

## Pediatric deep venous thrombosis



Christopher O. Audu, MD, PhD, Thomas W. Wakefield, MD, and Dawn M. Coleman, MD, *Ann Arbor, Mich*

### ABSTRACT

**Background:** Deep venous thrombosis (DVT) in the pediatric population is rare, occurring in about 10 to 14 out of 10,000 pediatric admissions annually, but with serious consequences such as pulmonary embolism and/or post-thrombotic syndrome. There is a dearth of surgical literature regarding this entity, its pathophysiology, its treatment and its long-term sequelae.

**Methods:** An extensive search of available surgical and medical literature in Medline, PubMed was obtained by searching terms synonymous with pediatric DVT. Case reports and opinion articles were excluded. Ongoing clinical trials were culled from clinicaltrials.gov by searching for pediatric DVT studies. Institutional guidelines, where available, were included in this summary.

**Results:** We provide a clinically relevant summary with the aims of improving prevention, early identification and treatment of pediatric DVT.

**Conclusions:** Although rare and frequently with subtle presentations, pediatric DVT can be serious. Early identification and treatment can be instrumental in limiting sequelae and in improving outcomes for these patients. (*J Vasc Surg: Venous and Lym Dis* 2019;7:452-62.)

**Keywords:** Pediatric; DVT; Clot; Thromboembolism

Deep venous thrombosis (DVT) in the pediatric population is rare,<sup>1-3</sup> but has potentially serious consequences such as pulmonary embolism and post-thrombotic syndrome (PTS). The disease process exists in a bimodal distribution (neonates/infants vs adolescents) and is more frequently iatrogenic from the usage of central venous catheters.<sup>4-6</sup> There is a dearth of surgical literature regarding this entity, its pathophysiology, its treatment, and its long-term sequelae. Herein, we explore available literature (Table I) to provide a clinically relevant summary with the aims of improving prevention, early identification and treatment of this disease.

Pediatric DVT is rare, and in one study has been estimated to occur in 10 to 14 out of 10,000 pediatric admissions annually.<sup>23</sup> Although most incidences are associated with central venous catheterization,<sup>4-6,24</sup> there are many other risk factors to consider, including surgery, trauma, older aged children, congenital prothrombotic disorders (such as antiphospholipid syndrome, factor V Leiden, protein C, and protein S deficiency), acquired hypercoagulable states, use of oral contraceptives, inflammatory bowel disease, renal

comorbidities, short bowel syndrome, infection (owing to the activation of procoagulant pathways), and a positive family history of DVTs (especially because a family history of thrombosis is the most frequently missed risk factor in adults and warrants further study in the pediatric population).<sup>25</sup> Additionally, congenital anatomic variations such as inferior vena cava agenesis, atresia, occlusion, or azygous replacement can predispose patients to DVT development and should be pursued in pediatric DVT patients with no risk factors for thrombosis.<sup>24,26</sup> In pediatric patients with DVT, symptom development is often subtle. The most commonly reported symptoms include unilateral limb swelling with or without erythema, cellulitis, or unilateral limb pain. Phlegmasia is a very uncommon presentation. The diagnosis is usually made by compression color duplex ultrasound examination showing clot burden in the venous drainage of the affected limb.<sup>23,27</sup> Magnetic resonance venography and computed tomography venography may also be useful in evaluating upper extremity DVT as well as ilio caval DVT, balancing the risk of anesthesia (when required), radiation, and contrast use.<sup>28</sup> Although the use of heparinized saline flushes and close surveillance with serial imaging and/or duplex studies for children with indwelling catheters is recommended, there have been efforts to identify biomarkers that could aid in the diagnosis. There are some data to suggest that trending D-dimer levels in any child with a central venous catheter while hospitalized and raising one's suspicion for values greater than 500 ng/mL<sup>13,29</sup> for an active thrombotic process. Although other biomarkers that hold promise, including factor VIII, lupus anticoagulant, and serum homocysteine, may be useful in risk assessment,<sup>7</sup> further research

From the Section of Vascular Surgery, Department of Surgery, Michigan Medicine, University of Michigan.

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Correspondence: Dawn M. Coleman, MD, Section of Vascular Surgery, Department of Surgery, Michigan Medicine, 1500 E Medical Center Dr, 5172 Frankel CVC, Ann Arbor, MI 48109 (e-mail: dawnbarn@med.umich.edu).

