

CLINICAL PRACTICE GUIDELINES

Initiation and Maintenance of Enoxaparin (Lovenox)

Disclaimer: These clinical practice guidelines are based upon the opinions of staff members of The Children's Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient

A. General Information

These guidelines apply to the use of enoxaparin for the prevention and treatment of thromboembolic disorders. We have organized the information by phase of care: Initiation of therapy & inpatient management and Discharge & follow-up planning.

Low Molecular Weight Heparin (LMWH) has become the anticoagulant agents of choice in many pediatric patients, both for primary prophylaxis and treatment of thromboembolism. At CHOP Enoxaparin is the LMWH that is on formulary. The potential advantages of LMWH for pediatric patients include the need for minimal monitoring, lack of interference by other drugs or diet (unlike warfarin), reduced risk of Heparin-induced thrombocytopenia (HIT), and reduced risk of osteoporosis with long-term use compared to that with the use of heparin.

For patients with renal disease and creatinine clearance < 30 mL/min the preferred anticoagulants are unfractionated heparin (uFH) and warfarin (see guideline recommendation links for [Unfractionated heparin](#) and [Warfarin](#)). There is limited data on using enoxaparin chronically in adult and pediatric patients on dialysis, and it is not FDA approved for use in dialysis patients. UFH is preferred for patients with acute life threatening thrombosis to allow better titration of anticoagulation, and for patients with reasonable access. For patients in whom uFH is not feasible, LMWH may be considered as a bridge to warfarin. For patients in whom warfarin is not an option for long term therapy, enoxaparin may be considered on a case by case basis.

B. Baseline Monitoring (To be completed prior (< 48 hrs) to or upon initiation of enoxaparin)

Baseline labs are to be completed to ensure patient has a normal baseline coagulation state:

- CBC
 - Thrombocytopenia is a relative contraindication to anticoagulant therapy and should be corrected to $\geq 75,000/\text{mL}$ before use.
- PT
- PTT
- Creatinine (Cr)

If the patient has abnormal coagulation studies, or thrombocytopenia, the hematology team should be consulted for further recommendations. If the patient has an elevated Cr, the hematology and clinical pharmacy teams should be consulted for further recommendations.

C. Dosing

Considerations:

- The half-life of enoxaparin is 4 hours.
- Peak enoxaparin levels occur 3 to 5 hours following a subcutaneous injection.
- Enoxaparin is renally cleared and adjustments to dosage may be required if calculated CrCl is

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<30 mL/minute. Consult hematology or clinical pharmacy for dose adjustments or consider alternative therapy (unfractionated heparin or warfarin) in patients with decreased renal function.

- Infants < 3 months of age or weight < 5 kg have increased requirements per kilogram, which likely is due to a large volume of distribution and low antithrombin levels. Prior published enoxaparin dosing recommendations are often inadequate for neonates. The doses recommended in this document have been updated to reflect current practice and are more likely to achieve the therapeutic range.
- Obese patients: (BMI > 30) should receive lower dose ~ 0.8 mg/kg
- Patients with chylous drainage via pleural catheter may have AT3 losses that effect enoxaparin dosing
- **DOSES SHOULD BE ROUNDED UP TO THE NEAREST WHOLE MILLIGRAM**

Initial Dose:

- < 3 months: 1.7 mg/kg Sub-Q q 12 hours
- 3 months - 2 years: 1.2 mg/kg Sub-Q q 12 hours
- > 2 years: 1 mg/kg Sub-Q q 12 hours
- Obese patients ~ 0.8 mg/kg Sub-Q q12 hours-**Maximum dose 170 mg**

Dosage Adjustment for Renal Impairment: All dose adjustments should be discussed with clinical pharmacy

- CrCl > 30 mL/min: no adjustment
- CrCl < 30 mL/min (not dialysis dependent):
 - Initiate load with normal weight based dosing x once (see above "[Initial Dose](#)" section), then reduced subsequent doses as follow (give 12 hours after initial dose)
 - CrCl 10-30 mL/min: decrease dose by 30% and maintain interval of 12 hours
 - CrCl < 10 mL/min: decrease dose by 50% and maintain interval of 12 hours
- Dialysis dependent (all age):
 - Peritoneal dialysis: initiate load with normal weight based dosing x once (see above "[Initial Dose](#)" section), then decrease subsequent doses by 30%, give 12 hours after initial dose, and maintain interval of 12 hours
 - Intermittent hemodialysis: initiate 1 mg/kg every 24 hours

