Venous thromboembolism (VTE) is the inappropriate formation of a blood clot within a vein that reduces or completely obstructs venous blood flow. VTE-associated harms are significant and include loss of venous access, pain at the site of thrombosis, infection, pulmonary embolism (PE) (which can be life-threatening), and postthrombotic syndrome. VTE in hospitalized pediatric patients is a rapidly increasing problem, with an increase from 5.3 events per 10,000 hospital admissions in the early 1990s to a current estimate of 58 events per 10,000 hospital admissions.\(^1\)\(^3\) The epidemiological pattern of VTE in pediatrics is bimodal, revealing a peak in the neonatal and then the adolescent age groups.\(^1\) The overall mortality rate associated with VTE is 2.2%.\(^4\)

The majority of hospitalized children who develop VTE are critically ill. Although technological and therapeutic advances have increased survival in critical illness, many also place patients at increased risk for VTE. While the pathogenesis of pediatric VTE is multifactorial, and 95% of VTE cases are related to an underlying disorder,\(^2\)\(^4\) the presence of a central venous catheter (CVC) remains the single most important risk factor for developing VTE.\(^5\) In children admitted to ICUs, the prevalence of clinically apparent deep vein thrombosis and PE is at least 9.3 per 1,000 patients.\(^6\) This is a significant burden of disease in terms of morbidity and mortality. In addition, children with hospital-acquired VTE have an attributable increased length of stay (8.1 days) and an attributable cost of $27,000.

Although previously viewed by some as “the cost of doing business,” thrombosis is now considered by many to be a potentially preventable complication. A nationwide collaborative, Solutions for Patient Safety (SPS), has identified VTE as the second most common hospital-acquired condition throughout the more than 130 hospitals that participate in the collaborative, leading to increased interest in prevention and quality improvement initiatives.

**Hemostasis**

A basic understanding of hemostasis is necessary to appreciate why severely ill patients are prone to thrombosis. Many disease processes in critical illness involve inflammation, infection, and physical disruption of the endothelium, with resultant derangement of the finely balanced hemostatic system. The process of hemostasis stops bleeding at the site of vascular injury through the formation of an impermeable platelet and fibrin plug. Three key mechanisms facilitate hemostasis: vascular constriction, primary platelet plug formation (primary hemostasis), and clot propagation through fibrin formation (secondary hemostasis). Vascular constriction decreases blood flow at the site of injury. Concurrently, platelets adhere to the exposed subendothelium, facilitated through von Willebrand factor tethering, forming an initial platelet plug. Coagulation is initiated through the exposure of tissue factor at the site of endothelial injury. Tissue factor binds and activates factor VII, which activates the coagulation cascade, resulting in a small thrombin burst. This small thrombin burst stimulates further platelet activation and the activation of coagulation on the platelet surface. On this increased platelet surface, a large amount of thrombin is
formed that converts fibrinogen to fibrin. Fibrin, the final procoagulant protein in the coagulation pathway, is cross-linked by factor XIII, forming a stable clot.

This hemostatic process is balanced by anticoagulant and fibrinolytic proteins. The anticoagulant proteins include protein C, protein S, antithrombin, thrombomodulin, heparin cofactor II, and tissue factor pathway inhibitor. Anticoagulant proteins limit further clot formation. Clot degradation is facilitated through the fibrinolytic system, which includes plasminogen, tissue plasminogen activator (tPA), and urokinase plasminogen activator. Plasminogen is converted to plasmin, by either tPA or urokinase plasminogen activator, and cleaves cross-linked fibrin, leading to clot dissolution.

In the neonate, these hemostatic processes are in place but with different concentrations of both procoagulant and anticoagulants compared with adults. In normal postnatal development, many values normalize by 6 months of age, although changes can still be seen throughout childhood. With the onset of puberty, the coagulation system is similar to that of an adult.

