Venous Thromboembolism Prophylaxis – Pediatric – Inpatient

Consensus Care Guideline

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Introduction

Venous thromboembolism (VTE) is a life-threatening condition associated with increased morbidity, mortality, duration of hospital stay, and health care expenditures.[1] In the pediatric population, VTE is increasingly being recognized as a complication of contemporary health care.[2] The estimated annual incidence of VTE among hospitalized pediatric patients is upwards of 60 events per 10,000 admissions and has been increasing over time. Infants are at the greatest risk of thromboembolism, with a second peak in incidence noted during adolescence. Although VTE is far less common in children than adults, several underlying factors place children at risk for developing VTE. One of the greatest risks for VTE in children is the insertion of central venous catheters, which is common in the inpatient setting. Other acquired conditions frequently associated with VTE in children include infection, trauma, surgery, and immobility.

There is no standardized and validated thromboprophylaxis risk tool established in the pediatric population. This guideline provides recommendations on the evaluation of both risk of VTE and risk of bleeding in pediatric patients based on identified risk factors, as well as appropriate VTE prophylaxis modalities if applicable.

Scope

Intended Users: Physicians, advanced practice providers, pharmacists, and nurses who provide care to hospitalized pediatric patients

Objective: To provide recommendations and guidance for the prevention of VTE in hospitalized pediatric patients.

Target Population: Any pediatric patient admitted to the hospital who is 6 months of age or older. The recommendations for pharmacologic strategies used to prevent VTE would apply to pediatric patients receiving unfractionated heparin (UFH), low molecular weight heparin (LMWH), or a direct oral anticoagulant (DOAC).

Patients younger than 6 months of age are excluded from this guideline due to insufficient data to describe screening for VTE and prophylactic anticoagulation use in this population.

This guideline is not intended to provide recommendations for the treatment of VTE.

Recommendations

1. Prevention of VTE in hospitalized pediatric patients[3]
    - 1.1 All hospitalized patients 6 months of age or older should be evaluated for both bleeding and VTE risk within 24 hours of admission, upon transferring level of care, and periodically during hospital stay (every 48-72 hours).[4-6] (*UW Health GRADE Low quality evidence, strong recommendation*)
2. Evaluation of Bleeding Risk
    - 2.1 There is no universally validated model or tool to assess bleeding risk with the use of chemical DVT prophylaxis in pediatric patients.
    - 2.2 Recommendations for specific factors associated with increased bleeding risk are included in Table 1.[4-8] (*UW Health GRADE Very low quality evidence, strong recommendation*)
        - 2.2.1 If a patient meets at least one of the following criteria of the "*Chemical Prophylaxis NOT Recommended*" list in Table 1, avoid chemical prophylaxis as risk outweighs benefit. (*UW Health GRADE Very low quality evidence, strong recommendation*)
        - 2.2.2 If patient meets at least one of the following criteria in the "*Consider Avoiding Chemical Prophylaxis*" list in Table 1, consider avoiding chemical prophylaxis. (*UW Health GRADE Very low quality evidence, conditional recommendation*)
            - 2.2.2.1 Consider consulting hematology for recommendations if patient considered at high risk for VTE, but also with high bleeding risk.[6]
            - 2.2.2.2 Uncontrolled hypertension is defined as systolic or diastolic blood pressure greater than 95th percentile for age, height, and gender.[4]

2.2.2.3 Coagulopathy is defined as INR >1.5, APTT >44 seconds, fibrinogen <100 g/dL, or platelet <50,000/microliter.[4]

Table 1: Bleeding Risk Factors

Chemical Prophylaxis NOT Recommended	Consider Avoiding Chemical Prophylaxis
Intracranial hemorrhage	Intracranial mass
Brain ischemia/acute stroke	Recent lumbar puncture (< 24 hours ago)
Active bleeding	Coagulopathy
Recent thrombolytic therapy (< 24 hours)	Neurosurgical procedure
	Pelvic fracture within past 48 hours
	Uncontrolled hypertension
	Recent aspirin or antiplatelet use (< 5-7 days ago)