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**Table I.** Select studies of pediatric deep venous thrombosis (DVT)/venous thromboembolism (VTE) culled from the surgical and nonsurgical literature

Author, title, year	Method	Conclusions
<b>Reviews</b>		
Jaffray and Young, <sup>5</sup> Deep Vein Thrombosis in Pediatric Patients, 2017	Literature review	<p>Efforts of the Children's Hospitals Solution for Patient Safety are underway to prevent VTE in children</p> <p>Data from the Kids' Inpatient Database shows tertiary centers have increased rates of DVT over community hospitals.</p> <p>CVCs are strongly associated with DVT in pediatrics although there is no consensus on which type is most responsible</p> <p>In addition to anticoagulation, thrombolysis can also be considered given adequate benefit to risk ratio.</p> <p>PTS is a well-known sequela.</p> <p>Prophylaxis for DVT are yet to be deemed effective in children. The Children's Hospital Acquired Thrombosis study will help in identifying risk factor prediction model and determine prevention strategies.</p>
Zia et al, <sup>7</sup> Markers of coagulation activation, inflammation and fibrinolysis as predictors of poor outcomes after pediatric venous thromboembolism: A systematic review and meta-analysis, 2017	Systematic review and meta-analysis	<p>A close relationship exists between inflammation and thrombosis.</p> <p>Although limited, elevated D-dimer, FVIII and lupus anticoagulant in the acute setting and chronically (3-6 months after the incident) shows promise for predicting recurrent VTE and PTS in the pediatric population.</p>
Leeper et al, <sup>8</sup> VTE in pediatric trauma patients - 10 year experience and long-term follow up in a tertiary care center, 2017	Retrospective review of pediatric trauma admissions to ICU from 2005 to 2014.	<p>TBI therapy is closely linked to the development of DVT.</p> <p>Coagulopathy on admission is associated with hypercoagulability in the postinjury period.</p> <p>Treatment was not associated with improved VTE outcomes.</p>
Vu et al, <sup>3</sup> Determination of risk factors for DVT in hospitalized children, 2008	Cross-sectional study from Health Care Cost and Utilization Project Kids inpatient database for 1997, 2000, and 2003	<p>Discharge diagnosis of DVT of the lower extremities has increased since 1997.</p> <p>Risk factors include: age (15-17 years), obesity, IBD, hematologic malignancy, and surgery (thoracoabdominal or orthopedic).</p>
<b>DVT treatment</b>		
Newall et al, <sup>9</sup> Anticoagulant prophylaxis and therapy in children: current challenges and emerging issues, 2018	Literature review	<p>Pediatric/neonatal DVT is a growing problem with few guidelines to steer treatment.</p> <p>Patients in the ICU and neonates are at highest risk. A thorough risk benefit profile should be generated before anticoagulation.</p> <p>Common anticoagulation in this population centers on LMWH, UFH and vitamin K</p>

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Table I. Continued.

