

Antithrombotic Therapy

Blocked Central Venous Lines

The following are guidelines for management of blocked central venous lines. Modifications for individual circumstances may be necessary. In general, consultation from the Thrombosis Service should be obtained.

I. INDICATIONS

1. For central venous lines (CVL's) that are "blocked" and will not infuse properly.
2. For CVL's which require blood return as an essential function i.e. hematology/oncology catheters, hemo-dialysis catheters.
3. All patients with clinical symptoms such as: head/neck swelling, respiratory distress, bluish colour, collateral circulation should be evaluated by objective tests such as venography, ultrasound and ventilation perfusion lung scans, as appropriate.

II. INITIAL MANAGEMENT

1. Complete CXR to visualize line placement.

	CHEMICAL-RELATED BLOCKAGE	BLOOD-RELATED BLOCKAGE
INDICATIONS	Infusion running then sudden unexplained occlusion	Blood sampling Blood administration Blood back-up infusion
INITIAL ACTION	1. Attempt to aspirate. 2. Flush with 0.9% NaCl. 3. Follow HCl guidelines. 4. If no blood return, follow guidelines for alteplase. If unsuccessful clearing the CVL contact the Vascular Access Service. 5. If able to flush the line but no blood return, proceed to diagnostic work-up if clinically indicated. 6. If unable to flush line, contact Vascular Access Service.	1. Attempt to aspirate. 2. Flush with 0.9% NaCl. 3. Follow guidelines for alteplase. If unsuccessful clearing the CVL contact the Vascular Access Service. 4. If able to flush line, but unable to get blood return, proceed to diagnostic work-up, if clinically indicated. 5. If unable to flush line, contact the Vascular Access Service.

III. GUIDELINES FOR LOCAL INSTILLATION

	CHEMICAL OCCLUSION	BLOOD RELATED OCCLUSION	
Type of Catheter	Hydrochloric Acid 0.1M	Size of Patient	Alteplase (tPA)
<i>Single Lumen</i> (e.g., Hickman, Cook Roko, PICC)	2 mL	>10kg	1 mg/mL. Use amount required to fill volume of line, to maximum 2 mL=2 mg.
		≤10kg	1 mg diluted to 2 mL. 1 mL=0.5 mg.
<i>Double Lumen</i> (e.g., Hickman, Cook, Quinton)	2 mL <i>per lumen</i>	>10kg	1 mg/mL. Use amount required to fill volume of line, to maximum 2 mL=2 mg <i>per lumen</i> . Treat one lumen at a time.
		≤10kg	1 mg diluted to 2 mL per lumen. 1 mL=0.5 mg.
Subcutaneous Ports (e.g., Port-A-Cath, PASport)	3 mL	>10kg	2 mg diluted with NS to 3 mL 1 mL=0.65 mg.
		≤10kg	1.5 mg diluted with NS to 3 mL. 1 mL=0.5 mg.
Haemodialysis Catheters -small Quinton, Cook -large Quinton, Uldall For <i>non</i> -Nephrology patients use double Lumen guidelines	1 mL 1.5 mL	>10kg	See guidelines above for single lumen catheter.
		≤10kg	0.75mg diluted to 1.5 mL

Note: After a minimum of 2 hours instillation of each drug, withdraw drug, if possible flush the catheter with 0.9% NaCl attempt to aspirate blood.

Please refer to guidelines in the Nursing Procedure Manual Section L.23 for alteplase (tPA) and Section L.24 for hydrochloric acid.

IV. DIAGNOSTIC WORK-UP

Investigation of a blocked CVL is necessary if the line fails to function properly after two doses of alteplase (tPA) or if it has blocked for a second time. In certain situations, detailed investigation may be warranted even outside of these guidelines.

1. **Perform a lineogram to determine the following:**
 - a) Location of the CVL.
 - b) Potential occlusion at the tip of CVL.
 - c) Presence of retrograde flow.
 - d) Potential leak.
 - e) Lineogram cannot rule out the presence of large vessel clot, therefore must proceed as follows:
2. **Perform a venogram:**
 - a) if the venogram is normal and the CVL is not functioning then local occlusion must be present
 - b) if the venogram is abnormal proceed to treatment as outlined below section V.
3. **If a venogram (the “gold standard” investigation) cannot be readily obtained,** perform a doppler ultrasound evaluation of the large vessels near and including the CVL. However, the sensitivity and specificity of this technique for detection of large vessel thrombus in the upper venous system is poor (20%). Venography remains the recommended investigation. Doppler is very sensitive (80%) in diagnosing neck vessel thrombosis.
 - a) If the doppler ultrasound and lineogram are normal but there is still no blood return from the CVL, consider using the CVL for instillation only. Venogram is strongly recommended to rule out large vessel clot.
 - b) If the doppler ultrasound and/or lineogram are abnormal ie. obstruction of flow related to occlusion at the tip of the catheter or retrograde flow around the catheter, it is recommended to proceed to a venogram to rule out proximal clot.

V. TREATMENT

Please consult the [Vascular Access Service](#) and the Thrombosis Service.

VI. EXTENSIVE DEEP VEIN THROMBOSIS

- a) A ventilation/spiral CT scan may be helpful to determine if pulmonary embolization has occurred. (30% of children with DVT have pulmonary embolism and are asymptomatic)
- b) The following are options for management:
 - 1) Leave the CVL in place and attempt systemic thrombolytic therapy if there are no contraindications. See p. 248.
 - 2) [Contact Vascular Access Service](#) and the Thrombosis Service to remove the CVL. Begin anticoagulation as indicated and consult Thrombosis Service.