3. Evaluating VTE risk in medical, surgical, and trauma patients
   - 3.1 There is no universally validated model or tool to assess VTE risk in medical, surgical, or trauma pediatric patients.
   - 3.2 Table 2 and Table 3 should be used to assess VTE risk.[4-6,8-18](*UW Health GRADE Very low quality evidence, strong recommendation*)
     - 3.2.1 Reduced mobility is defined as decrease in movement from baseline or those unable to participate in physical therapy.
     - 3.2.2 Active infection includes diagnostically confirmed bacterial infections and/or viral infections including COVID-19 infection.
     - 3.2.3 Central venous access device is defined as a non-tunneled catheter, tunneled catheter, or peripherally inserted central catheter (PICC).
     - 3.2.4 Major burn is defined as more than 50% of body surface area.
     - 3.2.5 Major surgery is defined as an operation lasting longer than 45 minutes.
     - 3.2.6 Critically ill is defined as patients in the critical care setting or ICU (inotropic support, mechanically ventilated, etc.).
     - 3.2.7 Autoimmune disorders associated with thrombosis include Kawasaki's disease, inflammatory bowel disease, systemic lupus erythematosus, nephrotic syndrome, multisystem inflammatory syndrome in children (MIS-C), etc.
     - 3.2.8 Thrombophilic conditions include defects of antithrombin, protein C or S deficiency, factor V Leiden, homocystinuria, or prothrombin gene mutation.
     - 3.2.9 Active malignancy is defined as receiving chemotherapy and/or radiation in the previous 6 months.
     - 3.2.10 Estrogen therapy includes oral contraceptives or estrogen replacement currently taking or taken within the past 2 weeks.
     - 3.2.11 Obesity is defined as BMI greater than 95th percentile for age.
   - 3.3 Risk Factor Stratification definitions
     - 3.3.1 Low VTE risk:
       - No altered mobility and 0-2 risk factors
     - 3.3.2 Moderate VTE risk:
       - No altered mobility and 3-4 risk factors
       - Altered mobility and 0-2 other risk factors
     - 3.3.3 High VTE risk:
       - No altered mobility and ≥ 5 risk factors
       - Altered mobility and ≥ 3 other risk factors

Table 2: VTE Risk Factors

Acute Conditions
Reduced mobility longer than 48 hours
Central venous access device
Active infection
Major trauma or burn
Major surgery
Pregnancy
Critically ill
Hypoalbuminemia
Blood transfusion within previous 48 hours
Chronic Medical Conditions
Post-pubertal and/or age 12 years or older
Autoimmune disorders associated with thrombosis
Thrombophilic condition
Active malignancy
Smoking
Estrogen therapy
Obesity
Historical Factors
Asparaginase within previous 30 days
Recent surgery within past 30 days
History of thrombosis*
Family history of VTE in a 1st degree relative < 40 years old at time of clot

**For patients with prior history of central line-associated VTE, see section 6.3 below*

Table 3: VTE Risk Assessment[8]

Risk Factor Stratification	Recommendation
Low VTE Risk	• Early Ambulation • No prophylaxis necessary
Moderate VTE Risk High VTE Risk and High Bleed Risk	• Early Ambulation • Mechanical Prophylaxis
High VTE Risk and Low Bleed Risk	• Early Ambulation • Mechanical Prophylaxis and consider pharmacologic Prophylaxis

4. VTE prophylaxis options
   - 4.1 Mechanical prophylaxis: methods may include sequential compression device (SCD), graduated compression stockings (GCS), or consulting physical therapy and/or occupational therapy to assist with movement of the patient.[4-6,8,10,11,19]
     - 4.1.1 Contraindications to mechanical prophylaxis[4,19] (*UW Health GRADE Low quality evidence, strong recommendation*)
       - Extremity has acute fracture
       - Extremity has peripheral IV access
       - Skin condition affecting extremity (i.e. dermatitis, burn, etc.)
       - Unable to achieve correct fit due to patient size
       - Lower extremity peripheral arterial insufficiency

4.2 Patients identified as high VTE risk should be evaluated to possibly receive the corresponding prophylaxis based on individual considerations. (See Table 4) (*UW Health GRADE Low quality evidence, strong recommendation*)
- 4.2.1 Enoxaparin is the preferred pharmacologic prophylaxis agent for pediatric patients.[20,21] (*UW Health GRADE Low quality evidence, strong recommendation*)
  - 4.2.1.1 Use of subcutaneous (SQ) injections is preferred due to lack of evidence of intravenous administration in the prophylactic setting.
  - 4.2.1.2 Avoid enoxaparin or heparin if patient has hypersensitivity to enoxaparin, heparin, pork products, or any component of the formulation.[4] (*UW Health GRADE Low quality evidence, strong recommendation*)

Table 4: VTE Prophylaxis Regimens* in High VTE Risk Patients[1,4,7,8,21-24]

