Therapeutic Dosing of Unfractionated Heparin – Adult – Emergency Department/Inpatient Clinical Practice Guideline

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Pharmacy & Therapeutics Committee (Last Periodic Review: 06/16/2016)
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Executive Summary

Guideline Overview

This clinical practice guideline is intended to provide a standardized process for the initiation, maintenance and monitoring of intravenous unfractionated heparin. Practices considered include guidance on selection of dosing nomograms, initial and maintenance monitoring of heparin infusions, initial and maintenance heparin dose adjustments, and transitioning between dosing nomograms.

Key Revisions

1. Removal of recommendations for heparin monitoring and dose titrations using PTT

Key Practice Recommendations

1. Select the dose adjustment nomogram based on indication for UFH use
    - 1.1 Gradual heparin nomogram
        - 1.1.1 Patients treated with alteplase in the past 24 hours
        - 1.1.2 New mechanical valve (valve placed during current admission)
        - 1.1.3 High bleeding risk (recent surgery, trauma, hepatic dysfunction)

    - 1.2 Rapid heparin nomogram
        - 1.2.1 Venous Thromboembolism (deep vein thrombosis, pulmonary embolism)
        - 1.2.2 Ventricular or atrial thrombus
        - 1.2.3 Atrial fibrillation
        - 1.2.4 History of mechanical valve

2. Initiation of UFH Infusion
    - 2.1 Initial starting rate should be based on actual body weight – see Table 1.

Table 1. Initial dosing UFH bolus and infusion

Nomogram	Bolus Dose (units/kg)	Maximum Bolus (units)	Initial Infusion (units/kg/hr)
Rapid	80	10,000	18
Gradual	None	NA	12

3. Titration of UFH Infusion *(Class IIb, Level C)*
    - 3.1 Adjust the rate as indicated using the appropriate dosing table

Gradual Anticoagulation Nomogram by anti-Xa

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
<0.1	Bolus 20 units/kg & inform MD	↑ by 2 units/kg/hr
0.1 – 0.29	0	↑ by 1 units/kg/hr
0.3 – 0.7	0	NO CHANGE; Therapeutic Range
0.71 – 0.8	0	↓ by 1 units/kg/hr
0.81- 1.7	Hold infusion 1 hr	↓ by 2 units/kg/hr
> 1.7	Hold infusion 1½ hr & inform MD	↓ by 3 units/kg/hr

Rapid Anticoagulation Nomogram by anti-Xa

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
< 0.1	Bolus 40 units/kg & inform MD	↑ by 3 units/kg/hr
0.10 - 0.19	Bolus 20 units/kg	↑ by 2 units/kg/hr
0.2 - 0.29	None	↑ by 1 unit/kg/hr
0.3 - 0.7	0	No Change; Therapeutic Range
0.71 - 0.8	None	↓ by 1 unit/kg/hr
0.81 - 1.7	Hold infusion 1 hr	↓ by 2 units/kg/hr
> 1.7	Hold infusion 1½ hr & inform MD	↓ by 3 units/kg/hr

Companion Documents
1. Venous thromboembolism diagnosis and treatment – adult – inpatient/ambulatory/emergency department – clinical practice guideline

Scope

Disease/Condition(s): Hospitalized adult patients receiving intravenous unfractionated heparin intended for therapeutic dosing

Clinical Specialty: Classify the clinical specialties that might use the guideline (e.g. Primary Care, Neurology, Cardiology, Nursing, PT/OT, Respiratory Therapy, etc.)

Intended Users:
- Registered Nurses
- Pharmacists
- Advanced Practice Providers
- Physicians

Objective(s): This clinical practice guideline is intended to provide a standardized process for the initiation, maintenance and monitoring of intravenous unfractionated heparin.

Target Population: The recommendations within this guideline would apply to adult patients receiving intravenous unfractionated heparin infusions in the inpatient or emergency department setting.

Interventions and Practices Considered: The clinical interventions and practices recommended in this guideline are intended for patients receiving intravenous unfractionated heparin:
- Initial infusion rate
- Infusion rate titrations
- Monitoring
- Transitioning between therapies and dosing nomograms/algorithms

Major Outcomes Considered: The major outcomes considered in this guideline are for the safe and effective dosing of IV unfractionated heparin through the use of standardized dosing and monitoring nomograms, and documentation. Efficacy is measured by achieving a

therapeutic goal within 24 hours of initiation for the rapid nomogram and within 36 hours for the gradual nomogram. Safety is measured by bleeding outcomes and critical values.

Methodology

Methods Used to Collect/Select the Evidence:
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

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** in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix A for the rating scheme(s) used within this document.

