

Date published/posted: August 7, 2009

Management of Therapeutic Unfractionated Heparin (UFH)

Clinical Question

P (population/problem): In patients at a pediatric institution requiring systemic anticoagulation with unfractionated heparin (UFH) for the prevention or treatment of thrombo-embolic events,
 I (intervention): what are the appropriate medication doses and laboratory monitoring parameters
 O (outcome): to prevent under-coagulation and over-anticoagulation complications?

Target Population

Inclusion: Patients receiving systemic unfractionated heparin therapy at a pediatric institution
Exclusion: Patients on extracorporeal membrane oxygenation (ECMO)
 Patients receiving heparin flushes/infusions for central catheter patency

Recommendation(s)

Laboratory Monitoring

1. It is recommended that activated partial thromboplastin time (aPTT) be used as the standard laboratory measurement for the management of UFH therapy as discussed in Table 1 (*Local Consensus [5], Hirsh 2008a [5a]*).

Table 1: Recommendations for aPTT monitoring during UFH therapy (*Local Consensus [5], Hirsh 2008a [5a]*)

Patient Type/Age	Obtain Baseline aPTT (Prior to initiation of UFH ¹)	Repeat aPTT every 4 hours during treatment until therapeutic range achieved ²	Goal aPTT Range
< 1 year	Yes	Yes	75 to 115 seconds
1 to 16 years	Yes	Yes	
> 16 years	Yes	Yes	
Post-op CT Surgery Patients	No: Intra-op heparin not reversed with protamine Yes: Intra-op heparin reversed with protamine ³	Yes	60 to 80 seconds
s/p Cardiac Catheterization	Consider ⁴	Consider ⁴	40 to 60 seconds
s/p Liver Transplantation	Consider ⁴	Consider ⁴	40 to 60 seconds

¹UFH therapy may be started while awaiting the results of the aPTT test, if a delay in therapy initiation could result in an adverse patient outcome (*Local Consensus [5]*).

²Extend aPTT testing to once daily when aPTT values are in therapeutic range and relatively stable (*Hirsh 2008a [5a]*).

³CT Surgery patients who received heparin within the 6 hours prior to starting a heparin infusion who were not reversed with protamine after surgery, will not have a valid baseline aPTT, because of starting therapy early. CT Surgery patients who were reversed with protamine after surgery should have a baseline aPTT level prior to the start of a heparin infusion (*Local Consensus [5]*).

⁴UFH infusion rates of 15 units/kg/hour or less are considered prophylactic dosing and aPTT are not required (*Hirsh 2008a [5a]*).

Note 1: Some patients may have a lower goal aPTT range, based upon UFH usage and indication.

Note 2: aPTT value in the range of 75 to 115 seconds reflects anti-factor Xa levels of 0.3 to 0.7 unit/ml in most patients (*Local Consensus [5]*).

Note 3: There is a wide variation in the responsiveness of the aPTT to UFH between various reagents and instruments. Each laboratory must determine their own therapeutic range for the aPTT to correspond to a therapeutic heparin level of 0.3 to 0.7 anti-factor Xa units (*Hirsh 2008a [5a]*).

2. It is recommended to obtain the following laboratory studies:
 - Baseline: Complete Blood Count (CBC) with differential and prothrombin time (PT) (*Hirsh 2008a [5a]*).
 - Evaluation of thrombophilic disorders: Consider other tests (for example, fibrinogen, D-dimer, fibrin split products), as clinically indicated, prior to the initiation of UFH therapy (*Hirsh 2008a [5a]*).
 - CBC: Every other day until day 14 of therapy or until UFH therapy is stopped, whichever occurs first, to monitor for heparin-induced thrombocytopenia (HIT). If platelet count drops to greater than 50% below baseline or below $150 \times 10^9/L$, suspect HIT and notify the hematologist (*Hirsh 2008a [5a]*).

Note: The risk of HIT is greater after 5 days of therapy (*Hirsh 2008a [5a]*).
 - Anti-factor Xa: Obtain a level for dose guidance if the patient requires large daily doses of UFH without achieving a therapeutic aPTT (*Hirsh 2008a [5a]*).

