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Guidelines for the use of anticoagulants and Thrombolytic agents in children

[Adapted from 1-800-noclots, Antithrombotic Therapy in Neonates and Children in Chest 2008 and The Hospital for Sick Children's Stroke Guidelines 2008]

APPHON/ROHPPA supportive care guidelines are developed by Atlantic Provinces health professional specialists using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

Supportive Care

Children and families, who have supportive care needs that are not addressed in the APPHON/ROHPPA guidelines for the use of anticoagulants and thrombolytic agents in children (e.g., access to medication; difficulty coping with the stresses and worries of this condition), can contact the hematology family care coordinators at the tertiary care centres for assistance. Supportive care consists of the provision of services to meet children and families' physical, social, emotional, nutritional, informational, psychological, spiritual and practical needs throughout the illness experience (Fitch 1994, 2000).

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Guidelines for unfractionated heparin therapy [UFH]

The following are guidelines for initiating and monitoring unfractionated heparin [UFH] therapy. Modifications for individual clinical circumstances may be necessary. In general, consultation from the Pediatric Hematology/Oncology Service should be obtained.

Heparin in concentration greater than 1,000 units/ml is considered a potentially toxic drug. Most concentrations of heparin less than 1,000 units/ml are used only for the flushing or heparinization of central lines [arterial or venous]. However, any concentration of heparin, if administered in large enough volume, could expose a child to an increased risk of bleeding.

Guidelines:

UFH may be administered IV or Subcutaneous. The nomogram for intravenous UFH presented below has been modified from a nomogram that ensures adequate aPTT prolongation in greater than 90% of adult patients within 48 hours of initiation of therapy. This protocol has been studied in pediatric patients.

Within the IWK Health Centre, there are two forms of UFH- one measured in USP units [pre-mixed bags of 50 units UFH/ml] and vials of more concentrated UFH [measured in BP units] for use in neonates or patients with fluid restrictions. USP and BP units **are not** equivalent and care must be taken in switching from one brand to another.

Intravenous UFH dosing [therapeutic]:

- The loading dose of UFH is 75-100 units/kg IV over 10 minutes [maximum 5,000 units/ dose]. Neonates are generally bolused with 75 units/kg.
- The initial maintenance dose of UFH is age related:
  - children less than 12 months of age*: 28 units/kg/hour continuous infusion
  - children greater than or equal to 12 months of age: 20 units/kg/hour continuous infusion
  - Older children and adults: 18 units/kg/hour continuous infusion
  - The maximum initial rate is 1000 units/hour

  *corrected for gestational age.
- Obtain blood for an aPTT at least 4 hours after the administration of the UFH loading dose [not earlier] and then 4 hours after every change in the infusion rate.
- Adjust the UFH infusion to maintain aPTT values of 60-85 seconds as shown in the following nomogram.

APTT [s]	Anti-factor Xa [units/mL]	Bolus [units/ml]	Hold [minutes]	Rate change [units/kg/hr]	Repeat aPTT
less than 50	less than 0.1	50	0	increase by 20%	4 hours
50-59	0.1-0.34	0	0	increase by 10%	4 hours
60-85	0.35-0.70	0	0	no change	24 hours
76-95	0.71-0.89	0	0	decrease by 10%	4 hours
96-120	0.90-1.20	0	30	decrease by 10%	4 hours
greater than 120	greater than 1.20	0	60	decrease by 15%	4 hours

- Obtain blood for aPTT 4 hours after administration of the heparin loading dose and 4 hours after every change in the infusion rate.
- Obtain anti-factor Xa level within 48 hours of initiating UFH therapy. If anti-factor Xa level and aPTT do not correspond [see above nomogram], adjust UFH to maintain anti-factor Xa levels between 0.35-0.7 units/ml.
- Low molecular weight heparin [LMWH] may be used instead of UFH.
- The rate changes suggested above are to be calculated as a fraction of the total infusion [units/kg/hour] and not the number of ml/hr at which the IV is infusing.
- There should be a dedicated IV for UFH administration. This IV must not be stopped or interrupted for the infusion of other medications as the therapeutic level of heparin will fall acutely.

Intravenous UFH dosing [prophylactic]:

- Bolus dose is not required.
- Neonates, infants and children:
  - 10 units/kg/hour by continuous infusion

Subcutaneous UFH dosing [therapeutic or prophylactic]:

- UFH can be administered twice daily [q12h] as a subcutaneous injection.
- The total dose is calculated based on the usual requirement per kg per hour per day.
- Multiply the dose of UFH per hour by 24 hours, and then divide the dose by 2 to obtain the dose to administer q12h.

- The dose is adjusted based on the aPTT obtained 6 hours after the morning dose.
- The target mid-interval aPTT value [6 hours post dose] is the same as for IV UFH and the nomograms for IV UFH changes can be used [but, no bolus dose].

Bridge therapeutic subcutaneous UFH:

- UFH may be administered subcutaneous as a bridge anticoagulant in patients receiving either LMWH or warfarin therapy prior to an anticipated interruption of therapy [e.g. interventional procedure, surgery].
- For patients receiving LMWH, the usual evening dose of enoxaparin and daily dose of tinzaparin can be replaced by subcutaneous UFH (Give the UFH dose the evening prior to the procedure) .
- For patients receiving warfarin, the warfarin should be stopped 3 days prior to the interventional procedure or surgery and subcutaneous UFH administered the day prior to surgery [i.e. following the omission of 2 previous doses of warfarin with the subcutaneous UFH dose calculated as above].

Monitoring of therapy:

- For most children, UFH is monitored with aPTT.
- Anti-factor Xa levels should be used to monitor UFH in:
  - children less than 12 months of age
  - children whose aPTT and anti-factor Xa levels do not correlate
  - pregnant women
  - patients with Lupus erythematosus
- Once a therapeutic aPTT is achieved, obtain daily aPTT. The coagulation laboratory should receive the sample to be tested before noon. Obtain a CBC twice weekly.
- Anti-factor Xa levels should be measured at the same time as an aPTT during the first 48 hours of therapy to ensure the aPTT is reflecting the child's heparin concentration. If there is no correlation between the anti-factor Xa level and the aPTT, the anti-factor Xa level should be used to monitor UFH therapy. Anti-factor Xa levels for UFH should be between 0.35-0.7 units/ml.
- Once the anti-factor Xa level and the aPTT are known, the aPTT can often be used to monitor therapy, especially during the night.
- If the infusion of UFH during the maintenance phase is interrupted for greater than one hour, re-establish the UFH maintenance infusion as the previous rate. Obtain an aPTT 4 hours later. Once the aPTT result is available, adjust the infusion rate as indicated above.
- Measure the platelet count twice weekly. If the platelet count drops by 50%, determine if the decrease in platelet count is likely related to the underlying

disease or is potentially secondary to the UFH therapy. A red top tube and a blue top tube should be sent to the lab for a HIT [heparin induced thrombocytopenia] screen. The risk of HIT is very low in children. In adults, HIT usually occurs after at least 5 days of treatment unless there has been a previous exposure to heparin.

- Where possible, avoid intramuscular injections and arterial punctures during UFH or LMWH therapy. If needed, hold the injection/puncture area for an extended period of time.
- For DVT in children, UFH [or LMWH] is usually administered for a minimum of 5-7 days. Maintenance warfarin therapy can be started on day 1 or 2 of UFH therapy.
- If the DVT is extensive or the child has a massive pulmonary embolus, administer UFH [or LMWH] for 7-14 days and delay warfarin therapy until approximately day 5. Neonates may be treated for 10-14 days without warfarin. This decision should be individualized.
- Avoid aspirin or other anti-platelet drugs if possible during UFH or LMWH therapy. If analgesia is required, acetaminophen is preferred.

Conversion of UFH to LMWH:

- Administer the dose of subcutaneous LMWH at the same time as discontinuing the UFH infusion.
- Measure an ant-factor Xa assay 4 hours after 2nd dose of LMWH and adjust dose of LMWH according to nomogram.

Heparin 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 the UFH. If an immediate effect is required, consider administering protamine sulfate.
- Protamine sulfate inactivates UFH by neutralizing its positive charge.
- Following IV administration of protamine sulfate, neutralization of UFH occurs within 5 minutes.
- The dose of protamine sulfate required to neutralize UFH is based on the amount of UFH received in the previous two hours as follows:

Time since end of IV heparin infusion (min)	Dose of protamine (mg) to neutralize 100 units of heparin*
less than 30	1
30-60	0.5-0.75
61-120	0.375-0.5
greater than 120	0.25-0.375

***Heparin received within previous 2 hours.**

- The maximum dose of protamine sulfate, regardless of the amount of UFH received is 50 mg except for reversal of UFH following cardiopulmonary bypass.
- Protamine sulfate is usually administered in a concentration of 10 mg/ml at a rate not to exceed 5 mg/minute. If administered too quickly, protamine sulfate may cause cardiovascular collapse. Patients with known hypersensitivty to fish or those who have received protamine-containing insulin or previous protamine sulfate therapy may be at risk of hypersensitivity reactions. Do not administer intramuscularly.
- Obtain blood for aPTT and/or anti-factor Xa level and PT/INR 15 minutes after the administration of protamine sulfate.

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Procotcol for low molecular weight heparin [LMWH] therapy with enoxaparin and tinzaparin

The following are guidelines for initiating and monitoring low molecular weight heparin. Modifications for individual clinical circumstances may be necessary. These dosage guidelines apply to enoxaparin and tinzaparin only. They cannot be directly extrapolated to other LMWHs. Consultation from the Pediatric Hematology/Oncology Service should be obtained prior to initiating anticoagulation treatment in children.

Unfractionated heparin (UFH) and LMWH prevent extension of established clots but do not dissolve an established thrombus. Rather, the patient's own thrombolytic enzymes help to break down the clot.

Indications:

The use of LMWHs should be considered for most patients requiring therapeutic or prophylactic anticoagulation.

Low molecular weight heparin doses:

- Prior to initiating LMWH, obtain baseline bloodwork [CBC, PT/INR, aPTT and creatinine] and patient's weight. If applicable, do a pro-thrombotic work-up.

Age-dependent dose of enoxaparin, mg/kg q12h
(enoxaparin has 110 anti-factor U/mg)

Pediatric dose*	Age less than 2 months**	Age 2 months-18 years
Initial treatment dose	1.75 mg/kg/dose q12h	1 mg/kg/dose q12h
Prophylactic dose	0.75 mg/kg/dose q12h or 1.5 mg/kg/dose q24h	0.5 mg/kg/dose q12h or 1 mg/kg/dose q24h

***pre-term infants [less than 37 weeks gestation] require up to 2 mg/kg/dose q12h mg/kg;**
**** for neonates, use corrected age.**

- The use of higher doses per kg may be deemed necessary for some patients. This can only be done with the assistance of the Pediatric Hematology/Oncology Service.
- Tinzaparin 175 u/kg q24h for children 10 years and older.