Definitions

Gradual Anticoagulation Nomogram – Initiates unfractionated heparin at a lower initial infusion rate with the intent to achieve a therapeutic range within 24-36 hours. This nomogram is typically reserved for patients receiving concomitant thrombolytics, who have a new mechanical valve during current admission or when concerns for bleeding outweigh the need for quickly reaching a therapeutic goal[1,2].

Rapid Anticoagulation Nomogram – Initiates unfractionated heparin with the intent to achieve a therapeutic range within 18-24 hours. This nomogram is typically reserved for venous or atrial thrombosis, acute coronary syndrome, history of mechanical valves or when therapeutic anticoagulation is needed quickly[3,4].

Introduction

Unfractionated heparin (UFH) is used intravenously when therapeutic anticoagulation is warranted and low molecular weight heparin is not a suitable option. Intravenous (IV) UFH has an immediate onset of action but requires monitoring and infusion rate adjustments in order to achieve a targeted therapeutic range[5]. The following guideline provides recommendations for how to initiate, dose adjust and monitor a UFH infusion.

There is literature to suggest that monitoring IV UFH with anti-Xa levels may achieve a time to therapeutic range faster and warrant less lab testing than monitoring with aPTT. Additionally, there are less extrinsic factors that can affect the anti-Xa level making it more representative to the level of heparin.[7-12] These guidelines use anti-Xa as the preferred method for monitoring UFH infusions.

UFH is a high alert medication. An additional double-check is required as specified in Hospital Administrative Policy 8.33 must be performed on all boluses, when IV pump programming is outside of the established IV pump decision support software (Alaris Guardrails®) limits, when a new bag of heparin is hung and at each shift change.

In addition UFH infusions should be used with caution in patients with hypersensitivity to heparin, who are actively bleeding or have increased risk for hemorrhagic complications, who have severe thrombocytopenia or who have had a hemorrhagic stroke in the past 4 weeks[5].

Recommendations

Unfractionated Heparin – Therapeutic Use
IV UFH infusions with the intent for titration to a therapeutic goal must be ordered via the IP/ED Heparin Anticoagulation – Adult – Supplemental Order Set. No modifications of these nomograms are allowed. While discouraged, if patient circumstances require heparin dosing that differs from established nomograms, specific orders must be written. While not specified in this guideline, built within this order set are specific titration orders for UFH infusions with IIb/IIIa inhibitors used for acute coronary syndromes. Separate order sets are available for extracorporeal membrane oxygenation and ventricular assist devices.

1. Select the dose adjustment nomogram based on indication for UFH use
    1.1 Gradual heparin nomogram[1,2,4] *(UW Health moderate quality evidence, weak/conditional recommendation)*
        1.1.1 Patients treated with alteplase in the past 24 hours
        1.1.2 New mechanical valve (valve placed during current admission)
        1.1.3 High bleeding risk (recent surgery, trauma, hepatic dysfunction)

    1.2 Rapid heparin nomogram[3-5] *(UW Health high quality evidence, strong recommendation)*
        1.2.1 Venous Thromboembolism (deep vein thrombosis, pulmonary embolism)
        1.2.2 Ventricular or atrial thrombus
        1.2.3 Atrial fibrillation
        1.2.4 History of mechanical valve

2. Baseline monitoring of UFH infusions[5] *(UW Health low quality evidence, strong recommendation)*
    2.1 Collect baseline aPTT and PT/INR prior to initiating UFH infusion if not already available
    2.2 Collect baseline CBC and platelet prior to initiating UFH infusion if not already available
    2.3 Do NOT monitor UFH infusion with both aPTT and anti-Xa

3. Initiation of UFH Infusion
    3.1 Initial bolus doses are indicated in the rapid nomogram[3-5] *(UW Health moderate quality evidence, strong recommendation)*
        3.1.1 Bolus doses are based on actual body weight – see Table 1.
        3.1.2 Round bolus dose to the nearest 100 units for ease of preparation

3.1.3   Use heparin 1000 units/mL vial from floor stock for bolus dose

3.2   Initial starting rate should be based on actual body weight[1-5] – see Table 1 *(UW Health high quality evidence, strong recommendation)*

Table 1. Initial dosing UFH bolus and infusion

Nomogram	Bolus Dose (units/kg)	Maximum Bolus (units)	Initial Infusion (units/kg/hr)
Rapid	80	10,000	18
Gradual	None	NA	12

3.3   Use heparin 25,000 units/500 mL D5W premixed bags
3.3.1   Other heparin concentrations are not allowed for use

4. Maintenance monitoring of UFH Infusion[5] *(UW Health low quality evidence, strong recommendation)*
    4.1   Check anti-Xa 6 hours after initiation and/or 6 hours after any rate change
    4.2   Once 3 consecutive anti-Xa levels are within therapeutic range, order daily level with the morning labs
        4.2.1   If a rate adjustment becomes necessary recheck anti-Xa in 6 hours and repeat above process 4.1-4.2
    4.3   If the infusion is held for an elevated level and restarted check anti-Xa 6 hours after the infusion has been restarted
    4.4   If the infusion is held for a procedure, restart at the previous infusion rate and check anti-Xa 6 hours after the infusion has been restarted
    4.5   If goal is not reached within 24 hours for rapid nomogram or 36 hours for gradual nomogram, with correct titration, the patient may not be an appropriate candidate for adjustments based on these heparin nomograms. Recommend consultation with Pharmacy and/or Hematology for assistance with dosing.