For children \leq 12 months:

Weight (kg) x 28u/kg/hr x volume of solution (χ mL)= units of heparin un χ mL of solution.

1 mL/hr= 28 u/kg/hr

For children > 12 months:

Weight (kg) x 10u/kg/hr x volume of solution (χ mL)= units of heparin in χ mL of solution.

1 mL/hr= 10 u/kg/hr

2 mL/hr= 20 u/kg/hr

Fluid restricted patients such as neonates, or patients in renal failure, may receive more concentrated heparin solutions upon request.

5. **Dedicated IV for UFH administration. This IV must not be stopped or interrupted for other medication.**

SUBCUTANEOUS UNFRACTIONATED HEPARIN

1. For subcutaneous UFH, the total daily dose in units/kg is divided into 2 doses given q12h. Subcutaneous UFH is monitored using either the APTT or Anti-Factor Xa level (see #3) measured at 6 hours after the SC dose. Dosing is adjusted according to the nomogram above.

If the APTT is <50 seconds, increase the subcutaneous dose by 20%. Obtain an APTT 6 hrs post subcutaneous dose and continue as per the nomogram.

2. UFH can be used as a “bridge” anticoagulant in patients receiving a low molecular weight heparin or warfarin prior to anticipated interruption of therapy (e.g., before surgery). Consult the Thrombosis Service for more information.

III. MONITORING OF THERAPY

1. Prior to the initiation of UFH therapy, obtain blood for CBC and APTT. If appropriate, obtain blood for prothrombotic workup (see protocol for deep vein thrombosis).
2. Once patients have achieved a therapeutic APTT, it is recommended to obtain blood for CBC, APTT daily. The coagulation laboratory would prefer to receive the samples before noon (standard Anti-Factor Xa assay times: 06:00, 12:00, 20:00).
3. If the infusion of UFH during the maintenance phase is interrupted for more than one hour, re-establish the UFH maintenance infusion at the previous rate. Obtain an APTT 4 hours later. Once the APTT is available, adjust the infusion rate as indicated above.
4. It is recommended to measure platelet counts daily. If the platelet count drops by 50% or more from baseline platelet count, please take a red top tube and a blue top tube and send to the coagulation lab for a heparin-induced thrombocytopenia (HIT) screen. Call the Thrombosis Service.
5. Where possible, avoid IM injections and arterial punctures during anticoagulation therapy. Clinical situations may warrant the use of arterial punctures (for example, ventilated patients). Appropriate precautions, including the use of extended periods of external pressure should be used.

- The duration of UFH therapy is dependent upon the primary problem. For DVT in children, UFH is usually administered for a minimum of 7 days. Maintenance warfarin therapy may be instituted on day 1 or 2 of UFH therapy. Alternatively, patients may be discharged on low molecular weight UFH. See Section IV. Conversion of Unfractionated Heparin to Enoxaparin.

Note: If the thrombus is extensive or massive PE present, administer heparin for 7-14 days and begin warfarin therapy on day 5.

Note: Newborns may be treated for 10 to 14 days without warfarin. This decision should be individualized.

- In general avoid aspirin or other antiplatelet drugs during UFH therapy. If analgesia is required, acetaminophen is preferred.

IV. CONVERSION OF UNFRACTIONATED HEPARIN TO ENOXAPARIN

- Administer the dose of subcutaneous enoxaparin at the same time as standard UFH infusion is discontinued.
- Do an anti-Factor Xa level (low molecular weight heparin level) 4 hours after the morning dose and adjust the dose of enoxaparin according to the nomogram on p.240.

V. UFH ANTIDOTE

If anticoagulation with UFH needs to be discontinued for clinical reasons, termination of the UFH infusion will usually suffice because of the rapid clearance of UFH. If an immediate effect is required, consider administering protamine sulfate.

Protamine sulphate neutralizes heparin activity by virtue of its positive charge. Following IV administration, neutralization occurs within 5 minutes. The dose of protamine sulphate required to neutralize UFH is based on the amount of UFH received in the previous two hours as follows:

Time since last heparin dose or end of infusion	Protamine per 100 units unfractionated heparin received (maximum 50mg/dose)
<30 min	1 mg
30-60 min	0.5-0.75 mg
61-120 min	0.375-0.5 mg
>120 min	0.25-0.375 mg

Except for reversal of UFH following cardiopulmonary bypass, the maximum dose of protamine sulfate, regardless of the amount of UFH received, is 50 mg. Protamine sulphate should be administered in a concentration of 10 mg/mL at a rate not to exceed 5 mg/min. If administered too quickly protamine sulphate 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 sulphate.

Obtain blood for APTT, 15 minutes after the administration of protamine.

Antithrombotic Therapy

Note: Heparin is a descriptive term referring to all heparins including: unfractionated Heparin (UFH) and low molecular weight heparin (LMWH)

Management of Heparin-Induced Thrombocytopenia

The following are guidelines for the management of heparin-induced thrombocytopenia. Modifications for individual circumstances may be necessary. In general, consultation with the Thrombosis Service should be considered.

