PROTOCOLS FOR ANTICOAGULANT AND THROMBOLYTIC THERAPY

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References:

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Contents:

PROTOCOL FOR HEPARIN THERAPY

(for patients > 1 month of age)

- Always obtain baseline PT/INR, APTT, CBC and fibrinogen before starting therapy
- Once APTT is in the therapeutic range, repeat APTT daily; CBC and platelets are to be checked twice weekly

LOADING DOSE:

75 units/kg (maximum: 5000 units/dose)
-infuse IV over 10 minutes by syringe pump

INITIAL MAINTENANCE DOSE:

< 1 year of age:	28 units/kg/hr
≥ 1 year of age:	20 units/kg/hr
Adolescents and adults	18 units/kg/hr (maximum 1000 units/hr)

Obtain APTT 4 hours after loading dose and adjust dose according to nomogram.

APTT (sec.)	Bolus (units/kg)	Holdtime (min.)	Rate Change	Repeat APTT
< 40	50	0	↑ 20%	4 hr
40 – 49	0	0	↑ 10%	4 hr
50 – 75	0	0	0	4 hr then next day
76 – 85	0	0	↓ 10%	4 hr
86 – 95	0	30	↓ 10%	4 hr
> 95	0	60	↓ 15%	4 hr

USUAL CONCENTRATION FOR MAINTENANCE HEPARIN:

- 50 units/mL for majority of patients
- 100 units/mL for patients who are severely fluid restricted
- Use D5W (but also compatible with saline)

CORRECT WRITING OF ORDERS:

Write orders as:

"Heparin infusion (50 units/mL) in D5W; infuse IV at ____mL/hr (____ Units/kg/hr)"

The use of the anticoagulant monitoring sheet during therapy is strongly encouraged.

PROTOCOL FOR WARFARIN THERAPY

- Always obtain baseline PT/INR, APTT, CBC and fibrinogen before starting treatment.
- Maximum initial loading dose 0.2 mg/kg. **Reduce this to 0.1 mg/kg in patients post-Fontan surgery, liver dysfunction or severe renal impairment.**
- Usual maintenance dose is about 0.1 mg/kg/day
- Once daily dosing; to be given at 1800 hrs. Round dose to nearest 0.5 mg.
- The rate of INR change influences dosing changes: if INR increases quickly be **conservative** with subsequent dose increases.

LOADING DOSE:

Day	INR	Dose of warfarin
Loading dose Day 1	1-1.3	0.2 mg/kg
Day 2-4	1.1- 1.3	0.2 mg/kg
	1.4-1.9	0.1 mg/kg (50% of initial loading dose)
	2 – 3	0.1 mg/kg (50% of initial loading dose)
	3.1-3.5	0.05 mg/kg (25% of initial loading dose)
	>3.5	Hold dose until INR < 3.5; then restart at 50% less than previous dose

LONG-TERM MAINTENANCE DOSAGE GUIDELINES:

Day	INR	Dose of warfarin
Day 5 and beyond (dose dependent on INR)	1.1 - 1.4	Increase dose by 20%
	1.5 - 1.9	Increase dose by 10%
	2 - 3	no change
	3.1 - 3.5	Decrease dose by 10%
	> 3.5	hold until INR < 3.5, restart at 20% less than previous dose

PROTOCOL FOR ENOXAPARIN THERAPY

- Enoxaparin is the only low molecular weight heparin (LMWH) on formulary at C & W
- Obtain baseline INR, aPTT, fibrinogen, CBC and renal function.

Dosing: Use with caution and dose may need to be adjusted in renal failure.