Patient Population	Weight	VTE Prophylaxis Regimens
Normal Renal Function	< 60 kg	• Enoxaparin 0.5 mg/kg SQ every 12 hours (max 60 mg/day)[a]
	≥ 60 kg	• Enoxaparin 40 mg SQ every 24 hours[b] (consider 30 mg SQ every 12 hours for total knee arthroplasty) • Heparin 5000 units SQ every 12 hours[a]
Renal Impairment (CrCl < 30 mL/min/1.73m^2)	< 60 kg	• Enoxaparin 0.5 mg/kg SQ every 24 hours[a]
	≥ 60 kg	• Enoxaparin 30 mg SQ every 24 hours[a] • Heparin 5000 units SQ every 12 hours[a]

[a]*UW Health GRADE Low quality evidence, strong recommendation*
[b]*UW Health GRADE Low quality evidence, conditional recommendation*
**For patients with prior history of central line-associated VTE, see section 6.3 below*

5. Rivaroxaban, an oral anticoagulant with FDA approval in the pediatric population, may be considered for prophylaxis in patients with high VTE risk if appropriate based on patient characteristics.[25-27] *(UW Health GRADE Low quality evidence, conditional recommendation)*
   - 5.1 Consider rivaroxaban for VTE prophylaxis in patients appropriate for use based on below criteria due to emerging evidence in the pediatric population, and consider hematology consult if needing assistance determining appropriateness. *(UW Health GRADE Very low quality evidence, conditional recommendation)*
   - 5.2 Rivaroxaban may be used based on individual considerations.[26] *(UW Health GRADE Low quality evidence, strong recommendation)*
     - 5.2.1 Only use rivaroxaban in infants weighing at least 2.6 kg whose serum creatinine is less than the 97.5th percentile and children or adolescents with eGFR ≥ 50 mL/min/1.73 m^2 *(UW Health GRADE Low quality evidence, strong recommendation)*
     - 5.2.2 Patients should receive at least five days of parenteral anticoagulation and at least ten days of enteral feeding prior to starting rivaroxaban for VTE prophylaxis. *(UW Health GRADE Low quality evidence, strong recommendation)*
     - 5.2.3 See Lexicomp drug monograph for rivaroxaban dosing based on patient age, weight, and interacting medications (i.e. certain antiseizure medications, etc.)
6. VTE prophylaxis in unique pediatric populations
   - 6.1 Rivaroxaban for thromboprophylaxis after Fontan procedure[28]
     - 6.1.1 Rivaroxaban may be used for thromboprophylaxis after Fontan procedure based on individual considerations listed under 5.2.1 and 5.2.2. *(UW Health GRADE Low quality evidence, strong recommendation)*
     - 6.1.2 See Lexicomp drug monograph for rivaroxaban dosing based on patient age and weight
   - 6.2 Pediatric patients with COVID-19 infection[29]

6.2.1 Pharmacologic VTE prophylaxis is recommended in patients aged 12 years and older who are hospitalized for COVID-19 infection, unless contraindicated. *(UW Health GRADE Low quality evidence, strong recommendation)*
6.2.1.1 If pharmacologic VTE prophylaxis is contraindicated, consider mechanical VTE prophylaxis. *(UW Health GRADE Low quality evidence, strong recommendation)*
6.2.1.2 For patients less than 12 years old, follow usual VTE prophylaxis recommendations. *(UW Health GRADE Low quality evidence, strong recommendation)*
6.2.2 Consider checking D-dimer, and if elevated but the patient does not have an active thromboembolism, consider starting VTE prophylaxis at any patient age.[30,31] *(UW Health GRADE Very low quality evidence, conditional recommendation)*

6.3 Pediatric patients with history of central line-associated thrombosis
6.3.1 Prior history of thrombosis, whether associated with a central line or not, is a known risk factor for subsequent thrombosis
6.3.2 Consider therapeutic anticoagulation with heparin or enoxaparin, rather than prophylactic anticoagulation, in patients with a history of central-line associated thrombosis if any future central line is placed based on emerging evidence and if appropriate for the patient[32] *(UW Health GRADE Low quality evidence, conditional recommendation)*
6.3.3 If using therapeutic anticoagulation, reference UW Health documents "Therapeutic Dosing of Unfractionated Heparin – Pediatric/Neonatal – Inpatient/Emergency Department" and "Enoxaparin Dosing and Monitoring for Therapeutic Use – Pediatric – Inpatient" for guidance on dosing and required monitoring

7. Anticoagulation monitoring[3,22]
7.1 Complete blood count (CBC)
7.1.1 Obtain baseline CBC within 48 hours of initiation of enoxaparin or heparin. (*UW Health GRADE Very low quality evidence, strong recommendation*)
7.2 Anti-Xa[5,21]
7.2.1 Routine anti-Xa levels are not recommended with the use of enoxaparin, heparin, or rivaroxaban at prophylactic doses.[1]
7.2.2 May consider checking anti-Xa level if the patient experiences active bleeding or has evidence of renal dysfunction while receiving enoxaparin.[22] (*UW Health GRADE Very low quality evidence, conditional recommendation*)
7.2.3 If an anti-Xa level is deemed necessary, it should be drawn 4-6 hours after enoxaparin administration with a target anti-Xa goal of 0.1-0.3 units/mL.[21]