GUIDELINES

Heparin-induced thrombocytopenia (HIT) is an uncommon complication of heparin therapy, and can cause significant morbidity and mortality. The incidence of HIT is about 3% in adult patients receiving UFH. The incidence of HIT in pediatric patients has been estimated to be the same as in adults. In adults HIT usually begins 5-7 days after commencing heparin therapy (median 10 days) but can occur earlier in patients with prior exposure to heparin. In children, HIT occurs on average 22 days after commencing heparin therapy. An abrupt decrease of platelet count (e.g. decrease of platelet count by half in 1-2 days) should raise suspicion of HIT.

DIAGNOSTIC WORKUP

Any source of heparin, including low molecular weight heparin [LMWH] (though it rarely causes HIT) and low dose UFH infusions or boluses to maintain patency of intra-arterial or intravenous lines, should be discontinued if the suspicion of HIT is high.

Blood samples from patients should be tested by requesting a HIT screen.

TREATMENT

If there is no evidence of thrombosis and no indication for continuation of anticoagulant therapy, discontinuation of heparin will usually result in the platelet count returning to normal. If there is a thrombus and continuation of anticoagulation therapy is required in children. Danaparoid (Orgaran®) is currently the agent of choice.

Danaparoid (Orgaran®)

Danaparoid consists mainly of heparin sulphate, a small quantity of dermatan sulphate and a minor amount of chondroitin sulphate, and does not contain any heparin fragments. Danaparoid has a much higher anti-Xa/anti-IIa ratio compared to heparin and LMWH. Danaparoid has a decreased cross-reactivity rate (<10-20%) with heparin-induced antibody as compared to LMWH (>90%).

Intravenous Dose: Loading dose:30 units/kg body weight IV
 Initial maintenance dose:
 1.2-2 units/kg/hr continuous IV infusion

Subcutaneous Dose: 18 units/kg SC q12h

Monitoring: Anti-Factor Xa activity can be monitored 6 hrs following the IV bolus or SC dose. Once the therapeutic level of 0.4-0.8 units/mL has been achieved, monitor Anti-Factor Xa levels daily.

Danaparoid is predominantly removed from the circulation through the kidney. Consequently, danaparoid is contraindicated in patients with severely impaired renal function.

Warfarin

Use of warfarin is considered to be contraindicated by some experts in the field because of an initial decrease of protein C that can contribute to the prothrombotic state.

Initiation of warfarin can be considered after the platelet counts return to normal.

Antithrombotic Therapy

Note: Heparin is a descriptive term referring to all heparins including: unfractionated heparin (UFH) and low molecular weight heparin (LMWH)

Low Molecular Weight Heparin (LMWH) Use in Children and Neonates

The following are guidelines for initiating and monitoring enoxaparin therapy. Modifications for individual clinical circumstances may be necessary. These dosage guidelines apply to enoxaparin only and cannot be directly extrapolated to other LMWH's. The treatment and prophylactic doses of enoxaparin in children are extrapolated from the adult clinical trials and a cohort study in children. In general, consultation from the Thrombosis Service, should be obtained.

I. INDICATIONS

The use of low molecular weight heparins should be considered in most patients requiring anticoagulation for therapy or prophylaxis.

II. ENOXAPARIN (LOW MOLECULAR WEIGHT HEPARIN) DOSE

(see nomogram next page)

1. Obtain patients weight.
2. Prior to the initiation of enoxaparin therapy, obtain blood for CBC, APTT and creatinine. If appropriate do a prothrombotic workup.

	Age ≤ 2 months	Age ≥ 2 months - 18 years
Initial Treatment Dose	1.5 mg/kg/dose SC q12h	1 mg/kg/dose SC q12h
Initial Prophylactic Dose	0.75 mg/kg/dose SC q12h or 1.5 mg/kg/dose SC once daily	0.5 mg/kg/dose SC q12h or 1mg/kg/dose SC once daily
Maximum Dose	3 mg/kg/dose SC q12h	2 mg/kg/dose SC q12h

3. Dose of enoxaparin:

- a) Enoxaparin can be administered once daily SC as prophylaxis.
- b) Monitoring of Anti-Factor Xa levels for prophylaxis is not required unless renal failure is present. Consult the Thrombosis Service.

III. NOMOGRAM FOR ADJUSTING ENOXAPARIN TREATMENT

Adjust the dose of enoxaparin according to the following nomogram. Depending on the anti-factor Xa level achieved, successive actions are indicated, including whether to hold the next scheduled dose whether any dose change is indicated and when the next anti-factor Xa level should be drawn.

Anti-Factor Xa level	Hold next dose?	Dose change?	Repeat anti Xa level?
<0.35 units/mL	No	increase by 25%	4 hours post next morning dose
0.35-0.49 units/mL	No	increase by 10%	4 hours post next morning dose
0.5-1 units/mL	No	0	1x per week at 4 hours post morning dose
<1.20 units/mL	No	decrease by 20%	4 hours post next morning dose. Hold dose. Do a trough level. If trough <0.5 at 10 hrs post dose, administer scheduled dose at 20% of previous dose.

The above nomogram assumes that there is no bleeding or renal compromise.

Note: Dose adjustment may be limited by commercially available concentration of enoxaparin. Dose adjustments must be ordered in 0.5 mg increments for doses < 5 mg and in 1.0 increments for doses > 5 mg.

*Note: A subcutaneous catheter can be used in children ≥ 3 kg but must be closely monitored for depot site hematoma. If problems occur, remove catheter (Insuflon) and use direct SC injection.

*Note: Enoxaparin is provided in insulin syringes where 1mg of drug corresponds to 1 unit.

