How I Treat Venous Thrombosis in Children

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Abbreviations used:

CSVT  central nervous system sinus venous thrombosis
CT    computerized tomography
CTA   computerized tomography angiography
DVT   deep venous thrombosis
IVC   inferior vena cava
MR    magnetic resonance
MRA   magnetic resonance angiography
PTS   post thrombotic syndrome
SVC   superior vena cava
US    ultrasound
Introduction:

Evidence-based medicine for pediatric thrombosis is in its infancy. As recently as ten years ago antithrombotic therapy for infants and children largely was based on individual empiric experience, small case series, or was extrapolated 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 sequellae in this age group (5-7). Most published reports failed to describe therapeutic dosing or duration, and documentation of anticoagulant activity achieved was almost non-existent. 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 non-invasive 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 twenty-five 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 (i.e. non-echogenic) 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 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 utilize 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 cave (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 (PE). A positive helical CT scan confirms the diagnosis of PE while a normal ventilation perfusion (VQ) scan rules it out. In the adult literature, CT is more often obtained in patients in patients at high risk of PE, while 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 in Children to Base Choice of Initial Antithrombotic Therapy:

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 (18). Recently we have proposed a more proactive goal of optimizing vascular outcome.

The post-thrombotic syndrome (PTS) is a clinical constellation of pain, swelling, visible collateral vein formation and skin abnormalities that range from
hypermelaninization 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. As compared to 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 six to nine 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% while 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 two therapies, direct comparison is not possible. Otherwise-
healthy children treated with appropriate regimes 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 as
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 (noted on
Table I) 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 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
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 on Table II. 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 within thirty 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 twelve years or greater at the time of thrombosis in children is associated with an increased risk of PTS, while elevations in plasma factor VIII and D-dimer, whether at diagnosis or following three to six 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 fourteen 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 on Table III. Standard risk DVT is generally non-occlusive and affected children do not manifest all three high-risk features of occlusiveness, elevated factor VIII and elevated D-dimer at the time of presentation.

Examples of how we tailor antithrombotic therapy based upon risk stratification are shown on Table IV. 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 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 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 and a clotting activation marker, such as D-dimer or fibrin(ogen) degradation products (FDP) should be obtained before starting any antithrombotic therapy. It is my practice to maintain fibrinogen 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, UH:

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 one 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 time to heparin concentration, is present in 2% of otherwise well 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. using UH documented its very short half-life in neonates (42). 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/hr 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 on Table V.

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 (unpublished data). 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 extra
vascular compartment. Subsequent to antithrombin infusion, infants have achieved the therapeutic range by anti-Xa activity testing on 15 to 20 U/kg/hr 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, LMWH:**

LMWHs are being utilized 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. call for a therapeutic anti-Xa activity range of 0.6 to 1.2 U/mL in adults (32). 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 on Table
Children from twelve to twenty-one years are consistently in the therapeutic range when treated with an initial enoxaparin dose of 1.25 mg/kg/dose while 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 four 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 less than three months can require up to 2.0 mg/kg/dose; children from one to six 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 anti-thrombin as well as anti-Xa activity, while 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 up to six months using the Insuflon® catheter (Insuflon, 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 IV 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 twenty-four hours prior to invasive procedures, especially lumbar puncture. Thus LMWH is not first-line therapy for certain pediatric patients.

Thrombolysis using Tissue Plasminogen Activator, TPA:

Systemic thrombolytic therapy should be strongly considered in children with high risk clots which present within two weeks of symptomatic onset. Both TPA and UK have been used successfully in children (15, 23). Currently, UK is not available in the US. 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/hr) 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/hr) 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 two weeks of symptomatic clot onset, and only partially effective beyond two weeks (15, 23). An initial infusion of TPA for twenty-four hours has improved our success using interventional thrombectomy in a number of refractory cases. Contraindications to thrombolytic therapy are displayed on Table I and a suggested dosing schedule is shown on Table V.

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/hr (0.12 mg/kg/hr for neonates) if there is no evidence of improvement in blood flow. Coagulation screening tests including PT, aPTT, fibrinogen, plasminogen and D-dimer or FDP, 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). If no clot lysis is
determined at 24 hours, substantial elevation in D-dimer or FDP and/or fall in fibrinogen and plasminogen 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) or the Amplantz Clot Buster system (EV3) 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 six months following symptomatic onset. Although our experience with
invasive thrombolysis and interventional thrombectomy is relatively recent, early results have been encouraging. Surgical thrombectomy currently is reserved for children with life or limb-threatening thrombi that have failed or are not amenable to interventional approach, e.g. SVC occlusion resulting in a hemodynamically unstable decrease in cardiac venous return.