- The appropriate dose for children less than 10 years has not been established.

<u>Nomogram for LMWH treatment [therapeutic dosing]</u>:

- Adjust the therapeutic dose of LMWH according to the following nomogram. Depending on the anti-factor Xa level achieved, the nomogram guides successive actions 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 next anti-Xa level
less than 0.35 units/ml	no	increase by 25%	4 hours post next am dose
	no	increase by 10%	4 hours post next am dose
0.5-1 units/ml **[therapeutic range]**	no	no change	One week later, then monthly while on LMWH (if anti-Xa level in therapeutic range) at 4 hours post am dose
1.1-1.5 units/ml	no	decrease by 20%	4 hours post next am dose
1.6-2 units/ml	Hold for 3 hours	decrease by 30%	trough level before next dose and 4 hours post next dose (base subsequent dose change on the 4 hour level NOT on the trough level)
greater than 2 units/ml	Yes, until anti-Xa is less than or equal to 0.5 units/ml	decrease by 40%	Trough level before next dose and if not less than 0.5 units/ml, repeat before each dose is due

The above nomogram assumes that the patient is not bleeding.
* For doses of Enoxaparin less than 10 mg and for Tinzaparin less than 1,000 units; increase or decrease dose by 1mg or 100 units respectively.

<u>Monitoring of LMWH</u>:

- All blood from patients should be drawn by fresh venipuncture. There must be no contamination from UFH [e.g. from an arterial or central venous line].

- A blood sample should be drawn 4 hours after the subcutaneous administration of LMWH. If therapeutic, a monthly and before discharge check on anti-factor Xa level is sufficient while in hospital.
- After discharge, monthly levels are sufficient unless patient has renal insufficiency.
- The anti-factor Xa level for therapeutic heparinization is 0.5-1 units/ml. In certain situations, patients may require anti-factor Xa levels greater than 1 unit/ml.
- For patients on long term LMWH therapy [greater than 3 months], consider bone denistometry studies at baseline and then every 12 months to assess for possible osteoporosis.
- LMWH is excreted renally. If renal function changes, creatinine levels should be checked along with anti-factor Xa levels.
- For adult patients, monitoring of anti-factor Xa levels is not required except for patients with renal insufficiency, obesity, very low body weight or pregnancy.

Ongoing follow-up:

- It is recommended that Aspirin or other anti-platelet drugs be avoided during LMWH. If analgesia is required, it is preferable to use acetaminophen or opioids.
- In general, avoid IM injections and arterial punctures during anticoagulation.
- Measure platelet counts regularly. If the platelet count drops greater than 50% from baseline, determine if the decreased count is likely related to an underlying disorder or is potentially secondary to the heparin therapy. Send a HIT screen to determine if heparin-induced thrombocytopenia [HIT] is present.
- The duration of LMWH therapy is dependent on the primary problem. For Deep vein thrombosis [DVT] in children, LMWH is usually administered for a minimum of 5 to 7 days. Warfarin can be instituted on day 1 or 2 of LMWH. If the DVT is extensive or massive pulmonary embolus [PE] is present, administer LMWH for 7-14 days and begin warfarin therapy on day 5. Newborns may be treated for 10-14 days without warfarin. LMWH can also be used for 3 months for treatment of DVT instead of warfarin.

Conversion of enoxaparin to unfractionated heparin [UFH]:

- UFH should not be initiated until at least 8 hours after a dose of subcutaneous LMWH.
- If UFH is started 8-12 hours after subcutaneous LMWH, do not administer a bolus dose of UFH.

- If UFH is started greater than12 hours after subcutaneous LMWH, initiate with either an IV bolus followed by an IV drip or as a subcutaneous q12h dose [see unfractionated heparin guidelines].
- Measure aPTT 6-8 hours after starting UFH, and then follow the guidelines for UFH.

Antidote for LMWH:

- If anticoagulation with LMWH needs to be discontinued for clinical reasons, termination will usually suffice. If immediate reversal is required, protamine sulfate reverses most, but not all, of the anti-factor Xa activity. Equimolar concentrations of protamine sulfate neutralize the anti-factor IIa activity, but results in only partial neutralization of the anti-factor Xa activity. However, studies in experimental animal models indicate that increased microvascular bleeding produced by very high concentrations of LMWH is neutralized by protamine sulfate.
- The dose of protamine sulfate is dependent on the dose of LMWH used and the time of administration. If protamine is given within 3-4 hours of the LMWH, then a maximum neutralizing dose is 1 mg of protamine per 100 units or 1 mg of LMWH given in the last dose (maximum dose 50 mg).
- **Do not administer protamine sulfate intramuscularly; use an infusion pump.**
- Administer protamine sulfate in a concentration of 10 mg/ml at a rate not to exceed 5 mg/minute. If administered too quickly, protamine sulfate may cause cardiovascular collapse. Patients with known hypersensitivity reactions to fish, those who have received protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions. Obtain blood for anti-factor Xa level 15 minutes after administration of protamine sulfate.
- If the measured anti-factor Xa level is greater than 5 units/ml, consider a continuous infusion of protamine sulfate at 0.02 mg/kg/hr and continue to measure anti-factor Xa levels while the infusion is running.

Spinal tap/lumbar puncture (LP):

- LMWH should be delayed until 8-12 hours after insertion of spinal needle.
- Insertion of a spinal needle should be delayed until 10-12 hours after a dose of LMWH.
- For twice daily, LMWH must omit 2 doses prior to LP (i.e. the night before and morning of procedure).
- For once daily dosing, omit the day of procedure (this is based on giving the LMWH in the am).

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Guidelines for warfarin therapy

The following are guidelines for initiating and monitoring warfarin therapy. Modifications for individual circumstances may be necessary. Consultation with the Pediatric Hematology/Oncology Service should be obtained.

It is suggested that warfarin not be used for infants less than 12 months of age [other than for mechanical valves] because of the potential development of osteopenia, difficulty reaching a target INR, variable sensitivity to warfarin related to inconsistent intake and the challenge of administering oral medications.

Guidelines:

- Obtain a baseline PT/aPTT/INR as well as LFT, CBC prior to initiating therapy.
- Steady state warfarin levels are achieved usually in 3-5 days.
- Start warfarin on day 1 or 2 of heparin therapy. UFH or LMWH should be continued for a minimum of 5 days. However, if treating an extensive DVT with or without pulmonary embolus, start warfarin on day 5 of UFH or LMWH therapy and continue UFH or LMWH until a therapeutic INR is achieved for 2 days.
- If the patient is receiving TPN, discontinue vitamin K supplementation in the TPN.
- If the child is receiving formula, consider changing the child's formula to one with the lowest vitamin K concentration. If the child is exclusively breastfed, consider supplementation with a small amount of standard formula per day for a constant intake of vitamin K. The required daily amount of vitamin K is 1 microgram/kg/day, equivalent to about 120 ml of standard formula daily.
- Aim for an INR between 2 and 3 for most patients. Children with mechanical valves require an INR between 2.5 and 3.5.
- When an INR is greater than 2 for 2 consecutive days, heparin may be discontinued. Usually the INR decreases by a small percentage the following day due to discontinuation of the heparin.
- Heparin and the presence of a lupus anticoagulant may spuriously prolong the INR obtained by some reagent-instrument combinations.
- In general, warfarin should be avoided in infants less than 12 months of age except for infants with mechanical valves.
- Discuss risks and benefits of and cautions for warfarin with the child/parents (Appendix 1).

Recommended range for oral anti-coagulation therapy

Indication		Target INR (Range)
Deep venous thrombosis/PE		2.5 (2-3)
Fontan		2.5 (2-3)
Tissue heart valve		(2-3)
Rheumatic heart valve		(2-3)
Atrial fibrillation		(2-3)
High-risk surgery		(2-3)
Homozygous protein C or protein S deficiency		3.5 (3-4)
Mechanical prosthetic valve	Aorta	(2-3)
	Mitral	2.5-3.5

Contraindications for warfarin treatment:

Absolute:
- presence of a severe or active bleeding diathesis
- non-compliance
- first trimester pregnancy

Relative:
- warfarin allergy or intolerance [acute rash, hepatitis, diarrhea, nausea]
- hemorrhage [withhold for 4-6 weeks following non-CNS bleeds; longer for CNS bleeds]
- active peptic ulcer disease
- known coagulation defects
- thrombocytopenia [platelets less than 50,000] or platelet dysfunction
- recent hemorrhagic stroke
- uncontrolled hypertension
- excessive alcohol intake
- daily use of NSAIDs
- planned invasive procedure or major surgery [especially involving the nervous system, spine or eye]
- second and third trimester of pregnancy
- severe liver disease

Therapeutic warfarin- initial dosing, day 1:

The usual initial dose is 0.2 mg/kg orally as a single daily dose, with a maximum of 5 mg. Infants may require an average of 0.33 mg/kg, whereas teenagers may require as little as 0.09 mg/kg to maintain an INR of 2-3. Reduce the dose to 0.1 mg/kg for patients with liver dysfunction or in children having undergone a Fontan procedure or severe renal dysfunction [e.g. receiving hemodialysis].

Patients should take their warfarin once a day, preferably at the same time every day. The INR testing should be performed at the same time of day each time it is measured and preferably about 16 hours following the last dose.

Therapeutic warfarin- initial dosing, day 2-4:

- Monitor PT/INR daily until INR in target range for 2 consecutive values.
- The subsequent loading doses are based on the INR response as follows. The dose reductions indicated below are critical to avoid "overshooting" the target range.
- If the INR is not greater than 1.5 on day 4, the patient should be reassessed and the dose per kg increased based on the individual clinical need.

INR	Warfarin adjustment – initial loading days 2-4
1.1 – 1.3	repeat initial dose x 1, if INR remains less than 1.2, then increase dose by 20% and continue as per nomogram
1.4 – 1.9	50% of initial dose
2 - 3	50% of initial dose
3.1 - 3.5	25% of initial dose
greater than 3.5	Hold until INR less than 2.5, and then restart at 50% less than the previous dose. See guidelines for over-anticoagulation

Long-term therapeutic warfarin maintenance dosing:

These guidelines apply primarily to medically stable patients already established on long-term maintenance therapy. Medically unstable patients or those completing 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.

Fluctuations of INR beyond the patient's target range should always be investigated and corrected where possible. Consider causes such as change in dose of warfarin, patient adherence, medication profile, diet or intercurrent illness.

See Appendix 2 for a list of foods with high vitamin K content. See Appendix 3 for a list of medications commonly used in pediatrics that influence warfarin

dosing. See Appendix 4 for a list of over the counter medications & herbals of concern for hematology patients.