IV. MONITORING OF LOW MOLECULAR WEIGHT HEPARIN

1. Bloodwork to be done after drug administration: PLEASE draw blood from fresh venipuncture. THERE MUST BE NO CONTAMINATION from UFH, e.g., from an arterial or central venous line.
2. On day 1 and/or day 2, a blood sample should be drawn 4 hours after the SC administration of enoxaparin. If therapeutic, a weekly check (q Monday) on the anti-factor Xa (low molecular weight heparin) level is sufficient, while in hospital.
3. The therapeutic anti-factor Xa level for **treatment dose** therapy is **0.5-1 units/mL**. In certain situations, patients may require Anti-Factor levels ≥ 1.0 units/mL, in consultation with the Thrombosis Service.
4. For patients on long term enoxaparin therapy (>3 months), consider bone densitometry studies at baseline and then every 6 months to assess for possible osteoporosis.
5. Enoxaparin may accumulate in the body over time and therefore adjustments in dosage may be required. Continue as per the nomogram above.
6. Enoxaparin is excreted renally. In patients with unstable renal function, creatinine should be checked along with Anti-Factor Xa levels. Consult Thrombosis Service.

V. ONGOING FOLLOW UP

1. In general avoid aspirin or other antiplatelet drugs if possible during low molecular weight heparin therapy. If analgesia is required, acetaminophen or opioids are recommended.
2. In general, avoid IM injections and arterial punctures during anticoagulation.
3. Measure platelet counts regularly. An abrupt decrease of platelet count (e.g., decrease of platelet count by half in 1-2 days) should raise suspicion of heparin-induced thrombocytopenia (HIT). See p.237 for more information. If HIT is suspected, send blood in a red top tube and a blue top tube to the lab for a HIT screen.
4. The duration of low molecular weight heparin therapy is dependent upon the primary problem. In children with DVT, LMWH is usually administered for a minimum of 3 months. Duration of therapy in neonates is guided by ultrasound. An ultrasound is recommended prior to discharge or after 4 weeks of therapy. Note that LMWH therapy may be used instead of warfarin therapy for DVT.

VI. CONVERSION OF ENOXAPARIN TO UNFRACTIONATED HEPARIN

1. Heparin should not be initiated until at least 8 hours after the last dose of enoxaparin.
2. If heparin is started 8-12 hours after the last dose of enoxaparin, do not administer a bolus of heparin. Start the heparin infusion at the appropriate dose (units/kg/hour) for age.
3. If heparin is started >12 hours after the last dose of enoxaparin, initiate with the IV bolus of heparin followed by an infusion.
4. Measure the APTT 6-8 hours after initiating the heparin infusion, then follow the protocol for heparin.

VIII. ENOXAPARIN ANTIDOTE

If anticoagulation with enoxaparin needs to be terminated for clinical reasons, discontinuation of enoxaparin injections will usually suffice. If an immediate reversal of effect is required, protamine sulphate reverses most but not all of the anti-Factor Xa activity of low molecular weight heparins. However, studies in experimental animal models indicate that increased microvascular bleeding produced by very high concentrations of low molecular weight heparins is neutralized by protamine sulphate.

The dose of protamine sulphate is dependent on the concentration of enoxaparin in the circulation. The recommendations for the neutralization of low molecular weight heparins are different than for unfractionated heparin. A maintenance protamine infusion may be warranted: the Thrombosis Service must be consulted for recommendations.

Antithrombotic Therapy

Warfarin (Coumadin®)

The following are guidelines for initiating and monitoring warfarin therapy. Modifications for individual clinical circumstances may be necessary. In general, consultation from the Thrombosis Service should be obtained.

I. GUIDELINES

Obtain a baseline PTT/INR prior to initiating warfarin therapy.

The loading period is approximately 3-5 days for most patients before a stable maintenance phase is achieved.

Patient must be taking full PO, including food prior to initiating warfarin to prevent the INR from increasing to dangerously high levels.

Start warfarin on Day 1 or 2 of unfractionated heparin therapy. Heparin should be continued for a minimum length of 5 days duration. **Exceptions:** If treating an extensive DVT with or without pulmonary embolism, start warfarin on Day 5 of heparin therapy.

If the patient is receiving TPN, remove vitamin K from the solution before or as warfarin therapy begins.

In general, warfarin should be avoided in infants less than 12 months of age except in infants with mechanical valves, and should not be used as the primary treatment of heparin-induced thrombocytopenia.

If the patient is receiving formula, consider changing the patient to a formula containing the least amount of vitamin K. If the patient is *exclusively* breastfed, consider supplementation with a small amount of standard formula per day for a constant intake of vitamin K (required vitamin K is 1 microgram/kg/day, which is equivalent to about 120 mL of standard commercial formula daily).

If the patient is receiving other medications, i.e., antibiotics, which can affect warfarin, the loading dose must be adjusted.

Aim for an INR between 2.0-3.0 for the vast majority of patients. Children with mechanical valves in place require an INR between 2.5-3.5.

Ideally when the INR is greater than 2.0 for 2 consecutive days, heparin can be discontinued. Usually the INR decreases by a small percentage the following day.

II. WARFARIN LOADING DOSE DAY 1

The usual loading dose is 0.2 mg/kg po as a single daily dose, maximum 5mg. Reduce dose to 0.1 mg/kg po in patients with liver dysfunction or Fontan or severe renal dysfunction (i.e.hemodialysis). If patient receives > 5mg as a daily dose Thrombosis must be consulted.