**Oral anticoagulation:**

Although use of warfarin is not popular generally for children under the age of one 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 INR when loading doses of 0.3 to 0.4 mg/kg were used at initiation (59). Loading doses of 0.2 mg/kg/day 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 two 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 two readings, biweekly for two 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 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 < 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 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/day of warfarin therapy. Infants less than a year require higher doses of warfarin, up to 0.5 mg/kg/day and an occasional older child or teenager requires as little as 0.05 mg/kg/day. Using this approach, a retrospective review of our data base 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 by 2 or more grams/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 four 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 ruptured 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 (20).

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 $\geq 100\text{mg/dL}$, platelet count of $\geq 50,000/\mu\text{L}$, 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 non-activated prothrombin complex concentrates if avoidance of vitamin K administration is desired. Life-threatening hemorrhage has been controlled with 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) based on evidence for efficacy in prevention of PTS in adults (62). Compliance with use of compression stockings has been exceedingly problematic and fewer than 50% of adolescents exhibit consistent use. Stasis ulcers developing in adolescent patients with lower extremity DVT have been very difficult to manage. Pre-existing 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 on Table IV.

*Low risk for Recurrence/Progression:*
All children are treated with UH or LMWH as initial therapy for at least five 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 three months of anticoagulant therapy is longer than required. A randomized clinical trial formally comparing six weeks to three months of anticoagulation in children with early resolution of catheter-related thrombosis has been undertaken by 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.

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 seven 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 seven days and converting to warfarin for six months of total therapy or for twelve months if clot persists at six 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 two studies suggest that children with multiple trait
thrombophilia have an increased risk for thrombus recurrence (35, 64). Three aggregated US registries 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 two 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 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, e.g. 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 twelve 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 one or two 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 twelve months of anticoagulation. Even in the presence of three 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 (66). Children with thrombophilia and severe manifestations in multiple family members often develop recurrent thrombosis around puberty.

Renal vein thrombosis in newborn infants carries a very high rate of organ infarction and dysfunction despite heparin anticoagulant therapy (67). 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 (68). Two small trials have demonstrated the efficacy of anticoagulation for CSVT (69). While larger clinical trials are needed to determine optimal therapy for CSVT in children, I advocate antithrombotic therapy in this setting.

**Heparin-induced Thrombocytopenia (HIT)**

Heparin-induced thrombocytopenia is recognized in approximately 1% of at-risk pediatric patients (70,71). 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 on Table III. 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/hr) or LMWH (0.5 mg/kg/q12h) beginning twelve to twenty-four
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/hr. 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, multi-disciplinary 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 (72). 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.
<table>
<thead>
<tr>
<th>Table I. Contraindications to Specific Antithrombotic Therapies in Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfractionated Heparin</strong></td>
</tr>
<tr>
<td>Known allergy</td>
</tr>
<tr>
<td>History of HIT(T)s</td>
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<tr>
<td>Invasive procedure &lt; 24 hours</td>
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</table>
### Table II: Risk Assessment for Persistence or Recurrence of Venous Thrombosis in Children

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Risk</th>
<th>Standard Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Trigger resolved/removed</td>
<td>FVIII $\leq$ 150 U/dL</td>
<td>FVIII $&gt; 150$ U/dL</td>
</tr>
<tr>
<td></td>
<td>Transient underlying medical</td>
<td>D-dimer $\leq$ 500 ng/mL</td>
<td>D-dimer $&gt; 500$ ng/mL</td>
</tr>
<tr>
<td></td>
<td>condition</td>
<td>$&lt; 3$ Trait Thrombophilia*</td>
<td>$\geq 3$ Trait Thrombophilia*</td>
</tr>
<tr>
<td>Thrombus</td>
<td>Resolved within 6 weeks</td>
<td>Atrial</td>
<td>Vena Cava</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-occlusive DVT</td>
<td>Occlusive DVT</td>
</tr>
</tbody>
</table>

* Thrombophilias include genetic and acquired prothrombotic traits that can be determined in blood, and are listed on Table III.
**Table III. Risk Factors for Thrombosis in Children**

**Time-Limited Risk Factors:**
- Indwelling Catheters
- Infection
- Post-infectious Antiphospholipid Antibodies
- Surgery
- Surgically Correctable Congenital Heart Disease

