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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