Author, title, year	Method	Conclusions
		<p>antagonists, taking special note of differences in pharmacodynamics and pharmacokinetics compared with their adult counterparts.</p> <p>DOACs do not have pediatric dosing yet although Pediatric Investigation Plans for these drugs are in the early stages.</p>
Tarango et al, <sup>10</sup> Pediatric thrombolysis: a practical approach, 2017	Mini-review	<p>Thrombolysis is indicated in the setting of life-/limb-threatening thrombosis and can rapidly improve venous patency and may improve long term outcomes such as PTS.</p> <p>There are no high-quality clinical trials of thrombolysis in pediatric thrombosis.</p> <p>Thrombolysis is used in acute cases (&lt;14 days of onset) of vessel occlusion</p> <p>Recombinant tPA (alteplase) is most commonly used due to its short half-life. Dosing is not standardized.</p> <p>The authors recommend anticoagulation with thrombolysis owing to the release of active thrombin with lysis procedures.</p> <p>Contraindications: active bleeding, bleeding diathesis, recent major surgery, cranial hemorrhage, right-to-left shunt, extreme prematurity.</p> <p>Systemic and endovascular thrombolysis (infusion, catheter directed, PMT; PPMT) are most common approaches though no head to head comparisons are available now.</p> <p>Cryoglobulin is to be used for immediate reversal if bleeding occurs; protamine for UFH and TXA as needed.</p> <p>Thrombolysis in children is not benign and treatment must be a multidisciplinary effort.</p>
Lungren et al, <sup>11</sup> Endovascular thrombolysis to salvage central venous access in children with catheter-associated upper extremity DVT: technique and initial results, 2015	Cohort study	<p>Nine patients with average age of 8.3 years (range, 20 days to 17 years) with catheter associated UE-DVT underwent thrombolysis with access salvage as goal.</p> <p>tPA was used for thrombolysis in addition to balloon angioplasty, and mechanical thrombectomy.</p> <p>Endovenous thrombolysis for catheter associated upper extremity DVT in children may be safe and effective and could be considered particularly in patients in whom long term venous access is needed.</p>
Andrade-Campos, <sup>12</sup> Dosing and monitoring of enoxaparin therapy in children: experience in a tertiary care hospital, 2013 <sup>88</sup>	Cohort study	<p>A retrospective study from January 2005 to March 2012 involving patients &lt;16 years old treated with LMWH for DVT monitored by anti-factor Xa level (target, 0.5-1.0 U/mL at 4-6 hours post diagnosis).</p> <p>Dose increases were needed early in patients &lt;6 years old and neonates/infants required an initial higher dose to become therapeutic.</p> <p>All patients achieved DVT resolution.</p>

**Table I.** Continued.

Author, title, year	Method	Conclusions
Thompson et al, <sup>6</sup> Venous thromboembolism prophylaxis in the pediatric trauma population, 2013	Literature review	<p>Incidence of VTE in pediatric trauma patients is low (~0.02% of all admissions).</p> <p>Older (&gt;13 years) and more severely injured patients are at greater risk for VTE.</p> <p>Patients with major vascular injury and those with spinal cord/spine injury benefit the most.</p>
Goldenberg et al, <sup>13</sup> Percutaneous mechanical and pharmacomechanical thrombolysis for occlusive DVT of the proximal limb in adolescent subjects, 2011	Institution based prospective inception cohort study of pediatric VTE	<p>Institutional prospective cohort study experience with PMT/PPMT in adolescent subjects judged to be at high risk for PTS development.</p> <p>Local recurrent VTE following PMT/PPMT was observed.</p> <p>Recommend aggressive periprocedural anticoagulation.</p>
Leary et al, <sup>14</sup> Low dose systemic thrombolytic therapy for DVT in pediatric patients, 2010	Retrospective cohort study	<p>Twenty-three pediatric patients (median age, 12 years) received low-dose tPA initiated at 0.03-0.06 mg/kg/h for 24 hours with thrombus resolution (partial or complete) in 36%.</p> <p>The rest were treated at higher dosing with 75% response.</p> <p>Low-dose tPA administration leads to a substantial response rate although the risk of bleeding remains unclear.</p> <p>Neonates were not studied.</p>
Tousovská et al, <sup>15</sup> Treatment of DVT with LMWH in pediatric cancer: safety and efficacy, 2009	Cohort study	<p>Neither patency rates nor the risk of PTS showed a positive correlation with the achievement of therapeutic anti-factor Xa activity.</p> <p>Treatment schedule of LMWH at an initial dose of 1.2-1.5 mg/kg twice daily for the first 7-10 days followed by 1.5 mg/kg once daily, for 3 months duration proved to be well-tolerated and efficient in treating DVT in children undergoing chemotherapy.</p>
Stine et al, <sup>16</sup> Treatment of DVT with LMWH in pediatric cancer patients receiving chemotherapy, 2007	Cohort study	<p>Seven patients aged 4-17 undergoing immunotherapy with diagnoses of ALL, Hodgkin's disease, anaplastic large cell lymphoma, rhabdomyosarcoma were treated with LMWH titrated to an anti-factor Xa levels of 0.5-1.5 IU/mL until clot resolution.</p> <p>Dose was decreased to daily for total of 3-6 months of treatment. By 1-2 months, 100% of patients had resolution of thrombus.</p>
Merkel et al, <sup>17</sup> Long term treatment of thrombosis with enoxaparin in pediatric and adolescent patients, 2006	Cohort study	<p>In this pilot study, 27 children with DVT were treated with LMWH at a dosage of 1.5 mg/kg bid in neonates and 1 mg/kg bid in children.</p> <p>Eighty-five percent of patients responded well to LMWH therapy. The mean duration of the therapeutic phase was 16.5 days, which was followed by LMWH prophylaxis for 9.8 months.</p>

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**Table I.** Continued.

