**Definition:** Venous thrombosis is a blood clot that forms in a vein deep in the body. Venous thrombi are composed of large amounts of fibrin containing numerous erythrocytes, platelets, and leucocytes. (1) Venous thrombosis can produce a significant obstruction to blood flow, with the most serious pulmonary embolism. (1) Technologic advances in pediatrics have resulted in increasing numbers of patients being at risk for deep vein thrombosis (DVT) requiring antithrombotic therapy.

**Etiology:** Below is a list of some of the more common, important risk factors for DVT classified by time course, (1)

**Risk Factors for DVT** (1)
- History of DVT
- Cancer and chemotherapy
- Congenital heart disease
- Sickle cell anemia, Beta thalassemia
- Inflammatory diseases (Systemic Lupus Erythematosus [SLE], Inflammatory Bowel Disease)
- Renal disorders (Nephrotic syndrome)
- Pregnancy or combined oral contraceptive use
- Obesity
- Aberrant venous anatomy
- Genetic thrombophilic traits
  - Decreased antithrombin, protein C, protein S
  - Factor V Leiden, Prothrombin G20210A mutation
  - Factor 9, 11 and fibrinogen levels, homocysteine, Lp(a)
- Acquired thrombophilic traits
  - Antiphospholipid Antibodies (APA)- lupus anticoagulant, anticardiolipin antibodies, anti-β2GP1 antibodies
  - Acquired abnormalities in antithrombin, protein C, protein S
  - Elevated Factor 8 with systemic inflammatory states (such as SLE)

**Inclusion Criteria**
- Patients ≤21 years of age with signs and symptoms concerning for venous thrombosis

**Exclusion Criteria**
- Pregnancy

**Diagnostic Evaluation** (2)

**History:** Obtain a detailed history that includes previous central venous access, underlying medical conditions, subsequent planned medical or surgical management of any primary condition (may impact on any anticoagulation therapy), previous central nervous system insults, surgery, trauma or bleeding symptoms (bleeding risk if anticoagulated), medication compliance history, and social circumstances (impact on ability to deliver safe anticoagulation after hospital discharge). In adolescents, assess use of contraceptives. Obtain a detailed family history of thrombosis, including the circumstances of any documented thrombosis or miscarriages.

**Physical Examination**

Signs and symptoms of a DVT are dependent upon the location. DVT occurs in the upper extremities in approximately 60% of children due to the increased incidence of CVC-related thrombotic complications. Table 1 summarizes the clinical signs and symptoms of a DVT in relation to the location.

**Table 1. Clinical Signs and Symptoms and Location** (3,4)

<table>
<thead>
<tr>
<th>DVT Location</th>
<th>Clinical Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Venous Line Site (CVC)</td>
<td>CVC dysfunction</td>
</tr>
<tr>
<td></td>
<td>Limb swelling distal to a CVC insertion site</td>
</tr>
<tr>
<td></td>
<td>Superficial new collateral vein development adjacent to a CVC insertion site</td>
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<tr>
<td></td>
<td>Recurrent CVC sepsis, especially with the same organism</td>
</tr>
<tr>
<td>Extremity</td>
<td>Extremity pain, discoloration, swelling</td>
</tr>
<tr>
<td></td>
<td>Collateral vein development</td>
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<tr>
<td></td>
<td>Infrequently, fever and abdominal or inguinal pain in lower extremity</td>
</tr>
<tr>
<td>Superior Vena Cava</td>
<td>Swelling of neck and face, bilateral periorbital edema</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Internal Jugular</td>
<td>Unilateral swelling in neck and face, pain</td>
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<tr>
<td></td>
<td>Periorbital edema</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>Unexplained SOB</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Pleuritic chest pain</td>
</tr>
<tr>
<td></td>
<td>Hypoxemia</td>
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<tr>
<td></td>
<td>Fever</td>
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<tr>
<td></td>
<td>Pallor</td>
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<tr>
<td></td>
<td>Cyanosis, hemoptysis</td>
</tr>
<tr>
<td></td>
<td>Sudden collapse</td>
</tr>
<tr>
<td>Renal Vein Thrombosis</td>
<td>Hematuria, flank mass, thrombocytopenia (all three may not be clinically obvious at diagnosis), proteinuria, uremia, oliguria</td>
</tr>
<tr>
<td>Portal Vein</td>
<td>Splenomegaly</td>
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<tr>
<td></td>
<td>GI bleeding</td>
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<tr>
<td></td>
<td>Gastroesophageal varices</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Other</td>
<td>Large left iliofemoral vein thrombosis – consider May-Thurner Syndrome</td>
</tr>
<tr>
<td></td>
<td>Spontaneous upper venous thrombosis – consider Paget-Schroetter Syndrome (Thoracic Outlet Syndrome)</td>
</tr>
</tbody>
</table>