	Age ≤ 2 months	**Age > 2 months**
Enoxaparin treatment dose	1.5 mg/kg/dose SC Q12H	1 mg/kg/dose SC Q12H

Monitoring

- Therapeutic range of low molecular weight heparin level (anti Xa): 0.5 – 1 unit/mL
- Low molecular weight heparin (anti Xa) levels should be drawn 4 hours after the second dose, or the second new dose, if changed. Thereafter weekly for inpatients, monthly for outpatients, or as clinically indicated.
- Draw level via venous sample
- If a venous draw is not feasible and sample is drawn from a heparinized line, draw a PTT to rule out contamination. If patient is well and PTT is prolonged, redraw Anti XA via peripheral route
- If the patient is unwell (febrile, new infection <within two weeks> or MD discretion), draw an INR & fibrinogen along with the PTT as an increase in PTT might be due to coagulopathy and not heparin contamination.
- 30 unit insulin syringes can be used to measure small doses;
- **In insulin syringes 1 mg = 1 unit (order whole numbers of mg ie 5 mg NOT 5.5 mg)**
- Prior to invasive procedures such as lumbar punctures, omit 2 previous doses of enoxaparin

LMWH (anti Xa) level at 4 hours (units/mL)	Dose change	Obtain Next Level
< 0.35	Increase by 25%	4 hours post 2 doses after change
0.35 - 0.49	Increase by 10%	4 hours post 2 doses after change
0.5 - 1.0	0	4 hours post am dose once weekly
1.1 - 1.5	Decrease by 20%	4 hours post 2 doses after change
1.6 – 2.0	Hold dose for 3hr; decrease by 30%	Trough level before next dose, then 4 hours post 2 doses after change
> 2.0.	Hold until heparin level 0.5 then decrease by 40%	Trough level before next dose and if not <0.5 U/mL continue to hold and repeat before each dose is due

Conversion between low molecular weight heparin (LMWH) and unfractionated heparin (UFH)

1. LMWH to UFH

- No heparin bolus
- Start UFH infusion 8 - 12 hours after last LMWH dose
- Measure aPTT 6 hours after start of UFH infusion and monitor as per unfractionated heparin guidelines

2. UFH to LMWH
    - Stop UFH infusion
    - Give LMWH at the same time as stopping infusion.

PROTOCOL FOR SYSTEMIC THROMBOLYTIC THERAPY

* Hematology consult required*

Alteplase (tissue plasminogen activator, tPA)

- **No loading dose**
- **Infuse IV at 0.5 mg/kg/hr x 6 hours. Do not continue infusion beyond 6 hours.**
- Consider heparin at 10 units/kg/hr during alteplase infusion (do not give a heparin loading dose). Start as soon as possible, aiming for several hours of heparin prior to starting alteplase. If patient is already on therapeutic heparin, reduce the infusion rate to 10 units/kg/hr 30 minutes prior to starting alteplase. (Judicious use of IV heparin infusion is indicated to prevent thrombin generation.)
- Re-evaluate with objective testing (radiographically or return of pulses and BP for arterial thrombi) following 6 hours of infusion.
- 30 – 60 minutes after alteplase infusion is finished, start titrating heparin infusion up toward therapeutic APTT without bolus doses
- If no response, measure the plasminogen level. If low, administer FFP at 20 mL/kg every 8 hours.
- A repeat alteplase infusion can be considered 12-24 hours after completing initial course.

Monitoring

- Aim to decrease fibrinogen by 20-50% with increase D dimers to achieve a systemic thrombolytic state.
- **At 4-6 hours**: CBC (platelets), PT, APTT, fibrinogen, D dimer (to ensure lytic state achieved) then measure fibrinogen every 6 hours if possible
- Consider measuring plasminogen level at the end of the 6 hour infusion if no response, or prior to another course (keep in mind that added venous punctures increase the risk of bleeding).
- Maintain fibrinogen levels > 100 mg/dL; give cryoprecipitate (1 unit/5 kg) for severe hypofibrinoginemia.
- Give FFP 20 mL/kg Q6-8H if plasminogen is low.
- Maintain platelet count > 100,000
- **Daily:** PT, APTT, fibrinogen, D dimmer, CBC

If severe bleeding:

