion presents the individual approach of one pediatric hematologist that has developed over 25 years of clinical practice, clinical research, and review of the results of others. Literature is cited to support treatment practices and recommendations, as available. Where not otherwise supported, the treatment decisions are based upon the author's personal experience and professional judgment.

Diagnosis of thrombosis in children

Most newer imaging techniques have not been validated in children; results are extrapolated from studies in adults. Venous compression US is the cornerstone for diagnosis of DVT in the lower extremity in adults.[14] Compression and Doppler US are easily performed in children. We image the common femoral, femoral, and popliteal veins and their tributaries in transverse and longitudinal scans.[15] With the transducer over the common femoral vein in a transverse projection, the vein is compressed so that it collapses and disappears in comparison to the artery, which does not compress. Failure of the vein to collapse suggests the presence of thrombus; bulging of the vein supplements the diagnosis of thrombus. Failure to image intravascular thrombus suggests fresh (ie, nonechogenic) thrombus. Color-flow and pulsed Doppler images are then acquired throughout the full course of the vein. Flow deficits can be easily detected on color-flow Doppler. While the pulsed Doppler is being performed, augmentation of flow is achieved by squeezing the calf or change in flow is achieved by Valsalva maneuver. Both of these maneuvers result in flow change in patent veins. Reversal of flow on Valsalva maneuver indicates valvular insufficiency.

Imaging upper-extremity DVT is more problematic. Gray scale, color-flow, and pulsed Doppler are also the modality of first choice to evaluate the upper extremity.[16,17] Thrombi in the jugular, axillary, and distal subclavian veins can be detected reliably by US. Atrial and proximal superior vena cava (SVC) clots are also amenable to US diagnosis using echocardiography. Results of the PARKAA (Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia [ALL] Treated with L-asparaginase) study, which showed diagnostic insensitivity of US for SVC and proximal subclavian thrombi and insensitivity of venography for internal jugular thrombi, underscore the limitations of a "one size fits all" diagnostic approach to DVT.[18] MRA is excellent for thrombus imaging in the SVC and proximal subclavian veins. In addition, MRA with or without gadolinium can be used in patients with renal insufficiency or iodine allergies. CT is also quite good for vascular imaging and less expensive than MRA, but CTA does require intravenous iodinated contrast material. Although it is the "gold standard," we rarely use venography in children except during interventional procedures, due to challenging technical difficulties, requirement for iodinated contrast, and possibility of extending thrombus.

We use US as the first-line imaging technique for DVT of the extremity, SVC, and inferior vena cava (IVC), if possible. Echocardiography is our second technique of choice for cardiac and proximal vena cava thrombi. We use CT, without contrast if possible, as the modality of choice for upper-system thrombi as well as abdominal and pelvic vascular imaging in children when

US imaging is not possible. Diffusion MR is our first-line imaging technique of choice for CSVT, with MRA added as needed.

There is no single "best" imaging technique for pulmonary emboli (PEs). A positive helical CT scan confirms the diagnosis of PE whereas a normal ventilation perfusion (VQ) scan rules it out. In the adult literature, CT is more often obtained in patients at high risk of PE, whereas VQ is often obtained in patients at clinical low probability of PE with negative D-dimer.[19,20] Pulmonary angiography is reserved for interventional procedures and diagnostic dilemmas due to its invasiveness. We employ CTA as a first-line modality in children with suspected PE.

Rationale for risk stratification upon which to base choice of initial antithrombotic therapy in children

In the absence of data from randomized clinical trials, the choice of initial antithrombotic therapy for venous thrombosis in children has been dependent upon the experience and comfort of the pediatric hematologist. The classic rationale for antithrombotic therapy has been to prevent death, thrombus progression, or pulmonary embolism. Infants and children exhibit a low mortality from thrombosis or therapy-related complications[5,12,13,15,21-23] although the rate of pulmonary emboli has been reported at approximately 20% and remains the same in my pediatric patients with DVT.[21] Recently we have proposed a more proactive goal of optimizing vascular outcome.

The postthrombotic syndrome (PTS) is a clinical constellation of pain, swelling, visible collateral vein formation, and skin abnormalities that range from hyperpigmentation and induration to stasis ulcers. PTS has been reported in 10% to 60% of children following venous thrombosis.[12,15,23-26] The wide variation has been due, in part, to a lack of standardization among assessment tools used to evaluate children. A pediatric scale for PTS has recently been adapted from the adult international scale and validated in children.[24] The pathophysiology of PTS includes both obstructed and refluxed blood flow resulting in venous hypertension. Two prospective studies in adults suggest a positive relationship between clot persistence and the development of PTS.[27,28] Rapid restoration of vascular patency by clot dissolution might decrease the risk of PTS. Compared with adults, children require a far greater vascular capacity for age-appropriate activities including running and aerobic sports. Although thrombosis usually develops in children with significant underlying disorders, the survival rates for these disorders in childhood is approximately 80% and, unlike adults, most affected children can be expected to live 6 to 9 decades following an episode of thrombosis.[5,12,13,21] The implications of thrombosis outcome on long-term morbidity, cost, and quality of life are therefore far more profound in pediatric patients. Because of its potential to restore venous flow rapidly, thrombolysis is conceptually attractive for the treatment of children. However, not all children require thrombolysis to achieve a good outcome following thrombosis nor is the risk of bleeding associated with thrombolysis acceptable for all pediatric patients.