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Laboratory Tests

### Initial Laboratory Studies
- CBC
- DIC panel (includes PT, PTT, thrombin time, fibrinogen, D-dimer, heparine PTT as needed, and platelet count)
- Antithrombin (AT) for patients <6 months of age

### Diagnostic Imaging
Consultation with radiologist to choose appropriate imaging is recommended.

1. Internal jugular DVT – Doppler ultrasound (US) imaging; MR Venogram (MRV) as alternate

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**Critical Points of Evidence**

**Recommendations Adopted or Adapted from the American Society of Hematology Guideline**

- Administration of anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE). – Strong recommendation
- To use thrombolysis followed by anticoagulation in pediatric patients with DVT. As Texas Children’s Hospital is a center with access to pediatric interventional radiology, local thrombolysis may be appropriate given the location, size, and clinical impact of the thrombus. – Conditional recommendation
- To offer anticoagulation in pediatric patients with sub-massive PE. – Strong recommendation
- To use thrombolysis followed by anticoagulation in pediatric patients with pulmonary embolism with hemodynamic compromise. – Strong recommendation
- To use anticoagulation alone in patients with symptomatic DVT or PE. – Conditional recommendation
- To not use antithrombin replacement therapy in addition to standard anticoagulation in pediatric patients with DVT or PE. – Conditional recommendation
- To use antithrombin replacement therapy in addition to standard anticoagulation rather than standard anticoagulation alone in pediatric patients with DVT/CSVT/PE who have failed to respond clinically to standard anticoagulation treatment and in whom subsequent measurement of AT concentrations reveals low AT levels based on age appropriate reference ranges. – Conditional recommendation
- To not remove a functioning CVAD in pediatric patients who continue to require venous access. – Conditional recommendation
- To remove a non-functioning or unneeded CVAD in pediatric patients with symptomatic CVAD-related thrombosis. – Strong recommendation
- To delay CVAD removal after initiation of anticoagulation in pediatric patients with central line-related thrombosis. – Conditional recommendation
- To not remove a functioning CVAD in patients with symptomatic CVAD-related thrombosis with worsening symptoms who continue to require venous access. – Conditional recommendation
- To use either low molecular weight heparin or vitamin K antagonist in pediatric patients with symptomatic DVT or PE. – Conditional recommendation
- To use anticoagulation for 3 months in pediatric patients with provoked DVT or PE. – Conditional recommendation
- To use anticoagulation for 6 weeks in neonates with provoked DVT or PE. – Conditional recommendation
- To use anticoagulation for a minimum of 6 months in patients with unprovoked DVT or PE. Anticoagulant therapy may be prolonged for recurrent VTE in pediatric patients. – Conditional recommendation
- To consider using either anticoagulation or no anticoagulation in pediatric patients with CVAD-related superficial vein thrombosis. – Conditional recommendation
- To use anticoagulation in pediatric patients with right atrial thrombosis. – Conditional recommendation
- To not use thrombolysis or surgical thrombectomy followed by standard anticoagulation; rather, anticoagulation alone should be used in pediatric patients with right atrial thrombosis. – Conditional recommendation
- To use anticoagulation in neonates with renal vein thrombosis. – Conditional recommendation
- To not use thrombolysis followed by standard anticoagulation in neonates with non-life threatening renal vein thrombosis. – Strong recommendation
- To use thrombolysis followed by standard anticoagulation in neonates with life threatening renal vein thrombosis. – Conditional recommendation
- To consider anticoagulation in patients with acute PVT. – Conditional recommendation
- To not use anticoagulation to treat PVT in patients post-liver transplant period and chronic PVT. – Conditional recommendation
- To use anticoagulation in pediatric patients with CSVT without hemorrhage. – Strong recommendation
- To use anticoagulation in pediatric patients with CSVT with hemorrhage. – Conditional recommendation
- To use anticoagulation alone in pediatric patients with CSVT. – Conditional recommendation

**Consensus Recommendations**

- The panel agreed that a pediatric hematologist or a pediatrician in consultation with a hematologist will be best suited to implement these recommendations given the complexity of the care involved in children with VTE. – Consensus recommendation
• Consult hematology for individualized treatment in pediatric patients with asymptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE). – Consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

**Condition-Specific Elements of Clinical Management**

**General:**
Treatment of thrombosis can involve anticoagulation, thrombolytic and/or antiplatelet therapy. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the primary anticoagulant choices available for acute treatment. Warfarin (Coumadin) is the most commonly used oral anticoagulant. Warfarin is not used as initial anticoagulation therapy. When conversion to warfarin is desired, a period of overlap between UFH or LMWH is recommended. Comparison of the advantages and disadvantages of the anticoagulants are described below.