D. Monitoring

- Enoxaparin is monitored by a peak heparin anti-Xa level using an assay for LMWH. It should be sent 4 hours (range 3-5 hours) after 2nd or 3rd dose upon initiation, after any dose change, and when there is concern that the patient may be bleeding. Trough anti-Xa is not routinely used to monitor enoxaparin. Patients on intermittent hemodialysis may use trough anti-Xa level to monitor enoxaparin due to inability to monitoring peak anti-Xa level as outpatient. The trough anti-Xa level may be helpful in determining drug-free interval in patients with high thrombosis risk(s).

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- Neonates and infants (< 1 yr): weekly while inpatient - if two anti-Xa levels are within therapeutic goal, then go to a schedule of every other week or more frequent with concerns about deteriorating renal function
- Children (1-17 yrs): every other week while inpatient or more frequent with concerns about deteriorating renal function
- Adults (≥ 18 yrs): monitoring of anti-Xa level is not required if the patient has normal renal function **and** non-obese (< 100 kg or BMI < 30 kg/m²) or non-malnourished (weight > 45 kg)
- Patients with renal impairment (CrCl < 30 mL/min) or on peritoneal dialysis:
 - Inpatient: every 3-4 days while inpatient for at least 2 levels, then weekly for at least 4 levels, then every 2 weeks
 - Outpatient: weekly for at least 2 levels, then every 2 weeks for at least 3 levels, then monthly
- Patients on intermittent hemodialysis (all age) send anti-Xa peak after 2nd or 3rd dose and adjust according to peak anti-Xa until within goal (see [Table 1](#) below). When peak anti-Xa is within goal, send a trough level prior to the next dose. Adjust dose to the trough level range 0.1-0.3 unit/mL (see [Table 2](#) below).
 - Inpatient: peak or trough every 3-4 days for at least 2 levels, then weekly for at least 4 levels, then every 2 weeks
 - Outpatient: weekly
- Patients with pleural catheters for chylous drainage who have changing output should be monitored at least weekly
- Enoxaparin dose may accumulate over the first few weeks, therefore anti-Xa levels should be monitored accordingly

Therapeutic Range: A guideline for therapeutic enoxaparin is a peak heparin anti-Xa level of 0.5 to 1 units/mL in a sample taken 4 hours (range 3-5 hours) following a subcutaneous injection. Anti-Xa levels up to 1.2 units/mL have been targeted for patients with high risk of thrombosis. Closer monitoring is needed (at least weekly anti-Xa).

Table 1. Nomogram for Adjusting Enoxaparin Dose for Peak Anti-Xa

Peak Anti-Xa Level	Dose Change	Repeat Anti-Xa Level
< 0.35 units/mL	Increase by 25%	4 h after 2nd dose
0.35-0.49 units/mL	Increase by 10%	4 h after 2nd dose
0.5-1 units/mL	None	See " Monitoring " section
1.1-1.5 units/mL	Decrease by 20%	4 h after 2nd dose
1.6-2 units/mL	Decrease by 30%	4 h after 2nd dose
> 2 units/mL	For these patients, check for decreased renal function. All further doses should be held, and the anti-factor Xa level measured q 12 h until the anti-factor Xa level is < 0.5 units/mL. Enoxaparin can then restarted for patients with CrCl > 30 mL/min at a dose 40 % less than recently prescribed dose	

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Table 2. Nomogram for Adjusting Enoxaparin Dose for Trough Anti-Xa in Patients with Renal Impairment as an Inpatient (20-24 hour after dose)

Trough Anti-Xa Level	Peak Anti-Xa Level	Dose Change	Repeat Anti-Xa Level
< 0.1 units/mL	0.5 – 0.75 units/mL	Increase by 10%	4 h after 2nd dose
	> 0.75 units/mL	Discuss with clinical pharmacy	
0.1-0.3 units/mL	0.5-1 units/mL	None	See “ Monitoring ” section
> 0.3 units/mL	0.5 – 0.75 units/mL	Recheck both peak and trough within 48 hours. If repeat peak and trough are similar to initial peak and trough, then adjust/monitoring according to peak recommendation	
	> 0.75-1 units/mL	Decrease by 10%	4 h after 2nd dose