There have been no head-to-head prospective randomized trials comparing thrombolysis with anticoagulation as initial therapy for infants and children. The rate of vascular patency following anticoagulant therapy in children has been reported at approximately 50% whereas that reported following thrombolysis of acute thrombi is greater than 90%.[15,23,29,30] However, because patient characteristics are not equivalent in reports of the 2 therapies, direct comparison is not possible. Otherwise-healthy children treated

with appropriate regimens of either anticoagulants or thrombolytics exhibit low rates of major bleeding.[15,23,29,30] Minor bleeding is more common with the use of tissue plasminogen activator (TPA) thrombolysis compared with low-molecular-weight heparin (LMWH)[22,23]; in addition, increased bleeding complications were not observed with the use of urokinase (UK) thrombolysis in children.[15] Both therapies appear to be safe when contraindications to use (Table 1) are appropriately followed.

One strategy to select optimal antithrombotic therapy for children with venous thrombosis may be to tailor treatment based upon assessed risk for an unfavorable clot outcome. Both patient-specific and thrombus-specific characteristics can be used to stratify the likelihood of poor outcome into low-, standard-, and high-risk categories. In 2001, a comprehensive thrombosis and thrombophilia program for children was formally organized through the Mountain States Regional Hemophilia & Thrombosis Center (a program of the University of Colorado School of Medicine and The Children's Hospital, Denver) with infrastructure support provided by a pilot grant from the Centers for Disease Control and Prevention and research protocol support provided by the National Institutes of Health (NIH) Pediatric Clinical Research Center. Since then a cohort of children with thrombosis and/or thrombophilia has been followed in the program. My colleagues and I agreed to evaluate, treat, and follow children with thrombosis on clinical pathways that were based upon guidelines recommended by the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy or expert consensus opinion.[31,32] Importantly, we agreed to assess outcomes using standardized tools and consistent time points. Using retrospective analyses of our clinical data, we developed "provisional" or "working" risk categories for children with thrombosis based upon our empiric observations. Future trials will be performed to validate our pilot data.

A suggested provisional schema for childhood thrombosis risk stratification is shown in Table 2. Children without underlying predisposing condition in whom a transient triggering event has resolved are classified as "low risk" because these children appear to have a lower risk for thrombus recurrence or PTS. Thrombi in these children usually develop in the hospital following surgery, trauma, or use of central catheters for resuscitation; are diagnosed without a long lag period; and resolve quickly. Clot resolution

Table 1. Contraindications to specific antithrombotic therapies in infants and children

Unfractionated heparin
Known allergy
History of HITs
Low-molecular-weight heparin
Known allergy
History of HITs
Invasive procedure within the previous 24 h
Systemic TPA
Known allergy
Active bleeding
Central nervous system ischemia/hemorrhage/surgery within the previous 10 d (includes birth asphyxia)
Surgery within the previous 7 d
Invasive procedure within the previous 3 d
Seizures within the previous 48 h
Thrombolysis by interventional radiology
Known allergy
In cases where needed, inability to place a vena cava filter
Limitations are size of involved vessels and experience of interventionalists

Table 2. Risk assessment for persistence or recurrence of venous thrombosis in children

Patient characteristics
Low risk
Trigger resolved/removed
Transient underlying medical condition
Standard risk
FVIII level 150 U/dL or less
D-dimer level 500 ng/mL or less
Fewer than 3 trait thrombophilias*
High risk
FVIII level greater than 150 U/dL
D-dimer level greater than 500 ng/mL
At least 3 trait thrombophilias*
Persistent antiphospholipid antibody
Thrombus characteristics
Low risk
Resolved within 6 weeks
Standard risk
Atrial
Nonocclusive DVT
High risk
Vena cava
Occlusive DVT

*Thrombophilias include genetic and acquired prothrombotic traits that can be determined in blood and are listed in Table 3.

Table 3. Risk factors for thrombosis in children

Time-limited risk factors
Indwelling catheters
Infection
Postinfectious transient antiphospholipid antibodies
Surgery
Surgically correctable congenital heart disease
Ongoing risk factors
Thrombophilia
Genetic thrombophilia
Factor V Leiden, prothrombin 20210 mutation
Deficient/dysfunctional antithrombin, protein C, protein S
Elevations in lipoprotein (a), homocysteine
Other less common genetic disorders of coagulation regulation or fibrinolysis
Acquired thrombophilia (genetic contributions are variable)
Markers of inflammation (elevations in factor VIII, D-dimer, C-reactive protein)
Primary antiphospholipid antibody syndromes (lupus anticoagulant, anti-β2GPI antibody, anticardiolipin antibody)
Acquired decreases in coagulation regulatory proteins (nephrotic syndrome, protein-losing enteropathy)
Indwelling catheters (eg, cystic fibrosis, long-term parenteral nutrition, hemophilia, sickle cell anemia)
Leukemia, cancer, and chemotherapy (eg, *L. asparaginase*)
Inflammatory diseases (systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis)
Prosthetic cardiac valves
Diabetes mellitus
Sickle cell anemia

within 30 days has been related to a low risk of PTS in adults[27,28] as well as in a retrospective review of our patients.[24] Adult patients with similar clinical profiles have been considered "low risk" based upon infrequent thrombus recurrence without analysis of functional outcome.[33]