3. It is recommended to avoid intramuscular injections and arterial punctures during UFH therapy. Consider appropriate precautions, including the use of extended periods of external pressure, if arterial punctures are warranted. (*Hirsh 2008a [5a]*)

Dose

4. It is recommended to initiate UFH therapy based on the recommendations in Table 2 (*Local Consensus [5]*, *Hirsh 2008a [5a]*, *Monagle 2008 [5a]*).

Table 2: Recommendations for dosing patients receiving UFH therapy (*Local Consensus [5]*, *Hirsh 2008a [5a]*, *Monagle 2008 [5a]*)

Patient Type/Age	UFH Loading Dose Administered Intravenously over 10 minutes (Maximum dose = 5000 units)	UFH Infusion Rate
< 1 year	75 units/kg*	28 units/kg/hour
1 to 16 years		20 units/kg/hour
> 16 years		18 units/kg/hour
Newborn following open heart surgery	Not indicated	15 to 20 units/kg/hour, based on clinical status
s/p Cardiac Catheterization	Not indicated	15 to 20 units/kg/hour, based on clinical status
s/p Liver Transplantation	Not indicated	10 units/kg/hour

s/p = status post,

*A larger loading dose may be indicated, dependent on the patient’s clinical condition (i.e., preceding cardiopulmonary bypass, limb-threatening thrombosis) (*Local Consensus [5]*)

Note: CCHMC uses a standard UFH concentration of 100 unit/ml in Normal Saline (0.9% Sodium chloride) for bolus and continuous therapeutic infusions. A lower concentration of 50 unit/ml is available for extremely low birth weight infants (*Local Consensus [5]*).

5. It is recommended to adjust the UFH dose based upon aPTT values according to the recommendations in Table 3 (*Hirsh 2008a [5a]*, *Monagle 2008 [5a]*).

Table 3: Recommendations for adjusting UFH dose based on aPTT values (*Hirsh 2008a [5a]*, *Monagle 2008 [5a]*)

aPTT (seconds)	Bolus (unit/kg)	Hold Infusion (minutes)	Rate Change (units/kg/hour)	Repeat aPTT
Less than 50	50	0	Increase dose rate by 10%	4 hours
50 to 74	0	0	Increase dose rate by 10%	4 hours
75 to 114	0	0	No change	24 hours
115 to 124	0	0	Decrease dose rate by 10%	4 hours
125 to 140	0	30	Decrease dose rate by 10%	4 hours
Greater than 140	0	60	Decrease dose rate by 15%	4 hours

- 6. It is recommended to continue the intravenous UFH infusion therapy without interruption unless authorized by a physician (*Hirsh 2008a [5a]*).
- 7. It is recommended to obtain an aPTT and re-establish the UFH maintenance infusion at the previous rate if the UFH infusion is interrupted for more than one hour (*Hirsh 2008a [5a]*).

Reversal of UFH

- 8. It is recommended to use intravenous protamine sulfate if rapid reversal (within 4 hours) of UFH is required as described in Table 4 (*Hirsh 2008a [5a]*).

Note 1: Protamine sulfate rapidly (within 5 minutes) neutralizes UFH activity (*Hirsh 2008a [5a]*).

Note 2: Patients with a known hypersensitivity to fish, and those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate (*Hirsh 2008a [5a]*).

Note 3: If rapid reversal of UFH is not required, termination of the UFH infusion may suffice (*Hirsh 2008a [5a]*).

- 9. It is recommended to administer protamine sulfate intravenously, over 10 minutes (*Hirsh 2008a [5a]*).

Note: Protamine sulfate may cause cardiovascular collapse if administered too quickly (*Hirsh 2008a [5a]*).

Table 4: Dosage of protamine sulfate (based on amount of UFH administered within 2 hours) (*Hirsh 2008a [5a]*)

Time since last UFH dose	Protamine sulfate dose per 100 units UFH received
< 30 minutes	1 mg
30 to 60 minutes	0.5 to 0.75 mg
60 to 120 minutes	0.375 to 0.5 mg
> 120 minutes	0.25 to 0.375 mg

- 10. It is recommended to obtain an aPTT and PT 15 minutes after the administration of protamine sulfate (*Hirsh 2008a [5a]*).