Author, title, year	Method	Conclusions
		No rethrombosis observed in follow-up at 2.3 years.
<b>PTS</b>		
Betensky and Goldenberg, <sup>18</sup> Post-thrombotic syndrome in children, 2018	Review	<p>PTS is a chronic condition characterized by the development of venous insufficiency that manifests clinically as extremity swelling, pain, cramping, stasis dermatitis, and ulceration of the affected limb. The incidence ranges from 3% to 70% for a median of 2 years after DVT.</p> <p>The inflammatory response to DVT contributes to PTS development.</p> <p>Risk factors are (1) patient-related (BMI, comorbidities, CVC use), (2) thrombus-related (DVT location, lack of resolution), (3) biomarkers (D-dimer, FVIII elevation); and (4) treatment-related factors (anticoagulation, PMT).</p> <p>PTS is a clinical diagnosis. The Manco-Johnson instrument and the modified Villalta scale are measures used to quantify/classify PTS.</p> <p>There are no preventative strategies proven to date.</p>
Baker et al, <sup>19</sup> Complications and 30-day outcomes associated with VTE in the Pediatric orthopaedic surgical population, 2016	Query of ACS NSQIP pediatric database queried for patients undergoing orthopaedic procedure between 2012 and 2013.	<p>Of &gt;14,000 cases, only 0.1% had a postoperative VTE.</p> <p>Surgery for infection had the highest VTE incidence. Other patient factors associated with VTE were hyponatremia, and GI, renal, and hematologic disorders.</p> <p>Complications associated with VTE: increased hospitalization length, central line-associated blood systemic infection, pneumonia, UTI, and unplanned intubation.</p> <p>In the absence of risk factors, thromboprophylaxis may not be necessary in this population.</p>
Avila et al, <sup>20</sup> Postthrombotic syndrome and other outcomes of lower extremity deep vein thrombosis in children, 2016	Retrospective, single institution study between January 2000 and December 2014.	<p>Line-related lower extremity DVT had more benign outcomes than non-line-related DVT.</p> <p>Sex, DVT triggering event, and DVT resolution predicted lower extremity PTS.</p>
Kumar et al, <sup>21</sup> Prevalence and risk factors for PTS after DVT in children - a cohort study, 2015	Prospective study using the Mayo Clinic Master Diagnostic Index	<p>More than 70% of children with DVT report subsequent symptoms or signs of PTS, although only 13% report clinically significant, moderate to severe PTS.</p> <p>For every doubling in the years since the incident DVT, the likelihood of PTS increases by a factor of 1.75</p> <p>Every extra vein segment thrombosed increases the likelihood of having PTS by factor of 1.4.</p>