Clot persistence has been shown to be a marker for development of PTS.[27,28] Clot occlusiveness at initial diagnosis in children has been shown in several retrospective case series to predict thrombus persistence.[25,26,29,30] Recent analyses have determined that an age of 12 years or older at the time of thrombosis in children is associated with an increased risk of PTS, whereas elevations in plasma factor VIII and D-dimer levels, whether at diagnosis or following 3 to 6 months of anticoagulant therapy, predict a composite poor outcome in children including PTS, clot persistence/progression, or recurrence.[24,34] Persistent vena cava thrombus increases the risk for PTS and has been associated with severe symptoms in pediatric patients.[25] In addition, combined genetic prothrombotic risk factors have been shown to increase the risk for thrombus recurrence in children as well as adults.[35,36] We classify children with the above clinical characteristics as high risk and give careful consideration to initial therapy with TPA thrombolysis. Based on our published experience, we usually begin systemic TPA for thrombi with symptomatic onset less than 14 days before initiation of treatment, and local thrombolysis with thrombectomy via interventional radiology for longer-seated thrombi or severe clinical presentations.[23] If systemic thrombolysis is unsuccessful in 24 to 48 hours, we may progress to interventional thrombectomy with or without thrombolysis.

We classify children with DVT as "standard risk" in cases where thrombi develop in association with underlying prothrombotic conditions such as inflammation, hormonal therapy, or genetic thrombophilia. The genetic thrombophilias are those inherited traits that increase the relative risk of thrombus development. Risk factors for thrombosis in children including common genetic thrombophilias are displayed in Table 3. Standard-risk DVT is generally nonocclusive and affected children do not manifest all 3 high-risk features of occlusiveness, elevated factor VIII level, and elevated D-dimer level at the time of presentation.

Examples of how we tailor antithrombotic therapy based upon risk stratification are shown in Table 4. It may soon be possible to assign additional determinants of outcomes in children who present with venous thrombosis. Such information will identify children at high risk for poor outcome, who are likely to benefit from more aggressive antithrombotic treatment, as well as low-risk children who may do well with less intensive or shorter-duration therapy.

Pathophysiologic mechanisms of various risk factors for thrombosis outcome

The cross-talk between coagulation and inflammation has been implicated in venous thrombosis. Inflammation results in increased

Table 4. Examples of therapeutic decision making for first-episode venous thrombosis in infants, children, and adolescents

Nonocclusive DVT, no ongoing trigger (eg, catheter is removed) or prothrombotic conditions → anticoagulation →
Thrombus resolved within 6 wk
Newborn: anticoagulation for 10 d or until clot resolves
Infant, child, adolescent: anticoagulation for 6 wk to 3 mo
Thrombus not resolved within 6 wk → anticoagulation until clot resolves, 3-12 mo*
Occlusive DVT, or nonocclusive central thrombus, symptoms less than 14 d → anticoagulation or systemic low-dose TPA → anticoagulation until clot resolves, 3 to 12 mo*
Occlusive superior or inferior vena cava or iliac, or hemodynamically significant cardiac clot, symptoms present no more than 14 d → systemic thrombolysis → if not resolved in 24-48 h → interventional radiology for catheter-directed thrombectomy/thrombolysis if clot persists, anticoagulation for 12 mo*
Occlusive superior or inferior vena cava or iliofemoral or cardiac, symptoms present more than 14 days → intervention radiology for catheter-directed thrombectomy/thrombolysis if clot persists, anticoagulation for 12 mo*

*Indefinite long-term anticoagulation for all persistent lupus anticoagulant or 3 trait or greater thrombophilia.

thrombin generation, and thrombin reciprocally activates inflammation through activations of monocytes, platelets, and endothelial cells; release of cytokines; initiation of the acute-phase response; and induction of apoptosis.[37] Markers of inflammation including elevations in D-dimer and factor VIII levels as well as inhibition of fibrinolysis have been correlated with thrombus persistence and recurrence in adults.[38-40] Recently, elevation of the inflammatory marker, C-reactive protein, which previously had been associated with arterial vascular events, has been correlated with the onset and severity of PTS following DVT in adults.[41]

Dosing of antithrombotic agents for infants and children

Baseline coagulation studies including the prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and a clotting activation marker, such as D-dimer or fibrin(ogen) degradation products (FDPs), should be obtained before starting any antithrombotic therapy. It is my practice to maintain the fibrinogen level at 100 mg/dL, platelet count at 50 000/μL, and PT within 3 seconds of the upper limit of normal, using transfusions if necessary, to prevent bleeding toxicity while on anticoagulant or thrombolytic therapy.