**On-Going 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, anticardiolipin antibody, Anti-β2GP1 antibody

Acquired decreases in coagulation regulatory proteins: nephrotic syndrome, protein losing enteropathy

Indwelling catheters: e.g. Cystic Fibrosis, Long-term Parenteral Nutrition, Hemophilia, Sickle Cell Anemia

Leukemia, Cancer and Chemotherapy

Inflammatory Diseases: Systemic Lupus Erythematosus, Inflammatory Bowel Disease, Rheumatoid Arthritis

Prosthetic Cardiac Valves

Diabetes Mellitus

Sickle Cell Anemia
Table IV. Examples of Therapeutic Decision Making for 1st Episode Venous Thrombosis in Infants, Children & Adolescents:

- Non-occlusive DVT, no on-going trigger (e.g. catheter is removed) or prothrombotic conditions → Anticoagulation →
  
  Thrombus resolved within 6 weeks
  
  → Newborn: Anticoagulation for 10 days or until clot resolves
  
  → Infant, child, adolescent: Anticoagulation for 6 weeks to 3 months
  
  Thrombus not resolved within 6 weeks → Anticoagulation until clot resolves, 3 to 12 months *

- Occlusive DVT, or non-occlusive Central Thrombus, symptoms < 14 days → Anticoagulation or Systemic Low-Dose TPA →
  
  Anticoagulation until clot resolves, 3 to 12 months *

- Occlusive Superior or Inferior Vena Cava or Iliac, or Hemodynamically Significant Cardiac Clot, Symptoms present ≤ 14 days → Systemic Thrombolysis → If not resolved in 48-96 hours → Interventional Radiology for Catheter-directed Thrombectomy/Thrombolysis

- Occlusive Superior or Inferior Vena Cava or Iliofemoral or Cardiac, Symptoms present > 14 days → Intervention Radiology for Catheter-directed Thrombectomy/Thrombolysis

* Indefinite long-term anticoagulation for all persistent Lupus Anticoagulant or ≥ 3 trait Thrombophilia
### Table V. Dosing for Antithrombotic Therapy in Children

| Drug                        | Continuous IV | Low Molecular Weight | Tissue Plasminogen
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Unfractionated Heparin</strong></td>
<td>Continuous IV</td>
<td><strong>Heparin</strong></td>
<td><strong>Activator</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lovenox®, enoxaparin</td>
<td>Continuous IV or Bolus*</td>
</tr>
<tr>
<td><strong>Loading Dose</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Newborn &lt; 37 weeks:</td>
<td>50 U/kg</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Newborn ≥ 37 weeks:</td>
<td>100 U/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant/Child &gt; 1 month:</td>
<td>50 U/kg</td>
<td></td>
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<tr>
<td><strong>Initial Maintenance Dose</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Newborn &lt; 37 weeks:</td>
<td>15 U/kg/hr</td>
<td>Newborn to &lt; 1 month:</td>
<td>Infants to &lt; 3 months:</td>
</tr>
<tr>
<td>(may require ≥ 25 U/kg/hr to achieve therapeutic anti-Xa level)</td>
<td></td>
<td>1.625 mg/kg</td>
<td>0.06 mg/kg/hr</td>
</tr>
<tr>
<td>Newborn ≥ 37 weeks:</td>
<td>28 U/kg/hr</td>
<td>Infants 1 month to &lt; 1 year:</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>(may need ≥ 50 U/kg/hr/hr to achieve therapeutic anti-Xa level)</td>
<td></td>
<td>1 year to &lt; 6 years:</td>
<td>1.375 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months to &lt; 21 years:</td>
<td></td>
</tr>
</tbody>
</table>
Infant/Child/Adolescent: 20 U/kg/hr

6 years to < 21 years: 1.25 mg/kg

(may need ≥ 30 U/kg/hr hr to achieve therapeutic anti-Xa level)

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Anti-Xa activity 0.3 – 0.7 U/mL</th>
<th>Anti-Xa activity 0.5 – 1.0 U/mL</th>
<th>Clot Lysis by imaging or decrease in extent</th>
<th>Increase in D-dimer or FSP</th>
</tr>
</thead>
</table>

- Lower doses of TPA are used in interventional catheter-directed procedures; higher doses of TPA are used by others. See text for dosing schedules. Bolus dosing of TPA can be used for massive PE

0.03 mg/kg/hr; max 2 mg/hr
References:


How I treat venous thrombosis in children

Marilyn J Manco-Johnson