III. WARFARIN LOADING DOSES DAYS 2-4

a) If your response is an INR of:

INR	1.1 - 1.4	repeat initial loading dose
INR	1.5 – 3.9	50% of initial loading dose
INR	>4.0	hold until INR <3.5 then restart 50% less than the previous dose

Note: These dose reductions are critical to avoid “overshooting” the target range.

Note: If INR is >3.0 on Day 1. Hold, repeat INR, then restart at 50% of previous dose.

b) If INR is not greater than 1.5 after 2 doses increase dose by 50% and follow above nomogram.

IV. LONG-TERM WARFARIN MAINTENANCE DOSE GUIDELINES

These guidelines apply primarily to medically stable patients already established on long-term maintenance therapy. Medically unstable patients or those completing the loading protocol may respond differently. Close daily monitoring with individualized dose adjustment of such patients is essential until they are clearly established on maintenance therapy.

INR	1.1-1.4	Check for compliance, if compliant increase by 20% of dose
INR	1.5-1.9	Increase by 10% of dose
INR	2.0-3.0	No change
INR	3.1-3.5	Decrease dose by 10%
INR	>3.5-4.0	Administer one dose at 50% less than maintenance dose. Then restart at 20% less than the maintenance dose.
INR	4.1-5.0	Hold x 1 dose then restart at 20% less than maintenance dose
INR	>5.0	Contact the Thrombosis Service

V. LONG-TERM WARFARIN MAINTENANCE DOSE FOR MECHANICAL VALVES

Use similar guidelines as for number IV but maintain the INR between 2.5 and 3.5.

INR	1.1-2.0	Check for compliance, if compliant increase by 20% of dose
INR	2.0-2.5	Increase by 10% of dose
INR	2.5-3.5	No change
INR	3.6-3.9	Administer one dose at 50% less than maintenance dose. Restart at 20 % less than maintenance.
INR	4.0-4.5	Hold x 1 dose then restart at 20% less than maintenance dose
INR	4.5-5.0	Contact the Thrombosis Service

VI. OUTPATIENT FOLLOW-UP

Ideally when the INR is greater than 2.5 for 2 consecutive days, the patient can be discharged. The Thrombosis Team must be consulted prior to the discharge of the patient from the hospital. The Thrombosis Team will follow all outpatients in the region and ensure that patients outside the region are monitored appropriately.

Patient's discharged home on warfarin should receive a prescription for vitamin K 10 mg, to be used as directed by thrombosis when INR's are dangerously high.

Monitor the INR within 3-4 days of discharge from hospital.

Always draw an INR 5 to 7 days after initiating a new dose. Use the maintenance guidelines for making changes in dosage.

Once the patient has 2 INR's between 2.0-3.0 (or 2.5 to 3.5 for mechanical valves) taken 7 days apart, the interval for checking the INR can be stretched to 2 weeks; then if stable, to 3 weeks; then if stable, to 4 weeks.

The INR should be monitored a **minimum** of once a month.

Instruct the patient/parent to inform you of any changes/additions in medication or diet.

The duration of therapy with warfarin will vary depending upon the underlying problem. Children with mechanical heart valves or repeated thromboembolic events will receive warfarin indefinitely. Children with a thrombotic event and a persistent, significant, underlying predisposing factor may be switched to low dose warfarin following 3 months of treatment with full dose warfarin, until the predisposing factor is no longer present. Children with uncomplicated DVT will receive warfarin for 3 months only.

Warfarin is teratogenic in early pregnancy and use of a reliable birth control method is recommended in female patients of childbearing age. If therapeutic amounts of warfarin are being used, oral contraceptives are permissible.

Many medications may affect the response to warfarin, Some of these medications are listed below. For information on interactions with other medications, consult the unit pharmacist or the Drug Information Service.

Drug Name		
Acetaminophen	ASA (acetylsalicylic acid)	Levofloxacin
Amiodarone	Omeprazole	Cefazolin
Metronidazole	Aminosalicylic Acid	Clarithromycin
Ceftriaxone	Ibuprofen	Penicillin G (IV high dose)
Erythromycin	Ketorolac	Ciprofloxacin
Piperacillin (IV high dose)	Celecoxib	Trimethoprim/Sulfamethoxazole
Sulfamethoxazole	Levothyroxine	Tetracycline
Doxycycline	Allo-purinol	Heparin
Rifampin	Spironolactone	Phenytoin
Carbamazepine	Ranitidine	Fluconazole
Valproate (vaproic acid)	Chloral Hydrate	Vitamin C (high doses)
Naproxen	Indomethacin	Vitamin K
Prednisone	ASA (acetylsalicylic acid)	Vitamin E

VII. WARFARIN ANTIDOTE

Vitamin K is the antidote for warfarin. The dose to be administered and concurrent use of FFP or Feiba® or factor VII concentrate are dependent on the clinical problem. The following are guidelines only and Thrombosis should be consulted for warfarin reversal.

1. NO BLEEDING

- a) If rapid reversal of warfarin necessary and the patient **will** require warfarin again in the near future: give vitamin K at a dose of 0.5 to 2 mg orally (not intramuscularly or intravenously), depending upon the patient's size.
- b) If rapid reversal of warfarin necessary and the patient **will not** require warfarin again in the near future: give vitamin K at a dose of 2-5 mg orally(not intramuscularly or intravenously).