Unfractionated heparin

Unfractionated heparin (UH) is a very effective drug in children when used appropriately. The short half-life of UH is an advantage for children at high risk for bleeding or likely to require invasive procedures because the effect diminishes rapidly after discontinuation. The greatest bulk of anticoagulant experience in children has been with UH and, owing largely to its half-life of 25 minutes in neonates to 1 hour in adults, it is remarkably safe.[42,43]

UH for therapy of acute thrombosis is given with a loading bolus injection and continuous infusion. In contrast to recommendations for adults, it is my practice to monitor UH in children using anti-Xa activity, as I have found the aPTT to be unsatisfactory for heparin monitoring in a proportion of children. The baseline aPTT is prolonged in neonates and infants due to low levels of contact factors[44]; the addition of heparin does not result in a linear further prolongation of the aPTT in these babies. The lupus anticoagulant, which also prolongs the aPTT and alters the relationship of aPTT to heparin concentration, is present in 2% of otherwise-healthy children,[45] up to 25% of children at the time of presentation with thrombosis,[21] and more than two thirds of children with acute varicella infection[46] or pulmonary emboli.[47] Antithrombin activity, necessary to mediate the anticoagulant effect of heparin, is decreased physiologically in well-term infants; severely decreased in sick preterm infants; and often decreased in children with extensive thrombi, nephrotic syndrome, secretory diarrhea, or chemotherapy with L-asparaginase. Unfortunately, assays to monitor heparin that are more specific than the aPTT are still not available on an as-needed basis for many pediatric services. As tertiary care centers are called upon to support increasing numbers of intensively supported infants and children, efforts should be made to ensure that tests needed to support anticoagulant therapy are available with a clinically relevant turnaround time. Although I do not use aPTT for heparin monitoring, if the baseline aPTT is within the normal range for age, aPTT can be used to monitor UH (if anti-Xa activity testing is not available), aiming for a prolongation to 2 to 3 times the baseline value.

The newborn infant poses special challenges in the use of UH. Early pharmacokinetic studies of McDonald et al[42] using UH documented its very short half-life in neonates. A low rate of bleeding and successful antithrombotic outcome using pharmacokinetically driven data for continuous infusion therapy were reported.[43] Because of physiologically low levels of antithrombin, rapid plasma elimination of UH, and remarkable hypercoagulability, term infants with venous thrombosis, particularly infants of diabetic mothers, have required 50 U/kg/h or more of UH to achieve the therapeutic range of 0.3 to 0.7 U/mL anti-Xa activity.[43,44]

Infants and children exhibit wide variations in dose requirements for UH and often require frequent dose adjustments to maintain a therapeutic anticoagulant effect. An effective schedule for UH loading and infusion is shown in Table 5.

Very high UH requirements have caused many pediatric hematologists to conclude that UH is ineffective or dangerous for use in the neonatal period. I find it to be a very effective therapy. In settings of extreme heparin resistance, requirements for "pharmacologic" as opposed to usual therapeutic doses of UH in newborn infants can be reduced by replacing antithrombin. I have given one vial of antithrombin concentrate (500 units, delivering the entire dose) to infants as small as 2.7 kg (M.J.M-J., unpublished data, approximately 5 cases, 1995-2005). Recovered plasma antithrombin activity following doses as high as 185 U/kg has not exceeded 1.0 U/mL. Plasma recovery of antithrombin in the sick newborn infant may be unexpectedly low because infused antithrombin is going to an endothelial or extravascular compartment. Subsequent to antithrombin infusion, infants have achieved the therapeutic range by anti-Xa activity testing on 15 to 20 U/kg/h of UH. The duration of effect of antithrombin concentrate, when used for this indication, was approximately 2 days. Of course, the combined use of UH and antithrombin concentrate requires meticulous monitoring to ensure safety.

Children treated with UH as an initial agent are generally transitioned to LMWH or warfarin to complete a prescribed course of anticoagulation.

Low-molecular-weight heparins

LMWHs are being used increasingly for initial therapy of acute thrombosis in children, especially outside of the intensive care setting. Based upon studies in adults, LMWHs are judged to have a more predictable dose response and require less monitoring.[48,49] Many adult patients are treated as outpatients using LMWH. Most venous thrombosis in children is treated in the hospital, at least initially, and the appeal of LMWH in this population owes mostly to its subcutaneous administration and reduced requirement for monitoring, especially given that venous access is often limited in infants and small children. Insufficient dosing data regarding LMWH, however, exists in children. Small pharmacokinetic studies of enoxaparin and dalteparin in pediatric patients demonstrate wide ranges of dose requirements, with neonates requiring the highest doses.[50-52] The recommendations of Hirsch et al[32] call for a therapeutic anti-Xa activity range of 0.6 to 1.2 U/mL in adults. Published pediatric series have typically achieved anti-Xa activity levels at or below the lower end of this published therapeutic range. Based upon a recent analysis of enoxaparin dose response in children, more specific age-related doses for enoxaparin can be recommended as shown in Table 5.[30] Children aged 12 to 21 years are consistently in the therapeutic range when treated with an initial enoxaparin dose of 1.25 mg/kg/dose, whereas the majority of neonates reach a therapeutic anti-Xa activity level using 1.625 mg/kg/dose. All patients are monitored by anti-Xa activity assay 4