**Risk Factors for Thrombosis**

Rudolf Virchow first described the risk factors for venous thrombosis as stasis of venous blood flow, hypercoagulability, and endothelial injury (Figure 1). Using this paradigm, one can see why critically ill patients are at increased risk for VTE (Table 1). As previously mentioned, pediatric VTE is commonly associated with the presence of multiple VTE risk factors, and this is highlighted in critically ill children who commonly are immobilized with a CVC but additionally may have disease processes associated with an increased risk for VTE.

Inherited prothrombotic disorders include deficiencies of anticoagulants (protein S, protein C, and antithrombin) as well as the factor V Leiden and prothrombin gene mutations. These congenital thrombophilias are all associated with an increased risk of VTE but not with an increased risk of arterial thrombosis. Figure 2 provides the relative risk for VTE associated with these disorders. Most pediatric patients, even those with a congenital thrombophilia, will have additional VTE risk factors at the time of their thrombotic event. An exception to needing additional risk factors includes homozygous protein S or C deficiency when at birth, patients present with severe clotting (purpura fulminans).

Acquired risk factors for thrombosis include chronic diseases such as congenital heart disease (CHD), active malignancy, nephrotic syndrome, inflammatory disorders (autoimmune diseases, inflammatory bowel disease, graph versus host disease) and sickle cell disease. Acute illnesses such as severe trauma, sepsis, systemic infection, and severe dehydration can also increase the thrombotic risk. Medical interventions for these conditions have an associated increased risk of VTE, including cannulation of large veins, immobilization, medications, and surgery. While the intent with these treatments is clearly to heal, the untoward side effect of increasing the VTE risk is notable and is associated with significant morbidity and mortality.
Table 1. Virchow’s Triad As It Relates to Critical Illness

<table>
<thead>
<tr>
<th>Virchow’s Triad</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stasis of blood flow</td>
<td>Prolonged immobility</td>
</tr>
<tr>
<td></td>
<td>Venous stasis from central line placement</td>
</tr>
<tr>
<td></td>
<td>Myocardial dysfunction</td>
</tr>
<tr>
<td>Endothelial injury</td>
<td>Medical devices: central venous line, vascular stents</td>
</tr>
<tr>
<td></td>
<td>Systemic infection</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>Diseases</td>
</tr>
<tr>
<td></td>
<td>Congenital cardiac disease</td>
</tr>
<tr>
<td></td>
<td>Inflammatory disorders (autoimmune disease, inflammatory bowel disease)</td>
</tr>
<tr>
<td></td>
<td>Active cancer</td>
</tr>
<tr>
<td></td>
<td>Graph versus host disease</td>
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<tr>
<td></td>
<td>Systemic infection</td>
</tr>
<tr>
<td></td>
<td>Polycythemia</td>
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<tr>
<td></td>
<td>Hyperviscosity from severe dehydration</td>
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<tr>
<td></td>
<td>Antiphospholipid antibody syndrome</td>
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<tr>
<td></td>
<td>Protein-losing disorders (nephrotic syndrome)</td>
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<tr>
<td></td>
<td>Sickle cell disease</td>
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<tr>
<td></td>
<td>Heparin-induced thrombocytopenia</td>
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<tr>
<td></td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td>Estrogen-containing oral contraceptive pills</td>
</tr>
<tr>
<td></td>
<td>Asparaginase</td>
</tr>
<tr>
<td></td>
<td>Activated factor concentrates (recombinant factor VIII, FEIBA)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Congenital thrombophilia</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant deficiency: antithrombin, protein S, or protein C</td>
</tr>
<tr>
<td></td>
<td>Factor V Leiden gene mutation</td>
</tr>
<tr>
<td></td>
<td>Prothrombin gene mutation</td>
</tr>
</tbody>
</table>

Although risk factors for VTE are multifactorial, the presence of a CVC is the greatest causal risk factor across all age groups and clinical conditions. Potential mechanisms for clot formation include flow disruption due to the catheter in the blood vessel, vessel wall trauma during catheter insertion, and endothelial damage from the indwelling line as well as infused irritants and vesicants. Further discussion of specific line-related factors is provided later in this chapter.