**Treatment Recommendations:**

**Unfractionated Heparin (UFH)**
- UFH Advantages: Rapid onset of action, short half-life, antidote available.
- UFH Disadvantages: Requires monitoring, may cause heparin-induced thrombocytopenia.

**Low Molecular Weight Heparin (LMWH)**
- LMWH advantages: Longer half-life than heparin and subcutaneous administration, less heparin-induced thrombocytopenia when compared to UFH, useful in patients needing long-term therapy. Less laboratory monitoring and adjustment.
- LMWH disadvantages: Subcutaneous route not appropriate for all infants/children. Cannot be used in heparin-induced thrombocytopenia. Requires monitoring and the antidote is only partially effective. In the setting of renal failure, more frequent monitoring is needed to adjust the dose.

**Warfarin (Coumadin)**
Warfarin advantages: Can be given as an oral medication, can be monitored by INR levels that are widely available, lower cost.
Warfarin disadvantages: Significant interactions with foods and drugs, significant intra- and inter-individual variability in dose response necessitating frequent monitoring, narrow therapeutic window, requires patient with reliable enteral intake, reduced bone density with prolonged use (>1 year), no safety or efficacy information for use in neonates, no suspension or liquid preparations, not used as initial anticoagulation therapy, requires conversion overlap of UFH or LMWH.

Note: Recent pharmacogenetic screening for specific studies show that polymorphisms of CYP2C9 and VKORC1 may predict individuals at risk for over- or under-anticoagulation.

**Thrombolytic Therapy**
- Refer to Texas Children’s Cancer and Hematology Centers Guidelines for thrombolysis using tissue plasminogen activator (tPA) in pediatric patients
- Hematology consultation recommended

- Consider consultation with other services:
  o Pediatric Surgery
  o Interventional Cardiology
  o Interventional Radiology

**Surgical Thrombectomy:** Surgical thrombectomy is rarely used in children since the recurrence rate of thromboembolism and the risk of long-term vascular damage are high. The risks and benefits need to be considered for each case. Contraindications to treatment in some patients, the need for anticoagulation therapy necessitates treatment despite contraindications. Consultation with a hematologist is recommended.

Contraindications to treatment with tissue plasminogen activator (e.g., pharmacologic thrombolysis, alteplase) include known allergy, active bleeding, significant potential for local bleeding (e.g., tumor surrounding vessel with clot), General Surgery within the previous 7 days, Neurosurgery within the previous 10 days, invasive procedures within the previous 3 days or seizures within the previous 48 hours. The risk vs. benefit of therapy must be carefully considered in these patients.

**General Precautions (Clinical indications may outweigh risks)**
- Avoid use of aspirin and NSAIDs for pain/fever (exceptions: SLE, APS, and arterial thrombosis patients)
- No rectal temperatures
- Use soft toothbrush or water-irrigating device
- Apply direct pressure to cuts for 10 minutes
- Avoid arterial punctures if possible

**Consults/Referrals**
- Hematology
- Interventional Radiology
- Interventional Cardiology

**Measures**
- Number of children diagnosed with VTE
- Time from start of anticoagulation therapy to attaining therapeutic range
- Number of patients who received thrombolysis or surgical thrombectomy
Clinical Algorithm for Deep Vein Thrombosis (DVT)

Diagnosis and Initiation of Thrombosis Therapy

Begin

Is patient hemodynamically stable?

Yes

Thrombosis Present or still high suspicion based on clinical assessment and/or history?

Yes

Echocardiogram shows right ventricular strain?

Yes

Non-massive Pulmonary Embolus identified & patient is hemodynamically stable

Consult Hematology for recommendations for treatment

Reference PE Consensus Management Guideline & Algorithm (non-massive)

Begin

Suspect Pulmonary Embolism?