Table 5. Dosing for antithrombotic therapy in children

	Loading dose, U/kg	Initial maintenance dose	Monitoring
Unfractionated heparin by continuous IV[4,24]			
Neonates less than 28 wk gestation	25	15 U/kg/h (may require ≥ 20 U/kg/h to achieve therapeutic anti-Xa level	Anti-Xa activity: 0.3-0.7 U/mL
Neonates 28-37 wk gestation	50	15 U/kg/h(may require ≥ 25 U/kg/h to achieve therapeutic anti-Xa level)	Anti-Xa activity 0.3-0.7 U/mL
Infants at least 37 wk gestation	100	28 U/kg/h (may need ≥ 50 U/kg/h to achieve therapeutic anti-Xa level)	Anti-Xa activity 0.3-0.7 U/mL
Infants and children older than 1 mo	75	20 U/kg/h (may need ≥ 30 U/kg/h to achieve therapeutic anti-Xa level)	Anti-Xa activity 0.3-0.7 U/mL
Low-molecular-weight heparin[30] and			
subcutaneous enoxaparin, q12h			
Newborns under 1 mo old	None	1.625 mg/kg	Anti-Xa activity 0.5-1.0 U/mL
Infants 1 mo to less than 1 y old	None	1.5 mg/kg	Anti-Xa activity 0.5-1.0 U/mL
Children 1 y to less than 6 y old	None	1.375 mg/kg	Anti-Xa activity 0.5-1.0 U/mL
Children 6 y to less than 21 y old	None	1.25 mg/kg	Anti-Xa activity 0.5-1.0 U/mL
Tissue plasminogen activator by continuous[23]			
IV or bolus*			
Infants less than 3 mo old	None	0.06 mg/kg/h	Clot lysis by imaging or decrease in extent; increase in D-dimer or FSP level
Children 3 mo to less than 21 y old	None	0.03 mg/kg/h; max 2 mg/h	Clot lysis by imaging or decrease in extent; increase in D-dimer or FSP level

*Lower doses of TPA are used in interventional catheter-directed procedures; higher doses of TPA are used by others. See "Thrombolysis using tissue plasminogen activator" for dosing schedules. Bolus dosing of TPA (1 mg/kg with a maximum of 50 mg) can be used for massive PE.

hours after the first or second dose of enoxaparin. Using these initial age-specific enoxaparin doses, a median anti-Xa level of 0.6 U/mL has been achieved in all pediatric age groups.[30] Following the initial dose, subsequent dosing is adjusted based upon anti-Xa activity and increased by 0.125 mg/kg/dose; most children have achieved the targeted therapeutic range following no or one dose adjustment. Children younger than 3 months can require up to 2.0 mg/kg/dose; children aged 1 to 6 years can require as little as 1.25 mg/kg/dose but often require higher doses. Very few pediatric patients exceed 1.0 anti-Xa activity units/mL on 1.25 mg/kg/dose. Using this dosing schema, clot resolution has been achieved in 50% of children with venous thrombosis.[30]

The therapeutic range of anti-Xa activity for LMWH is higher than that for UH because UH exhibits antithrombin as well as anti-Xa activity, whereas the action of LMWH is primarily anti-Xa. Because the effects of LMWH on thrombin are minimal, the aPTT prolongation by LMWH is correspondingly small. Some of my colleagues judge that their coagulation laboratory can correlate small increases in aPTT by LMWH with anti-Xa activity. I have no experience with use of aPTT to monitor LMWH and thus cannot personally advocate its use.

Although children are notoriously reluctant to receive medications by injection, enoxaparin has been successfully administered for a duration of up to 6 months using the Insuflon catheter (Maersk Medical, Lynge, Denmark; distributed by Chronimed, Minnetonka, MN). The Insuflon is a soft plastic infusion device placed under the skin via a small-diameter metal cannula and covered with an adhesive plastic dressing. Doses of LMWH are administered through a small plastic hub. The Insuflon catheter is replaced weekly. Local hematomas are common but can be reduced by applying pressure following injection. Approximately 25% of patients at the Children's Thrombosis/Thrombophilia Program complete a course of anticoagulation using LMWH. The remainder transition to warfarin to complete the prescribed anticoagulation course.

Because of the unique pharmacokinetics of enoxaparin, this agent can be given intravenously with plasma elimination equal to the subcutaneous route. In a rare situation where subcutaneous administration was contraindicated in a very small preterm infant with an infected atrial thrombus, intravenous enoxaparin was used successfully.[53]

LMWH must be withheld for 24 hours prior to invasive procedures, especially lumbar puncture. Thus LMWH is not first-line therapy for certain pediatric patients.

Thrombolysis using tissue plasminogen activator

Systemic thrombolytic therapy should be strongly considered in children with high-risk clots that present within 2 weeks of symptomatic onset. Both TPA and UK have been used successfully in children.[15,23] Currently, UK is not available in the United States. Thrombolytic agents can be administered systemically or locally. Systemic thrombolysis avoids the requirement for interventional radiologic procedures (often challenging in small children), a requirement for anesthesia, and the delay to therapy potentially encumbered during the organization of local invasive thrombolysis. Higher-dose TPA (0.1 to 0.5 mg/kg/h) in short courses of 6 to 48 hours are generally chosen for arterial clots and can also be used for venous thrombi. Low-dose (0.03 to 0.06 mg/kg/h) longer-duration systemic infusions of TPA for 12 to 96 hours have been shown effective for lysis of venous thrombi.[23] Venous thrombi occupy a larger clot volume than do arterial thrombi and occur in low flow states with rapid induction of collaterals. TPA is primarily cleared during the first pass through the liver; most TPA will bypass a completely obstructed venous segment. A longer infusion of TPA at a lower concentration theoretically increases the probability of drug contact with the clot. Systemic infusions of both TPA and UK have been shown to be highly effective in lysis of most pediatric clots when administered within 2 weeks of symptomatic clot onset and only partially effective beyond 2 weeks.[15,23] An initial infusion of TPA for 24 hours has improved our success using interventional thrombectomy in a number of refractory cases. Contraindications to thrombolytic therapy are displayed in Table 1 and a suggested dosing schedule is shown in Table 5.