Warfarin Dosing Nomogram: Maintenance Phase for Target INR 2-3 and 2.5-3.5

Warfarin Maintenance Doses for Long-Term Therapy INR Target 2 – 3		**Warfarin Maintenance Doses for Long-Term Therapy INR Target 2.5 – 3.5**	
INR	**Warfarin Adjustment**	**INR**	**Warfarin Adjustment**
1.1 – 1.4	Increase dose by 20%	1.1 – 1.9	Increase dose by 20%
1.5 – 1.7	Increase dose by 10%		
1.8 – 3.2	No Change	2 – 2.2	Increase dose by 10%
3.3 – 3.5	Decrease dose by 10%	2.3 – 3.7	No Change
3.6 – 4	Decrease does by 50% x 1 then decrease dose by 20% of maintenance	3.8 – 4	Decrease dose by 50% x 1 then decrease dose by 20% of maintenance
4.1 - 5	Hold x 1 dose then decrease dose by 20%	greater than 4	Contact Hematologist
greater than 5	Contact Hematologist		
Dose adjustments will be rounded to the nearest 0.25 mg			

This nomogram is intended for use once loading phase completed. Prior to each dose adjustment assess patient for medication change, illness (cold-flu), and adherence.

- Changes in warfarin dosage may take several days to affect INR. Hence frequent dose adjustment is not recommended.
- Adjustments may need to be modified in the presence of intercurrent illness.
- A 15% dose adjustment is expected to result in a change in INR of approximately 1.

<u>Prophylaxis with warfarin INR 1.4-1.9</u>:

- Nomogram for target INR values between 1.4-1.9. Warfarin can be administered prophylactically with a lower target range of 1.4-1.9. in this situation, an initial loading dose of 0.1 mg/kg is given on day 1. The following nomograms can be used to adjust both the loading and

maintenance doses. An INR value should be measured at approximately the end of the first week of therapy to ensure INR is not greater than 1.5.
- No routine monitoring of INR is required.

Very low dose prophylaxis with warfarin:

Warfarin can be administered prophylactically at a fixed dose of 1 mg per day in children who are greater than 12 years of age and approximately 50 kg or greater if these children are at high risk of thrombosis but who do not require therapeutic doses of anticoagulants. An INR value should be measured at approximately the end of the first week of therapy to ensure INR is not greater than 1.5.

Warfarin prophylaxis for air flights:

Children who are greater than 12 years of age and 50 kg or greater and at risk of thrombosis during a long air flight may receive warfarin in a dose of 1 mg orally for 3 days prior to the flight. No monitoring of INR is required.

Outpatient follow-up:

When the INR is greater than 2 for 2 consecutive days, the patient can be discharged. Alternatively, if the INR is close to 2, the patient may be discharged on therapeutic subcutaneous UFH or LMWH along with warfarin and the patient's warfarin dose can be adjusted according to the INR as an outpatient. The Pediatric Hematology/Oncology Service will follow all outpatients.

- Monitor the INR within 3 days of discharge from hospital if the patient is discharged with an INR of 2 or as per the Pediatric Hematology/Oncology Service, if the INR is sub-therapeutic on discharge.
- Always draw an INR 5 to 7 days after initiating a new dose. Use the maintenance guidelines for adjusting doses.
- Once the patient has 2 INRs between 2-3 [or 2.5-3.5 for mechanical valves] taken 7 days apart, the interval for checking the INR can be extended to 2 weeks. If continues to be stable, the interval can be extended to 3, then 4 weeks.
- The INR should be monitored minimally 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 on the underlying problem. Children with mechanical valves or repeated thrombotic events will receive warfarin indefinitely. Children with a thrombotic event and a persistent, significant underlying pre-disposing factor may be switched to low dose warfarin following 3 months of treatment with full dose warfarin, until

the pre-disposing factor is no longer present. Children with uncomplicated DVT will receive warfarin for 3 months only.
- Warfarin is teratogenic in early pregnancy and reliable birth control is recommended. If therapeutic amounts of warfarin are being used, oral contraceptives are permissible.

Complications of warfarin therapy:

- bleeding
- skin necrosis- day 3-8 of initiating therapy
- purple toe syndrome- week 3-10 after initiating therapy
- alopecia, osteoporosis, g.i. discomfort, rash

Conditions associated with *decreased* PT/INR response include:

- edema
- hereditary warfarin resistance
- hyperlipemia
- hypothyroidism

Conditions associated with *increased* PT/INR response include:

- cancer
- collagen disease
- congestive heart failure
- diarrhea
- elevated temperature
- hepatic disorder
- hyperthyroidism
- poor nutritional state
- steatorrhea
- vitamin K deficiency

See Appendix 2 for a list of foods with high vitamin K content.

See Appendix 3 for a list of medications commonly used in pediatrics that influence warfarin dosing.

See Appendix 4 for a list of over the counter medications & herbals of concern for hematology patients.

Guidelines for over-anticoagulation with warfarin

Antidote for warfarin:

Vitamin K is the antidote for warfarin. The dose to be administered and need for concurrent plasma or prothrombin concentrates [containing factors II, VII, IX and X] are dependent on the clinical condition. The following are guidelines only.

No bleeding:

- In event that rapid reversal of warfarin is necessary and the patient will require warfarin again in the near future, administer vitmain K, 0.5 to 2 mg subcutaneously [however, absorption unpredictable] or PO depending on patient's size. Do not give IM.
- In the event that rapid reversal of warfarin is necessary and the patient will not require warfarin again, administer vitamin K 2-5 mg subcutaneously or PO and consider giving prothrombin concentrate at a dose of 50 units/kg IV or factor VIIa IV [requires consult with Pediatric Hematology/Oncology Service].

INR less than 5:

- omit 1 dose of warfarin
- increase frequency of INR monitoring (2 to 3 times a week)
- resume therapy at 10-20% lower dose

INR 5-9:

- omit 1-2 doses of warfarin
- increase frequency of INR monitoring [daily]
- resume therapy at 10-20% lower dose when INR reaches patient's target range
- if the patient is at high risk of serious bleeding, consider administering vitamin K (2-3 mg orally)

INR greater than 9:

- hold warfarin
- consider giving vitamin K, 3-5 mg orally
- increase frequency of INR monitoring to daily and give additional vitamin K if INR is not substantially reduced by 24-48 hours
- resume therapy at 20% lower dose when INR reaches patient's target range and monitor INR closely until stable
- consider more frequent routine INR monitoring

Bleeding present:

- Discontinue warfarin
- Attempt local control of bleeding
- If significant but not life-threatening bleeding: give vitamin K 0.5–2 mg orally plus frozen plasma (20 mL/kg IV).
- If significant and life-threatening bleeding: Consult hematology and administer vitamin K 5 mg by very slow IV infusion [rate less than 1 mg/min] plus frozen plasma (20 mL/kg IV). Consider giving prothrombin concentrate, Octaplex (50 units/kg with a maximum dose per episode of 1000 IU Factor IX activity) or recombinant factor VIIa (requires consult with pediatric hematology/oncology service).
- Monitor INR q6h and treat with repeat dosing of vitamin K and/or plasma/ concentrate as needed.

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Guidelines for elective reversal of warfarin therapy

The following are guidelines for elective reversal of warfarin therapy. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Anesthesia considerations for patients on warfarin:

- local and general anesthetics can be safely administered to patients on warfarin
- avoid intramuscular drugs
- neuroaxial blocks, e.g. epidural analgesia and spinal anesthesia, should not be performed on patients on warfarin
- if central venous access is needed, a compressible site is preferred
- nasogastric tubes should be avoided

Low dose warfarin [INR 1.4-1.9]:

- if the INR is less than or equal to 1.5, no reversal is necessary for most surgeries
- the exceptions include high risk surgeries, [e.g. eye surgery, neurosurgery] where complete warfarin reversal is necessary
- hold the warfarin 72 hours prior to procedure

Full-dose warfarin:

Patients at risk of significant hemorrhage at the time of surgery include:

- major surgery or surgery in which a body cavity is entered
- percutaneous needle procedures in non-compressible sites, including organ biopsies
- any type of prosthetic surgery
- central nervous system and eye surgery

Low risk procedures include:

- percutaneous needle procedures in readily compressible sites
- most skin procedures
- routine dental procedures

Patients at high risk of thrombosis include:

- prosthetic mitral valve, old model aortic valve prosthesis
- atrial fibrillation with either a history of stroke or additional risk factors
- DVT/PE within the past 3 months
- hypercoagulable state with recent thrombotic episode, recurrent thrombosis or history of life-threatening thrombosis

Surgery to be done within less than 24 hours:

- discontinue warfarin and administer intravenous vitamin K or frozenplasma
- monitor INR closely

Surgery to be done in 24-96 hours:

- discontinue warfarin, administer vitamin K (2-3 mg) orally
- monitor INR q8-24 hours

Surgery to be done in greater than 96 hours:

- For patients where the risk of thrombosis is high in the absence of anticoagulant therapy [e.g. mechanical valves], after discussion with surgeon:

  - discontinue the warfarin 5 days prior to surgery
  - ensure no inadvertent/ongoing use of aspirin
  - if indicated, start therapeutic dose of UFH or LMWH 48 hours after discontinuing warfarin or the same day warfarin is held
  - check INR the day before procedure to ensure it adequately falls into near normal range [less than or equal to 1.5]
  - timing of the UFH infusion or last dose of LMWH dose will depend on the type and amount of specific agent and procedure-specific antithrombotic requirements
  - if the INR is greater than 1.5 within 12 hours before surgery, administer low dose vitamin K [1 mg PO/SubQ] and recheck the INR approximately 6 hours later or the morning of surgery
  - Discontinue IV UFH 4 hours prior to surgery. Send a stat PT/INR and aPTT 3 hours prior to surgery. Pre-op PT/INR, aPTT should be within normal limits.
  - in consultation with surgery, resume IV UFH 12 hours post-op at the pre-surgery rate or start SC UFH or SC LMWH. UFH or LMWH should be therapeutic

