PROTOCOLS FOR ANTICOAGULANT AND THROMBOLYTIC THERAPY

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TABLE OF CONTENTS **PAGE**

- Protocol for heparin therapy..... 2

- Protocol for warfarin therapy..... 4

- Protocol for enoxaparin therapy..... 7

- Protocol for systemic thrombolytic therapy..... 10

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/h
> 1 year of age:	20 units/kg/h
Adolescents and adults	18 units/kg/h

-Obtain aPTT 4 hours after loading dose and adjust dose according to nomogram.
-Nomogram is based on heparin therapeutic aPTT of 50 – 70 sec. at BCCH, which corresponds approximately to unfractionated heparin level (anti-Xa) of 0.35 – 0.7 units/mL. Use caution if lab heparin therapeutic aPTT is different.
-For patients not responding as predicted or with a high initial aPTT measure unfractionated heparin level (anti-Xa) (goal: 0.35 – 0.7 units/mL). Hematology or Hematopathology consult recommended

APTT (sec.)	Bolus (units/kg)	Hold time (min.)	Rate Change	Repeat APTT
<40	50	0	↑ 20%	4 hr
40-49	0	0	↑ 10%	4 hr
50-70	0	0	0	24 h
71-79	0	0	↓ 10%	4 hr
80-95	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 ____ units/kg/h"

ADDITIONAL INFORMATION:

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
- 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

Precautions

- 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 lumbar puncture or pacer wire removal
- Platelet count should be maintained above 50 x 10 ^9/L 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

Antidote: Protamine 1 mg/100 units of heparin received in previous 30 minutes. Refer to protamine monograph for further information about dosing beyond 30 minutes

PROTOCOL FOR WARFARIN THERAPY

- Hematology Consultation for warfarin strongly recommended. This program includes essential warfarin education for families and close INR monitoring
- 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, within 5 days of starting a new medication, acute illness (especially gastrointestinal), significant change in diet

INITIAL LOADING DOSE (day 1):
0.2 mg/kg orally (maximum: 5 mg/dose). Reduce dose to 0.1 mg/kg for patients with liver impairment, 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)
Most maintenance warfarin dosage adjustment is done by Hematology. Dose adjustment should be guided by indication for warfarin, bleeding risk, and patient circumstance in discussion with Hematology

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

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

b) 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 K_1 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] Recombinant Factor VIIa (Niastase) should be reserved for very severe emergencies and discussed with Hematology and Hematopathology

Desired therapeutic range:

- For most indications (eg. Fontan, Kawasaki Disease, antiphospholipid syndrome, longterm thromboprophylaxis) INR 2-3
- For mechanical valves: INR 2.5-3.5
- 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)
- Transient procoagulant effect on initiation of warfarin due to decreased Protein C and S. Bridging with heparin or low-molecular weight heparin may be required

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 show some resistance to warfarin
- Conversely, breast fed infants may be more sensitive to warfarin due to low amounts of Vitamin K in breast milk. If warfarin dosing is too low then vitamin K supplementation can be considered
- Metabolized by cytochrome P450 CYP2C9 resulting in many significant drug interactions.

Check for drug interactions when starting or stopping concomitant medications and check INR within 5 days of starting or stopping a medication

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 are eating and when further procedures are not planned

Discharge considerations:

- Warfarin teaching should be done, with information pamphlet and calendar
- Make arrangements for out-patient monitoring of INR – usually via Hematology consultation. If on long term anticoagulation, consider Point of Care INR testing
- Repeat INR at discretion of designated physician. Initially, check INR at weekly intervals or if there is a change in medication or dietary habits

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 indicated
- Immunizations can go ahead while on warfarin. Use smallest available needle and apply strong local pressure.

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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 creatinine

Dosing: Use with caution in patients with renal impairment as dose may need to be adjusted

	Age ≤ 2 months	**Age > 2 months**
Enoxaparin treatment dose	1.5 mg/kg/dose SC Q12H	1 mg/kg/dose SC Q12H May consider maximum starting dose 100 mg Q12H
Enoxaparin prophylaxis dose	0.75 mg/kg/dose SC Q12h May consider 1.5 mg/kg/dose SC Q24h if no prohibitive bleeding risk	0.5 mg/kg/dose* SC Q12H May consider 1 mg/kg/dose* SC Q24h if no prohibitive bleeding risk

*No maximum dose

- **Round up to nearest whole number of mg (eg. 6 mg NOT 5.5 mg)**
- 30 unit insulin syringes can be used to measure small doses; **with insulin syringes 1 mg = 1 unit**
- Prior to invasive procedures such as lumbar punctures, omit enoxaparin for 24 hours prior (2 doses if twice daily dosing, 1 dose if once daily dosing)

Monitoring (for treatment dosing)

- 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 on day 2 of treatment, 4 hours after the morning dose, and on day 2 following a dose change 4 hours after morning dose
- Draw level via venous sample
- If a venous draw is not feasible and sample is drawn from a heparinized line, draw aPTT 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

LMWH (anti Xa) level at 4 hours (units/mL)	Dose change	Obtain Next Level
< 0.35	Increase by 25%	4 hours post 2-3 doses after change
0.35 - 0.49	Increase by 10%	4 hours post 2-3 doses after change (after next AM dose)
0.5 - 1.0	0	4 hours post AM dose once weekly
1.1 - 1.5	Decrease by 20%	4 hours post 2-3 doses after change (after next AM dose)
1.6 – 2.0	Hold dose for 3hr; decrease by 30%	Trough level before next dose, then 4 hours post 2-3 doses after change (after next AM dose)
> 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

Monitoring (for prophylaxis dosing)

- Monitoring is not usually required for prophylaxis but may be considered in patients with obesity, high bleeding risk, or abnormal renal function
- Therapeutic range of low molecular weight heparin level (anti Xa) for prophylaxis is not well established: peak 0.2 – 0.49 unit/mL, or trough level ≥0.1
- Consult pharmacist and/or hematology for dose adjustments based on levels

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

ADDITIONAL INFORMATION

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 impairment – discuss with Pharmacist and Hematology
- 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
- Pharmacokinetics may be altered in critically ill children and obese children

Administration

- Monitor injection sites 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 x 10^9/L while on therapeutic dosing of enoxaparin (or adjust dose in discussion with hematology when platelets <50)
- 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 8 hours, give 1 mg of protamine per mg of enoxaparin, by slow IV infusion. Protamine may cause anaphylaxis and hypotension

Discharge considerations

- Pharmacare Special Authority needs to be obtained 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 and inpatient bedside 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 x 10^9/L 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, uncontrolled hypertension
- General surgery or lumbar puncture 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/h x 6 hours

HEPARIN addition during alteplase infusion

- Concurrent heparin infusion recommended to prevent thrombin generation. Run at 10 units/kg/h during alteplase infusion (do not give a heparin loading dose). Start as soon as possible, if possible start prior to starting alteplase
- If patient is already on therapeutic heparin, reduce the infusion rate to 10 units/kg/h 30 minutes prior to starting alteplase
- 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
- 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 ≥100 x 10^9/L

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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