The most relevant monitoring during thrombolytic therapy is clot lysis as determined by objective imaging. Clots should be imaged prior to and at the conclusion of thrombolytic therapy, at the least. If complete clot lysis is determined on Doppler US, then no marker of biochemical thrombolytic effect is necessary. Using low-dose TPA, we repeat imaging at 24 hours and may double the hourly rate of TPA to 0.06 mg/kg/h (0.12 mg/kg/h for neonates) if there is no evidence of improvement in blood flow. Coagulation screening tests including PT, aPTT, fibrinogen level, plasminogen concentration, and D-dimer or FDP levels, obtained at baseline and every 24 hours while on therapy, are important to ensure hemostatic levels of platelets and fibrinogen and to determine baseline fibrinolytic potential (plasminogen concentration) and activation (D-dimer or FDP levels). If no clot lysis is determined at 24 hours, substantial elevation in D-dimer or FDP levels and/or fall in fibrinogen and plasminogen levels suggest a systemic fibrinolytic effect, in which case higher doses of TPA are unlikely to be more efficacious. If markers do not indicate systemic fibrinolysis, the dose can be increased. Fresh frozen plasma at a dose of 10 mL/kg may be infused daily to replenish plasminogen for plasma concentrations less than 50%. Infusions of thrombolytic agents should be discontinued as soon as clot lysis has been achieved, as there is no potential for further improvement and bleeding complications increase with increasing dose and duration of thrombolytic therapy.

More recently, local delivery of TPA by pulse spray into clots has been used in combination with mechanical clot disruption and thrombectomy, based on encouraging results in adults.[54,55] Increasingly, adolescents and larger children with high-risk clots are being referred to interventional radiology for endovascular thrombectomy using the Angiojet system (Possis, Minneapolis, MN) or the Amplatz Clot Buster system (EV3, Plymouth, MN) and/or local thrombolysis as primary therapy. Smaller children with high-risk clots, particularly SVC obstructions, can be treated with catheter-directed thrombolysis by pediatric cardiologists or radiologists skilled in interventional procedures.

Venous stents have been placed in our pediatric patients to prevent recurrent PE, similar to procedures developed for adults.[56,57] Temporary Greenfield or Tulip filters are placed most commonly in children with large vena cava thrombi who have unstable cardiopulmonary function from recent massive PE, in order to prevent further showering of the lungs with emboli during interventional thrombectomy. Using local thrombolysis, clinically significant restoration of blood flow has been achieved even when therapy is initiated up to 6 months following symptomatic onset. Although our experience with invasive thrombolysis and interventional thrombectomy is relatively recent, early results have been encouraging. Surgical thrombectomy is currently reserved for children with life- or limb-threatening thrombi that have failed or are not amenable to interventional approach (eg, SVC occlusion resulting in a hemodynamically unstable decrease in cardiac venous return).

Oral anticoagulation

Although use of warfarin is not generally popular for children under the age of 1 year, it has been used successfully beginning in the first week of life.[58] However, warfarin adjustment during infancy does require very observant parents and more frequent monitoring. Children treated with warfarin have been reported by the Canadian childhood thrombosis group to exhibit a high risk for exceeding the target international normalized ratio (INR) when loading doses of 0.3 to 0.4 mg/kg were used at initiation.[59] Loading doses of 0.2 mg/kg/d have been reported by this same group to achieve a therapeutic INR within a week. Unfortunately, warfarin

anticoagulation in infants and young children is difficult, even in the context of a comprehensive pediatric anticoagulation clinic, and requires frequent monitoring with dose adjustments.[59]

At the Children's Thrombosis/Thrombophilia Program in Denver, all children on anticoagulation are followed by a multidisciplinary team. The pharmacist carries primary responsibility to record INR values and recommend dose adjustments. Oral anticoagulation with warfarin is routinely started using a maintenance dose of 0.1 mg/kg. The INR is first measured after 3 to 5 days of therapy. Heparin is not discontinued until the INR is greater than the target for 2 consecutive readings. Dose adjustments are made by small increments, usually of 0.5 mg/dose. Frequency of INR determinations is based upon the stability of warfarin effect in an individual child. However, for an average child, the INR is determined twice weekly until the target range is achieved, then weekly for 2 readings, biweekly for 2 determinations, and then monthly. The target INR is 2 to 3 for standard courses of anticoagulation in children; this represents two thirds of children whom I treat. A higher INR target of 2.5 to 3.5 is maintained for children on anticoagulation for certain valvular cardiac disease or for antiphospholipid antibody syndrome. An unusual pediatric patient, such as a teenager with severe protein C deficiency, may require a target INR of 3 to 4. A small number of my patients, approximately 10%, are treated with "mini-dose" warfarin with a target INR of lower than 2, usually 1.5 to 2.0. This unproven dose range is used for the occasional young child with multiple-trait thrombophilia who manifests a persistently elevated D-dimer level but no thrombosis in a steady state, without evidence of infection or inflammation, or a rare child with a high risk for bleeding on standard-intensity warfarin. Most children require 0.1 to 0.15 mg/kg/d of warfarin therapy. Infants younger than a year require higher doses of warfarin, up to 0.5 mg/kg/d, and an occasional older child or teenager requires as little as 0.05 mg/kg/d. Using this approach, a retrospective review of our database indicates that the INR is in the target range 60% of the time, low 25%, and high 15%. In the average children for whom target INR is 2 to 3, extreme values, less than 1.5 or greater than 4.0, each are found on approximately 3% of determinations.

