In Brief

Thrombotic Disorders

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Author Disclosure

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Thrombosis historically has been considered a disorder of older adults, in whom it has an incidence of 2.5% to 5%. In comparison, the overall incidence of thrombosis in pediatrics is only 0.07 per 10,000 children, with neonates and adolescents affected most commonly. Advances in pediatric critical care, with survival of sicker children, coupled with the frequent use of central venous lines, have contributed to the growing prevalence of thrombotic disorders. The incidence of thrombosis in hospitalized children is reported to be 5.3 per 10,000 children, greatly increased from previous reports, but still 2 logs lower than in adults. The small numbers of patients, as well as the difficulty of sampling blood, particularly in neonates, have been impediments to pediatric-specific clinical trials. As a result, evidence-based treatment for thrombotic disorders in childhood is largely in its infancy. Treatment frequently has been extrapolated from studies performed in adults, often with disappointing results. The more recent development of national and international registries holds great promise as emerging data reveal potentially important differences in outcomes in children.

Hemostasis is a balance between the tendencies to bleed and to clot and results from an equilibrium between procoagulant and anticoagulant factors. A perturbation in any of these components can lead to an increased tendency for thrombosis. The Virchow triad describes the three broad categories of such disruptions: damaged endothelium, interrupted or decreased blood flow, and abnormalities in blood composition. Damage to the endothelium can be caused, for example, by trauma from a central catheter or from inflammation, as in vasculitis. Decreased blood flow can result from arrhythmias or from immobilization leading to stasis. Abnormalities in the blood most commonly result from defective or deficient coagulant proteins. Very often these predisposing factors, either inherited or acquired, work in concert, providing a cumulative risk of thrombus formation. Acquired risk factors may be transient, such as pregnancy, surgery, and the presence of a central catheter. Genetic thrombophilia is obviously longstanding and has implications for the health of other family members as well. Table 1 provides a more detailed list of potential causes of thrombophilia.

The signs and symptoms of venous and arterial thrombosis vary by the location and extent of vessel occlusion. Many of the acute symptoms of venous thrombosis result from vessel obstruction, stasis, and decreased venous return, leading to pain and swelling distal to the site of obstruction. One third of venous thrombotic events in children involve the upper extremities, a significantly higher proportion than in adults because of the disproportionately larger number of catheter-related thromboses in children. An obstructing thrombus in the superior vena cava (SVC) can lead to SVC syndrome, consisting of upper extremity and facial swelling. Sinus venous thromboses often present with headache, sometimes occurring with additional neurologic symptoms such as blurry vision and even seizures.

Arterial thrombi usually present with obvious signs of decreased perfusion. In the peripheral arteries, pallor and coolness may progress rapidly to cyanosis and tissue necrosis. Cerebral arterial thrombi present dramatically with new-onset neurologic deficits. Pulmonary artery thrombi often are asymptomatic but can lead to hypoxia, tachypnea, pleuritic chest pain, respiratory failure, and circulatory collapse, depending on size and location.

Venous hypertension from chronically obstructed and refluxed flow leads to significant morbidity. Approximately 10% to 60% of children who have thrombi of the extremity develop post-thrombotic syndrome, a clinical con-

Table 1. Causes of Thrombophilia

Acquired Thrombophilia/Risk Factors
Indwelling catheter, trauma, recent surgery, immobilization, congenital heart disease, prosthetic valves, diabetes, sickle cell anemia, chemotherapy, infection, oral contraceptives, smoking, dehydration, nephrotic syndrome, inflammatory bowel disease, antiphospholipid syndrome, elevated factor VIII, malignancy, autoimmune disease
Genetic Thrombophilia
Protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin 20210 mutation, factor V Leiden mutation, elevated homocysteine/MTHFR, elevated lipoprotein A

MTHFR=methylenetetrahydrofolate reductase gene

stellation of symptoms that includes pain, swelling, visible collateral vein formation, hyperpigmentation, induration, and stasis ulcers. Similarly, visceral thrombosis can lead to organ dysfunction over the long term.

Definitive diagnosis of thrombosis requires appropriate imaging studies and is dependent on the location of the thrombus. Ultrasonography is the first-line imaging technique for a deep venous thrombosis of the extremity, especially of the lower limb. Echocardiography is used to view cardiac and proximal vena cava thrombi. Imaging upper extremity thrombosis can be problematic, and detection of clots in the proximal veins requires either computed tomography (CT) scan or magnetic resonance imaging. Thrombi in the central nervous system vasculature are imaged best by magnetic resonance angiography. No one test is best for imaging pulmonary emboli. CT angiography is often the first-line approach for children suspected of having pulmonary emboli (PE). Helical CT frequently is obtained in adults at high risk for PE because it has high specificity, and a ventilation-perfusion scan often is performed in patients at low risk because of its high negative predictive value.

In addition to imaging, measurement of D-dimer has demonstrated utility as a nonspecific marker of thrombosis. D-dimer is generated from the action of naturally occurring fibrinolytic enzymes on cross-linked fibrin within the thrombus. A positive D-dimer test result is worrisome for the presence of a thrombus but should be considered in conjunction with imaging test results.