**Table I.** Continued.

Author, title, year	Method	Conclusions
Avila et al, <sup>22</sup> PTS following upper extremity DVT in children, 2014	Cohort study investigating the occurrence, characteristics, and predictors of UE-PTS	Despite its relatively estimated high occurrence, the characterization of pediatric UE-DVT and UE-PTS is lacking. The most common triggering events in the cohort of 158 children were effort-related in primary events (87%), and central lines in neonates (100%) and non-neonates (92%). Pediatric UE-PTS frequency and severity depend on UE-DVT pathogenesis and on patient's age. Line-related PTS had a more benign course in neonates.
<b>Program development</b>		
Kukreja et al, <sup>1</sup> Developing a pediatric endovascular thrombolysis program: a single center experience, 2013	Process paper	Creating a thrombolysis center requires a multidisciplinary approach with significant buy in. This institution used pediatric hematology, VIR, critical care, anesthesiology and vascular surgery. Stringent inclusion criteria: thrombosis involving IVC, deep pelvic veins, lower extremity proximal to calf veins. Exclusion criteria: pregnancy or <10 days post-partum, serum creatinine >2 mg/dL, concurrent bleeding diathesis, major surgery/trauma, cerebrovascular hemorrhage/infection, intracranial aneurysm, uncontrolled SBP >180 mm Hg or DBP >100 mm Hg, atrial fibrillation, known left to right shunt, pericarditis, history of HIT, history of anaphylactic reaction to contrast dye. Heparin was infused before, during and after thrombolysis with eventual transition to LMWH. Clinical exam more telling than radiographic images days after the procedure for evaluating treatment success. Follow-up was in 3 and 6 months.
<p><i>ACS</i>, American College of Surgeons; <i>ALL</i>, acute lymphocytic leukemia; <i>bid</i> two times per day; <i>BMI</i>, body mass index; <i>CVC</i>, central venous catheter; <i>DBP</i>, diastolic blood pressure; <i>DOAC</i>, direct antithrombin anticoagulant agents; <i>FVIII</i>, factor VIII; <i>GI</i>, gastrointestinal; <i>HITT</i>, heparin-induced thrombocytopenia with thrombosis; <i>IBD</i>, inflammatory bowel disease; <i>ICU</i>, intensive care unit; <i>IVC</i>, inferior vena cava; <i>LMWH</i>, low-molecular-weight heparin; <i>NSQIP</i>, National Surgical Quality Improvement Program; <i>SBP</i>, systolic blood pressure; <i>PMT</i>, percutaneous mechanical thrombolysis; <i>PPMT</i>, percutaneous pharmacomechanical thrombolysis; <i>PTS</i>, post-thrombotic syndrome; <i>TBI</i>, traumatic brain injury; <i>tPA</i>, tissue plasminogen activator; <i>TXA</i>, tranexamic acid; <i>UE-DVT</i>, upper extremity deep venous thrombosis; <i>UE-PTS</i>, upper extremity post-thrombotic syndrome; <i>UTI</i>, urinary tract infection.</p>		

is needed to elucidate the usefulness of these biomarkers to predict adverse outcomes after VTE in children.

Once diagnosed, there are two mainstays of treatment: anticoagulation with continued monitoring or thrombolysis.<sup>30</sup> For acute and subacute DVT, anticoagulation therapy is preferred. Current recommendations are to use lovenox or heparin with target anti-Xa levels of 0.3 to 0.7 IU/mL for a duration of 3 to 6 months, with subsequent continuation of therapy determined by the persistence of clinically significant prothrombotic risk factors.<sup>8,15-17,31</sup> Lovenox has the advantages of increased DVT efficacy, less intracranial hemorrhage as well as a

longer half-life than unfractionated heparin. After the initiation of heparin therapy, warfarin is the agent of choice for longer term (>3 months) therapeutic intensity anticoagulation in children. This recommendation is subsequent to the complication of heparin-induced osteoporosis and fractures associated with longer term low-molecular-weight heparin therapy.<sup>32,33</sup> The target international normalized ratio depends on the underlying disorder but in children with thromboembolism, the target international normalized ratio is 2.0 to 3.0, similar to the adult population.<sup>34</sup> There is no consensus for the use of the newer direct antithrombin anticoagulant agents such as rivaroxaban, apixaban, edoxaban, or dabigatran

because these medications were not developed with children in the study groups and the lack of reversible agents for most of these medications has prevented early adoption (although dabigatran and the anti-Xa agents now have reversal agents that are approved by the US Food and Drug Administration).<sup>9,35</sup> Several studies are ongoing regarding their usage in the pediatric population (Table II).

For patients with significant acute symptoms of pain and swelling who fail to respond to anticoagulation and those with perceived limb threat, systemic thrombolysis, usually with tissue plasminogen activator, followed by months of anticoagulation is increasingly reported. One study which evaluated systemic thrombolysis with anticoagulation for pediatric patients ages 11 to 21 with lower extremity DVTs reported a markedly decreased odds of PTS at 18 to 24 months compared with standard anticoagulation alone.<sup>13,29</sup> The role of catheter-based pharmacomechanical thrombolysis depends on the clot burden, with larger clots being more suited for this treatment modality.<sup>1,10,11,13,14,36</sup> Contraindications to either form of thrombolysis include the following: surgery or invasive procedure within 7 to 14 days of therapy, central nervous system hemorrhage/trauma/surgery within the preceding 2 months, severe asphyxia event within 7 days of therapy, current central nervous system pathology, seizure history, severe bleeding, uncontrolled or uncorrectable coagulopathy (inability to maintain fibrinogen >100 mg/dL or platelets >75,000–100,000 × 10<sup>9</sup>/L), systemic septicemia, contrast allergy, and serum creatinine of greater than 2 mg/dL.<sup>13,37,38</sup> The role of systemic or catheter-based thrombolysis in neonates for venous thrombi nonthreatening to life, organ, or limb is not established and, as such, is relatively contraindicated.<sup>39</sup>