Bleeding toxicity of antithrombotic therapy in children

Hemorrhage occurs as a complication of any antithrombotic therapy. Fortunately, infants and children seem to have a low rate of major bleeding toxicity, and major hemorrhage, defined as that causing a drop in hemoglobin level by 20 or more g/L (2 or more g/dL), requiring red cell transfusion or return to the operating room, intracranial or intraperitoneal, is very uncommon when proper care is taken in patient selection. Great care should be taken in treating any child who is actively bleeding prior to antithrombotic therapy or who has tissue injury from recent surgery, trauma, or invasive procedures. We have treated 170 children with antithrombotic therapy for venous thrombi over the past 4 years. One child each developed a hemorrhagic complication on LMWH (1 epidural hemorrhage/90 children treated), TPA (1 peritoneal hematoma related to a femoral catheter/20 children treated), and coumadin (1 hemorrhagic ovarian cyst/551 patient months). No child developed hemorrhage related to UH.

"Nuisance" bleeding, primarily oozing around indwelling catheters, occurs in 25% of children treated with TPA and appears to be independent of dose.[23]

Many children treated for thromboses are very ill and undergoing intensive supportive care. In order to minimize bleeding complications related to antithrombotic therapy, I use transfusion support to maintain a fibrinogen concentration of at least 100 mg/dL, platelet count of at least 50 000/μL, and prothrombin time within 3 seconds of the upper limit of normal.

UH has a plasma half-life of less than one-half hour in neonates and excessive levels can usually be controlled by stopping the infusion. However, accidental overdose of UH heparin can be reversed by calculating heparin load based on assayed plasma concentration and administering 1 mg of protamine for each 100 U of UH. LMWH is only 70% neutralized by protamine. TPA, owing to its very short half-life is cleared minutes after stopping an infusion. Coumadin toxicity can be treated with transfusion of fresh frozen plasma or nonactivated prothrombin complex concentrates if avoidance of vitamin K administration is desired. Life-threatening hemorrhage has been controlled with recombinant activated factor VII (rFVIIa).[60,61]

Adjuvant therapies for children with limb DVT

In addition to choice and duration of specific antithrombotic agents, pediatric patients are evaluated for adjuvant therapies. All children and adolescents are referred for fitted compression stockings (Jobst BSN, Charlotte, NC) based on evidence for efficacy in prevention of PTS in adults.[62] Compliance with use of compression stockings has been exceedingly problematic and less than 50% of adolescents exhibit consistent use. Stasis ulcers developing in adolescent patients with lower-extremity DVT have been very difficult to manage. Preexisting obesity has been present in adolescents who developed venous stasis ulcers, similar to reports in adults.[63] Nutritional and exercise counseling are part of standard care for our children and adolescents with DVT.

Risk-stratified duration of therapy for children with thrombosis

Historically, the duration of antithrombotic therapy for children was adapted from adult recommendations. Clinical experience has indicated that not all pediatric thrombi have the same potential for progression or recurrence and that future therapy may be individualized based upon risk factors for good or poor thrombotic outcome. Example recommendations for decision making regarding the duration of anticoagulant therapy based upon perceived risk are shown in Table 4.

Low risk for recurrence/progression

All children are treated with UH or LMWH as initial therapy for at least 5 days. Children with catheter-related thrombosis without a significant inflammatory condition in whom the clot resolves rapidly after the trigger is removed appear clinically to have a low rate of clot recurrence. Common examples of transient risks in children include central venous catheters placed for fluid resuscitation, antibiotic delivery, and interventional procedures. It is possible that the standard 3 months of anticoagulant therapy is longer than required. A randomized clinical trial formally comparing 6 weeks to 3 months of anticoagulation in children with early resolution of venous thrombosis has been undertaken by Dr Neil Goldenberg and our team in collaboration with the Hemophilia and

Thrombosis Research Society and will begin enrolling patients shortly. Eligibility for this study is limited to children with first-episode acute venous thrombosis without multiple thrombophilia traits or other potent risk factors for poor outcome.

Venous thrombi in newborn infants, while of significant potential morbidity, often resolve rapidly and have a low recurrence risk.[4,5] We usually discontinue therapy in neonates when the thrombus is resolved.

Standard risk for recurrence/progression

The risk of recurrent thrombosis in children was reported to be 23% at 7 years in a series of Dutch children with DVT.[64] The majority of children with standard-risk thrombosis are treated with anticoagulation using LMWH or UH for at least 7 days, converting to warfarin for 6 months of total therapy or for 12 months if clot persists at 6 months. There is no evidence regarding clot recurrence relative to duration of therapy in children, and a randomized, prospective clinical trial is urgently needed. Data from 2 studies suggest that children with multiple-trait thrombophilia have an increased risk for thrombus recurrence.[35,64] Three aggregated registries in the United States determined a very low rate of thrombus recurrence in children, including children with thrombophilia.[65] Children with multiple-trait thrombophilia were not analyzed separately in the latter report. While the risk of thrombus recurrence is not yet definitively resolved, I base duration of antithrombotic therapy for thrombophilic children with a first DVT on clot resolution and persistence of inflammatory markers.