Mortality from thrombosis in children is low compared with that in adults. Most affected children survive and can be expected to live for decades following a thrombotic event. Thus, the impact on long-term morbidity and quality of life is greater in children. Rapid treatment to prevent complications must be balanced carefully with the risk of bleeding. Anticoagulants form the mainstay of therapy (Table 2). Unfractionated heparin (UH) or low-molecular weight heparin (LMWH) is used initially for at least 5 to 7 days. In stable patients, therapy is completed by either continuing LMWH or switching to warfarin.

Because of its short half-life, UH has been used commonly as the first-line agent in patients who have a high risk for bleeding or a need for invasive procedures. For the same reason, UH must be administered as a continuous intravenous infusion. LMWH appears to be effective, with fewer adverse effects than UH, and is being used increasingly as front-line therapy. LMWH works largely by inhibiting factor Xa, so dosing must be titrated to anti-Xa activity, not to the activated partial thromboplastin time. Warfarin, a vitamin K antagonist, requires very frequent monitoring, which may offset its advantage as an oral agent. The need to crush the medication, which is not available as a liquid preparation, leads to significant dose-to-dose variability, making warfarin impractical for use in very young children.

Whereas the anticoagulants block the formation of clots, tissue plasminogen activator (TPA) is a thrombolytic agent that promotes clot breakdown by activating plasminogen to plasmin, thus tipping hemostatic balance in favor of increased fibrinolysis. Systemic thrombolytic therapy should be strongly considered for clots that have a high risk of morbidity and mortality. The rate of vascular patency following anticoagulant therapy in children has been reported at 50%; following thrombolysis, it is greater than 90%. Systemic TPA is effective when administered within 2 weeks of symptomatic clot onset and only partially effective beyond 2 weeks. TPA can be delivered locally to the site of the thrombus via catheter-directed administration and has been effective even in clots that persist several months from diagnosis. Contraindications to the use of thrombolytic agents include active bleeding, recent surgery, and cerebral ischemia or hemorrhage. Surgical thrombectomy is an option for treating life- or limb-threatening thrombi when thrombolysis is contraindicated or has failed.

Antiplatelet agents such as aspirin are used in certain cardiac disorders, arterial ischemic stroke, and Kawasaki disease. Several anticoagulant-deficient states, such as antithrombin III deficiency and homozygous protein C disease, require specific protein concentrate replacement therapy. Adjuvant therapies include fitted compression stockings, nutritional and exercise counseling to reduce obesity, and adequate control of comorbid conditions. Estrogen-containing oral contraceptives should be avoided in at-risk patients, especially those who carry the

Table 2. Commonly Used Anticoagulants and Thrombolytics

Agent	Mechanism of Action	Pros	Cons	Monitoring
Unfractionated heparin (UH)	Binds to antithrombin III and accelerates inhibition of thrombin and factor Xa	Rapid onset of action, short half-life, easy reversibility, effective antidote (protamine)	Continuous infusion. Risk of bleeding, HIT, osteoporosis	Anti-factor Xa concentration (goal: 0.3 to 0.7) PTT (goal: two to three times baseline)
Low-molecular weight heparin	Inhibits factor Xa	Long half-life, twice a day subcutaneous administration (allows for outpatient treatment), stable pharmacokinetics allows infrequent monitoring and lowers risk of bleeding	Subcutaneous injections. Protamine reversal not complete, HIT (lower than in UH), osteoporosis	Anti-factor Xa concentration 4 hours after second dose (goal: 0.6 to 1.0)
Vitamin K antagonists (warfarin)	Reduces the concentrations of vitamin K–dependent factors: II, VII, IX, and X	Long half-life, oral administration, effective antidote (vitamin K)	Many food and medication interactions and unpredictable concentrations, requires frequent titration	INR (goal: 2 to 3) dependent on indication
Tissue plasminogen activator	Activates plasminogen to plasmin, rapidly promoting clot break down	Rapid onset of action, active lytic agent for high-risk clots	Higher risk of bleeding, requires frequent monitoring, only administered in inpatient setting	Monitor clot by serial imaging. D-dimer increases. Fibrinogen decreases

HIT=heparin-induced thrombocytopenia, INR=international normalized ratio, PTT=partial thromboplastin time

factor V Leiden mutation or have antithrombin deficiency.

Thromboembolic events in children have increased and are a significant cause of morbidity and mortality. Ongoing multi-institutional research should generate the evidence necessary for tailored therapy rather than the "adult-size fits all" approach. Active debate still centers on whom to test, the timing of testing, and which tests to order for children at risk for thrombosis. Novel oral anticoagulant agents with improved safety profiles are needed and are in development.

Comment: Progress comes at a price, and with advances in neonatal and pediatric critical care, particularly with the widespread use of central venous catheters, we are seeing more thrombotic complications affecting children than in the past. However, even with their growing prevalence, thromboses remain relatively uncommon in pediatrics. As with so many other uncommon conditions, the good news of rarity spawns the bad news that evidence sufficient to guide therapy is difficult to gather. Depending on data from the treatment of adults is not ideal because we know children are different. The paradigm for dealing with this frequent problem in pediatrics is provided by the collaborative efforts that over the past few decades have transformed the prognosis for acute lymphoblastic leukemia. We need to encourage as standard procedure the development of national and international databases and study protocols for the multitude of individually uncommon conditions that collectively affect so many children.

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Editor, In Brief