Table 3. Nomogram for Adjusting Enoxaparin Dose for Trough Anti-Xa in Patients with Renal Impairment as an Outpatient (12->20 hour after dose)

Trough Anti-Xa Level	Dose Change	Repeat Anti-Xa Level
< 0.2 units/mL	Increase by 10%	Prior to next HD session
0.2-0.4 units/mL	None	See “ Monitoring ” section
0.41-0.6 units/mL	Decrease by 20%	Prior to next HD session
> 0.6 units/mL	For these patients, all further doses should be held. If enoxaparin is continued, measure anti-factor Xa level daily until the anti-factor Xa level is < 0.2 units/mL. Enoxaparin can then restarted at a dose 40 % less than recently prescribed dose.	

- Ideally, blood samples for the heparin anti-Xa level should be drawn by venipuncture. Heparin **contamination in the central line or IV may affect the level.** In the case where a level is drawn from a line through which heparin has been administered, ensure that an adequate amount of “waste” is withdrawn from the line before drawing the lab [at least twice the volume of the catheter].

E. Administration

- Administer by subcutaneous injection to the anterolateral/posterolateral abdominal wall, upper arm, or thigh. (an illustration of potential sites can be found in the enoxaparin educational booklet and the nursing procedure for administration of subcutaneous injections)
Do NOT administer IM.
- Insuflon™ catheters may be used to administer enoxaparin in children ≥5kg.

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F. Safety

- Bleeding! The major adverse event related to enoxaparin is bleeding. If a patient on enoxaparin develops bleeding, stop enoxaparin and urgently seek a Hematology consult.
- Heparin Induced Thrombocytopenia (HIT) - Though rare, HIT does occur in children. This should be suspected in any patient on heparin, uFH or LMWH, with unexplained drop in platelet count > 50% from baseline or with thrombocytopenia. **Hematology should be consulted immediately if HIT is suspected.**
- Long term use (≥ 1 year) of heparin or LMWH may increase the risk of osteoporosis. Consider obtaining a baseline DEXA scan in patients > 5 years of age.
- Avoid IM injections and arterial punctures during anticoagulant therapy. When such procedures are clinically necessary, ensure that adequate external pressure is applied post-procedure.
- Other invasive procedures that may result in bleeding in a patient who is anticoagulated and should be carefully considered include NG tube insertions, intubation, and rectal temps.
- **Avoid drugs that affect platelet function** (eg, aspirin, NSAIDs, dipyridamole) as they may potentiate the risk of hemorrhage.

G. Enoxaparin Reversal

- Protamine sulfate can be used – However, **it does not fully reverse LWMH** – (about 70% reversal).
- Protamine combines with the strongly acidic heparin to form a stable salt complex neutralizing the anticoagulant activity.
- Protamine requires a high level of caution when being prescribed and administered Protamine should be administered intravenously in a concentration of 10 mg/mL at a rate not to exceed 5 mg/minute. If administered too quickly it may cause cardiovascular collapse. Patients with known hypersensitivity reactions to fish, and those who have received protamine containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions to protamine sulfate.
- The dosage of protamine sulfate is based on the both the amount of enoxaparin and the time since the last dose, as follows:

Table 4. Nomogram for Enoxaparin Reversal

Time Since Last Enoxaparin Dose	Protamine Dose per 1 mg Enoxaparin Received
< 4 hours	1 mg per 1 mg enoxaparin received
4-8 hours	0.5-0.75 mg per 1 mg enoxaparin received
8-12 hours	0.25-0.5 mg per 1 mg enoxaparin received
> 12 hours	Do not give protamine

Max dose: 50 mg

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H. Converting from LMWH to uFH:

- Begin unfractionated heparin (uFH) no earlier than 8 hours after the last dose of LMWH.
 - If starting within 8-12 hours, **do not use** bolus dose of uFH.
 - After 12 hours, consider bolus dose of uFH followed by maintenance dose per protocol.

I. Elective Procedures

- Consult the provider conducting the procedure for specific direction of holding anticoagulation. In general, hold at least 1 LMWH dose for minor procedure and 2 LMWH doses prior to major procedure such as invasive **surgical** procedure or **lumbar puncture** (list not all inclusive).