A special mention should be given to children with cardiac disease. Children with CHD have altered levels of hemostatic proteins in addition to the known abnormalities in blood flow, blood composition, and vessel wall integrity, rendering them very vulnerable to thrombosis. Recently, Giglia et al. published a nearly 100-page scientific statement in *Circulation* on the prevention and treatment of thrombosis in pediatric CHD. This article thoroughly describes the propensity for thrombosis in CHD and discusses the classes...
of recommendations and levels of evidence behind anticoagulation in specific patient populations, such as palliated CHD, prosthetic valves, cardiopulmonary bypass and extracorporeal membrane oxygenation, arrhythmias, Kawasaki disease, cardiomyopathy, complication of cardiac catheterization, and pulmonary hypertension.

Prevention of Venous Thromboembolism

VTE prevention strategies include early mobilization and mechanical and pharmacologic prophylaxis. Prevention interventions in adults have been stratified based on VTE risk, and similar strategies have been applied in pediatrics. Faustino and Raffini conducted a systematic review of the published guidelines on VTE prevention in hospitalized children. The authors identified a total of 5 published guidelines, and all of the prevention strategies targeted adolescents. The focus on adolescents for VTE prevention is not surprising and is supported by epidemiological data demonstrating that similar to adults, hospitalized adolescents are at increased risk for non-CVC-associated VTE.

Early data suggest that these interventions are effective at VTE prevention in the adolescent population. Interestingly, the presence of a CVC was not a prominent factor in these risk stratifications, likely because of multiple negative randomized clinical trials on pharmacologic prophylaxis to prevent catheter-associated VTE in children.

The national SPS collaborative has recently implemented a non-catheter-related VTE prevention bundle (http://www.solutionsforpatientsafety.org/wp-content/uploads/SPS-Recommended-Bundles.pdf). This bundle is directed at screening hospitalized patients older than 12 years for their VTE risk and targeting prevention interventions based on their VTE risk. Specifically, these interventions include encouraging early and frequent ambulation for all patients, using sequential compression devices for at-risk and high-risk patients, and considering prophylactic anticoagulation for high-risk patients (Figure 3). Like prior published guidelines, the SPS VTE risk stratification does not include the presence of a CVC.

Available data do not support the use of systemic anticoagulation for the primary prevention of catheter-related thrombosis in children. Three randomized clinical trials have studied primary CVC prophylaxis in pediatric patients using prophylactic dosing of either low-molecular-weight heparin (LMWH) (anti-Xa goal, 0.1-0.3 U/mL), unfractionated heparin (UFH) (10 U/kg/h), or warfarin (international
THROMBOSIS IN PEDIATRIC CRITICAL ILLNESS

limiting the number of line days is paramount. The knowledge of Virchow’s triad supports that using the smallest diameter catheter relative to the vein would optimize blood flow. Similarly, reducing endothelial injury by limiting needlesticks during insertion might reduce endothelial injury and decrease the risk of thrombus formation. Latham and Thompson\cite{16} conducted a literature review to find data to guide the anesthesiologist in reducing CVC-associated VTE. Other than removing the CVC as soon as possible, the data were not definitive. Table 2 lists factors the authors identified that trend toward a lower incidence of CVC-associated VTE. Other investigators have evaluated factors associated with CVC location and insertion technique.\cite{17} Three factors achieved statistical significance for increasing CVC-associated VTE risk: left-sided catheter placement (compared with right), subclavian catheter location (compared with internal jugular), and percutaneous placement (compared with a surgical cutdown). Currently, several “insertion factors” are being tested by the SPS collaborative to determine whether they can reduce the incidence of catheter-associated VTE with these targeted interventions.