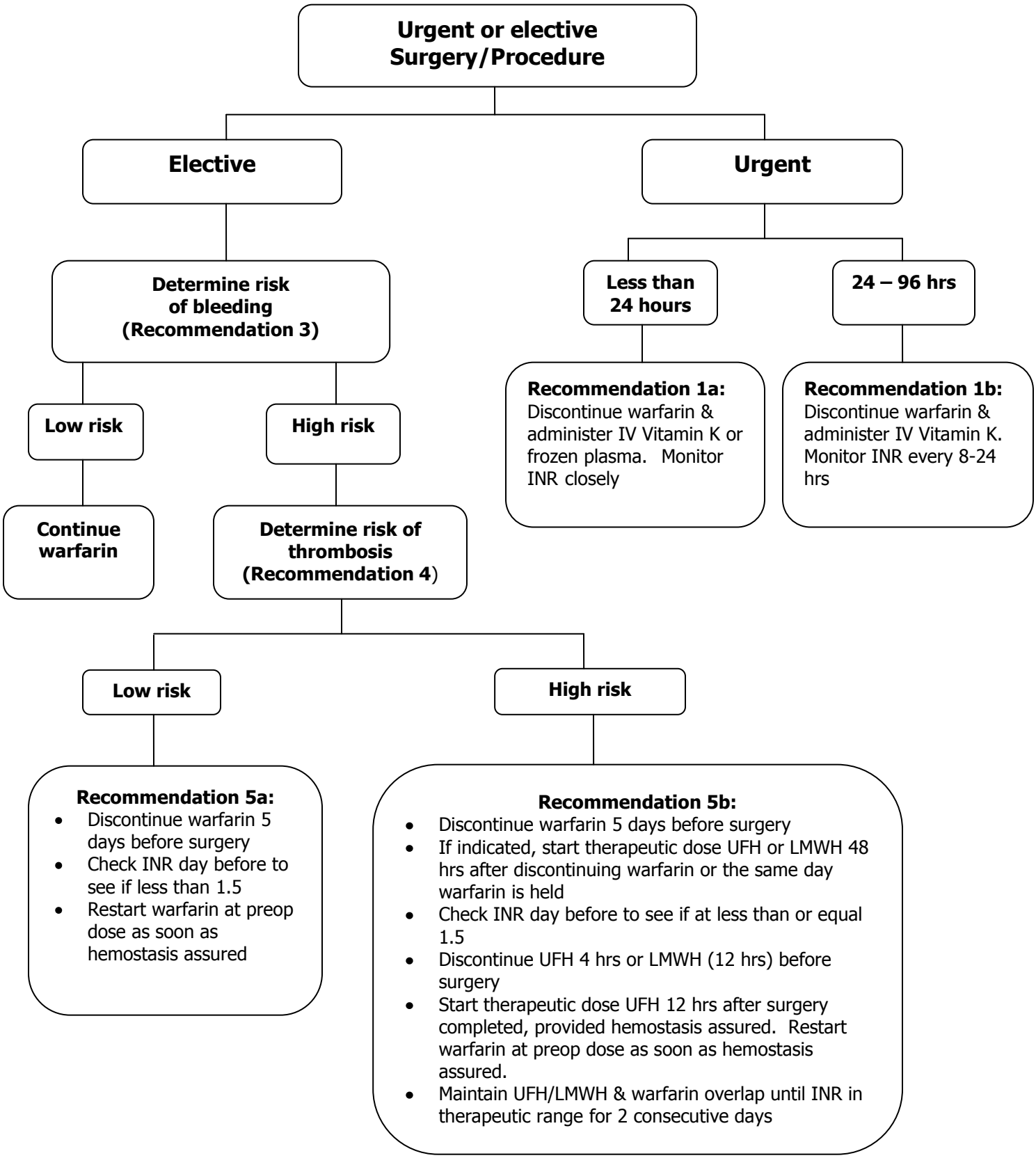
- if the patient develops any signs of bleeding, discontinue UFH or LMWH immediately
- restart warfarin at pre-op dose as soon as hemostasis assured
- maintain UFH/LMWH and warfarin overlap until the INR is in therapeutic range for 2 consecutive days
- in consultation with surgery, oral warfarin may be resumed post-operatively on the evening following surgery
- discontinue UFH or LMWH when warfarin reaches the therapeutic range with the INR between 2-3 or for mechanical valves between 2.5-3.5

- For patients where the risk of thrombosis is low in the absence of anticoagulant therapy [e.g. thrombotic event occurred several weeks ago and anticoagulant therapy has been ongoing], after consultation with surgeon:

  - discontinue the warfarin 5 days prior to surgery because the anticoagulant effects of warfarin will persist for 2-3 days
  - ensure no inadvertent/ongoing use of aspirin
  - Admit the patient on the day of [or evening before] surgery, as would be the usual practice. Measure the aPTT/INR on admission to obtain the results prior to surgery.
  - Measure INR the day prior to surgery to ensure it is in near normal range [usually less than or equal to 1.5]. If greater than 1.5, discuss with surgeon and pediatric hematologist/oncologist.
  - restart warfarin at pre-op dose as soon as hemostasis assured or at the end of procedure-related anticoagulation

Bridging anticoagulation for invasive procedure and need for anticoagulation peri-operatively

Days @ procedure	Warfarin	INR	LMWH or UFH
5 days prior	Last dose of warfarin if regular target INR @3	Check if not done within 1 week prior	Start once INR below target level
4 days prior	Last dose of warfarin if regular target INR @2.5	Check if not done within 1 week prior	Start once INR below target level
3 days prior	None	None	AM and PM dose
2 days prior	None	None	AM and PM dose
1 day prior	None	Check INR [aim 1-1.5]; oral vitamin K if INR greater than 1.5	AM dose only- stop at least 18 hours before procedure
Procedure	Resume at regular dose (evening after surgery)	As indicated by surgeon	Start at least 12 hours post procedure
1 day post	Regular dose	Daily as needed	Restart if/when hemostasis achieved
2 days post	Regular dose	Daily as needed	Continue until INR greater than minimally acceptable level x 1 day
3 days post	Regular dose	Daily as needed	Continue until INR greater than minimally acceptable level x 1 day


Urgent or elective Surgery/Procedure
Elective
Urgent
Determine risk of bleeding (Recommendation 3)
Less than 24 hours
24 – 96 hrs
Low risk
High risk
Recommendation 1a: Discontinue warfarin & administer IV Vitamin K or frozen plasma. Monitor INR closely
Recommendation 1b: Discontinue warfarin & administer IV Vitamin K. Monitor INR every 8-24 hrs
Continue warfarin
Determine risk of thrombosis (Recommendation 4)
Low risk
High risk
Recommendation 5a:
• Discontinue warfarin 5 days before surgery
• Check INR day before to see if less than 1.5
• Restart warfarin at preop dose as soon as hemostasis assured
Recommendation 5b:
• Discontinue warfarin 5 days before surgery
• If indicated, start therapeutic dose UFH or LMWH 48 hrs after discontinuing warfarin or the same day warfarin is held
• Check INR day before to see if at less than or equal 1.5
• Discontinue UFH 4 hrs or LMWH (12 hrs) before surgery
• Start therapeutic dose UFH 12 hrs after surgery completed, provided hemostasis assured. Restart warfarin at preop dose as soon as hemostasis assured.
• Maintain UFH/LMWH & warfarin overlap until INR in therapeutic range for 2 consecutive days

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Guidelines for systemic thrombolytic therapy

The following guidelines are for initiating and monitoring systemic thrombolytic therapy. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Initial evaluation:

- The initial evaluation will vary depending on the location and vessel involved. For deep venous thrombosis [DVT] please see the protocol for DVT.
- Consult the Pediatric Hematology/Oncology Service.

Indications:

- Systemic thrombolytic therapy is indicated for arterial occlusion, massive pulmonary embolism, pulmonary embolism not responding to heparin therapy and threat of organ and limb viability. Thrombolytic therapy may also be indicated for acute, extensive deep vein thrombosis.
- In neonates less than 6 months of age with arterial occlusion following cardiac catheterization, thrombolytic therapy must be used with caution. Begin with UFH as per protocol and, in general, assess the limb for a minimum of 24 hours before considering thrombolytic therapy. If avulsion or dissection is diagnosed, consult cardiovascular/plastic surgery immediately.

Contraindications:

- active bleeding
- significant potential for local bleeding [e.g. tumor surrounding the vessel containing the clot]
- general surgery within the previous 10 days
- neurosurgery within the previous 3 weeks
- hypertension
- arteriovenous malformations and recent severe trauma
- in some patients, the need for thrombolytic therapy necessitates treatment despite the contraindications

Precautions:

- do not administer intramuscular injections during therapy
- there should be minimal manipulation of the patient during thrombolytic therapy [e.g. no bathing, physiotherapy]
- avoid concurrent use of warfarin or antiplatelet agents

- do not perform urinary catheterization, rectal temperatures or arterial punctures during thrombolytic therapy
- Blood sampling must be taken from a superficial vein or indwelling catheter. If blood sampling is difficult due to poor venous access, insert an indwelling catheter for blood sampling prior to thrombolytic therapy.

Thrombolytic therapy:

- tissue thromboplastin activator [tPA]:
  1. Children less than 1 year give fresh frozen plasma (10 mg/kg) 30 minutes before tPA infusion to ensure adequate plasminogen and fibrinogen.
  2. Give a UFH infusion at 10 units/kg/hr during tPA infusion. Commence as soon as possible aiming for a number of hours of UFH prior to tPA. If the patient is already receiving therapeutic UFH, reduce the infusion to 10 units/kg/hr 30 minutes prior to starting the tPA infusion.
  3. Give tPA as an infusion at a rate of 0.5 mg/kg/hr intravenously for 6 hours.
  4. Re-evaluate the patient radiographically following 6 hours of tPA infusion [for arterial thrombi, use the return of pulses and blood pressure to pre-thrombus values]. If no response, administer frozen plasma 20 ml/kg IV q8h.
  5. A repeat infusion of tPA can be considered 12-24 hours after completing the initial course.
- streptokinase is not recommended for children

Monitoring:

- alert bloodbank that patient in on thrombolytic therapy to ensure cryoprecipitate is available
- monitor the response to thrombolytic therapy by the PT/INR, aPTT and fibrinogen level 4 hours following the onset of the infusion and every 6-8 hours thereafter
- 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 cyroprecipitate [1 bag/5 kg] OR if major bleeding occurs
- if the fibrinogen concentration is less than 1 g/L and the patient is still receiving an infusion of tPA, decrease the dose of the thrombolytic agent by 25%
- if there is no change in the fibrinogen concentration, check D-Dimer level to ensure that a thrombolytic state has been achieved
- maintain a platelet count greater than 100 x 10^9/L
- If a patient has received tPA therapy for more than 6 hours, consider treating with UFH alone for 24 hours before re-instituting tPA therapy. There may be

ongoing thrombolysis even in the absence of continued administration of tPA therapy.