The treatment of DVT in the pediatric population can be stratified by location of disease and its etiology. An algorithmic approach to management is presented in the Fig, divided into upper extremity DVT, lower extremity DVT, and visceral DVT.<sup>40</sup>

The sequelae of DVT in the pediatric population can be devastating and can be subdivided into short and long term. Short-term sequelae include limb edema, pain, discoloration, and pulmonary embolism, whereas long-term sequelae include recurrence, PTS (ie, pain, swelling, skin induration, and ulcers), the development of varices, loss of vein access, and ultimately death (although rare). Recurrence of DVT in children carries a lower risk than in adults, with cumulative incidences at 1 to 2 years of 6% to 11% vs 12% to 22%, respectively. Recurrence is treated for 6 to 12 months in the presence of an underlying reversible risk factor, 12 months to lifelong when idiopathic, and lifelong when a chronic risk factor persists.<sup>41</sup> The risk for PTS in children who have DVT of the limbs, however, seems at least as great as that in adults

(cumulative incidences at 1-2 years of 33%-70%, vs 29%, respectively).<sup>41</sup> However, severe PTS is a rare occurrence in children and infants.<sup>42,43</sup> There is a role for compression stocking usage in treating PTS in children, and this modality is often the first line of treatment, although its use is beset by concerns similar to the adult population, namely, discomfort, lack of patient/parent understanding of their condition, difficult application of stocking, and appearance.<sup>44,45</sup> Recanalization of chronically thrombosed veins in children is not studied outside of portal vein thrombosis recanalization associated with hepatic transplantation. The overall mortality in children with DVT is often owing to associated comorbidities; mortality owing to DVT itself is approximately 2%.<sup>41</sup>

DVT in the neonatal population is exceedingly rare (approximately 0.51 for every 10,000 live births per year)<sup>46</sup> and occurrences are frequently owing to the use of central venous catheters in the intensive care setting. Other reported causes are trauma, overwhelming sepsis, and underlying congenital disease. Most thromboembolic treatment protocols during the neonatal period are from expert opinion because there are no randomized, controlled trials. Nonetheless, standard low-molecular-weight heparin can be used in neonatal DVT with shortened duration compared with children.<sup>32</sup>

## PROPHYLAXIS AND NEW INITIATIVES

Given the sequelae and prevalence of DVTs in the pediatric population, preventative measures become important.<sup>5,9</sup> For patients with significant risk factors, several investigators recommend prophylaxis with antiplatelet agents, such as aspirin, and lovenox (<2 months, 0.75 mg/kg/dose subcutaneous twice daily; >2 months old, 0.5 mg/kg/dose subcutaneous twice daily).<sup>2,5,8-10,17,28,31</sup> There is no guideline for the use of inferior vena cava filters for prophylaxis in children and, as mentioned, the use of direct antithrombin anticoagulant agents as oral anticoagulant agents for prophylaxis in children is not recommended at this time.<sup>9</sup>

New initiatives are being developed at various centers to care for pediatric DVTs. The development of a Comprehensive Pediatric Thrombosis center that specializes in the notification, prevention, treatment, and follow-up of pediatric DVT cases with devoted resources has been advocated.<sup>2,36,47</sup> Additionally, several institutions have created guidelines for the treatment of pediatric DVTs. Given the rarity of this disease, this may become the trend wherein centers of excellence with devoted resources are aimed at this significant but rare clinical problem.