2. SIGNIFICANT BLEEDING

- a) Significant bleeding requires treatment with fresh frozen plasma 20 mL/kg IV or Factor VIIa, 50 u/kg IV.

Antithrombotic Therapy

Reversal of Anticoagulant Therapy

The following are guidelines for elective reversal of warfarin therapy. Modifications for individual clinical circumstances may be necessary. In general, consultation from the Thrombosis Service should be obtained.

Identified categories noting risk of thrombosis:

High Risk	Low Risk
Congenital Prothrombotic disorders	Old DVT
APLA +	Cardiomyopathy with no clot
Thrombi in the heart	Fontan with no clot
Kawasaki disease	CVL prophylaxis
Mechanical valves	Atrial fibrillation
New DVT (<5 weeks since diagnosis)	Pulmonary stenosis
Stroke	
Stents	
BT shunts	
Arterial thrombosis	
Pulmonary hypertension	

I. LOW-DOSE WARFARIN (INR 1.4 – 1.8)

- If $INR \leq 1.5$ – no reversal necessary for most surgeries: exceptions include high risk surgeries, i.e., eye surgery, neurosurgery – use full-dose warfarin reversal.
- Hold warfarin 72 hours prior to procedure.

II. FULL-DOSE WARFARIN (INR 2.0-3.0); OR (INR 2.5-3.5)

Patients on full dose warfarin are at risk of significant hemorrhage at the time of Surgery, therefore reversal is required.

Where risk of thrombosis is high. The following suggestions should be discussed with Surgery Service.

- Discontinue warfarin 72 hours prior to surgery.
- Prior to surgery initiate unfractionated heparin therapy **without** a bolus at appropriate dose for age. (This may be given IV or SC). SC heparin may be administered at home to avoid hospital admission. To calculate UFH dose see p.217
- If the INR is greater than 1.5 before surgery, administer FFP.
- Draw PTT pre-op to ensure normal. If not in normal range call the Thrombosis Service.
- In consultation with Surgery, resume IV heparin 6-12 hours post-op at previous rate. Aim for therapeutic range, see p.217. Enoxaparin may be used instead of UFH. Please consult the Thrombosis Service.

- f) If the patient develops any signs of bleeding, discontinue heparin IV.
- g) Oral warfarin can be resumed post-operatively in consultation with the Thrombosis Service. Warfarin can be restarted at 1.5x maintenance dose x 2 days followed by maintenance dose. Check INR 5 days after resuming warfarin.
- h) Discontinue IV heparin when warfarin reaches the therapeutic range of an INR between 2.0 – 3.0 or for mechanical valves 2.5 - 3.5 for 2 days.

Where risk of thrombosis is low.

- a) Discontinue warfarin 72 hours prior to surgery because the effects of warfarin are prolonged.
- b) Admit day of surgery. Measure INR with results available prior to surgery.
- c) Depending upon surgery, initiate 1.5 x maintenance dose of warfarin for 2 days. Then resume maintenance dose. Repeat INR within 3-5 days of resuming maintenance dose.

III. ENOXAPARIN

Where risk of thrombosis is high, the following suggestions should be discussed with surgery service.

- a) Hold 2 doses of Enoxaparin prior to surgery (night before and morning of) and administer subcutaneous heparin in the evening prior to surgery with no dose in the morning.
- b) Enoxaparin can be restarted post-op at previous dose.

Where risk of thrombosis is low, or with Enoxaparin prophylaxis.

- a) Hold 2 doses of Enoxaparin and no bridge heparin needed.
- b) Enoxaparin can be restarted post-op at previous dose.

Antithrombotic Therapy

Note: Heparin is a descriptive term referring to all heparins including: unfractionated heparin (UFH) and low molecular weight heparin (LMWH).

Systemic Thrombolytic Therapy

The following are guidelines for initiating and monitoring systemic thrombolytic therapy. Modifications for individual clinical circumstances may be necessary.

I. INITIAL EVALUATION

This will vary depending on the location and vessel involved. **For deep venous thrombosis (DVT) please see page 251.**

II. INDICATIONS

Systemic thrombolytic therapy is indicated for arterial occlusions, massive pulmonary embolism and pulmonary embolism not responding to heparin therapy. It may also be indicated for acute, extensive deep vein thrombosis and should be limited to situations where there is a risk for loss of life, organ or limb due to thrombosis. An urgent Thrombosis Service consult is strongly advised for all patients receiving thrombolytic therapy. However, treatment should be started without delay when indicated. The Thrombosis Service will offer assistance for continuation of the infusion and laboratory monitoring of the patient when requested.

In neonates less than 6 months of age with arterial occlusion: Following cardiac catheterization, thrombolytic therapy must be used with caution. Begin Unfractionated heparin as per protocol and assess the limb for a minimum of 24 hours before considering thrombolytic therapy. If possible, perform a head CT or cranial ultrasound prior to initiating lytic therapy. If avulsion or dissection of the vessel is diagnosed, consult cardiovascular/plastic surgery immediately.

If the viability of the limb or organ is in doubt then all investigations and consultations must be expedited.

III. CONTRAINDICATIONS

Active bleeding, significant potential for local bleeding (e.g., tumor surrounding vessel with clot), general surgery within the previous 10 days, neurosurgery within the previous 3 weeks, hypertension, AV malformations, and recent severe trauma. However, in some patients the need for thrombolytic therapy necessitates treatment despite the contraindications.