- Stop alteplase infusion, give cryoprecipitate (usual dose 1 bag/5 kg body weight or 5-10 mL/kg) and give IV tranexamic acid 10 mg/kg/dose

HEPARIN INFORMATION SHEET

- Requires a dedicated line for IV infusion. A separate peripheral line will be required for drawing of APTT levels and administration of incompatible medications.
- Blood for APTT shoud NOT be drawn on the extremity where heparin drip is infusing.
- Avoid IM injections, arterial punctures and, where possible, antiplatelet agents such as ASA, NSAIDs (eg ketorolac).
- Stop heparin 4 hours prior to invasive procedures such as LP or pacer wire removal.
- Platelet count should be maintained above 60,000 during therapy.
- If there is an abrupt decrease in the platelet count (e.g. 50% decrease) suspect heparin-induced thrombocytopenia (HIT).
- If transitioning to oral anticoagulation, start on day 1 of heparin and overlap for 5 days. Post-op cardiac patients can be initiated on oral anticoagulation once pacer wires are out.

Heparin Resistance

An anti Xa level is indicated if APTT is unreliable (e.g. presence of lupus anticoagulant) or if patient's heparin requirement is unusually high (> 40 U/kg/hr).
Therapeutic anti Xa range: 0.35 – 0.7 units/mL.
Consider Xa measurement in neonates who have a naturally prolonged APTT.

Mechanism of Action

Heparin binds to antithrombin which enhances the inactivation of thrombin (IIa) and factor Xa (as well as activated coagulation factors IX, X, XI, XII) and prevents the conversion of fibrinogen to fibrin.

Pharmacokinetics

- Heparin is not absorbed via the oral route, therefore intravenous (continuous infusion) and subcutaneous (intermittent) routes are necessary
- For immediate anticoagulation an intravenous bolus followed by a continuous infusion is given since there is a delay in absorption/onset via the SC route
- Heparin clearance is mostly renal so consider a reduced heparin dose in renal dysfunction
- The half-life of heparin is dose-dependent (in the therapeutic range, the half-life is about 1 hour)
- APTT reaches a steady state in approximately 4 hours in children

Adverse Effects

- The risk of heparin-induced thrombocytopenia is greater after the first 5 days, though it is sooner in patients with prior heparin exposure (eg heparin in cardiac bypass solutions)
- Hypersensitivity to heparin or any component (some preparations contain sulfites or benzyl alcohol which can be sensitizing)

Contraindications

- Severe thrombocytopenia, suspected intracranial hemorrhage, severe hypotension or uncontrolled bleeding.

Antidote: Protamine 1 mg/100 units of heparin received in previous 2 hours.

WARFARIN (COUMADIN) INFORMATION SHEET

ELECTIVE REVERSAL FOR WARFARIN*:*

INR > 8 and No bleeding :

a) Patient may require warfarin again in the near future: 0.5 - 2 mg vitamin K_1, PO or SC
b) Patient may not require warfarin in the near future: 2 - 5 mg vitamin K_1 PO or SC
c)

Significant bleeding:

a) Non-life threatening: 0.5 - 2 mg vitamin K_1 SC and consider 20 mL/kg of FFP.
b) Life-threatening and will cause significant morbidity: (obtain haematology consult)
   - 5 mg vitamin K_1 by slow intravenous infusion over 10 - 20 minutes (give slowly to reduce risk of anaphylaxis)
   - 20 mL/kg of FFP
   - consider giving prothrombin complex (contains Factors II, VII, IX, X) [50 units/kg IV) or recombinant Factor VIIa (Niastase)

Desired therapeutic range:

- INR 2-3
- For mechanical mitral valves: INR 2.5-3.5
- For Fontan surgery: INR 2.5
- Changes in INR reflect warfarin doses given 2-3 days ago. Anticoagulant activity is related to both the half life of warfarin (24-48 hr) and the Vitamin K clotting factors, which are relatively long (Factor VII: 6 hr; Factor IX: 24 hr; Factor X: 10-40 hr; Factor II: 60-100 hr). Despite onset of action within 36-72 hours, full steady state is not reached for 5 to 7 days.

