

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Vascular Thrombosis: Venous Thrombosis
Evidence-Based Guideline

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 leukocytes. ⁽¹⁾ Venous thrombosis can produce a significant obstruction to blood flow, with the most serious pulmonary embolism. 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.

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)

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

Laboratory Tests

Initial Laboratory Studies

- CBC
- DIC panel (includes PT, PTT, thrombin time, fibrinogen, D-dimer, heparinase 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

2. Extremity DVT – US, consider adding MRV to MR if imaging mass or infection
3. Pulmonary Embolism (PE) – Ventilation-perfusion scan (V/Q scan) if chest x-ray normal with no cardiopulmonary disease; CT angiogram (CTA) for symptomatic patient with abnormal chest x-ray findings; MR pulmonary angiogram combined with MRV to eliminate radiation exposure
4. Renal or portal vein DVT – US; MRV or CT to evaluate extension
5. Central venous system DVT – US for initial study; MRV for definitive diagnostic study; consider ECHO if concern for extension into right atrium

Critical Points of Evidence*

Recommendations Adopted or Adapted from the American Society of Hematology Guideline⁽⁵⁾

- 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 UHF or LMWH is recommended. Comparison of the advantages and disadvantages of the anticoagulants are described below.

Treatment Recommendations: ⁽⁶⁾

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:

- Pediatric Surgery
- Interventional Cardiology
- 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 for UFH, LMWH and warfarin include known allergy and history of heparin-induced thrombocytopenia. Existence of coagulopathy, thrombocytopenia, recent/active bleeding or invasive procedures within the past 24 hours should be carefully evaluated prior to initiation of treatment with UFH or LMWH.