Figure 3. Solutions for patient safety recommendations for venous thromboembolism (VTE) prevention based risk assessment in hospitalized patients 12 years or older

<table>
<thead>
<tr>
<th>Mobility Status</th>
<th>Low Risk</th>
<th>At risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of VTE Risk Factors</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Altered</td>
</tr>
<tr>
<td>Interventions: with no contraindications present</td>
<td>0</td>
<td>1 or more</td>
<td>0-1</td>
</tr>
<tr>
<td>Encourage highest degree of mobility</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SCD</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: SCD, sequential compression device.

normalized ratio goal (INR), 1.3-1.9), and all were negative studies.\cite{12-14} Massicotte et al\cite{12} conducted a randomized clinical trial comparing thrombotic outcomes in pediatric patients with newly placed CVCs who received either standard of care or low-dose LMWH. Venography failed to reveal a difference between treatment groups for either asymptomatic or symptomatic thrombosis. Schroeder et al\cite{13} randomized infants who had CVCs after surgery for CHD to receive either placebo or continuous UFH at 10 U/kg/h. No difference was found in thrombosis rates (on serial ultrasonographic examination) or in catheter malfunction. Ruud et al\cite{14} randomized 73 children with cancer and CVCs to either low dose warfarin (INR goal 1.3-1.9) or standard of care and they were unable to demonstrate a difference in thrombotic outcomes. Additionally, Vidal et al\cite{15} systematically evaluated 10 trials on pediatric central line prophylaxis, concluding that none of the interventions studied (a heparin-bonded catheter, UFH, LMWH, warfarin, antithrombin concentrate, and nitroglycerin) reduced the risk for CVC-associated thrombosis.

Sparse literature is available regarding non-anticoagulant VTE prevention strategies for CVCs in children. Clearly, like prevention for central line-associated bloodstream infection,
With limited studies specifically addressing VTE prevention in critically ill pediatric patients, care can vary significantly. Faustino et al.\(^\text{18}\) conducted a study of VTE prophylaxis practices in 59 PICUs. This prospective, multinational, cross-sectional study identified that a majority of patients (86.9%) had at least one risk factor for VTE. Mechanical prophylaxis was used in 23.8% of children 8 years of age or older, and pharmacologic VTE prophylaxis was used in only 34.7% of patients in whom there were consensus recommendations for using prophylaxis. The authors concluded that VTE prophylaxis is infrequently used in critically ill children worldwide.

Efforts have been made to standardize the approach to VTE prophylaxis in pediatric trauma patients. Hanson et al.\(^\text{19}\) led a multidisciplinary group of experts in the development of a consensus statement (given there is no evidence on which to base guidelines) regarding VTE prevention in critically ill pediatric trauma patients, a population in which the risk-benefit equation is complicated by inherent bleeding risk. The experts came to several areas of agreement regarding VTE prophylaxis: patients younger than 12 years do not require VTE prophylaxis, patient ambulation is not exclusively protective against VTE, mechanical prophylaxis has a role for those in whom pharmacologic prophylaxis is contraindicated, and strong consideration should be given to pharmacologic prophylaxis if a patient has a personal history of VTE.\(^\text{19}\)

### Detection and Diagnosis of Venous Thromboembolism

Despite prevention efforts, thrombotic events can still occur in hospitalized pediatric patients, and it is imperative that VTE remain a consideration when concerning clinical signs and symptoms are present. The signs and symptoms of VTE are dependent on the site and degree of venous occlusion. When an extremity is affected, the clinical signs include swelling and pain of that extremity. A patient with PE may develop a sudden onset of pleuritic chest pain, shortness of breath, and/or persistent tachycardia. A large PE can present as acute respiratory and cardiac failure. In a patient who is intubated and unable to report symptoms, a PE could present as an acute respiratory decompensation. For those patients with an abnormal connection between the right and left sides of the heart, a venous embolism could become a paradoxical embolism with resultant stroke or distal ischemia to the gastrointestinal tract, kidneys, or limbs.

