PROTOCOLS FOR ANTICOAGULANT AND THROMBOLYTIC THERAPY

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PROTOCOL FOR HEPARIN THERAPY

(for patients > 1 month of age)

- Obtain baseline INR, aPTT, fibrinogen, CBC, urea, creatinine before starting therapy
- Once aPTT is in the therapeutic range, repeat aPTT daily; CBC twice weekly
- Requires a dedicated line. Blood for aPTT should NOT be drawn from the extremity infusing heparin

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.

Titrate according to table. For patients not responding as predicted or with a high initial aPTT measure unfractionated heparin level (goal: 0.35 – 0.7 units/mL). Hematology or Hematopathology consult recommended.

APTT (sec.)	Bolus (units/kg)	Holdtime (min.)	Rate Change	Repeat APTT
<50	50	0	↑ 20%	4 hr
50-59	0	0	↑ 10%	4 hr
60-85	0	0	0	24 hr
86-95	0	0	↓ 10%	4 hr
96-120	0	30	↓ 10%	4 hr
>120	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 ____ units/kg/hr"

Last update: August 2018

HEPARIN INFORMATION SHEET

- Requires a dedicated line for IV infusion. Venous blood draws or a separate peripheral line will be required for drawing of aPTT levels and administration of incompatible medications.
- Obtain baseline INR, aPTT, fibrinogen, and CBC prior to initiating unfractionated heparin
- 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 50,000 during therapy.
- Obtain CBCs twice weekly. 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 unfractionated heparin 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).

If patient has an unusually high heparin requirement consider checking an antithrombin level. (Hematology/Hematopathology consult suggested)

Therapeutic unfractionated heparin level: 0.35 – 0.7 units/mL.

Consider monitoring unfractionated heparin levels in neonates who have a physiologically 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 (e.g. heparin in cardiac bypass solutions)
- Hypersensitivity to heparin or any component (some preparations contain sulfites or benzyl alcohol which can be sensitizing)

CONTRAINDICATIONS

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

ANTIDOTE:

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

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PROTOCOL FOR WARFARIN THERAPY

- Always obtain baseline INR, aPTT, CBC and fibrinogen before starting treatment.
- 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.
- Onset of action 24-72 hrs, peak effect 5-7 days
- Obtain INR whenever there is bleeding, new medication, acute illness (especially gastrointestinal), significant change in diet

INITIAL LOADING DOSE (day 1):
0.2 mg/kg orally, maximum 5 mg. Reduce dose to 0.1 mg/kg for patients with liver dysfunction, post-Fontan surgery or severe renal impairment.

LOADING DOSES for days 2 – 4 of warfarin therapy based on INR:

INR	Dose of warfarin
1.1- 1.3	Repeat initial loading dose
1.4-1.9	50% of initial loading dose
2 – 3	If after only 1-2 days of warfarin hold dose for 1 day then restart at 50% of initial loading dose. If after 3 – 4 days then continue with 50% of initial loading dose
3.1-3.5	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: (For Goal INR 2-3)

INR	Warfarin dose adjustment
1.1 - 1.4	Increase dose by 20%
1.5 - 1.7	Increase dose by 10%
1.8 – 3.2	no change
3.3 - 3.5	Decrease dose by 10%
> 3.5	hold until INR < 3.5, restart at 20% less than previous dose

Last update: August 2018

WARFARIN (COUMADIN) INFORMATION SHEET

ELECTIVE REVERSAL FOR WARFARIN:

The following are guidelines only. Hematology Consult recommended. Caution in using Vitamin K in patients with prosthetic valves.

NO BLEEDING

a) **If rapid reversal not required hold warfarin and repeat INR in 24 hours**
b) If rapid reversal required and patient may require warfarin again in the near future: 0.5 - 2 mg vitamin K_1, PO or SC
c) If rapid reversal required and patient may not require warfarin in the near future: 2 - 5 mg vitamin K_1 PO or SC

BLEEDING:

a) Non-life threatening: 0.5 - 2 mg vitamin K1 PO/SC/IV and consider 20 mL/kg of FFP.

b) Life-threatening or risk of significant morbidity: (obtain haematology consult)
- 20 mL/kg of FFP
- 5 mg vitamin K_1 by slow intravenous infusion over 10 - 20 minutes (give slowly to reduce risk of anaphylaxis)
- 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 dependent 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),Protein C and S (anticoagulant proteins)

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.
- Metabolized by cytochrome P450 CYP2C9 resulting in many significant drug interactions:
  - **anticoagulant effect potentiated by:** amiodarone, clarithromycin, cotrimoxazole, erythromycin, fluconazole, metronidazole, omeprazole, prednisone, propafenone, propranolol, dong quai, gingko baloba, 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 (brands: 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 renal impairment
- 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.

PROTOCOL FOR ENOXAPARIN

- 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.

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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.

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SYSTEMIC THROMBOLYTIC THERAPY USING ALTEPLASE

* Hematology consult and PICU Admission required

PREPARATION OF PATIENT FOR ALTEPLASE INFUSION

- Baseline CBC, INR, aPTT, fibrinogen and D dimers, group and screen
- Ensure that platelet count is > 100,000 and fibrinogen is > 1 g/L
- For children < 1 year of age, give plasma (15 mL/kg) prior to alteplase to replace naturally low plasminogen
- Notify blood bank of alteplase infusion so they are aware that blood products may be needed.
- 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.

CONTRAINDICATIONS:

- Active bleeding or significant potential for local bleeding (e.g. tumor surrounding vessel with clot), GI bleed, head injury, hypertension.
- General surgery or LP within previous 10 days.
- Neurosurgery within previous 3 weeks, stroke, AV malformations, TIA.
- Brain tumor.

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.

HEPARIN ADDITION DURING ALTEPLASE INFUSION

- 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, consider giving plasma at 15 mL/kg every 8 hours.
- A repeat alteplase infusion can be considered 12-24 hours after completing initial course.

MONITORING

At 4 hours and Q6-8H thereafter:

- CBC, INR, aPTT, fibrinogen, D dimer

Expect fibrinogen to decrease and d-dimer to increase with thrombolysis.

Maintain fibrinogen > 1 g/L with cryoprecipitate infusions (1 unit/5 kg) as needed.
If no response to alteplase, consider administration of plasma (15 mL/kg) Q8H.

Maintain platelets at 50-100,000.

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)

BLEEDING COMPLICATIONS:

- Major bleeding occurs in 10-30% of children.
- Management depends on severity.
- Consider:
    - stopping alteplase and heparin
    - local hemostatic measure
    - cryoprecipitate (to reverse alteplase)
    - protamine sulfate (to reverse unfractionated heparin)
    - for life-threatening bleeding consider rFVIIa

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