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

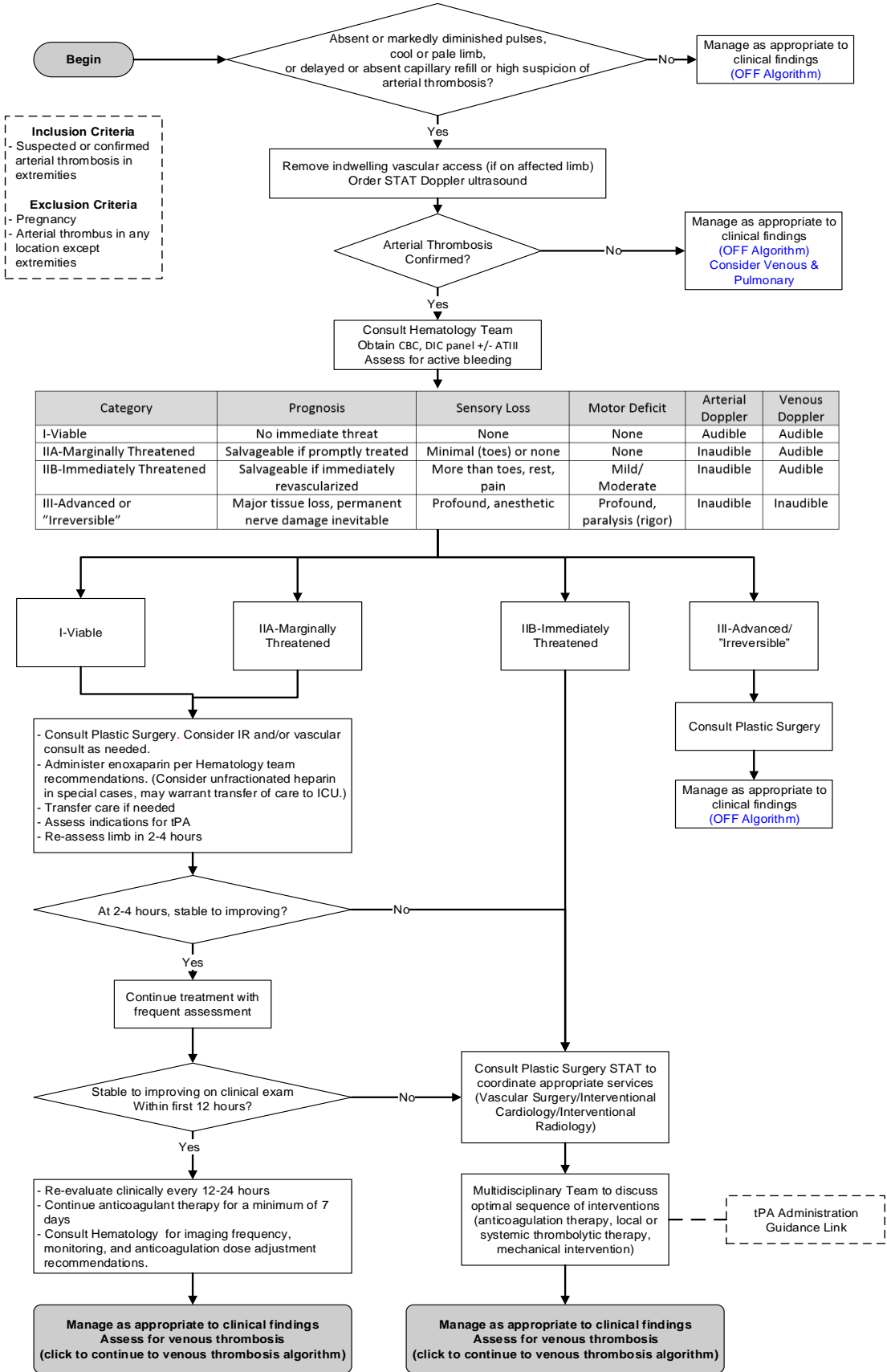
Consults/Referrals

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

**Texas Children's Hospital Evidence-Based Outcomes Center
Clinical Algorithm for Vascular Thrombosis
Diagnosis and Initiation of Treatment for Arterial Thrombosis**



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.

