

**Date published/posted: August 7, 2009**

## **Management of Low Molecular Weight Heparin Therapy (LMWH)**

### **Clinical Question**

- P (population/problem): In patients at a pediatric institution requiring systemic anticoagulation with low molecular weight heparin (LMWH) for treatment or prophylaxis
- I (intervention): what are the appropriate medication doses and laboratory monitoring parameters
- O (outcome): to prevent under-coagulation and over-anticoagulation complications?

### **Target Population**

Patients receiving low molecular weight heparin therapy (LMWH) at a pediatric institution

**Recommendations** (See Table of Recommendation Strength following references)

#### **Laboratory Monitoring**

##### *Laboratory studies required for LMWH therapy*

1. It is recommended to use the anti-factor Xa level as a measurement of efficacy for LMWH .  
**Note:** Cincinnati Children's Hospital Medical Center (CCHMC) identifies anti-factor Xa levels as "LMWH Level" in the clinical laboratory system.
2. It is recommended to check the anti-factor Xa level 4 to 6 hours following the subcutaneous administration of a dose. Draw the anti-factor Xa level from a fresh venipuncture so that there is NO CONTAMINATION from standard heparin left in the intravenous line tubing (*Hirsh 2008a [5a]*).

##### *Therapeutic Values for anti-factor Xa*

3. It is recommended to maintain an anti-factor Xa range of 0.5 to 1 unit/ml in patients receiving every 12 hour treatment of LMWH therapy (*Monagle 2008 [5a]*).
4. It is recommended to maintain an anti-factor Xa range of 0.1 to 0.3 unit/ml in patients receiving prophylactic LMWH therapy (*Monagle 2008 [5a]*).
5. It is recommended to monitor anti-factor Xa at frequencies noted in Table 1 (*Hirsh 2008a [5a], Monagle 2008 [5a]*).

##### *Baseline Laboratory Studies*

6. It is recommended to draw the following prior to the start of LMWH therapy:
  - Complete Blood Count (CBC) with differential
  - Activated Partial Thromboplastin Time (aPTT)(*Hirsh 2008a [5a]*).
7. It is recommended to consider obtaining blood for the evaluation of thrombophilic disorders and other tests (for example, Fibrinogen, D-dimer, Fibrin split products), as clinically indicated, prior to the initiation of LMWH therapy (*Hirsh 2008a [5a]*).

*Monitoring of Therapy*

8. It is recommended to monitor platelet counts regularly (minimum of once every 2 weeks) while a patient is receiving LMWH therapy. Suspect heparin-induced thrombocytopenia (HIT) if platelet count drops below  $150 \times 10^9/L$  (Hirsh 2008a [5a]).  
**Note:** The risk of HIT is rare with LMWH therapy, but can occur (Hirsh 2008a [5a]).
9. It is recommended to consider bone densitometry studies at baseline and then at regular intervals (approximately every 12 months) in patients expected to be on long-term LMWH therapy (> 3 months) (Local Consensus [5], Hirsh 2008a [5a]).

**Dosing and Administration**

10. It is recommended to administer LMWH via subcutaneous injection (Hirsh 2008a [5a]).  
**Note:** In the neonatal population, intravenous administration is acceptable (Cravy 2008 [4b]).
11. It is recommended to initiate LMWH therapy with treatment and prophylactic enoxaparin as described in Table 1 (Hirsh 2008a [5a], Monagle 2008 [5a]).  
**Note:** Enoxaparin is the LMWH of choice at CCHMC. If a patient receives a LMWH other than enoxaparin, modify dosing according to the manufacturer’s product information for that specific medication.