Finally, there are clinical trials aimed at further understanding the pathogenesis and treatment of pediatric DVTs (Table II). The information gleaned from these

**Table II.** Current clinical trials targeting pediatric venous thromboses. Accessed from [clinicaltrials.gov](http://clinicaltrials.gov) by searching for pediatric deep venous thrombosis (DVT)<sup>a</sup>

Trial Name	Summary	Primary outcomes	Sponsor	Stage
Pediatric High Risk Deep Venous Thrombosis Lytic Outcomes Trial (PHLO)	Evaluating the use of adjunctive catheter-directed thrombolysis, which includes the intrathrombus administration of recombinant tPA (activase/alteplase) and its ability to prevent PTS in pediatric patients compared with standard anticoagulation alone	Development of PTS within 24 months after randomization.	University of Colorado, Denver	Recruiting
Pediatric Pharmacokinetics/ Pharmacodynamics (PK/PD) Study	Phase I, open-label, multiple center study in pediatric patients from 0 to 18 years of age, trialing a single dose of edoxaban (30 vs 60 mg)	PK – Apparent systemic clearance (CL/F). PK – Apparent volume of distribution (V/F). PK – AUC for edoxaban and metabolites PK-Metabolite/parent ratios for AUC	Dalichi Sankyo Inc	Recruiting
Hokusai Study in Pediatric Patients with Confirmed VTE	An event-driven, prospective, randomized, open-label, blinded end point evaluation parallel group study in subjects with confirmed VTE to study the pharmacokinetics and pharmacodynamics of edoxaban in relation with standard of care.	Symptomatic recurrent VTE Death as a result of VTE No change or extension of thrombotic burden	Dalichi Sankyo, Inc	Recruiting
Thrombosis Outcomes in Pediatric Venous Thromboembolism (TOP) Study	Prospective cohort study looking to develop better prognostic biomarkers and to identify children at higher risk of adverse thrombotic outcomes very early in the course after an initial VTE. The study will compare biomarkers in children who develop poor VTE outcomes after an initial VTE with those who do not develop such outcomes.	PTS, symptomatic recurrent venous thromboembolism, and postpulmonary embolism impairment	Children's Medical Center, Dallas, Tex	Recruiting
Prevalence and Risk Factors of Venous Thromboembolism in Hospitalized Pediatric Patients	Evaluation of the prevalence of venous thromboembolism in hospitalized pediatric patients, and to identify if there are subgroups of patients who may be at higher risk. Two working hypothesis include that individual risk factors for VTE include age, obesity, black race, female sex, presence of a central venous line, traumatic mechanism of injury, orthopedic surgery and the use of OCPs. The second hypothesis is that risk factors have an additive effect such that risk	Documented VTE in patients aged ≤18 years of age who were hospitalized at MSMHC from January 1, 2000, to December 31, 2008.	Penn State University	Completed November 2017

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**Table II.** Continued.

Trial Name	Summary	Primary outcomes	Sponsor	Stage
	stratification can be developed to identify those patients with the highest risk.			
Incidence of Venous Thromboembolism in Children Undergoing Elective Neurosurgical Procedures	To determine frequency of clot development in the deep veins of children undergoing elective neurosurgery procedures,	Number of participants with postoperative ultrasound without evidence of thromboembolism.	James Whitcomb Riley Hospital for Children, Indianapolis, Ind	Complete