When VTE is suspected, the imaging modality selected is dependent on the site of thrombosis. Historically, venography was the gold standard, but it has fallen out of favor, being replaced by other imaging modalities like ultrasonography, computed tomography, or magnetic resonance venography.\(^\text{20}\) Ultrasonography, which is commonly used, is noninvasive, and a VTE diagnosis is classically made by noncompressibility of the venous lumen. Figure 4 shows an ultrasonographic image that demonstrates thrombosis in an internal jugular vein. Doppler ultrasonography can further delineate between a completely occlusive versus a nonocclusive thrombus. Echocardiography is commonly used to diagnose superior vena cava, proximal inferior vena cava, or cardiac

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**Table 2. Recommendations to Reduce Catheter-Related Thrombosis**

<table>
<thead>
<tr>
<th>Data support</th>
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<tbody>
<tr>
<td>- Decrease CVC duration.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trend toward lower incidence of thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Place catheter in the right internal jugular vein.</td>
</tr>
<tr>
<td>- Place CVC tip at the caval-atrial junction rather than more proximal sites.</td>
</tr>
<tr>
<td>- Use as small a CVC as clinically warranted.</td>
</tr>
<tr>
<td>- Use static ultrasonography to assess prepuncture patency and anatomic status of vessel.</td>
</tr>
<tr>
<td>- Use real-time ultrasonography during placement to decrease the number of intimal disruptions of the vein.</td>
</tr>
</tbody>
</table>

*Data from Latham and Thompson.\(^\text{16}\)  
Abbreviation: CVC, central venous catheter.*
mural thrombi. In addition, in a patient with a PE, echocardiography can provide intensivists additional information regarding the presence of right-sided ventricular strain. Computed tomography with pulmonary angiography is most commonly used for diagnosing a PE and allows for pulmonary vessel and parenchymal imaging. In children with hypoplastic left-side heart syndrome and a staged repair, a computed tomography with pulmonary angiography is challenging to interpret due to the surgical alteration in pulmonary blood flow. The D-dimer test has not been validated in pediatric clinical trials for the diagnosis of VTE.

**Thrombosis Treatment**

**Anticoagulation**

Early recognition and diagnosis of VTE will ensure prompt treatment to minimize VTE-associated harms. The standard of care for patients with VTE is anticoagulation unless there is a contraindication such as ongoing bleeding or a high risk of bleeding. The goal of anticoagulation is to stop clot propagation and prevent embolism (pulmonary and paradoxical). Additional potential benefits of anticoagulation include preservation of vascular access and the prevention of bacteremia.

The American College of Chest Physicians has published evidence-based clinical practice guidelines for antithrombotic therapy in neonates and children. This is an excellent resource for intensivists, as it provides evidence-based recommendations on anticoagulant choice, dosing, therapeutic levels, and duration of therapy. Acutely, anticoagulation should be initiated as soon as possible with a form of heparin, either UFH or LMWH, and later, if clinically appropriate, converted to warfarin. In pediatric patients, LMWH is favored due to minimal monitoring requirement, lack of significant drug interactions, reduced incidence of heparin-induced thrombocytopenia, and a reduced risk of osteoporosis with long-term use compared with UFH. UFH is favored over the use of LMWH in some clinical situations including but not limited to renal failure, a high risk of bleeding, or concurrent thrombolytic therapy. Currently, direct oral anticoagulants are not approved by the Food and Drug Administration for pediatric use, and clinical trials are underway to assess safety and efficacy.