Texas Children's Hospital Evidence-Based Outcomes Center Clinical Pathway for the Diagnosis and Initiation of Treatment for Pulmonary Embolism

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

Exclusion Criteria
Pregnant patients, patients > 21 years of age and ACHD patients

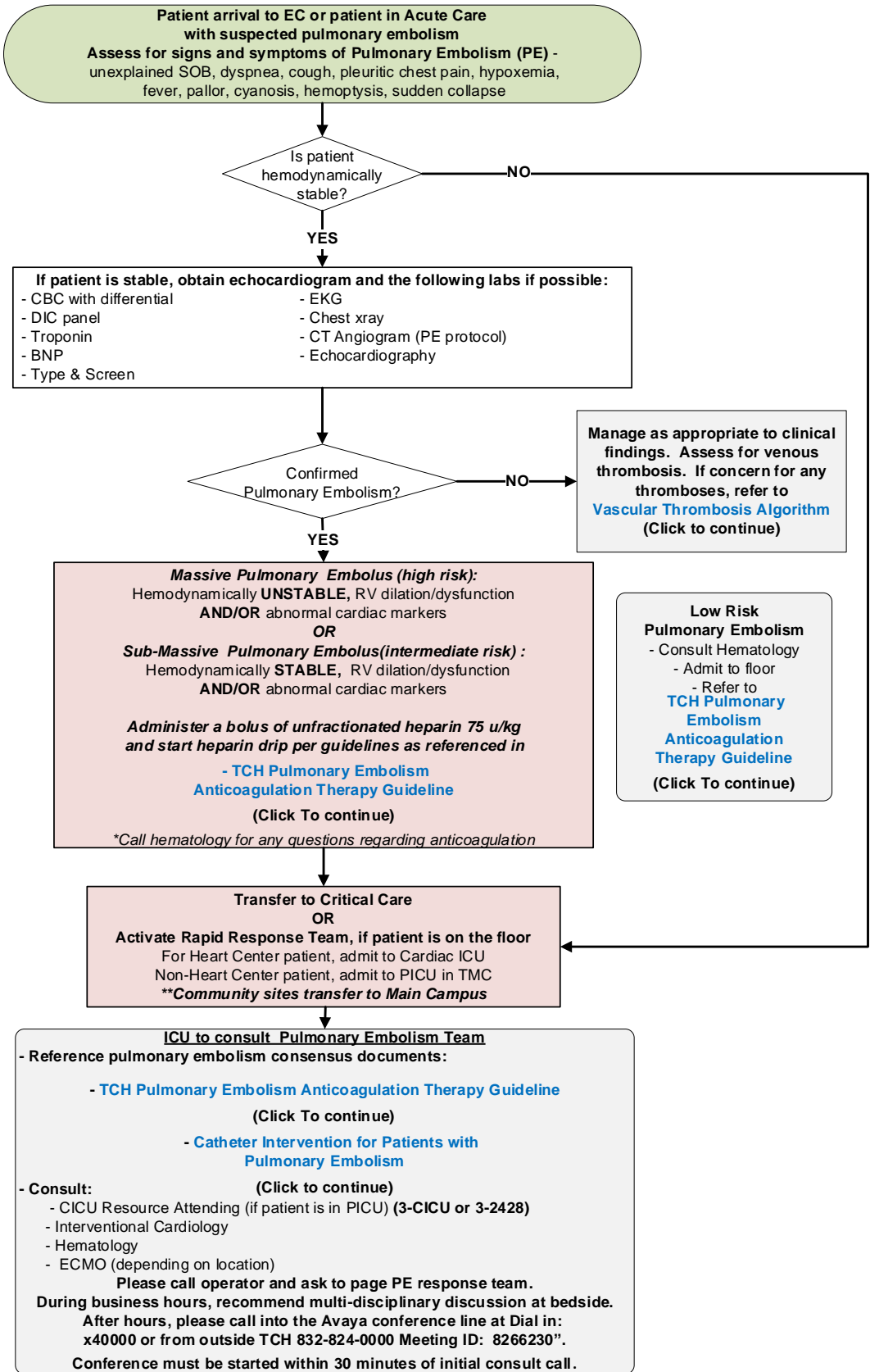
See PFW and ACHD PE algorithm for PE in pregnant women, ACHD patients or patients >21 years of age