Yes

If patient is unstable, obtain echocardiogram and the following labs if possible:

- CBC with platelets
- DIC Panel
- Troponin
- BNP
- Type & Screen

Manage as appropriate to clinical findings, assess for venous thrombosis algorithm

If concern for any thromboses, refer to other algorithms (Click to continue)

Evaluate for other respiratory diagnoses

If patient is unstable, obtain echocardiogram and the following labs if possible:

- CBC with platelets
- DIC Panel
- Troponin
- BNP
- Type & Screen

Massive Pulmonary embolus (RV dilation or dysfunction, abnormal cardiac markers, and hemodynamically unstable)

OR

Unable to complete evaluate because patient in profound shock

OR

Sub-massive Pulmonary embolus with RV dilation or dysfunction, abnormal cardiac markers, but hemodynamically stable

Consults for Pulmonary Embolism

- CICU Resource Attending
  - 3-CICU or 3-2428
- Interventional Radiology
- Interventional Cardiology
- Hematology
- Transfusion Medicine
- RV Failure
- ECMO

Transfer to Critical Care
For Heart Center patient, admit to Cardiac ICU
For Non-Heart Center patient, admit to PICU in TMC

Confirm pulmonary embolus with CT when stable
Consider surgical thrombolysis and systemic anticoagulation

Manage as appropriate to clinical findings

Risk factors for PE
- Central venous catheter in place
- Congenital heart disease (e.g. HLHS s/p Fontan)
- Oral contraceptive use
- Pregnancy or post-partum period
- Trauma
- Immobility
- Hypercoagulable states
- Vascular malformations
- Inherited thrombophilia
- Malignancy
- Nephrotic syndrome

Inclusion Criteria
- Patients ≤ 21 years old with signs and symptoms concerning for venous thrombosis

Exclusion Criteria
- Pregnant patients
  For pregnant patients, please refer to PFW Venous Thromboembolism in Pregnant/Postpartum Women Protocol (link).
- Neonates
  For neonates, please refer to BCM Neonatology Guidelines (link).

Suggested Evaluation
- Initial Labs:
  - CBC with platelets
  - DIC Panel
  - Troponin
  - BNP
  - Type & screen
- EKG
- Chest X-Ray
- CT Angiogram PE Protocol
- Echocardiogram (assess RV/LV ratio)

Assess for signs and symptoms of Pulmonary Embolism (PE): unexplained SOB, dyspnea, cough, pleuritic chest pain, hypoxemia, fever, pallor, cyanosis, hemoptysis, sudden collapse

Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.
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**Clinical Algorithm for Vascular Thrombosis**

Diagnosis and Initiation of Treatment for Venous Thrombosis

**Inclusion Criteria**
- Patients ≤ 21 years old with signs and symptoms concerning for venous thrombosis

**Exclusion Criteria**
- Pregnant patients

For pregnant patients, please refer to PFW Venous Thromboembolism in Pregnancy/Postpartum Women Protocol (link).

For neonates, please refer to BCM Neonatology Guidelines (link).

---

**Begin**

Patient presents with signs and symptoms concerning for venous thrombosis

Any signs or suspicions for Pulmonary Embolism not previously assessed or treated?

- Yes
  - Refer to Pulmonary Embolism Algorithm (Click to continue to algorithm)

- No
  - Consider Hematology or appropriate consult

**Initial Labs**

- CBC with platelets,
- DIC Panel (PT, PTT, TT, fibrinogen, D-dimer, platelet, PTT heparmye)

**Imaging**

Consider Radiology consult to choose appropriate imaging
- Doppler Ultrasound
- MRV if also imaging mass/infection
- CT Angiogram or CT venogram (if MRI contraindicated)

Thrombosis Present?

- No
  - OFF algorithm

- Yes
  - Pulmonary Embolism Present?

  - No
    - OFF algorithm

  - Yes
    - Life/Limb Threatening Embolus Present?

      - No
        - Consult Hematology Team
        - Order additional lab studies per consultation
        - Initiate anticoagulation therapy

      - Yes
        - Contraindications to antithrombotic therapy present?

          - No
            - OFF algorithm

          - Yes
            - Anticoagulation necessary?

              - No
                - OFF algorithm

              - Yes
                - Manage as appropriate to clinical findings

---

Administer low molecular weight heparin or unfractionated heparin per hematology recommendations

Thrombolysis and/or surgical/mechanical intervention may be beneficial if:
- Life, limb or organ threatening
- Massive PE
- Bilateral RVT
- Extensive thrombus burden
- No improvement in symptoms after 24-48 h of appropriate therapy

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Note: Clinical standards are developed for 80% of the patient population with a particular disease. Each practitioner must use his/her clinical judgment in the management of any specific patient.
References
Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines

DATE: February 2020
Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

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