Mechanism of Action

- Warfarin interferes with the cyclic interconversion of Vitamin K resulting in the decreased functional plasma concentration of the Vitamin K dependent clotting factors (Factors II, VII, IX, X)

Pharmacokinetics

- Warfarin is highly bound to albumin and this may be significant in severe hypoalbuminemia.
- Warfarin is rapidly and completely absorbed via the gastrointestinal tract; absorption is not affected by food
- Many infant formulas contain small amounts of Vitamin K to prevent hemorrhagic disease of the newborn. Formula fed infants may therefore be resistant to warfarin.
- Conversely, breast fed infants may be more sensitive to warfarin due to low amounts of Vitamin K in breast milk.
- Metabolism is by the cytochrome P450 system resulting in many significant drug interactions:
  - ***anticoagulant effect potentiated*** by: amiodarone, clarithromycin, cotrimoxazole, erythromycin, fluconazole, metronidazole, omeprazole, prednisone, propafenone, propranolol, dong quai, gingko balbo, ginseng.
  - ***anticoagulant effect counteracted*** by: barbiturates, carbamazepine, penicillin, phenytoin, rifampin, sucralfate, St. John's wort, Coenzyme Q10

Heparin overlap and when to start warfarin

- Start warfarin on day 1 or 2 of heparin, continue heparin for 5 days and INR > 2 for 2 days.
- For post-op cardiac patients, start warfarin when patients tolerate PO and pacer wires are removed

Discharge considerations:

- Warfarin teaching should be done, with information pamphlet and calendar.
- Make arrangements for out patient monitoring of INR.
- Repeat INR at discretion of designated physician. Initially, check INR at weekly intervals or if there is a change in medication or dietary habits.

Tablet colours

(Coumadin, Apo, Taro, Gen-Pharm)

1 mg (pink)	2 mg (lavender)
2.5 mg (green)	3 mg (tan)
4 mg (blue)	5 mg (peach)

Contraindications

- Hypersensitivity to warfarin
- Severe liver or kidney disease
- Recent or contemplated surgery
- Overt or uncontrolled bleeding
- Spinal puncture

Precautions

- Avoid NSAIDs, but ASA may need to be prescribed concomitantly for antiplatelet effect where necessary.

ENOXAPARIN INFORMATION SHEET

- Enoxaparin is more expensive than unfractionated heparin but it can be given more conveniently on an outpatient basis with much less monitoring. As enoxaparin does not cause platelet dysfunction, the risk of bleeding is lower than with unfractionated heparin. The risk of heparin induced thrombocytopenia and osteoporosis is reduced.

Mechanism of Action

- Enoxaparin binds to antithrombin and inhibits Xa. Unlike unfractionated heparin, enoxaparin has reduced effect on anti IIa and does not prolong APTT

Pharmacokinetics

- Enoxaparin is excreted mainly by the kidneys so a reduced dose or increased dosing interval is required in renal failure
- Enoxaparin does not bind to plasma proteins, therefore has a longer half-life (2-3 hours) with predictable pharmacokinetics, compared to unfractionated heparin.
- Absorption may be variable in neonates with inadequate adipose tissue.
- Maximum effect after SC dose is seen in 3 to 5 hours; duration is 12 hours.

Monitoring

- A venous sample is required to measure low molecular weight heparin level (anti Xa) in citrate tube (do not overfill)
- If a venous draw is not feasible and sample is drawn from a heparinized line, draw a PTT to rule out contamination. If patient is well and PTT is prolonged, redraw Anti XA via peripheral route
- If the patient is unwell (febrile, new infection <within two weeks> or MD discretion) draw an INR & fibrinogen along with the PTT as an increase in PTT might be due to coagulopathy and not heparin contamination
- Levels can be checked weekly when the desired range is achieved. For long term therapy, level can be checked every 2 to 4 weeks to avoid accumulation.