Some children with standard-risk thrombi are treated initially with thrombolysis with almost uniformly good outcome. These 2 approaches can both be justified and should appropriately be subjected to a randomized clinical trial for formal comparison.

High risk for recurrence/progression

Using clot progression on therapy, recurrence off therapy, or the development of signs and symptoms of PTS as criteria for poor thrombotic outcome, completely occlusive clots as well as elevations of factor VIII and/or D-dimer level have been shown to predict a poor clot outcome in pediatric patients.[29,30,34] Central thrombi occupying the superior or inferior vena cava also appear to convey a worse outcome.[25] Infants with congenital heart disease requiring cardiac catheterization are at risk for stenotic or atretic proximal veins and IVC, sometimes presenting in later childhood and adolescence, suggesting that some cases of atretic IVC may have been preceded by asymptomatic thrombosis.[25,64] Vascular anomalies (eg, May-Thurner anomaly) predispose affected patients to thrombus recurrence and PTS and should be treated as high risk for a poor thrombotic outcome. We treat children at high risk for progression or recurrence with anticoagulation for at least 12 months.

Special cases

Although multiple prothrombotic traits are a risk factor for thrombus recurrence,[35,64] most young children with thrombosis are treated with a finite course of anticoagulation, even if they are found to carry 1 or 2 thrombophilic traits. Children are treated with indefinite anticoagulation if they suffer recurrent thrombosis, have a strongly positive family history of recurrent venous thromboembolism, especially pulmonary embolism, or have a persistently positive D-dimer after 12 months of anticoagulation. Even in the

presence of 3 or more thrombophilic traits, recurrent thrombosis and PTS occur most commonly in children with obstructed and refluxed venous flow, such that mechanical impediments to venous return may be as or more important than thrombophilia in predicting clot recurrence. Antiphospholipid antibody syndrome in children is associated with a very high rate of thrombus recurrence off therapy, and most affected children are treated for an indefinite time period.[47] Children with thrombophilia and severe manifestations in multiple family members often develop recurrent thrombosis around puberty, suggesting that initiation of indefinite-duration anticoagulation may be considered for these patients at puberty.

Renal vein thrombosis in newborn infants carries a very high rate of organ infarction and dysfunction despite heparin anticoagulant therapy.[66] Careful attention should be given to aggressive antithrombotic therapies for renal vein thrombosis, including thrombolysis.

Children with systemic inflammatory disorders including systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis are at risk for thrombus recurrence when their inflammatory process is exacerbated. Children with systemic inflammation and a history of thrombosis are treated prophylactically until the inflammation is under control.

Children with CSVT suffer a high rate of residual cognitive and motor deficits.[67] Two small trials have demonstrated the efficacy of anticoagulation for CSVT.[68] While larger clinical trials are needed to determine optimal therapy for CSVT in children, I advocate antithrombotic therapy in this setting.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is recognized in approximately 1% of at-risk pediatric patients.[69,70] No clinical trials of therapy for HIT in children have been reported; however, therapy with alternative anticoagulants, including argatroban and leptirudin, has been extrapolated from adult recommendations.

Prophylactic anticoagulation in high-risk children

Most symptomatic thrombosis in children presents in the setting of defined risk factors, as displayed in Table 3. Genetic prothrombotic traits are being diagnosed in many asymptomatic children as a result of family studies. To date there are no data upon which to base recommendations for prophylactic anticoagulation for children with a positive diagnosis of one or more thrombophilic traits or for asymptomatic children with a history of previous DVT. In the absence of objective evidence, it appears reasonable to treat thrombophilic children prophylactically periprocedurally as well as during identified time-limited risk periods. I generally treat thrombophilic children with prophylactic doses of UH (10 U/kg/h) or enoxaparin LMWH (0.5 mg/kg/q12h) beginning 12 to 24 hours after surgery, depending on the nature of the procedure, and continuing for days to weeks until perioperative inflammation has subsided and the child has become fully ambulatory. In the highest-risk cases, surgery has been performed with a continuous UH infusion of 10 U/kg/h. Children with trauma are treated from the time hemostasis is achieved until they are ambulatory. Children with a history of previous DVT are treated with similar prophylaxis if their initial thrombotic event had not been related to a risk factor that has resolved. Estrogen-containing oral contraceptives are avoided in affected adolescents, especially those carrying the factor V Leiden mutation or antithrombin deficiency.

Conclusions

While still rare in comparison to incidence in adults, thrombosis is being recognized in children with increasing frequency. The development of comprehensive, multidisciplinary coagulation services to evaluate and treat children with thrombosis and thrombophilia has promoted consistency in diagnosis and management and should result in improved outcomes, similar to results reported for comprehensive hemophilia programs.[71] Descriptive studies have helped to define several epidemiologic and clinical features of pediatric thrombotic disease. However, many important questions regarding optimal prevention and treatment cannot be answered from retrospective studies. Currently, there is an urgent need recognized for the conduct of prospective, randomized clinical trials for infants and children with thrombosis. Creativity is required in design of such studies so that the relatively small number of children available for clinical trials will not impede progress toward achieving optimal outcomes for children with thrombosis.

Acknowledgments

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