**Table 1: Enoxaparin\* monitoring and initial dosing in patients at a pediatric institution (Hirsh 2008a [5a], Monagle 2008 [5a])**

Patient Type/Age	Enoxaparin Dosing		LMWH Level Monitoring Frequency		Comments/Notes
	Prophylaxis	Treatment	Prophylaxis	Treatment	
< 2 months	0.75 mg/kg/dose every 12 hours	1.5 mg/kg/dose every 12 hours SC [Max dose = 2 mg/kg]	Not recommended	After second or third dose and weekly after therapeutic dose achieved	
2 months to 18 years or ≤ 50 kg	0.5 mg/kg/dose every 12 hours SC	1 mg/kg/dose every 12 hours SC (Max dose = 2 mg/kg)	Not recommended	After second or third dose and weekly after therapeutic dose achieved	Pediatric patients greater than 50 kg can be considered adult for prophylaxis dosing, and receive recommended adult dosing.
> 18 years or > 50 kg to 125 kg	40 mg once daily SC or 30 mg every 12 hours SC	1 mg/kg/dose every 12 hours SC (Max dose = 150 mg every 12 hours)	Not recommended	Not recommended	<ul style="list-style-type: none"> <li>• The mg/kg dose has been validated for enoxaparin for total body weight up to 144 kg (Hirsh 2008a [5a]).</li> <li>• Patients &gt; 18 years of age can alternatively receive a dose of 1.5 mg/kg/dose once daily</li> <li>• Maintain the antifactor-Xa level at greater than 1 unit/ml at 4 to 6 hours following a dose (Hirsh 2008a [5a]).</li> </ul>
> 125 kg	40 mg every 12 hours SC		Not recommended	Not recommended	
Renal Dysfunction	Consider decreasing dose	Consider starting dose at 50% of the normal starting dose	Consider	After second or third dose and weekly after therapeutic dose achieved	Consider increased monitoring of anti-factor Xa levels.
Pregnancy	40 mg once daily SC or 30 mg every 12 hours SC	1 mg/kg/dose every 12 hours SC (Max dose = 150 mg every 12 hours)	Not recommended	After second or third dose and weekly after therapeutic dose achieved	

\*Enoxaparin is the LMWH of choice at CCHMC. If a patient receives a LMWH other than enoxaparin, modify dosing according to the manufacturer’s product information for that specific medication.

Max = Maximum; SC = subcutaneous injection

**Note 1:** Use commercially available unit dose sized products when available.

**Note 2:** CCHMC prepares a 20 mg/ml enoxaparin product for low-weight patients requiring therapy with enoxaparin.

12. It is recommended to adjust LMWH treatment based on anti-factor Xa levels. Enoxaparin therapy can be adjusted as described in Table 2 (*Monagle 2008 [5a]*).  
**Note:** Enoxaparin is the LMWH of choice at CCHMC. If a patient receives a LMWH other than enoxaparin, modify dosing according to the manufacturer’s product information for that specific medication.

**Table 2: Recommendations to adjust dosing treatment with Enoxaparin\* (*Monagle 2008 [5a]*)**

Anti-factor Xa level	Dose Change	Repeat Anti-factor Xa level
< 0.35 units/ml	Increase dose by 25%	4 hours following new dose
0.35 to 0.49 units/ml	Increase dose by 10%	4 hours following new dose
0.5 to 1 units/ml	No changes	Once a week at 4 hours following dose
1.1 to 1.5 units/ml	Decrease dose by 20%	4 hours following new dose
1.6 to 2 units/ml	Decrease dose by 30%	4 hours following new dose
> 2 units/ml	<ul style="list-style-type: none"> <li>• Hold all further doses</li> <li>• Measure anti-factor Xa level every 12 hours until level is 0.5 units/ml</li> <li>• Restart enoxaparin at a dose 40% less than what was originally prescribed</li> </ul>	

\*Enoxaparin is the LMWH of choice at CCHMC. If a patient receives a LMWH other than enoxaparin, modify dosing according to manufacturer’s product information for that specific medication.

13. It is recommended to follow these precautions when administering LMWH:
- Avoid intramuscular injections and arterial punctures during LMWH therapy. If arterial punctures are warranted, consider appropriate precautions, including the use of extended periods of external pressure (*Hirsh 2008a [5a]*).
  - Avoid aspirin or other antiplatelet drugs during LMWH therapy. If analgesia is required, acetaminophen is the preferred drug (*Hirsh 2008a [5a]*).
  - In patients having a lumbar puncture, delay the lumbar puncture until two consecutive doses of LMWH have been held (at least 18 hours from last injection). Do NOT use LMWH in patients receiving continuous epidural anesthesia (*Ansell 2008 [5a]*).
- Note:** Perispinal hematomas and paralysis have been reported in patients having a lumbar puncture while receiving LMWH (*Hirsh 2008a [5a]*).