Heparin therapy:

- concurrent UFH therapy is recommended for all thrombolytic agents
- Do not administer a bolus of UFH. Administer 10 units/kg/hr UFH
- do not adjust the UFH infusion to therapeutic levels during the tPA infusion
- if UFH is discontinued during the tPA therapy, restart a UFH infusion when possible and the fibrinogen concentration is greater than1 g/L
- When the tPA infusion is stopped, the UFH therapy must continue, but do not give bolus dose. Adjust the UFH infusion to keep the aPTT in the therapeutic range

Complications of therapy:

- Bleeding may occur in 30-50% of patients and is usually in the form of oozing from a wound or puncture site. These forms of bleeding can be treated with local pressure and supportive care.
- If major bleeding occurs, stop the infusion of tPA and UFH. If the fibrinogen concentration is less than 1 g/L, administer cryoprecipitate [1 bag/5 kg] to increase the fibrinogen concentration to greater than 1 g/L.
- Administer other blood products as indicated.
- If life threatening bleeding occurs, stop the infusion of tPA and UFH. Infuse cyroprecipitate as above and reverse the thrombolytic process by infusing tranexamic acid (Cyklokapron) intravenously at 10 mg/kg (maximum of 1 gram) 2-3 times daily over 10 minutes OR 45 mg/kg over 24 hours continuous infusion (children 1 month to 18 years) until bleeding stops. Protamine sulfate may be required to reverse the UFH [see UFH guidelines]. Consideration may be given to the use of factor VIIa only on the advice of the Pediatric Hematology/Oncology Service.

References:

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Guidelines for management of pediatric patients with Deep Vein Thrombosis/Pulmonary Embolism (DVT/PE)

The following guidelines are for the management of children and adolescents with DVT or PE. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

General:

- Obtain detailed history and physical examination, including patient's weight, specific information on potential precipitating factors, pro-thrombotic risk factors, medication, recent illnesses and family history.
- Symptoms suggestive of pulmonary embolism include dyspnea, pleuritic chest pain, and tachypnea. Uncommon symptoms are cough, hemoptysis, fever, syncope, diaphoresis, apprehension, rales, wheezing, hypotension, tachycardia, cyanosis, pulmonary rub.

Tests:

Diagnostic:

- For a suspected DVT in the upper venous system, venography is required.
- For a suspected clot in the jugular veins, compression ultrasound should be used as venography is relatively insensitive for detection of DVT in these veins.
- For a suspected DVT in the lower proximal venous system, doppler/ultrasound may be sufficient. If negative, and suspicion high, perform a venogram.
- Ventilation/perfusion scan [V/Q] or CT scan for investigation of PE should be carried out in all children with cardio-respiratory abnormalities to determine if PE present. This may not be possible in young children.
- In addition, for children suspected to have a pulmonary embolus, a chest x-ray, arterial blood gas and ECG are indicated. For some children, a high speed, high resolution CT scan of the chest can replace a V/Q scan. Consultation with a radiologist is required.

Laboratory tests:

- measure baseline CBC, PT/INR, aPTT and consider prothrombotic work-up including antithrombin, protein C, protein S, APCR, factor V Leiden, prothombin 20210a, MTHFR, antiphospholipid antibodies, lupus anticoagulant and anticardiolipin antibody, lipoprotein A, homocysteine, plasminogen and reptilase time

- individual clinical situations will dictate the appropriate tests and timing of work-up

Initial therapy:

- initial therapy can be either UFH or LMWH for a minimum of 5 days and for longer periods [10-14 days] in the presence of an extensive DVT or PE
- the loading dose of UFH is 75 units/ kg IV over 10 minutes
- the initial maintenance dose of UFH is age related [see UFH guidelines]
- adjust the UFH infusion to maintain an aPTT of 60-85 seconds [see UFH guidelines]
- Perform an anti-factor Xa level for patients receiving UFH to ensure the aPTT correlates with the anti-factor Xa level. If the anti-factor Xa does not correlate with the aPTT, continue measuring anti-factor Xa levels to monitor UFH [see UFH guidelines].
- LMWH may be used instead of UFH. Initiate LMWH as per LMWH guidelines

Duration of therapy:

- either LMWH or warfarin can be used for the duration of therapy following the initial treatment with either UFH or LMWH
- for a DVT secondary to an acquired insult, 3 months of therapy is usually sufficient
- for a calf DVT secondary to an acquired insult, a 6-week course is usually sufficient
- for idiopathic DVT, at least 6 months of therapy should be considered
- For recurrent DVT, consider indefinite anticoagulation. After 3 months of anticoagulation therapy, follow-up of thrombosis recommendations.

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Guidelines for management of pediatric patients with inherited thrombophilia

The following guidelines are for the prophylaxis and treatment of children and adolescents with inherited predisposition to thrombosis. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Asymptomatic:

- all children and adolescents with a past history of venous thromboembolism [VTE], with or without evidence of a thrombophilic defect, should be considered for short-term prophylaxis to cover periods of increased thrombotic risk- for example, surgery, trauma, plaster casting, immobilization.
- affected asymptomatic relatives of children and adolescents with thrombophilic disorder, who have had a VTE should be considered for short-term prophylaxis to cover periods of increased risk

Following an episode of VTE:

- the initial approach is as for any patient with a DVT/PE [UFH or LMWH for a minimum of 5 days, with initiation of warfarin therapy as per the guidelines] and treatment for 6 months to achieve an INR target of 2.5 [2-3]
- a shorter period of treatment may be acceptable when the thrombus is confined to a distal vein [e.g. calf] and if there is evidence of a temporary risk factor that is no longer present
- if there is a persisting additional risk factor or a high-risk thrombophilia present [combined defects, reactive site antithrombin deficiency], consideration should be given to extending the usual period of anticoagulation
- with recurrent DVT/PE that occurred when the patient was not on anticoagulation therapy, reintroduce warfarin to attain a target INR of 2.5 [2-3]
- with recurrent DVT/PE that occurred while the patient was on anticoagulation therapy, increase warfarin to attain a target INR of 3.5 [3-4]
- in general, patients who have had two or more apparently spontaneous DVT/PE require consideration for indefinite anticoagulation

Specific treatments:

- recombinant protein C concentrate is available for the treatment of purpura fulminans [homozygous protein C deficiency]
- some children with protein C deficiency may require long-term prophylaxis with protein C concentrates

- antithrombin concentrate is available for patients with DVT/PE secondary to antithrombin deficiency
- patients with homocystinemia/homocystinuria may benefit from prophylaxis with folic acid and/or vitamin B6
- patients with protein S deficiency and thrombosis may benefit from prophylaxis with frozen plasma

Condition	Acute treatment	Chronic treatment
Homozygous protein C def	Protein C concentrate, frozen plasma + heparin	Warfarin + protein C concentrate - indefinitely
Homozygous protein S def	Frozen plasma + heparin	Warfarin + plasma - indefinitely
Double heterozygotes withThrombosis	Heparin → warfarin	Warfarin - indefinitely
Double heterozygotes without thrombosis	Prophylaxis for high risk	None
Heterozygote with Thrombosis	Heparin → warfarin	Warfarin for 6 months
Heterozygote without thrombosis	May require prophylaxis for high risk	None
Antiphospholipid syndrome	Heparin → warfarin	Warfarin

References:

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Management of Blocked Central Venous Access Devices

The following are guidelines for the management of blocked central venous catheters [CVAD] in pediatric hematology/oncology patients. These guidelines are meant to be complementary to and used with the guidelines for tPA [tissue plasminogen activator] and for instillation of hydrochloric acid (HCl) in the Nursing Pharmacy Policies & Objectives Manual. Modifications for individual clinical circumstances may be necessary.

A "blocked" catheter is a catheter that is difficult to flush, with sluggish or no blood return [partial occlusion] or completely occluded. [see Signs & Symptoms of Catheter-related Thrombosis, Nursing Pharmacy Policy 30.52].

All patients with clinical symptoms- such as head and neck swelling, respiratory distress, bluish color, collateral circulation- should be evaluated by objective tests such as venography, ultrasound and ventilation/perfusion lung scans as appropriate.

Indications:

The management guidelines below should be instituted in the following situations:

- for CVADs that are "blocked" and will not infuse properly
- for CVADs that require blood return as an essential function [e.g. hematology/oncology CVADs, hemodialysis CVADs] when that blood return is absent or difficult

Initial management (Chest X-ray to visualize line placement)

	Blood related blockage	Chemical related blockage*
Indications	- Unable to draw blood sample - Unable to infuse blood - Blood back-up in infusion line	- Infusion running through line suddenly occludes
Action	• Attempt to aspirate, try positional and/or Valsalva maneuvers • Flush with 0.9% NaCl; do not use syringe smaller than 10 ml • If able to flush line, but unable to get blood return, proceed to diagnostic work-up if clinically indicated • If unable to flush or obtain blood return, call CVAD RN/6N clinical educator to follow tPA guidelines • If still unable to flush line, contact surgery and CVAD RN [during weekday work hours]	• Attempt to aspirate, try positional and/or Valsalva maneuvers • Flush with 0.9% NaCl; do not use syringe smaller than 10 ml • Follow Hydrochloric acid (HCl) guidelines • If unsuccessful, call CVAD RN/6N clinical educator to follow tPA guidelines • If able to flush line, but unable to get blood return, proceed to diagnostic work-up if clinically indicated • If unable to flush or obtain blood return, call CVAD RN/6N clinical educator to follow tPA guidelines • If still unable to flush line, contact surgery and CVAD RN [during weekday work hours]

***consider occlusion secondary to lipid deposits - use 70% ethanol instillation**

TPA/Alteplase^{R} and HCl guidelines for local instillation

	Single lumen CVAD	Double lumen CVAD	SC port-a-cath
HCl [0.1N]	Instill a maximum of 2 ml for 2-4 hours before attempting to aspirate	Instill a maximum of 2 ml for 2-4 hours before attempting to aspirate	Instill a maximum of 3 ml for 2-4 hours before attempting to aspirate
TPA	less than 10 kg: consult Pediatric Hematology/ Oncology; use 0.5 mg tPA/ ml; instill a maximum of 2 mL	less than 10 kg: consult Pediatric Hematology/ Oncology; use 0.5 mg tPA/ ml; instill a maximum of 2 ml per lumen	less than 10 kg: consult Pediatric Hematology/ Oncology; use 0.5 mg tPA/ml; instill a maximum of 2 ml per lumen
	greater than 10 kg: use 2 mg tPA/ml; instill a maximum of 2 ml	greater than 10 kg: use 2 mg tPA/ml; instill a maximum of 2 ml per lumen	greater than 10 kg: use 2 mg tPA/ml; instill a maximum of 2 ml per lumen
	If unsuccessful in obtaining blood return, repeat above once in 24 hrs.	If unsuccessful in obtaining blood return, repeat above once in 24 hrs. **Normally, treat one lumen at a time.**	If unsuccessful in obtaining blood return, repeat above once in 24 hrs.

NOTE: after 2 hours instillation of each drug, withdraw drug. If possible, flush catheter with 0.9% NaCl and attempt to aspirate blood.