UFH has no intrinsic anticoagulant effect but instead acts through the binding of antithrombin, which potentiates its anticoagulant activity more than 1,000-fold and inactivates coagulant factors IIa (thrombin), Xa, Xla, and XIIa. The half-life of UFH is short, estimated at 1.5 ± 0.5 hours. Unfortunately, UFH interacts with other plasma proteins, endothelial cells, and macrophages, which can alter the pharmacokinetics with a resultant high inter- and intrapatient dose response.
Intravenous UFH therapy is typically started as a bolus followed by the initiation of a continuous infusion. The two most common assays used to monitor UFH are the activated partial thromboplastin time (aPTT) and the UFH anti-Xa level. Both tests have pitfalls when used to monitor UFH as well as poor correlation. The therapeutic goal for aPTT is 1.5 to 2.5 times control, and the UFH anti-Xa goal is 0.3 to 0.7 U/mL. The aPTT is not a direct measure of the UFH effect and can be influenced by many other parameters that could result in either an overestimation or underestimation of the true UFH effect. For example, an elevated factor VIII or fibrinogen (acute phase reactants) will shorten the aPTT, making it appear that the patient is heparin resistant. Alternatively, a deficiency in a coagulation factor (eg, from liver failure or consumption) or the presence of an antiphospholipid antibody will prolong the aPTT, making it appear that the patient is in the therapeutic range for UFH when in fact he or she is not. The UFH anti-Xa level provides a more direct measure that is not affected by the above factors, although the UFH anti-Xa level does not reflect additional anticoagulant targets of UFH. The activated clotting time is a whole-blood clotting time that is simple to obtain with a rapid turnaround time. It is more sensitive to a wider range of heparin doses than the aPTT and is affected by the same factors as the aPTT; additionally, thrombocytopenia prolongs the activated clotting time. When UFH is being monitored, the blood samples for laboratory coagulation testing should be drawn from a nonheparinized source.

Full reversal of heparin can be obtained with the use of protamine sulfate, a basic protein that binds heparin and forms a salt. Approximately 1 mg of protamine will neutralize 100 units of UFH. Calculations should be made based on the total amount of heparin received in the prior 2 to 2.5 hours. Adverse events such as hypotension and bradycardia can be minimized with slow administration of protamine.

LMWHs are derived from UFH by chemical or enzymatic depolymerization and contain shorter length polysaccharide chains. Similar to UFH, LMWHs exert an anticoagulant effect through binding antithrombin and potentiating the anticoagulant activity; however, in contrast to UFH, LMWHs have a reduced inhibitory activity against factor IIa (thrombin) relative to factor Xa. LMWHs are administered as a subcutaneous injection. The pharmacokinetic properties are more stable than those of UFH. The half-life is 3 to 6 hours, and the LMWH anti-Xa levels peak 3 to 5 hours after dosing. LMWH is predominantly cleared by the kidneys. Dosing will vary based on the exact LMWH that is used. Similar to the use of UFH, if a patient has a low antithrombin level, higher doses of the LMWH may be required.

Routine monitoring in pediatric patients is recommended. An LMWH anti-Xa peak level is used with a goal of 0.5 to 1 U/mL (drawn 3-5 hours after an injection). LMWH can be partially reversed (approximately 70%) with protamine. LMWH should not be used in the setting of renal failure.

Duration of anticoagulation therapy is determined based on the type of thrombotic event, ongoing VTE risk factors, and a patient’s bleeding risk. In patients with a confirmed VTE associated with a CVC, the American College of Chest Physicians guidelines recommend removal of the catheter after 3 to 5 days of anticoagulant therapy if the catheter is no longer needed. This delay theoretically will decrease the risk of VTE embolization with catheter removal. If the CVC needs to remain in place to support ongoing therapy, further clot propagation despite anticoagulation is possible, and patients should be monitored accordingly.

**Thrombolysis**

Thrombolytic therapy should be considered in pediatric patients when the benefit of rapid clot dissolution outweighs the risk of major hemorrhage. Thrombolytic agents dissolve thrombi by activating plasminogen to plasmin, thus stimulating fibrinolysis. The agent of choice in pediatrics is tPA, a recombinant human protein
with a very short half-life of 5 minutes. Strong indications for thrombolysis include a venous thrombus causing tissue ischemia, superior vena cava syndrome, massive PE with cardiovascular instability, bilateral renal vein thrombosis, or cerebral sinovenous thrombosis with progressive neurological decline despite adequate anticoagulation.

The most serious complication of thrombolytic therapy is bleeding. Bleeding complications can range from minor (skin, mucosal, or puncture site bleeding) to major (intracranial hemorrhage, other organ hemorrhage, or hemorrhage requiring transfusion). Reported rates of bleeding have varied in pediatric publications, but preterm infants appear to have the highest risk of intracranial hemorrhage. Table 3 lists relative contraindications to thrombolytic therapy. These should be considered prior to initiating thrombolytic therapy.