Procedure	Optimal amount of time required between procedure and previous dose
Arterial line	12 hours
Biopsy (all)	24 hours
Bronchoscopy	24 hours
Broviac	24 hours
Chest tube	24 hours
Circumcision	24 hours
Dental (minor)	12 hours
Dental (major – extraction)	24 hours
Immunization Administration	12 hours
Epidural procedure	24 hours
Foley Placement	12 hours
Hernia repair	24 hours
Lumbar puncture	24 hours
NG/ND/NJ Placement	12 hours
Paracentesis	24 hours
PICC	24 hours

J. Complications

- The attending of record or the attending defined responsible for outpatient management will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc) in consultation with the division of hematology as deemed appropriate.
- Reporting of complications, including bleeding requiring transfusion, intracranial hemorrhage, and over-anticoagulation requiring reversal with protamine, into the electronic reporting system, KAPS, is highly recommended.

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K. Discharge & Follow-Up Planning

ALERT: Prescription insurance plans often require prior authorization of enoxaparin (Lovenox) as a condition of covering the drug. This process may take up to 3 days to complete. Case Management facilitates this process and should be alerted to help with enoxaparin arrangements in ample time as not to delay discharge.

Ordering Drug:

When writing discharge orders/instructions, appreciate that for standard therapy, injections are given every 12 hours. Needle gauge and length are important considerations.

- Doses should be rounded up to the nearest **WHOLE MILLIGRAM**
- Enoxaparin (Lovenox®) can be ordered as a **multidose vial 300 mg/3mL**. Most patients prefer **to use an insulin syringe with a 31 gauge, 5/16" needle** with the dose drawn from the multiple dose vial.
 - Insulin syringes are marked in units and were made for use with insulin. Enoxaparin is given in mg, not units. However, because 1 mg of enoxaparin is the same volume as 1 unit of insulin, the insulin syringe can be used. A 1 unit measurement in an insulin syringe is equivalent to 1 mg of enoxaparin.
 - Outpatient anticoagulation management service usually request/prefers the multidose vial with insulin syringes
 - You must order a syringe if ordering a multiple dose vial. Either choose the insulin syringe (30 units/0.3mL, 50 units/0.5 mL or 100 units/1 mL) or a standard needle. Be sure the family is educated prior to discharge to use the needle you prescribe for home use.
 - Some pharmacies prepare syringes (referred to as pre-drawn syringes)
- **Manufacturer's pre-filled syringes. The concentration is 100 mg/1 mL.** The needle is 27gauge, ½ inch length and is attached to the syringe.
 - **30 mg and 40 mg syringes** have NO graduation marks on the syringe barrel. They are ordered specifically for a dose that is fixed/not changing.
 - **60 mg, 80 mg and 100 mg syringes** – all are graduated; consequently some drug can be squirted out to achieve the ordered dose i.e. using a 60 mg prefilled syringe, for ordered dose of 48 mg, a patient could squirt out 12 mg prior to administering the injection.
 - Rarely to never used in pediatric patients are Manufacturer's pre-filled syringes at a concentration of 150 mg/1 mL. This information is included here for completeness and in the event that a morbidly obese patient requires an enoxaparin dose > 100 mg.
 - 120 mg and 150 mg syringes both have 27 gauge, ½ inch needles attached

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Ordering Patient/Family Education:

Prior to discharge, all patients and their families should receive education regarding the safe use of enoxaparin. There are educational booklets on enoxaparin available through hematology, cardiology, and the Connelly Center and as a PDF file through the CHOP intranet under Patient Family Education (PFE)

Arranging Follow up Planning:

All patients discharged on enoxaparin should have a follow-up appointment with the service responsible for managing the patient's enoxaparin therapy (i.e. hematology or cardiology),

- Including date, time scheduled, and location for outpatient follow-up in written discharge instructions
- An anti-Xa level should be ordered/arranged for within 1-2 weeks of discharge (within one week in patients < 20 kg)
 - Then every 4 to 12 weeks or sooner if bleeding symptoms or significant changes in weight or renal function occur in the interim
- The attending physician who will be responsible for outpatient management of the enoxaparin will be identified and documented.

Related Policy: #TX-7-19, [Anticoagulation Management Program Guidelines](#)