Diagnostic work-up:

Investigation of a blocked CVAD is necessary if the line fails to function properly after 2 doses of tPA or if it has blocked for a second time within several months, regardless of the number of tPA infusion or their effect. In certain situations, detailed investigations may be warranted even outside of these guidelines.

a. perform a lineogram to determine the following:

- location of CVAD tip
- potential occlusion at the tip of the CVAD
- presence of retrograde flow
- potential leak

A lineogram cannot rule out the presence of a large vessel clot.

b. venogram:

- if the venogram is normal and the CVAD is not functioning, a local occlusion may be present
- if the venogram is abnormal and a large vessel thrombus is seen, see guidelines for management of pediatric patients with deep vein thrombosis
- If a venogram cannot be easily obtained, perform a Doppler ultrasound evaluation of the large vessels near and including the CVAD. However, the sensitivity and specificity of this technique for detection of large vessel thrombus in the upper venous system is approximately 20%. Venography is the recommended investigation.
- If the Doppler ultrasound and the lineogram are normal but there is still no blood return from the CVAD, consider using the CVAD for instillation only. A venogram is strongly recommended to rule out large vessel clots
- if the Doppler ultrasound or lineogram are abnormal, proceed to a venogram

If associated with extensive deep vein thrombosis:

- obtain a ventilation/perfusion or CT scan to determine if pulmonary embolization has occurred
- If CVAD is no longer required or non-functioning, CVAD should be removed. Suggest using at least 3-5 days of anticoagulation prior to removal.
- one option is to leave the CVAD in place and attempt systemic thrombolytic therapy if there are no contraindications [see guidelines for thrombolytic therapy]
- if CVAD is still required and still functioning begin UFH therapy followed by 3 months of warfarin therapy or 3 months of LMWH as indicated

- for children with first CVAD related DVT, after the initial 3 months of therapy, suggest prophylactic doses of warfarin (INR 1.5-1.8) or LMWH (anti-factor Xa levels of 0.1 to 0.3) to be given until CVAD removed
- of initial therapy, suggest prophylactic doses of warfarin (INR 1.5-1.8) or LMWH (anti-factor Xa levels of 0.1 to 0.3) to be given until CVAD removed
- if the reoccurrence occurs while on prophylactic therapy, suggest continuing therapeutic doses until the CVAD is removed or for a minimum of 3 months
- See guidelines for UFH, warfarin and LMWH therapy. Follow-up should be arranged with the Pediatric Hematology/Oncology Service.

References:

1. Haire W, Atkinson JB, Stephens LC et al. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double blinded randomized trial. Thromb Hemost 1994; 72:545-547.
2. Choi M, Massicote P, Marzinotto V et al. The use of tissue plasminogen activator to restore patency of central venous lines in pediatric patients: a prospective cohort study. J Pediatr 2001; 139:152-156.
3. Public Health Service and Food and Drug Administration. Important drug warning regarding the use of Abbokinase [urokinase]. Anonymous. 1999; 1401 Rockville Pike, Rockville MD, 20582-1448.
4. Chesler L, Feusner JH. Use of tissue plasminogen activator [rtPA] in young children with cancer and dysfunctional central venous catheters. J Pediatr Hematol/Oncol 2002; 24:653-656.
5. IWK Nursing Pharmacy Policies. 30.59, 30.52, 30.58, 30.50.

Anticoagulation guidelines for patients with Fontan repair

Further clinical investigations are needed before recommendations for primary post-operative prophylaxis can be made. Current opinions include either ASA or therapeutic amounts of UFH, followed by warfarin therapy to achieve an INR of 2-3. The optimal duration of prophylaxis is unknown. Patients with fenestration may benefit from treatment until closure. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Anticoagulation with UFH:

- initiate low dose UFH starting 48 hours post-operatively at 10 units/kg/hr with no bolus
- do not adjust the UFH dose to achieve a therapeutic aPTT
- UFH should be stopped for 2 hours before intracardiac lines are removed.
- it is **NOT** required to hold anticoagulation therapy for the following procedures: removal of percutaneously inserted central venous catheters [PICCs], pacing wires, Jackson Pratt drains, peritoneal dialysis catheters, chest tubes or external central venous catheters
- anticoagulation therapy **MUST** be held for the removal of a Port-a-Cath

Anticoagulation with warfarin:

- Initiate warfarin therapy 48 hours after surgery and if oral intake has begun. The patient should be eating well before starting warfarin
- patients undergoing the Fontan procedure are known to be particularly sensitive to warfarin therapy
- in these patients, the loading dose of warfarin should be the same as the dose prior to the procedure
- the dosing of warfarin should be adjusted according to the nomogram [see warfarin guidelines] with the INR to be between 2-3
- long term follow-up of patients with Fontan repair should include transesophageal echocardiograms to assess for intracardiac thrombosis
- Long term anticoagulation of patients with Fontan repair remains controversial. Indications for the continuation of anticoagulation should be assessed on an individual basis

Anticoagulation with ASA:

- ASA is started as soon as oral intake is established and is continued indefinitely
- Low dose ASA is given: 1-5 mg/kg/day. One baby ASA contains 80 mg of acetylsalicylic acid

- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA.

References:

1. Stumper O, Sutherland G, Geuskens R et al. Transesophageal echocardiography in evaluation and management after a Fontan procedure. J Am Coll Cardiol 1991; 17:1152-1160. Monagle P, Chan A, Chalmers E, Michelson A. Chest 2004; 126:645S-687S.
2. Sharratt G, Lacson A, Cornel G et al. Echocardiography of intracardiac filling defects in infants and children. Pediatr Cardiol 1986; 7:189-194.
3. Monagle P, Bovil E, Michelson A, Andrew M. Antithrombotic therapy in children. Chest 2001; 119:344S-370S. Monagle P, Chan A, Chalmers E, Michelson A. Chest 2004; 126:645S-687S.
4. Monagle P, Cochrane A, MacCrindle B et al. Thromboembolic complications following Fontan procedures. The role of prophylactic anticoagulation. J Thorac Cardiovasc Surg 1998; 115:493-498.
5. Streif W, Andrew M, Marzinotto V et al. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. Blood 1999; 94:3007-3014.
6. Monagle P, Andrew M. Coagulation abnormalities after Fontan procedures. J Thorac Cardivasc Surg 1993; 113:989-993.

Anticoagulation guidelines for Blalock-Taussig shunts

The following are guidelines for initiating and monitoring anticoagulation for Blalock-Taussig shunts. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Anticoagulation with UFH:

- UFH anticoagulation begins in the operating room with a prophylactic dose of 10 units/kg/hr. No monitoring is required as a therapeutic aPTT is not the goal.
- LMWH may be used instead of UFH [see guidelines for LMWH prophylactic dosing].

Anticoagulation with ASA:

- ASA is started as soon as oral intake is established and is continued indefinitely
- Low dose ASA is given: 1-5 mg/kg/day. One baby ASA contains 80 mg of acetylsalicylic acid
- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA.

Further guidelines:

- This protocol includes all patients less than 1 year of age as well as patients with a Norwood shunt. Modifications may be indicated if there are concerns regarding shunt thrombosis risk

Reference:

1. Hall SM. Pubic Health Laboratory Services, Communicable Disease Surveillance Centre, London. Reye's syndrome and aspirin: a review. Brit J Clin Pharm 1990; 70:4-11.

Anticoagulation guidelines for valve replacement

The following are anticoagulation guidelines for patients with valve replacement. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be sought.

Mechanical valves:

- UFH to achieve a therapeutic aPTT of 60-85 secs starting at 48 hours post-operatively [see UFH guidelines]
- UFH should be stopped for 2 hours before intracardiac lines are removed
- the removal or insertion of chest tubes and percutaneously inserted central lines can be done while receiving UFH
- continue UFH until INR therapeutic for 2 days
- warfarin should be initiated 48 hours after oral intake is established
- the dose of warfarin is adjusted using the nomogram [see nomogram below] to keep the INR between 2.5-3.5
- in general, children with mechanical valves will also receive ASA (1-5 mg/kg/day) or dipyridamole (2-5 mg/kg/day) within 72 hours of valve placement

Suggested target INR for adults with mechanical prosthetic valves

Valve type	Position	Additional Clinical Factors	Target INR (range)
St.Jude Medical bileaflet	Aortic	Normal left atrium sinus rhythm	2.5 (2-3)
Carbomedic bileaflet Medtronic hall tilting disk Tilting disk Bileaflet	Mitral		3 (2.5-3.5)
Coged ball or caged disk	Any		3 (2.5-3.5) + ASA 1-5 mg/kg/day
Any valve	Any	Left atrial enlargement, atrial arrhyrhmias, endocardial damage, low ejection fraction	3 (2.5-3.5) + ASA 1-5 mg/kg/day
Any valve	Any	Previous valve thrombosis or evidence of systemic embolus despite therapeutic anticoagulation	3 (2.5-3.5) + ASA 1-5 mg/kg/day

Tissue valves:

Aortic valve replacement:

- warfarin is not required for patients with sinus rhythm
- ASA is started as soon as oral intake is established and is continued indefinitely
- Low dose ASA is given: 1-5 mg/kg/day. One baby ASA contains 80 mg of acetylsalicylic acid
- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA.

Mitral/tricuspid valve replacement:

- if the patient is in atrial fibrillation or has a proven intra-arterial thrombus, use full anticoagualtion with warfarin as per mechanical valve guidelines to achieve an INR of 2.5-3.5
- if the patient has normal sinus rhythm, use full anticoagulation with warfarin for 3 months [INR 2.5-3.5]
- ASA is started as soon as oral intake is established and is continued indefinitely
- Low dose ASA is given: 1-5 mg/kg/day. One baby ASA contains 80 mg of acetylsalicylic acid.
- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA.

Pulmonary valve replacement [including Dacron^{R} conduits]:

- There are no evidence-based recommendations available. Current therapies require evaluation in clinical trials.
- the current standard of practice is to give no anticoagulant therapy

Homograft valves:

- current therapies require evaluation in clinical trials
- the current standard of practice is to give no anticoagulant therapy

References:

1. Saour JN, Sieck J, Mamo LAR et al. Trial of different intensities of anticoagulation in patients with prosthetic valves. N Eng J Med 1990; 322:428-432.
2. Monagle P, Michelson A, Bovil E, Andrew M. Antithrombotic therapy in children. Chest 2001; 119:344S-370S. Monagle P, Chan A, Chalmers E, Michelson A. Chest 2004; 126:645S-687S.
3. Stein P, Alpert J, Bussey H et al. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 2001; 119:220S-227S.

Anticoagulation guidelines for patients with endovascular stents and vascular dilatation procedures

The following are guidelines for initiating and monitoring anticoagulation for patients with endovascular stents or having undergone vascular dilatation. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology Service should be obtained.