Transitioning UFH therapy

- 11. It is recommended to transition UFH to and from other anticoagulant medications as described in Table 5 (*Local Consensus [5], Douketis 2008 [5a], Hirsh 2008a [5a]*).

Table 5: Transitioning UFH to and/or from another anticoagulant medication (*Local Consensus [5], Douketis 2008 [5a], Hirsh 2008a [5a]*).

Transitioning Medication (Current to New)	Stop Current Medication	Start New Medication
UFH to Warfarin	Stop UFH after a minimum of 5 days or when warfarin INR is therapeutic	Start warfarin when clinically indicated and patient able to tolerate medication
UFH to LMWH	Stop UFH 4 hours after the first LMWH dose	Start LMWH when clinically indicated
Warfarin to UFH	Stop warfarin when clinically indicated or 5 days prior to procedure	Start UFH on the third day of holding warfarin
LMWH to UFH	Stop LMWH after UFH initiation	Start UFH 4 hours after the last LMWH dose

LMWH = Low Molecular Weight Heparin

Duration of Therapy

- 12. It is recommended to refer patient to a specialist for the ongoing management of UFH therapy (*Local Consensus [5]*).

Note: Duration of UFH therapy is dependent on the indication (*Hirsh 2008a [5a], Monagle 2008 [5a]*).

Discussion/summary of evidence

Based upon an AGREE evaluation of the *Chest* American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), we concluded that the working group published a well-developed guideline (*Hirsh*

2008c [5a]). The Applicability domain scored relatively low. This score takes into account discussions in the guideline of how to apply the recommendations to practice. While the guidelines do not specifically address how to apply them to clinical practice, all the recommendations are clearly identified, and the review team did not feel this decreased the validity of the guidelines.

Standardized AGREE domain scores:

Scope and Purpose	96%
Stakeholder Involvement	53%
Rigor of Development	95%
Clarity and Presentation	72%
Applicability	30%
Editorial Independence	94%

(Crary 2008 [4b], Local Consensus [5], Ansell 2008 [5a], Bates 2008 [5a], Douketis 2008 [5a], Guyatt 2008 [5a], Hirsh 2008a [5a], Hirsh 2008b [5a], Hirsh 2008c [5a], Kearon 2008 [5a], Monagle 2008 [5a], Schunemann 2008 [5a])

Health Benefits, Side Effects and Risks









Health Benefits: Following these recommendations when managing patients on UFH therapy may help to minimize both over-coagulation (thrombus formation) and under-coagulation (bleeding) (Hirsh 2008a [5a]).

Side Effects: Bleeding is the most common complication of UFH therapy. Osteoporosis can occur with prolonged (more than 6 months) use (Hirsh 2008a [5a]). A high-index of suspicion is required to diagnose heparin-induced thrombocytopenia (HIT) in patients receiving UFH.

Risks: The most important factor influencing the risk of bleeding is the intensity of anticoagulation therapy (Hirsh 2008a [5a]). The quality of management of anticoagulant therapy can be measured by determining the time blood values are within therapeutic range.

References (evidence grade in []; see Table of Evidence Levels following references)

Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

1. **Ansell, J.; Hirsh, J.; Hylek, E.; Jacobson, A.; Crowther, M.; and Palareti, G.:** Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 160S-198S, 2008, [5a]  [_____](#).
2. **Bates, S. M.; Greer, I. A.; Pabinger, I.; Sofaer, S.; and Hirsh, J.:** Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 844S-886S, 2008, [5a]  [_____](#).
3. **Crary, S. E.; Van Orden, H.; and Journeycake, J. M.:** Experience with intravenous enoxaparin in critically ill infants and children. *Pediatr Crit Care Med*, 9(6): 647-9, 2008, [4b]  [_____](#).
4. **Douketis, J. D.; Berger, P. B.; Dunn, A. S.; Jaffer, A. K.; Spyropoulos, A. C.; Becker, R. C.; and Ansell, J.:** The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 299S-339S, 2008, [5a]  [_____](#).
5. **Guyatt, G. H.; Cook, D. J.; Jaeschke, R.; Pauker, S. G.; and Schunemann, H. J.:** Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 123S-131S, 2008, [5a]  [_____](#).
6. **Hirsh, J.; Bauer, K. A.; Donati, M. B.; Gould, M.; Samama, M. M.; and Weitz, J. I.:** Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 141S-159S, 2008a, [5a]  [_____](#).
7. **Hirsh, J.; Guyatt, G.; Albers, G. W.; Harrington, R.; and Schunemann, H. J.:** Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 71S-109S, 2008b, [5a]  [_____](#).
8. **Hirsh, J.; Guyatt, G.; Albers, G. W.; Harrington, R.; Schunemann, H. J.; and American College of Chest, P.:** Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 110S-112S, 2008c, [5a]  [_____](#).