**Discontinuation of LMWH**

14. It is recommended to discontinue LMWH 24 to 36 hours prior to surgical procedures. Give the last dose of LMWH in the morning of the day before the procedure. (*Douketis 2008 [5a]*).
15. It is recommended to consider protamine sulfate if an immediate (within 3 to 4 hours of LMWH) reversal of LMWH is required.
- Dose of protamine sulfate is dependent on the last dose and time of LMWH given (*Hirsh 2008b [5a]*).
  - Maximal neutralizing dose is 1 mg of protamine sulfate per 100 units (1 mg) LMWH given at the last dose (*Hirsh 2008a [5a]*).
  - Administer intravenously over a 10 minute period, since rapid infusion can cause hypotension (*Hirsh 2008a [5a]*).
- Note 1:** There is limited information using protamine sulfate to reverse the effects of LMWH; in particular, it has NOT been shown to completely reverse LMWH (*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]*).

**Transitioning LMWH therapy**

16. It is recommended to transition LMWH to and from other anticoagulant medications as described in Table 3 (next page) (*Local Consensus [5], Douketis 2008 [5a], Hirsh 2008a [5a]*).

**Table 3: Transitioning LMWH to or from another anticoagulant medication (Local Consensus [5], Douketis 2008 [5a], Hirsh 2008a [5a]).**

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

\*Patients with a higher clotting risk may be started on LMWH immediately upon the discontinuation of warfarin (Local Consensus [5]).

UFH = Unfractionated Heparin

**Duration of Therapy**

- 17. It is recommended to refer patient to a specialist for the ongoing outpatient management of LMWH therapy (Local Consensus [5]).

**Note 1:** The duration of LMWH therapy is dependent on patient indications (Monagle 2008 [5a]).

**Note 2:** CCHMC sponsors a Thombophilia Program that manages patients receiving LMWH (Phone: 513-636-6213) (Local Consensus [5]).

**Discussion/summary of evidence**

Based upon an AGREE evaluation of *Chest* American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> Edition), we concluded that the working group published a well-developed guideline (Hirsh 2008b [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], Kearon 2008 [5a], Monagle 2008 [5a], Schunemann 2008 [5a])

**Health Benefits, Side Effects and Risks**


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











Potential benefits of LMWHs in pediatric patients include the need for minimal monitoring, lack of interference by other drugs or diet, reduced risk of heparin-induced thrombocytopenia (HIT), and the probable reduced risk of osteoporosis with long-term use (Monagle 2008 [5a]).

**Side Effects:** Bleeding is the main complication of LWMH therapy. The frequency of HIT is three times lower with LMWH therapy than with UFH (Monagle 2008 [5a]). The frequency of osteoporosis with LMWH is also lower when compared to UFH (Hirsh 2008a [5a]).

**Risks:** The most important factor influencing the risk of bleeding is the intensity of anticoagulation therapy. The quality of management of anticoagulant therapy can be measured by determining the time in the therapeutic range. This is expressed as the fraction of anti-factor Xa levels that are within therapeutic range (Hirsh 2008a [5a]).

**References/citations**

**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.; 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, 2008b, [5a] [\\_\\_\\_\\_\\_](#) .
8. **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] [\\_\\_\\_\\_\\_](#) .
9. **Local Consensus:** During BEST development timeframe. [5].
10. **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] [\\_\\_\\_\\_\\_](#) .
11. **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

Low molecular weight heparins (LMWHs) have rapidly become the anticoagulant agent of choice in pediatric patients, despite their undocumented efficacy. Enoxaparin is frequently the LMWH of choice in children, as the majority of available data is based upon this agent (*Monagle 2008 [5a]*).

LMWHs are prepared from unfractionated heparin (UFH) by enzymatic or chemical hydrolysis. LMWH inhibits factor Xa more potently than thrombin, where as UFH predominantly inhibits thrombin (*Hirsh 2008a [5a]*).

### 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), Enoxaparin, 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 measure: Percent of patients receiving initial dose of LMWH as recommended based on patient age and indication.

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](mailto: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](mailto: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.**