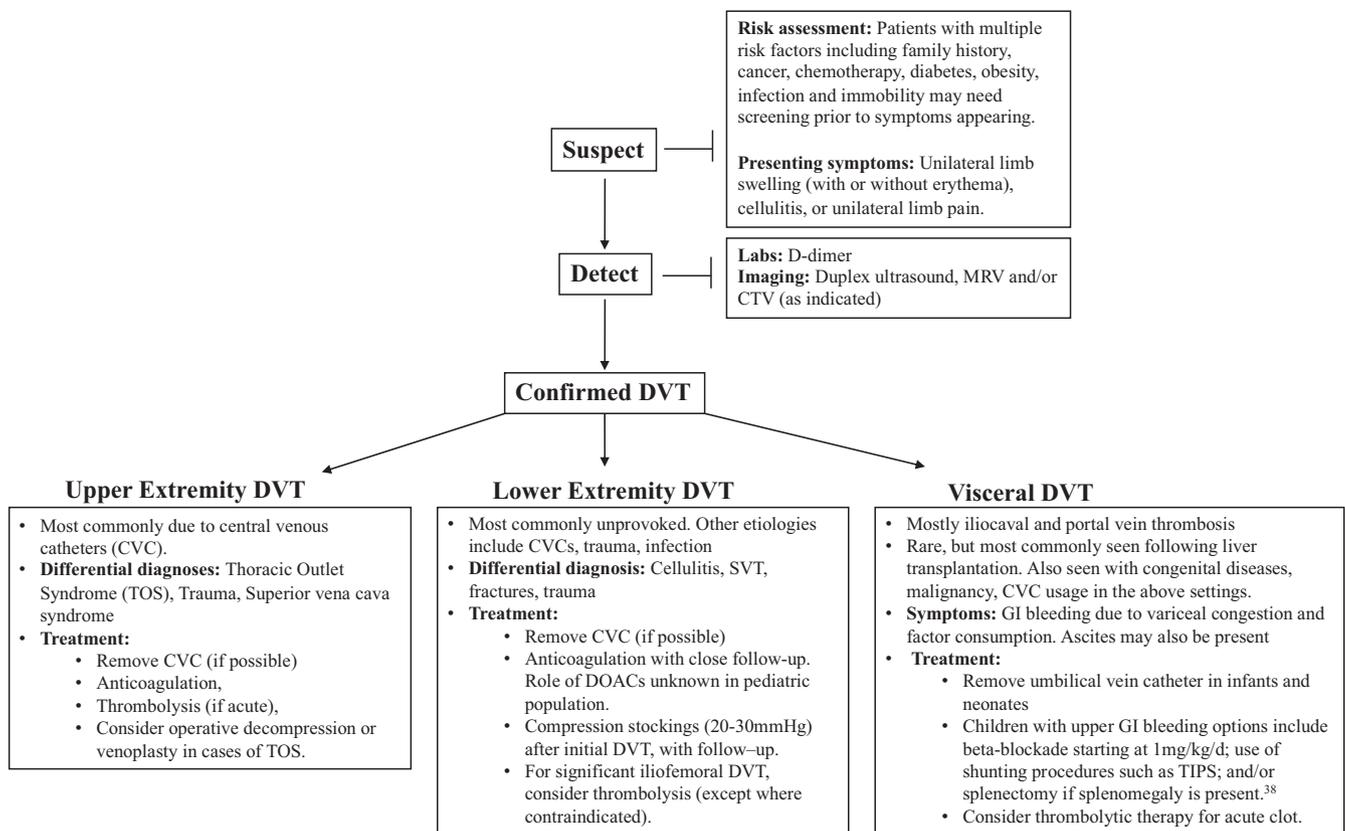
*AUC*, Area under the concentration-time curve; *OCP*, oral contraceptive pills; *PTS*, post-thrombotic syndrome; *tPA*, tissue plasminogen activator; *VTE*, venous thromboembolism.  
<sup>a</sup>Accessed on June 12, 2018.

studies will help to identify higher risk populations and tailor treatment to this group.

## CONCLUSIONS AND RECOMMENDATIONS

Although rare and frequently with subtle presentations, pediatric DVTs can be serious. Early identification and treatment can be instrumental in limiting sequelae and in improving outcomes for these patients.

There are limitations to this evidence summary. Chiefly, there is a dearth of prospective, randomized, controlled studies in this patient population regarding DVT and their treatment. This lack is partially due to the relatively low incidence of pediatric DVTs, and the increased ethical complexity surrounding any studies involving infants/children. Additionally, most trials on the study of anticoagulation agents did not involve infants and



**Fig.** Summary algorithm for approaching the management of pediatric deep vein thrombosis (DVT). CTV, computed tomography venography; GI, gastrointestinal; MRV, magnetic resonance venography; SVT, superficial vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

children in the pilot studies and hence extrapolation of treatment paradigms from the adult population is necessary.

Several take home recommendations are readily applicable for the daily practicing vascular surgeon who may encounter, or be consulted on, DVT in the pediatric population. An overview of such recommendations is presented in the Fig. Certain questions remain in the treatment of pediatric DVTs, such as the duration of treatment for unprovoked DVTs in these patients and the use of novel direct anticoagulant agents for prophylaxis and treatment. Studies are needed to help answer these questions.

### AUTHOR CONTRIBUTIONS

Conception and design: CA, DC, TW

Analysis and interpretation: CA, DC, TW

Data collection: CA

Writing the article: CA, DC, TW

Critical revision of the article: CA, DC, TW

Final approval of the article: CA, DC, TW

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