IV. PRECAUTIONS

1. No intramuscular injections during therapy.
2. Minimal manipulation of the patient, e.g., no bathing, physiotherapy.
3. Avoid concurrent use of warfarin or antiplatelet agents (e.g., aspirin, dipyridamole).
4. No urinary catheterization, rectal temperatures, or arterial punctures.
5. Take blood samples from a superficial vein or indwelling catheter. If blood sampling is difficult, insert an indwelling catheter for blood samples **prior** to thrombolytic therapy.

V. PREPARATION FOR INFUSION

1. CBC, platelet count, APTT, fibrinogen, d-dimer. Cross and type for 1 unit of PRBC.
2. Admit to the pediatric intensive care unit or a designated floor identified for thrombolytic therapy.
3. Consider sedation depending on the child and clinical circumstances.
4. Sign for head of bed indicating patient is receiving thrombolytic therapy.
5. Have the following available in case of localized bleeding: compresses (4x4), topical thrombin (retain in ward refrigerator).
6. Notify blood bank to ensure cryoprecipitate is available.
7. Order aminocaproic acid to have at bedside (Amicar® 100 mg/kg (max. 5g) IV bolus, then 30 mg/kg/hr (max. 1.25 g/hr) IV infusion until bleeding stops or until a maximum of 18 g/m²/day is given.)
8. Ensure good venous access for drug administration and for monitoring purposes.

VI. THROMBOLYTIC THERAPY

Give **alteplase (tPA)** as in infusion at a rate of **0.5 mg/kg/hr IV for 6 hours**.

If **catheter directed local alteplase (tPA)** is used decrease dose by 50%, **0.25 mg/kg/hr x 6 hrs**.

Re-evaluate radiographically following 6 hours of alteplase infusion (for arterial thrombi use the return of pulses and BP to pre-investigation values). If no response, suggest administering FFP 20 mL/kg IV q8h as a plasminogen source.

Streptokinase is not recommended in children.

VII. MONITORING

Monitor the response to thrombolytic therapy by the PT/INR, APTT, fibrinogen and d-dimer 4 hours following the onset of the infusion and every 6-8 hours thereafter.

If no response consider administering FFP 10-20 mL/kg q8h.

Expect the fibrinogen concentration to decrease by at least 20-50%; maintain the fibrinogen concentration at approximately 1 g/L or higher by infusions of cryoprecipitate (1unit/5kg).

If the fibrinogen concentration is < 1 g/L and the patient is still receiving an infusion of alteplase (tPA) decrease the dose of the thrombolytic agent by 25%.

Maintain the platelet count greater than 50-100 x 10⁹/L.

NB: If a patient has received thrombolytic therapy for more than 6 hours, consider treating with heparin alone for 24 hours before reinstating thrombolytic therapy. There may be ongoing thrombolysis even in the absence of continued administration of the thrombolytic agent.

VIII. UNFRACTIONATED HEPARIN THERAPY

Concurrent UFH therapy is recommended for all thrombolytic agents, UFH 10-20 u/kg/hr. If patient is not already on heparin, start infusion but do not give bolus dose.

If heparin administration was discontinued during thrombolytic therapy, restart heparin infusion whenever thrombolytic therapy is stopped and the fibrinogen concentration is > 1 g/dL. Do not give a bolus and aim for prolongation of the APTT 60-85s.

Use the heparin nomogram for adjusting heparin therapy.

IX. COMPLICATIONS OF THERAPY

Bleeding may occur in 30-50% of patients- usually this is oozing from a wound or puncture site and should be treated with local pressure and supportive care.

If severe bleeding occurs, stop the infusion of thrombolytic agent and heparin. Administer cryoprecipitate (usual dose of 1 bag/5kg). Consider Factor VIIa therapy.

If life threatening bleeding occurs: stop the infusion of the thrombolytic agent, infuse Cryoprecipitate as above, and reverse the lytic process by infusing aminocaproic acid (Amicar®) 100 mg/kg (max. 5g) IV bolus, then 30 mg/kg/hr (max. 1.25 g/hr) IV infusion until bleeding stops or until a maximum of 18 g/m²/day is given.) Protamine sulfate may be required to reverse the heparin. Consult the Thrombosis Service for more information. Consider Factor VIIa therapy.

Abbreviations: complete blood count (CBC);
activated partial thromboplastin time (APTT);
fresh frozen plasma (FFP).

Antithrombotic Therapy

Deep Vein Thrombosis

The following are guidelines for management of pediatric patients with deep vein thrombosis (DVT). Modifications for individual clinical circumstances may be necessary. In general consultation from the Thrombosis Service should be obtained.

I. GENERAL

Obtain detailed history and physical examination, including patient weight.

II. TESTS

1. For diagnosis of thrombus:

- a) For a suspected DVT in the upper central venous system, venography is recommended as ultrasound has a sensitivity of only 20% in this location.
- b) For a suspected clot in the jugular veins, compression ultrasound should be used because venography is relatively insensitive for the detection of DVT in these vessels.
- c) For a suspected DVT in the lower proximal venous system, Doppler/ultrasound may be sufficient.
- d) Ventilation perfusion scan (V/Q) or spiral CT chest should be considered in all cases (especially if cardiorespiratory abnormalities are present) to determine if pulmonary emboli are present, and for baseline assessment.