Administration

- Injection sites must be monitored closely for hematoma. The dose can be administered via the subcutaneous route using an ultrafine needle to minimize pain.
- Vials should be stored at room temperature with a 28 day expiry date once opened.

Precautions

- Hypersensitivity to enoxaparin or heparin
- Use with caution in patients with increased risk of bleeding, active bleeding, refractory/severe thrombocytopenia, coagulopathies, recent surgery, concomitant antiplatelet therapy or NSAIDs (ASA, ibuprofen or ketorolac) or recent epidural/spinal punctures.
- Aim to keep platelets above 50,000 while on enoxaparin
- Avoid IM injections and arterial punctures.
- Protamine does not completely neutralize the anti-Xa activity of enoxaparin. If the last dose of enoxaparin is given within 4 hours, give 1 mg of protamine per mg of enoxaparin, by slow IV infusion. Protamine may cause anaphylaxis and hypotension.

Discharge considerations

- Special Authority needs to be obtained (by physician) from Pharmacare for patients being discharged on enoxaparin.
- A teaching package is available for patients being discharged on enoxaparin. Teaching will be done by the ward pharmacist, cardiology clinic nurses or hematology nurses.

INFORMATION SHEET FOR THROMBOLYTIC THERAPY

In children, especially less than 1 year of age, or patients with low fibrinogen (<100 mg/dL) or low plasminogen for other reasons, consider replacement with FFP 10-20 mL/kg prior to starting alteplase. Fibrogen levels determine the need for cryoprecipitate and/or plasma replacement.

MECHANISM OF ACTION OF ALTEPLASE

- Alteplase (a.k.a. tissue plasminogen activator or tPA) is a recombinant enzyme which enhances the conversion of plasminogen to plasmin.
- It produces limited conversion of plasminogen in the absence of fibrin.
- Alteplase binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin.
- Plasmin cleaves fibrin and fibrinogen to form fibrin degradations products.
- D dimers are degradation products from broken down crosslinked fibrin.
- Half life of alteplase is less than 5 minutes therefore it is always given by continuous IV infusion.

CONTRAINDICATIONS:

- Active bleeding or significant potential for local bleeding (e.g. tumor surrounding vessel with clot), GI bleed.
- General surgery within previous 10 days.
- Neurosurgery within previous 3 weeks, stroke, intracranial or intraspinal surgery
- Brain tumor.
- Severe uncontrolled bleeding.

PREPARATION OF THE PATIENT FOR ALTEPLASE INFUSION:

- ICU admission.
- For children < 1 year of age give FFP prior to alteplase to replace naturally low plasminogen
- For children > 1 year of age, check fibrinogen and give FFP if low
- If fibrinogen <100 mg/dL in all children give cryoprecipitate.
- Baseline CBC, platelet count, PT, APTT, fibrinogen and D dimers.
- Ensure that platelet count is > 100,000 and fibrinogen is above 100 mg/dL
- Cross match and type for 1 unit of PRBC. Notify blood bank to have cryoprecipitate available.
- Ensure good venous access for blood sampling.
- Have compresses and topical thrombin available in case of localized bleeding.
- Consider sedation depending on the child and circumstances.
- An “Alteplase Infusion” sign should be posted on patient’s bed.

PRECAUTIONS:

- Minimal patient manipulation.
- No intramuscular injections, arterial punctures, urinary catheterization, rectal temperature.
- Avoid concurrent antiplatelet agents such as ASA, NSAIDs or dipyridamole.
- Reverse warfarin as needed.
- Blood sampling from superficial veins or indwelling venous catheter
- Monitor for bleeding in previous puncture sites (e.g. for cardiac catheter)

COMPLICATIONS OF THERAPY

- Bleeding may occur in 68% of children, usually from a wound or puncture site; 39% of bleeding patients require transfusions.