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline author and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Hand-searching journals, external guidelines, and conference publications

Time Period: All studies to date

Search Terms:

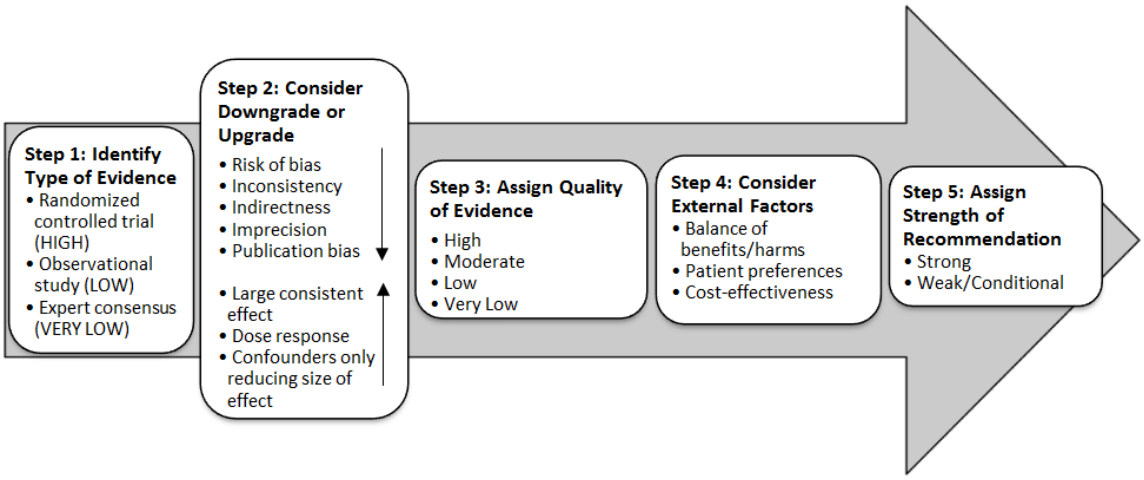
- VTE prophylaxis AND pediatrics
- VTE risk factors AND pediatrics
- Enoxaparin use in pediatrics for VTE prophylaxis
- Heparin use in pediatrics for VTE prophylaxis
- Direct oral anticoagulant use in pediatrics for VTE prophylaxis

Methods to Select the Evidence:
All observational studies, randomized clinical trials, and systematic reviews/meta analyses in English were considered for the guideline development.

Methods Used to Formulate the Recommendations:
The workgroup members created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

Recognition of Potential Health Care Disparities: None identified

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

- Prevention of VTE with the therapy that is most appropriate based on individual patient VTE and bleeding risk
- Rate of central venous catheter (CVC) related VTEs
- Rate of non-CVC VTE events

Appendix A. Pediatric VTE Prophylaxis Risk Factors and Assessment

Table 2: VTE Risk Factors

Acute Conditions
Reduced mobility longer than 48 hours
Central venous access device
Active infection
Major trauma or burn
Major surgery (during admission)
Pregnancy
Critically ill
Hypoalbuminemia
Blood transfusion within previous 48 hours
Chronic Medical Conditions
Post-pubertal and/or age 12 years or older
Autoimmune disorders associated with thrombosis
Thrombophilic condition
Active malignancy/cancer
Smoking
Estrogen therapy
Obesity
Historical Factors
Asparaginase within previous 30 days
Recent surgery within past 30 days
History of thrombosis*
Family history of VTE in a 1st degree relative < 40 years old at time of clot

**For patients with prior central-line associated VTE, see section 6.3 below*

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	≥ 60 kg	• Enoxaparin 40 mg SQ every 24 hours[b] (consider 30 mg SQ every 12 hours for orthopedic procedures) • Heparin 5000 units SQ every 12 hours[a]
Renal Impairment (CrCl <30 mL/min/1.73m^2)	< 60 kg	• Enoxaparin 0.5 mg/kg SQ every 24 hours[a]
	≥ 60 kg	• Enoxaparin 30 mg SQ every 24 hours[a] • Heparin 5000 units SQ every 12 hours[a]

[a]UW Health GRADE Low quality evidence, strong recommendation
[b]UW Health GRADE Low quality evidence, conditional recommendation
**For patients with prior central-line associated VTE, see section 6.3 below*

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