5. Titration of UFH Infusion *(UW Health low quality evidence, weak/conditional recommendation)*
    5.1   Prior to adjusting the UFH infusion, confirm the ordered nomogram
    5.2   Adjust the rate as indicated using the appropriate dosing table 2 or 3.

5.2.2   **Table 2. Gradual Anticoagulation Nomogram by anti-Xa**

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
<0.1	Bolus 20 units/kg & inform MD	↑ by 2 units/kg/hr
0.1 – 0.29	0	↑ by 1 units/kg/hr
0.3 – 0.7	0	NO CHANGE; Therapeutic Range
0.71 – 0.8	0	↓ by 1 units/kg/hr
0.81- 1.7	Hold infusion 1 hr	↓ by 2 units/kg/hr
> 1.7	Hold infusion 1½ hr & inform MD	↓ by 3 units/kg/hr

5.2.4 **Table 3. Rapid Anticoagulation Nomogram by anti-Xa**

Heparin Level by Anti-Xa (IU/mL)	Bolus/Hold	Infusion Rate Change
< 0.1	Bolus 40 units/kg & inform MD	↑ by 3 units/kg/hr
0.10 - 0.19	Bolus 20 units/kg	↑ by 2 units/kg/hr
0.2 - 0.29	None	↑ by 1 unit/kg/hr
0.3 - 0.7	0	No Change; Therapeutic Range
0.71 - 0.8	None	↓ by 1 unit/kg/hr
0.81 - 1.7	Hold infusion 1 hr	↓ by 2 units/kg/hr
> 1.7	Hold infusion 1½ hr & inform MD	↓ by 3 units/kg/hr

6. Acute coronary syndrome **with** IIb/IIIa inhibitors[13]
    6.1 Due to concern for increased bleeding risk in patients receiving both UFH and a IIb/IIIa inhibitor (ex. eptifibatide) a lower anticoagulation target range is preferred[1] *(UW Health moderate quality evidence, strong recommendation)*
    6.2 The target anti-Xa range for acute coronary syndrome with concomitant IIb/IIIa inhibitors is 0.1-0.3 IU/mL *(UW Health low quality evidence, weak/conditional recommendation)*
        6.2.1 This range should not be used for other indications *(UW Health low quality evidence, strong recommendation)*
        6.2.2 Once the IIb/IIIa inhibitor is discontinued the target anticoagulation goal for UFH should be changed to a therapeutic goal (0.3 – 0.7 IU/mL) *(UW Health low quality evidence, weak/conditional recommendation)*

7. Acute coronary syndrome **without** IIb/IIIa inhibitors[13]
    7.1 UFH bolus of 60 units/kg once (maximum 4,000 units) will be given at the start of the infusion
    7.2 Infusion will be started at 12 units/kg/hr and titration will be based off of the rapid nomogram *(UW Health moderate quality evidence, strong recommendation)*

8. Transitioning between nomograms and anticoagulants[14-18] *(UW Health low quality evidence, weak/conditional recommendation)*
    8.1 Gradual to Rapid (or vice versa) – continue with current heparin infusion rate. At time of next anti-Xa level titrate infusion using new nomogram
    8.2 Heparin to enoxaparin – give enoxaparin 2-4 hours after heparin discontinued
    8.2 Heparin to apixaban, rivaroxaban or dabigatran – give oral anticoagulant at the time heparin discontinued
    8.3 Heparin to fondaparinux – give fondaparinux 2-4 hours after heparin discontinued

9. Additional monitoring *(UW Health low quality evidence, strong recommendation)*
    9.1 Hemoglobin and platelets must be followed 24 hours after initiating UFH therapy and every other day thereafter for up to 14 days or until therapy is discontinued.
    9.2 Every 8 hours inspect line/surgical/wound sites for bleeding and check patient for symptoms indicating bleeding such as hematomas, bruising, and respiratory symptoms. Contact MD if any signs of bleeding.
    9.3 If patient is able to shower, it is recommended not to stop or pause the heparin infusion. It is preferred to maintain the infusion during the shower.