2. Bloodwork:

Baseline CBC, INR, APTT, Creatinine (LMWH renally cleared), Prothrombotic workup. Prothrombotic workup is carried out after completion of anticoagulation therapy and consists of:
ATIII, Protein C, Protein S, APCR, Factor V Leiden, Prothrombin gene defect, MTHFR, antiphospholipid antibodies, anticardiolipin, lipoprotein a, homocysteine, plasminogen and a reptilase time and thrombin time.

3. For other features:

Consider Ultrasound/CT of abdomen or chest for associated mass lesions where Indicated.

III. INITIAL THERAPY

1. Therapy can be initiated with either unfractionated heparin or a low molecular weight heparin (e.g., enoxaparin) for a minimum of 5-7 days, and for longer periods (10-14) days in the presence of an extensive DVT or PE.

IV. DURATION OF THERAPY

1. Either warfarin or low molecular weight UFH (enoxaparin) may be used for the duration of therapy following initial treatment with either heparin or low molecular weight heparin (enoxaparin).
2. For a DVT secondary to an acquired insult, 3 months duration of therapy is usually Sufficient.
3. For idiopathic DVT, at least 6 months duration should be considered.
4. For recurrent DVT, anticoagulation therapy is usually indefinite.
5. After 3 months of anticoagulation objective follow-up of the thrombosis is recommended.

Abbreviations: Complete blood count (CBC); activated partial thromboplastin time (APTT); ventilation perfusion scan (V/Q); computerized tomography (CT)

Antithrombotic Therapy

Cardiac Patients

This table is a summary only. For more information, refer to the complete guidelines, which are available from the Thrombosis Service or on the Cardiology nursing unit.

INDICATION	HEPARIN ^{a,b}	WARFARIN	ASA ^{c,d}
Fontan	10 units/kg/hr starting 2-3 days postop. Do not adjust dose.	Warfarin x 3-6 mos, or as per cardiology starting when patient able to take PO. If Fontan is fenestrated continue Warfarin. (NB:decreased loading dose). See guidelines for warfarin, p.243. Target INR: 2-3	(Study of warfarin vs. ASA is ongoing at HSC.) Call Dr. McCrindle, HSC for more information.
Endovascular Stent a) standard	Loading dose: 150 units/kg in cath lab. Maintenance: 10 units/kg/hr starting 48 hrs postop. Do not adjust dose.	--	Low dose ASA: 3-5 /kg/day x 6 mos. Consider Clopidigrel 1 mg/kg (in increments of 5 mg) PO per day.
b) Patient with stent ≤ 4 mm OR stent in Superior vena cava OR pulmonary vein stent	Standard dose heparin See guidelines for Heparin, p.234, or Enoxaparin, p.239	Enoxaparin, see guidelines for Heparin, p.217 or Enoxaparin, p.222 or Warfarin starting when patient able to take PO. See guidelines for Warfarin, p.243. Target INR: 2-3	Cardiology to decide when anticoagulation should be discontinued.
Blalock-Taussing Shunt (including pt< 1 yr or Norwood)	UFH followed by Enoxaparin. Consider treating until next stage cardiac surgery.	--	Consult with responsible cardiovascular surgeon for definitive therapy.

INDICATION	HEPARIN ^{a,b}	WARFARIN	ASA ^{c,d}
Mechanical Valve	Standard dose: See guidelines for heparin, p. 234. & enoxaparin p.239	Warfarin indefinitely, starting when patient able to take PO. See guidelines for Warfarin, p.243. Target INR: 2.5-3.5	Consult with Cardiovascular surgery to decide when to initiate therapy.
Tissue Valve a) Aortic	48 hours post op	Warfarin x3 mos or as per cardiology Starting when patient able to take PO. See guidelines for Warfarin, p.243. Target INR: 2.5-3.5	Low dose ASA: 3-5 mg/kg/day starting when patient able to take PO, x 3 mos.
b) Mitral/Tricuspid with atrial fibrillation or intra-atrial thrombus, or systemic embolis	Standard dose: See guidelines for UFH, p. 234. and enoxaparin p. 239	Warfarin indefinitely, starting when patient able to take PO. See guidelines for warfarin, p.243. Target INR: 2.5-3.5	—
c) Mitral/Tricuspid normal sinus rhythm	—	Warfarin x 3 mos or as per cardiology, starting when patient able to take PO. See guidelines for Warfarin, p.243. Target INR: 2-3	Low dose ASA: 3-5 mg/kg/day starting when patient able to take PO, and continuing indefinitely
d) Homograft Valve	—	—	—
e) Mitral valve ring or Gortex patch or Pulmonary Aterioplasty (6 weeks)	Therapeutic enoxaparin and/or warfarin (INR 2-3) are suggested post surgery. Discontinue after 6 weeks if no other indications		
f) Mitral valve ring or Gortex patch or Pulmonary Aterioplasty (1 month)	Therapeutic enoxaparin and/or warfarin (INR 2-3) are suggested post surgery. Discontinue after 1 month if no other indications		

- a) Heparin should be stopped for 2 hours before intracardiac lines are removed.
- b) Chest tube removal or insertion is not a contraindication for heparin.
- c) In patients with pacing wires in place, wires may be removed at the trough of enoxaparin or if the INR is less than 2. (Remove wires early for Fontan and mechanical valve patients without rhythm issues).
- d) ASA should be discontinued inpatients with viral illness, especially chickenpox and influenza, due to the risk of Reye's syndrome.
- e) Where possible, round Acetylsalicylic acid (ASA) dose to nearest 20 mg (1/4 tablet). Maximum: 325 mg/day