Anticoagulation with UFH:

- essentially all patients receive a bolus of 100-150 units/kg of UFH in the cardiac cath lab
- maintenance heparin therapy consists of prophylactic doses of UFH at 10-20 units/kg/hr
- UFH is not adjusted to achieve a therapeutic aPTT

Anticoagulation with ASA:

- low dose ASA therapy at 1-5 mg/kg/day for 6 months
- one baby ASA contains 80 mg of acetylsalicylic acid
- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA.

Further guidelines:

- Patients with stents will be heparinized using UFH or LMWH following placement of the stent. Long term anticoagulation may be provided using LMWH or warfarin [see LMWH and warfarin dosing guidelines]
- Dilatation of the portal vein, superior vena cava or any vessel at high risk of clotting will be followed by 2 weeks of full dose anticoagulant therapy. Following an ultrasound, anticoagulant therapy will be discontinued if the vessel is patent and stenting is not required.

Approach to acute cerebral arterial infarct

The following are guidelines for the diagnostic evaluation of children with an acute arterial infarct. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology and Neurology Services should be obtained.

- For neonates, the general approach for all strokes is supportive care.
- Anticoagulation is generally only indicated for neonates with an underlying risk factor.
- ASA is not indicated unless underlying cardiac risk factor.

General:

- obtain a general history
- check for recent head or neck injury, varicella infection within the past 12 months, oral contraceptive use, migraine, amphetamine use, tobacco use, history of head or neck irradiation, family history of early [age less than 55 years] stroke, heart attack, lipid problems, leg or lung clots, family history of first degree relatives of diabetes mellitus, deafness, ataxia or developmental delay. The latter are suggestive of metabolic disorders
- Conduct a detailed neurologic examination. Specially, check for carotid or head bruits, skin lesions or neurocutaneous disorders and clinical signs of cardiac disorders

Investigations:

- Conduct an in-depth radiographic assessment of the central nervous system including an MRI in all patients in addition to an initial CT scan. Preferably use a MRA [angiogram] to assess the circle of Willis, carotid and vertebral arteries at the level of the neck for evidence of vessel dissection.
- For most patients with arterial infarct, cardiac echocardiography is indicated. Other cardiac tests such as transesophageal echo and agitated saline ["bubble"] echocardiogram may be indicated as determined by the consulting neurologist and cardiologist.
- Measure baseline CBC, platelet count, PT/INR and aPTT
- Consider performing a work-up for hypercoagulable states: antithrombin, protein C, protein S, activated protein C cofactor resistance [APCR], factor V Leiden, prothrombin gene 20210a, antiphospholipid antibody, anticardioolipin antibody, lupus anticoagulant, plasminogen, thrombin time, reptilase time, fibrinogen, lipoprotein A and homocysteine. If the patient is receiving warfarin, protein C and protein S will be decreased due to the warfarin. The child should be tested after the warfarin has been discontinued. If the child is receiving LMWH, the hypercoagulable testing may be carried out as none

of the factors are affected by LWMH. UFH will affect the above tests with the exceptions of factor V Leiden, prothombin 2010a, lipoprotein A and homocysteine. Consider testing the child's parents.

- Further diagnostic evaluations for the etiology may be indicated and may include conventional angiography for patients with no clear etiology after MRA [MRA is inadequate to exclude vasculitis, large vessel dissection, MoyaMoya syndrome]
- The following tests for metabolic disorders predisposing to stroke may be indicated:
  - mitochondrial myopathy, encephalopathy, lactic acidosis and stroke–like episodes [MELAS]: serum lactate and pyruvate, CSF lactate and pyruvate, peripheral blood DNA analysis
  - Homocystinuria: serum or urine amino acids for potential homozygotes; plasma amino acids for heterozygotes
  - Fabry's disease: urinary ceramide trihexoside, leucocyte A-galactosidase
  - Hyperlipidemia: fasting serum cholesterol, triglycerides, HDL and LDL
  - Urea cycle enzyme defects: post-prandial plasma ammonia
  - Infections: serum and CSF studies for infection [bacterial, tuberculosis, viral], mycoplasma, cat-scratch fever, Rocky Mountain spotted fever, coxsackie virus B4 or A9, influenza A, varicella, HIV and parvovirus B19
- testing to diagnose systemic lupus or antiphospholipid antibody syndrome: ANA, non-specific PTT inhibitor, lupus anticoagulant and anticardiolipin antibody
- testing to diagnose other vasculitides: ESR, complement C3, C4, rheumatoid factor, CRP and ophthalmologic exam
- testing to diagnose sickle cell disease
- in neonates, thromboembolic strokes are increased with a patent foramen ovale or with right-to-left shunt from congenital cardiac lesions

Anticoagulant medications:

Anticoagulation may not be feasible if the infarct is associated with a significant hemorrhage, if the patient is hypertensive or the patient has other risks for bleeding.

For neonates, the general approach for all strokes is supportive care. Anticoagulation is generally only indicated for neonates with an underlying risk factor.

If anticoagulation indicated:

- LMWH or UFH for 7 days. No loading dose required
- CT on day 3 to rule out hemorrhage

Therapy based on the following etiologies:

1. Mild prothrombolic states as defined with neurology or hematology service.
2. Idiopathic stroke after initial investigations.
3. Cerebral arteriopathy (post varicella, Vasculitis, Moyamoya and idiopathic stenosis, complete occlusion of cerebral artery with no flow).
4. Most Congenital or acquired heart disease (e.g. Patent Formen Ovale, procedure related stroke).
5. Sickle cell anemia.

Switch to ASA 1-5 mg/kg/day after the initial 7 days of LMWH or UFH. Repeat MRI/MRA or in selected cases conventional angiogram in 3 months, to check for sub-clinical recurrent AIS or progressive vasculopathy prior to clinic visit.

For idiopathic stenosis, post-varicella, repeat MRI/MRA at 8 weeks post diagnosis.

Therapy based on the following etiologies:

1. Major prothombolic state as defined with the neurology or hematology service.
2. Recurrent stroke or TIA while on full dose ASA.
3. Definite or probable cervical/extra-cranial arterial dissection.
4. Severe (greater than 90%) arterial stenosis (non-occlusive) with slow blood flow on conventional angiogram.
5. Congenital or Acquired heart disease: considered at high risk for recurrent cardio embolism (e.g. intra-cardiac clot on echocardiogram).

Switch to warfarin or continue LMWH for 3-6 months or longer after initial 7 days of LMWH therapy.

Repeat MRI/MRA or in selected cases conventional angiogram in 3 months, prior to clinic visit. For arterial dissection repeat MRI/MRA or conventional angiogram in 6 weeks to determine treatment regimen.
Then switch to long-term ASA (1-5 mg/kg/day).

- Parents should be educated to stop ASA and use acetaminophen in the presence of fever and/or if their child has chickenpox. The latter is recommended because of the association of Reye syndrome with ASA. These children should receive an annual influenza vaccine.
- ASA should be held for neurosurgical and major cardiovascular surgery. ASA does not need to be held for lumbar puncture.

Intravascular thrombolysis

- intravascular thrombolysis for children with arterial ischemic stroke, should not be used outside of research protocols

Other treatment

- To minimize the extent of neuronal damage, fever, blood pressure and seizures should be controlled, normoglycemia should be maintained. Avoid sudden extreme reduction of blood pressure in order to maintain cerebral perfusion pressure.

References:

1. deVeber G. Hospital for Sick Children Stroke Guidelines 2008.
2. Monagle P, Chalmers E, Chan A et al. Antithrombotic therapy in neonates and children. Chest 2008; 133:887S-968S.
3. deVeber G. Cerebrovascular disease. In: Swaiman KF, Ashwal S [eds]. Pediatric Neurology: principles and practice. Philadelphia: CV Mosby, 1999.
4. Roach RS, Reila AR [eds]. Pediatric cerebrovascular disorders. 2nd edition. New York: Futura Publishing, 1995.
5. Einhaul KKM, Villringer A, Meister W et al. Heparin treatment in sinovenous thrombosis. Lancet 1991; 338:597-600.
6. Isler W. Stroke in childhood and adolescence. Eur Neurol 1984; 23:421-424.
7. Massicote P, Adams M, Marzinotto V et al. Low molecular weight heparin in pediatric patients with thrombotic disease: a dose finding study. J Pedaitrc 1996; 128:313-318.
8. Pessin MS, Estol CL, Lafranchise F et al. Safety of anticoagulation after hemorrhagic infarction. Neurol 1993; 43:1298-1303.
9. Sherman DG, Dyken ML, Gent M et al. Antitrhombotic therapy for cerebrovascular disorders. Fourth Antithrombotic Therapy Consensus Conference. Chest 1995; 108[suppl]:44S-46S.
10. Trescher WH. Ischemic stroke syndromes in childhood. Pediatr Ann 1992; 21:374-382.
11. Wizniter M, Masaryk T. Cerebrovascular abnormalities in pediatric stroke: assessment using parenchymal and angiographic magnetic resonance imaging. Ann Neurol 1991; 29:585-589.
12. Lanthier S, Carmant L, Labrisseau A et al. Etiology and outcome of stroke in children. Neurol 2000; 54:371-377.
13. Roach ES, deVeber G, Reila A et al. Recognition and treatment of stroke in children. NIH-NINDS electronic publication: acute stroke toolbox. Accessed 1998. [www.ninds.nih.gov/healinfo/disorders/strokeproceedin/chd-resp.htm]
14. Rivkin MJ, Volpe JJ. Strokes in children. Pediatr Res 1996; 17:265-278.

Cerebral sinovenous thrombosis

The following are guidelines for the diagnostic evaluation of children with sinovenous thrombosis [SVT]. Modifications for individual clinical circumstances may be necessary. Consultation from the Pediatric Hematology/Oncology and Neurology Services should be obtained.

