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### Background

#### What is Heparin?

Heparin is an anionic mucopolysaccharide.

Heparin acts as an anticoagulant by forming a complex with antithrombin (AT). This complex inhibits several activated blood coagulation factors: XIIa, XIa, IXa, Xa and IIa (thrombin). Heparin's onset of action is immediate. It is most often used in acute conditions and must be given parenterally.

Heparin therapy in children differs from that in adults; heparin clearance is faster in the young. Thus, children usually require more heparin. At birth, AT levels are 50% of adult values. The level is even lower in premature infants.

Pediatric patients often have serious underlying problems. Often other risk factors for bleeding are present.

### Practical Guidelines

#### UNFRACTIONATED HEPARIN

##### Intravenous regimen:

- Give IV bolus of 75 units/kg
- For infants <1year, start infusion with initial rate of 28 units/kg/hour
- For children >1year, start infusion with initial rate of 20 units/kg/hour

##### Monitoring of intravenous unfractionated heparin

- The aPTT is used to monitor the effects of unfractionated heparin treatment.
- aPTT reagents vary considerably in their sensitivity to heparin. Therefore your laboratory should establish a therapeutic range locally. In general, an adequate therapeutic effect would be achieved by an aPTT ratio of 2.0-2.5 time's control.
- Monitor aPTT every 4 hrs until therapeutic range has been achieved. Thereafter monitor aPTT and platelet count daily.
- Anti-Xa levels may be more reliable than aPTTs for monitoring heparin in newborns and some children: at birth, the aPTT is prolonged, reflecting the immaturity of the coagulation system. Children requiring heparin therapy frequently have underlying disorders that influence the baseline aPTT and therefore the response to heparin. Elevated factor VIII may cause sub therapeutic aPTT despite adequate anti-Xa level. In these children, aPTT may not correlate well with anti-Xa levels and thus checking both parameters may be helpful. In such conditions, anti-Xa should be used.

### Dosage Adjustments

As for adults, the use of a heparin dosing nomogram is encouraged because it helps achieve and maintain the aPTT in the therapeutic range efficiently. The following nomogram has been validated in children > 1 year old for a therapeutic range of 60 - 85 sec (correlating with an anti-factor Xa level of 0.35 - 0.7 U/mL).

## Clinical Guide: Heparin and LMWH in Children

**Initial Dose: 75 units/kg IV.**

**Initial Maintenance Dose: 20 units/kg/hour**

APTT (sec)	Bolus (units/kg)	Hold (min)	% Rate Change	Repeat APTT
< 50	50	0	+ 10%	4 hrs
50 - 59	0	0	+ 10%	4 hrs
60 - 85	0	0	0	next day
86 - 95	0	0	- 10%	4 hrs
96 - 120	0	30	- 10%	4 hrs
120	0	60	- 10%	4 hrs

### Subcutaneous regimen:

Subcutaneous (SC) injection of unfractionated heparin can be useful in pediatric patients with poor venous access. In adults, therapeutic heparin effects can reliably be achieved by subcutaneous injection as long as a sufficiently high dose is given. For children, the dose of SC heparin can be calculated from the IV requirements in the previous 24 hours and administered in two to three divided doses.

Monitoring should aim for a therapeutic aPTT 4-6 hours after a subcutaneous dose of unfractionated heparin. Subcutaneous catheters that remain in place for 7 days offer a relatively painless way for subcutaneous administration of heparin to children.

### LOW MOLECULAR WEIGHT HEPARIN (LMWH)

LMWH is now generally preferred except where reversal or alteration of anticoagulant effect may be needed rapidly i.e. post operative patient at risk for bleeding but requiring anticoagulation.. The only LMWH that is of bovine source is tinzaparin.