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

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

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



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.

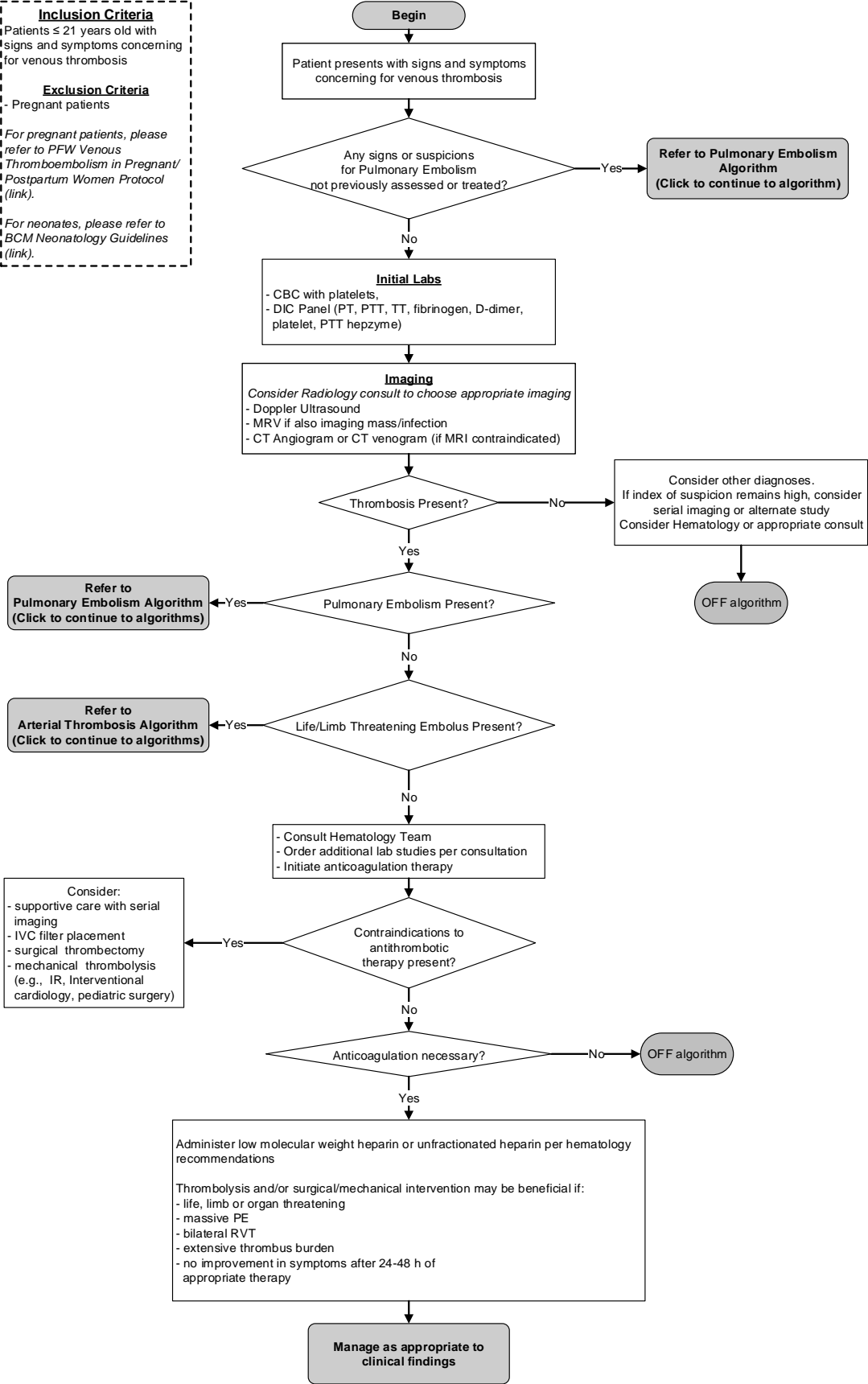
**Texas Children's Hospital Evidence-Based Outcomes Center
Clinical Algorithm for Vascular Thrombosis
Diagnosis and Initiation of Treatment for Venous Thrombosis**

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 Pregnant/ Postpartum Women Protocol (link).

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



References

1. Monagle, P., Cuello, C. A., Augustine, C., Bonduel, M., Brandao, L. R., Capman, T., ...Vesely, S. K. (2018). American Society of Hematology 2018 Guidelines for management of venous thromboembolism: Treatment of pediatric venous thromboembolism. *Blood Advances*, 2(22), 3292-3316.
2. Lanzkowsky, P, Lipton, J., & Fish, J. D. (Eds). (2016). *Manual of Pediatric Hematology and Oncology* (6th Ed.). Cambridge, MA: Academic Press.
3. Monagle, P., Chan, A. K. C., deVeber, G., et al. (2006). *Andrew's Pediatric Thromboembolism and Stroke*. Hamilton: BC Decker Inc.
4. Young, G. (2006). Diagnosis and treatment of thrombosis in children: General principles. *Pediatric Blood & Cancer*, 46(5), 540-546.
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6. Monagle, P., & Newall, F. (2018). Management of thrombosis in children and neonates: Practical use of anticoagulants in children. *Hematology: The American Society of Hematology Education Program*, 1, 399-404.

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
 - American Society of Hematology (2018) Guidelines for the management of venous thromboembolism: Treatment of pediatric venous thromboembolism
 - Chest Physicians (2012) Antithrombotic Therapy in Neonates and Children Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines
3. Literature Review of Relevant Evidence
 - Searched: Cochrane Reviews, Cochrane CENTRAL, PubMed
4. Critically Analyze the Evidence
 - One systematic review and meta-analysis and five nonrandomized studies
5. Summarize the Evidence

- Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in arterial thrombosis evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline. This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions. **"Evidence Supports"** provides evidence to support an intervention. **"Evidence Against"** provides evidence against an intervention. **"Evidence Lacking/Inconclusive"** indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*. The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis and initial management of venous thrombosis in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

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 should 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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Version History

Date	Comments
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Aug 2023	PE Algorithm updated (version 8)