9. **Kearon, C.; Kahn, S. R.; Agnelli, G.; Goldhaber, S.; Raskob, G. E.; and Comerota, A. J.:** Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 454S-545S, 2008, [5a] _____
10. **Local Consensus:** During BESt development timeframe. [5].
11. **Monagle, P.; Chalmers, E.; Chan, A.; DeVeber, G.; Kirkham, F.; Massicotte, P.; and Michelson, A. D.:** Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 887S-968S, 2008, [5a] _____
12. **Schunemann, H. J.; Cook, D.; and Guyatt, G.:** Methodology for antithrombotic and thrombolytic therapy guideline development: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 113S-122S, 2008, [5a] _____

Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life

Supporting information

Introductory/background information

UFH is a commonly used anticoagulant in pediatric patients. Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic parameters. Its molecular weight ranges from 3,000 to 30,000 daltons, with a mean molecular weight of 15,000. Only about one-third of an administered dose of heparin binds to antithrombin (AT), and this fraction is responsible for most of its anticoagulant effect (*Hirsh 2008a [5a]*).

Mechanism of Action: Heparin exerts antithrombotic activity by inducing a conformational change in the structure of AT that dramatically augments the ability of AT to neutralize thrombin, and, to a lesser extent, factor Xa and other coagulation factors. Heparin also impairs platelet function (*Hirsh 2008a [5a]*).

Plasma levels of AT are physiologically low at birth and do not increase to adult values until 3 months of age (*Monagle 2008 [5a]*). AT levels are even lower in sick premature infants. The clearance of UFH is faster in neonates than that for older children due to a larger volume of distribution (*Monagle 2008 [5a]*). Therefore, the dose of UFH required to achieve a therapeutic aPTT in neonates is higher compared to that in older children.

Group/team members

Group/Team Leader: Cynthia Barclay, PharmD, Pharmacy

Other group/team members:

Katherine Auger, MD, Chief Resident, General Pediatrics
Ranjit Chima, MD, Critical Care
Ralph Gruppo, MD, Hematology
Alexander Hamling, MD, MBA, Housestaff, General Pediatrics
Timothy Knilans, MD, Cardiology

Clinical Effectiveness Support:

Eloise Clark, MPH, MBA, Guidelines Program Administrator
Karen Vonderhaar, MS, RN, Guidelines Program Administrator, Methodologist

Search strategy

CHEST 2008 Anticoagulation Guidelines

In addition, a search was conducted for literature published subsequent to the Chest Guidelines:

OID MEDLINE; search terms: anticoagu\$ (explode), Heparin, Child, Treat\$ or Thera\$,
with limits and filters: English language, Humans, Age Range 0-18 years.

Known conflicts of interest

Conflicts of interest were declared and none were found.

Applicability Issues

Outcome measures:

- Percent of baseline aPTTs obtained prior to UFH initiation
- Percent of follow-up aPTTs obtained 4 to 6 hours after the start of the UFH infusion

Copies of this Best Evidence Statement (BEST) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>

Examples of approved uses of the BEST include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BEST may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any BEST adopted, adapted, implemented or hyperlinked by the organization is appreciated.

For more information about this CCHMC Best Evidence Statement and the development process, contact Cynthia Barclay, Pharm.D. in the Division of Pharmacy at: 513-636-4292 or cynthia.barclay@cchmc.org

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the

recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by: Clinical Effectiveness and Center for Professional Excellence.