### Examples of recommended doses of LMWH are:

<u>Enoxaparin</u>	<u>&lt; 2 months</u>		<u>2 months -18 yrs</u>	
Prophylactic dose	0.75 mg/kg/dose	q 12 hours	0.5 mg/kg/dose	q 12 hours
Treatment dose	1.5 mg/kg/dose	q 12 hours	1.0 mg/kg/dose	q 12 hours
<u>Dalteparin</u>	<u>All ages</u>			
Prophylactic dose	92 U/kg/dose	q 24 hours		
Treatment dose	129 U/kg/dose	q 24 hours		
Tinzaparin dose	Age dependent			
		0-2 months	275 U/kg q 24 hours	
		2-12 months	250 U/kg q 24 hours	
		1-5 yr	240 U/kg q 24 hours	
		5-10 yr	200 U/kg q 24 hours	
		10-16 yr	175 U/kg q 24 hours	

aiming for a therapeutic range of 0.5 to 1.0 U/ml 4 to 6 hours after the injection.

-- Dose requirements of enoxaparin may be higher for neonates (preterm neonates: 2 mg/kg 12 h; term neonates 1.7 mg/kg)

### Monitoring of LMWH

Anti-factor Xa is used to monitor the effects of LMWH. The samples should be taken 4 hours post-injection. The therapeutic range is regarded to be 0.5 – 1.0 u/mL (and the prophylactic range is regarded to be 0.1 – 0.3 U/mL). Dosage can be adjusted using a standardized nomogram such as the following:

## Nomogram for dosing LMWH in children

Anti-Xa Level (U/mL)	Hold next dose	Dose change	Next anti-Xa level
< 0.35	No	↑25%	Next day
0.35-0.49	No	↑10%	Next day
0.5-1.0	No	0	Next week
1.1-1.5	No	↓20%	Next day
1.6-2.0	3h	↓30%	Before next dose and next day
> 2.0	Until anti-Xa < 0.5 U/mL	↓40%	Before each dose until anti-Xa < 0.5 U/mL

## Overlap with Warfarin

Generally, warfarin can be started on the same day as heparin. In the presence of pulmonary embolism or extensive proximal DVT, the initiation of warfarin may be delayed for a few days. Warfarin and heparin should overlap for at least 3 to 4 days or until the INR value is within the therapeutic range for two consecutive days before heparin is discontinued. Therapeutic dose LMWH is a good alternative to warfarin in the treatment of venous thromboembolic disease.

## Teenage Pregnancy

Heparin is the anticoagulant of choice during pregnancy. Therapeutic anticoagulation with heparin can be achieved by subcutaneous injections twice daily. Secondary prevention in the post-partum period can be achieved with warfarin or SC heparin and is recommended for approximately 6 weeks after delivery or until treatment of the acute episode is complete. (See thrombosis in pregnancy.)

## Immunization

Patients can be immunized while they are on chronic anticoagulation therapy. For patient receiving LMWH, a safe strategy would be to immunize the patient before the next dose of LMWH is given, using the smallest gauge needle and applying firm pressure for 5 minutes.

## Adverse Effects

**Bleeding** is the most common adverse effect of heparin. If major bleeding occurs, discontinue heparin. The administration of IV protamine sulfate may be used to neutralize heparin's effects. With less critical bleeding, doses should be adjusted and underlying causes investigated.

**Osteoporosis** is a serious, but uncommon side-effect associated with prolonged use of high doses of heparin. The effect of heparin on bones in the growing child is not known. Any long-term use of heparin, including LMWH, (i.e. >3 months) should be accompanied with sensitive measurements of bone density.

**Thrombocytopenia** - The frequency of Heparin Induced Thrombocytopenia (HIT) in the child has been estimated at 2%. As in adults, HIT is often asymptomatic but may be associated with life-threatening or fatal arterial or venous thrombosis. It usually begins between 3 to 15 days after commencing therapy. **Should it occur, stop all sources of heparin and, if necessary, alternative treatment such as sodium danaparoid, hirudin or argatroban followed by warfarin may be used, based on anecdotal evidence. Platelet counts usually return to baseline within 4 days of stopping therapy.**

This guideline was developed in collaboration with the **Canadian Pediatric Thrombosis and Hemostasis Network** and reviewed by T.I.G.C. members, based on medical literature and on current Canadian medical practice.

## References:

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