Table 3. Relative Contraindications to Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Active bleeding</th>
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<tbody>
<tr>
<td>Inability to maintain platelet count &gt;75,000/μL</td>
</tr>
<tr>
<td>Inability to maintain fibrinogen &gt;100 mg/dL</td>
</tr>
<tr>
<td>Major surgery or hemorrhage within 7-10 days</td>
</tr>
<tr>
<td>Seizures within 48 hours</td>
</tr>
<tr>
<td>Central nervous system surgery, ischemia, trauma, or hemorrhage within 30 days</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
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<tr>
<td>Prematurity (infant of gestational age &lt;32 weeks)</td>
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A number of dosing strategies have been recommended for systemic tPA, but there is no consensus. Two common dosing strategies are “low” dose and “high” dose. Low-dose tPA is 0.03 mg/kg/h (with a maximum dose of 2 mg/h) and is better suited for venous thrombotic events that are non-life threatening. The dose can be increased up to a maximum of 0.06 mg/kg/h if there is no response to the initial dose and can be continued for a prolonged period (48-96 hours). Dose titration should be directed by the close monitoring of thrombolytic labs and serial imaging. High-dose tPA is 0.5 to 0.6 mg/kg/h and should be considered when more rapid clot resolution is required (i.e. arterial or more critical thrombotic events). The thrombus should be reassessed after 6 hours of high-dose tPA. A second, 6-hour infusion can be considered if further clot dissolution is required. In cases of frank cardiogenic shock from massive PE, tPA can be bolused initially during cardiopulmonary resuscitation (10 mg if patient weight is >60 kg); if return of spontaneous circulation is achieved, a longer 2-hour infusion (90 mg if weight >60 kg) can be administered. During resuscitation, bedside ultrasonography performed by well-trained practitioners can be used to quickly diagnose a saddle embolization with massive right-sided dilation to support the use of thrombolysis. In addition, tPA can be delivered via catheter directed thrombolysis and usually in combination with mechanical disruption of the clot by interventional radiology.

Ongoing monitoring of hematological parameters and thrombus response throughout thrombolytic therapy is imperative. Measurements of complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, and D-dimer should be obtained prior to the initiation of thrombolytic therapy and every 4 to 8 hours while the patient is receiving the infusion. An elevated D-dimer and a decrease in fibrinogen are indicative of a lytic state. To minimize the risk of bleeding, fibrinogen should be maintained greater than 100 mg/dL and the platelet count greater than 75,000/mL.

Invasive procedures (eg, arterial catheterization, intramuscular injections, urinary catheterization, and rectal temperatures) should be avoided during thrombolytic therapy. Neonates should undergo head ultrasonography prior to thrombolytic therapy to exclude intracranial hemorrhage. To maximize the lytic response to tPA, neonates should be administered fresh frozen plasma prior to the initiation of tPA infusion because of the decreased plasminogen levels in neonates.

Inferior Vena Cava Filter

Indications for an inferior vena cava filter include either an acute lower extremity deep vein thrombosis and a contraindication to
anticoagulation or a recurrent thrombosis or PE despite adequate anticoagulation. Inferior vena cava filters should be placed in children only if they weigh more than 10 kg.21 Retrievable filters are preferred and should be removed as soon as anticoagulation can be initiated. The filter itself serves as an ongoing nidus for thrombosis that can occur either above or below the filter.

Summary

Pediatric VTE is a frequent occurrence in critically ill children. As pediatric intensive care practitioners, we encounter the morbidity and sometimes the mortality associated with thrombosis. The ability to recognize and efficiently treat VTE is of utmost importance to limit propagation and potential loss of life. Some guidelines are available to aid us in these efforts. Solid data are quite sparse regarding how to prevent hospital-acquired thrombosis in pediatric patients. Collaborative efforts are being made to gather information on how best to reduce hospital-acquired VTE. Given the diversity of patient populations with modifiable and nonmodifiable risk factors, this is a formidable task.

REFERENCES