UW Health Implementation

Potential Benefits:
The benefits of implementation of this guideline include providing a standardized approach for the management and monitoring of UFH. It has been described in the literature that patients who reach a therapeutic heparin range within 24 hours have a decrease in both hospital and 30 day mortality.[3,5]

Potential Harms:
While it is anticipated that the overall safety and quality of UFH management will be improved after guideline implementation there is a risk for acute bleeding with any anticoagulant. The risk for bleeding associated with UFH increases as the UFH dose increases. There are also additional patient factors to consider that this CPG does not account for which may include but is not limited to: age > 60 years, history of bleeding within previous 3 months, thrombocytopenia, and supra-therapeutic anticoagulation test.[5]

Pertinent UW Health Policies & Procedures
1. UW Health Policy #: 8.33 High Alert Medication Administration

Guideline Metrics
Using a numbered list, describe metrics to assess compliance with the stated recommendations or to gauge improvement resulting from implementation of the guideline.
NOTE: All metrics required or reported externally should be included (consider guidance from QSI).
1. VTE Performance Measure – VTE 4 – UFH with dosage and platelet monitored by protocol
2. Guideline adherence
3. Time to achieve a target Xa level, supra-therapeutic Xa levels, bleeding and thrombotic events during heparin management

Implementation Plan/Clinical Tools
1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Guideline will be posted on the uwhealth.org/anticoagulation webpage.
3. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
4. Staff education will be coordinated by the Anticoagulation Stewardship Program.

Order Sets & Smart Sets
IP/ED Heparin Anticoagulant – Adult – Supplemental Order Set [4373]
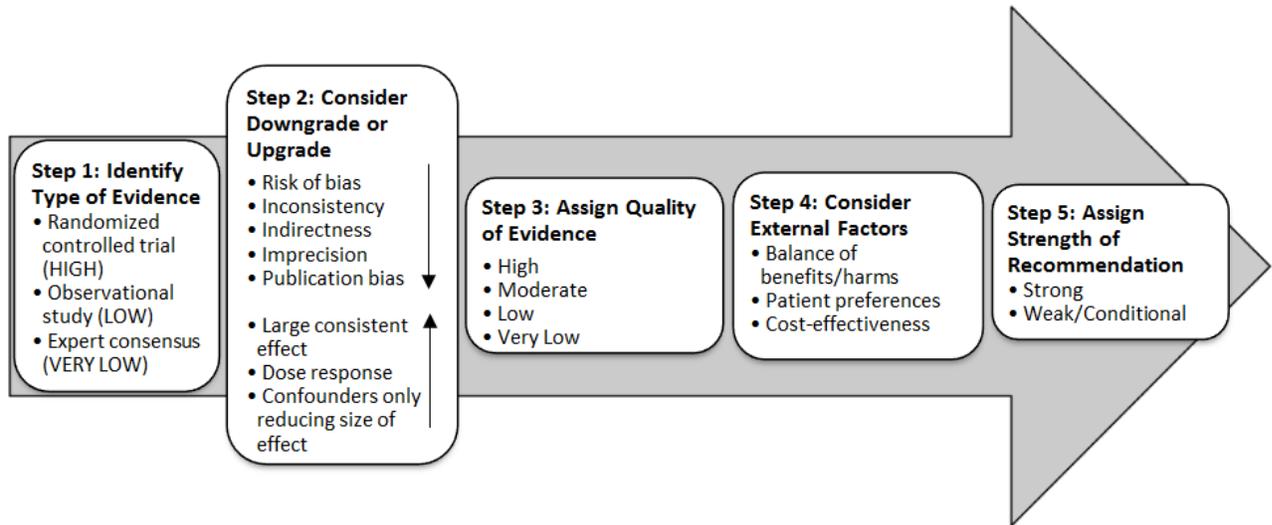
Practice Protocols
Protocol 4: Unfractionated heparin infusion titration practice protocol – Adult – Inpatient

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.

Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

Step 1: Identify Type of Evidence
- Randomized controlled trial (HIGH)
- Observational study (LOW)
- Expert consensus (VERY LOW)

Step 2: Consider Downgrade or Upgrade
- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

- Large consistent effect
- Dose response
- Confounders only reducing size of effect

Step 3: Assign Quality of Evidence
- High
- Moderate
- Low
- Very Low

Step 4: Consider External Factors
- Balance of benefits/harms
- Patient preferences
- Cost-effectiveness

Step 5: Assign Strength of Recommendation
- Strong
- Weak/Conditional

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	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Appendix B. Summary of Interim Revisions (As Appropriate)

Last Full Review	Summary of Revisions	Section (Page #)
MM/YY	List all revisions which were made between full periodic reviews.	

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