General:

- obtain a general history
- check for recent head or neck injury, oral contraceptive use, inflammatory bowel disease, family history of early [age less than 55 years] stroke, heart attack, lipid problems, leg or lung clots
- Conduct a detailed neurologic examination. Specifically, check for evidence of dehydration, papilledema, increased head circumference, head bruits, dilated facial or neck veins, Sturge-Weber syndrome, clinical signs of paranasal, facial or mastoid infection or clinical signs of cardiac disorders

Investigations:

- Conduct an in-depth radiographic assessment of the central nervous system including an MRI in all patients in addition to an initial CT scan. MR venograhpy is usually necessary to confirm SVT. In rare cases, angiography may be required.
- For most patients with arterial infarct, cardiac echocardiography is indicated. Other cardiac tests such as transesophageal echo and agitated saline ["bubble"] echocardiogram may be indicated as determined by the consulting neurologist and cardiologist.
- Measure baseline CBC, platelet count, PT/INR and aPTT.
- Consider performing a work-up for hypercoagulable states: antithrombin, protein C, protein S, activated protein C cofactor resistance [APCR], factor V Leiden, prothrombin gene 20210a, antiphospholipid antibody, anticardioolipin antibody, lupus anticoagulant, plasminogen, thrombin time, reptilase time, fibrinogen, lipoprotein A and homocysteine. If the patient is receiving warfarin, protein C and protein S will be decreased due to the warfarin. The child should be tested after the warfarin has been discontinued. If the child is receiving LMWH, the hypercoagulable testing may be carried out as none of the factors are affected by LWMH. UFH will affect the above tests with the exceptions of factor V Leiden, prothombin 2010a, lipoprotein A and homocysteine. Consider testing child's parents.
- The following tests for metabolic disorders predisposing to SVT may be indicated:
  - Homocystinuria: serum or urine amino acids for potential homozygotes; plasma amino acids for heterozygotes.

  - Hyperlipidemia [fasting serum cholesterol, triglycerides, HDL, LDL]
  - Infections: serum and CSF studies for infection [bacterial, tuberculosis, viral, fungal].
- testing to diagnose systemic lupus or antiphospholipid antibody syndrome-ANA, non-specific PTT inhibitor, lupus anticoagulant and anticardiolipin antibody
- testing to diagnose other vasculitides: ESR, complement C3, C4, rheumatoid factor, CRP and ophthalmologic exam
- testing to diagnose sickle cell disease

Anticoagulant medications:

Anticoagulation may not be feasible if the SVT is associated with a significant hemorrhage, if the patient is hypertensive or the patient has other risks for bleeding.

Anticoagulation remains controversial for pediatric patients with SVT. Anti-coagulation is currently recommended for adult patients.

Management of childhood cerebral sinovenous thrombosis (CSVT):

- Step 1: MRI/MRV or minimum CT venogram.
- Step 2: If no significant intra-cranial hemorrhage or other contraindication to anticoagulation, start anticoagulation. Anticoagulation in the neonate is controversial; the usual practice however is to treat.
- Step 3: CT on day 3 of therapy.
- Step 4: If new hemorrhage, consult Hematology and consider reversing anticoagulation.
- Step 5: If no new hemorrhage:
  1. Neonates: Continue with anticoagulation and reassess in 6 weeks with MRI/MRV or CT venogram.
  2. Older infant or Child: Continue with anticoagulation and reassess in 3 months with MRI/MRV or CT venogram.
- Step 6: If full resolution of thrombosis – Stop anticoagulation and only in selected cases do repeat follow up CT or MRV (e.g. prothrombotic disorder or other high risk for propagation of thrombosis off treatment.
- Step 7: If thrombosis not resolved – Continue with anticoagulation for full planned duration. Neonate 3 months; older child 6 months.
- Step 8: Follow-up in 3-6 months after diagnosis.

Intravascular thrombolysis

- There is limited experience with intravascular thrombolysis for children with SVT in whom progressive clinical deterioration occurs in spite of anticoagulation.

Other treatment

- To minimize the extent of neuronal damage, fever, blood pressure and seizures should be controlled, normoglycemia should be maintained. Avoid sudden extreme reduction of blood pressure in order to maintain cerebral perfusion pressure.

References:

1. deVeber G. Cerebrovascular disease. In: Swaiman KF, Ashwal S [eds]. Pediatric Neurology: principles and practice. Philadelphia: CV Mosby, 1999.
2. Roach RS, Reila AR [eds]. Pediatric cerebrovascular disorders. 2nd edition. New York: Futura Publishing, 1995.
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5. Horowitz M, Purdy O, Unwin H et al. Treatment of dural sinus thrombosis using selective catheterization and urokinase. Ann Neurol 1995; 38:58067.
6. Bousser MG, Russell RR. Cerebral sinus thrombosis. Major problems in neurology series, #33; 1997. WB Saunders, London, UK.
7. Mati B, Chakrabarti I. Study on cerebral venous thrombosis with special reference to efficacy of heparin. J Neurol Sci 1997; 150 [suppl]:S147.
8. Goddard-Finegold J. Stroke in the newborn. UpToDate 12.2, printed in November, 2004.
9. deVeber G. Hospital for Sick Children Stroke Guidelines 2008.

Appendix 1

Discuss risks, benefits of and cautions for warfarin with the child/parents:

- reason for prescribing warfarin and the duration of treatment
- the need to comply with recommended warfarin dosage
- the importance of monitoring and of the target INR
- the need to take warfarin once daily, preferably at the same time each day and the need to have the INR test performed in the morning
- the need for caution when initiating other medications or herbs, etc
- Always talk to your health professional before taking any over the counter or herbal products (notify them that you are taking warfarin)
- the importance of a consistent vitamin K content in the diet
- the need to avoid heavy or variable alcohol consumption
- the side effects, signs of bleeding to watch for and the potential of need for blood transfusion
- the influence of inter-current medications
- the need to avoid ASA, NSAIDS without consulting a pediatric hematologist
- the need to avoid contact sports, IM injections
- instructions for when to call the child's physician[s]
- medic alert
- various wafarin tablet strengths and appearences
- birth control
- dental hygiene
- missed doses
- relevant phone numbers

Appendix 2

Examples of foods with high vitamin K content:

- coriander or cilantro, cooked [1510 micrograms/100 grams]
- parsley cooked [900 micrograms/100 grams]
- Brussels sprouts
- spinach
- mint
- broccoli
- green apple with peel
- soybean oil

Appendix 3

Examples of medications commonly used in pediatrics that influence warfarin dosing

Drug	Effect on INR
Amiodarone	Increase
Acetaminophen [high dose]	Increase
Allopurinol	Increase
Azoles	Increase
Amoxicillin	Slight increase
Chloral hydrate	Increase
Carbenicillin	Increase
Cephalosporins	Increase
Cefaclor	Increase
Tegretol	Decrease
Dilantin	Decrease
Phenobarbitol	Decrease
Rifampin	Decrease
Cyclosporin	Decrease
Cloxacillin	Increase
Prednisone	Increase
Clotrimazole	Increase
Ranitidine	Increase
Erythromycin	Increase
Fluconazole	Increase
Darithromycin	Increase
Omeprazole	Increase
Metronidazole	Increase

***it must be assumed that all medications might affect warfarin metabolism and INR results.**

Appendix 4

Examples of OTC Medications & Herbals of concern for hematology patients

Medication/Herbal	Antiplatelet Effects	⇑ risk of bleeding	Anticoagulant Effects	Comments
Aspirin®	X	X		
Bufferin® Novasen® Asaphen® (ASA)	X	X		
Advil®/Motrin®/ ibuprofen				
Advil Cold & Sinus®, Sudafed Sinus Advance® (contains ibuprofen)	X	X		
Robaxisal® Methoxisal® + generics (ASA + methocarbamol)	X	X		
Robax Platinum® (ibuprofen + methocarbamol)	X			Monitor INR with warfarin
Lakota® products for joint pain				
222's (ASA +caffeine + codeine) + generics	X	X		
Midol® Regular (ASA + caffeine)				
Angelica	X			
Anise			X	
Dong Quai	X		X	May ↑ prothrombin time (PT)
Omega 3 (EPA & DHA, fish oils)	X			
Cod liver oil		X		
Kelp/focus		X	X	
Garlic	X	X		May add to effects of warfarin
Ginger	X	X		
Ginseng (Panax)	X		X	↓ effectiveness of warfarin
Gingko	X	X		
Vitamin E	X	X		Interferes with Vitamin K-dependent clotting factor
Alfalfa			X	
Black Cohosh	X			

Appendix 4 (continued)				
Examples of OTC Medications & Herbals of concern for hematology patients				
Medication/Herbal	**Antiplatelet Effects**	**⇑ risk of bleeding**	**Anticoagulant Effects**	**Comments**
Bromelain	**X**	**X**		
Capsicum		**X**		
Fenugreek	**X**		**X**	
Feverfew	**X**			
Licorice	**X**			
Onion	**X**	**X**		
Red clover		**X**	**X**	
Willow bark	**X**	**X**		
Caffeine	**X**	**X**		
Green tea	**X**	**X**		**has Vitamin K content, may ↓ effectiveness of warfarin**
Flaxseed	**X**	**X**		
Glucosamine ± chondroitin		**X**	**X**	**Chondroitin is heparin-like compound, may ↑ INR**
Evening Primrose Oil		**X**	**X**	
Melatonin		**X**		
Cranberry		**X**		**Has salicylic acid component, may ↑ INR**
Grapefruit				**May ↑ effect of warfarin**
Mango				**May ↑ INR when taken with warfarin**
Soy	**X**			**Contains Vitamin K, may ↓ effect of warfarin**
St John's Wort				**↓ effects of warfarin**
Co-Enzyme Q10				**Structurally similar to Vitamin K, ↓ effectiveness of warfarin**
L-Carnitine		**X**		
Milk Thistle		**X**		
Saw Palmetto		**X**		
Vitamin A		**X**		
Vitamin C		**X**		

Compiled by IWK Health Centre Pharmacy

Please note: this list is an unofficial guideline for parents and caregivers of hematology patients. It is not a complete list of over-the -counter products which may be of concern to Hematology patients, but includes many of the more common products found in pharmacies. Parents & patients should speak to their Physician or pharmacist about their specific condition and medications.

Guideline Development

Potential organizational barriers/cost implications to applying the recommendations found in this guideline include:

- inability to obtain medications due to expense (e.g. enoxaparin, tinzaparin)

Patient/family preferences:

- not considered applicable
- appropriate information and support will be provided

Key review criteria for monitoring/audit include:

- INR monitoring records
- Anticoagulant compliance
- Number of children requiring treatment for over anticoagulation
- Number of children requiring treatment for sub-therapeutic anticoagulation

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The individuals involved in the development of this guideline had no conflicts of interest with respect to the development of the guideline. The guideline was developed independently from any funding body.

The guideline was piloted at the IWK Health Centre in Halifax, Nova Scotia.

The guideline was externally reviewed by, pediatricians, hematologists, oncologists, and nurses.

The guideline will be reviewed in 3 years and at any time if significant information becomes available by the APPHON Guidelines Committee, and resubmitted to the APPHON Board and Cancer Care Nova Scotia Clinical Practice Guidelines Committee for ratification. If significant changes to anticoagulant and antithrombotic therapy in children, changes based on new evidence or best practice, develop prior to July 2015, the guideline will be updated to reflect those changes. As per the standard practice for APPHON guidelines, individuals will be assigned to regularly review applicable literature to monitor for significant changes. If literature documenting evidence-based or best practice based indications for changes to this guideline, the guideline will be updated with the applicable information as soon as feasible.