Miller Children's Hospital Warfarin Guideline
(Non-pharmacy regulated therapy)

Thrombotic events in the pediatric population are relatively uncommon. The low incidence of thrombotic events in the pediatric population may be related to a decreased ability to generate thrombin and other clotting factors, increased α_2- macroglobulin to inhibit thrombin, and enhanced anti-thrombotic potential of vessel walls. However, with recent advances in the treatment of critically ill children, an increase in thrombotic events has been observed. The annual incidence of thrombotic events in pediatrics has been reported as 0.07 - 0.14 per 10,000 children, or 5.3 per 10,000 hospital pediatric admissions, and 24 per 10,000 admissions to a neonatal intensive care unit. There are two age related peaks in thrombotic events: age < 1 year old and during adolescence. The all-cause mortality of thrombotic events in pediatrics is estimated to be between 1 to 2%.

The common denominator in clot formation is an imbalance between procoagulant and anticoagulant proteins leading to an event. Virchow's triad (stasis, injury, and hypercoagulable state) is a major factor in thrombus formation. Most thrombotic events in pediatrics are associated with underlying disease or risk factors. The most common risk factor for thrombotic event in pediatric population is placement of central venous catheters. Table 1 lists other established risk factors in pediatrics.

Table 1: Established Risk Factors for Thrombotic Events

Acquired Factors	**Persistent Factors**	**Congenital Factors**
Trauma	Malignancy	Protein C Deficiency
Immobilization	Hematological Disorders (i.e. Sickle Cell Disease)	Protein S Deficiency
Pregnancy	Rheumatologic Disease (i.e. Lupus)	Factor V Leiden
Nephrotic Syndrome	Antiphospholipid Syndrome	Prothrombin Gene Mutation
CVC/arterial line	Congenital Heart Disease	Antithrombin Deficiency
Drugs (hormones/chemo)	History of previous thrombosis	Hyperhomocysteine
Surgery, (i.e Fontan procedure, valve)	Inflammatory bowel disease	MTHFR Polymorphism
Infection (sepsis)		Elevated Lipoprotein(a)
Dehydration/Hypovolemia		Mutation in FVG1691A
Hemolytic Uremic Syndrome		Mutation in DTG22710a
Heparin-Induced Thrombocytopenia (type II)		Elevated Clotting Factors VII, VIII, IX, XI
Transcather stents/occluded devices		

Acute thrombotic events require prompt systemic anticoagulation most commonly with unfractionated heparin. Most patients are then bridged (transitioned) to either a low molecular weight heparin (LMWH) or oral anticoagulant (warfarin) for outpatient therapy, based on the physician's experience and clinical judgment. When transitioning to warfarin, the systemic anticoagulant needs to be adequately overlapped with warfarin therapy as discussed below. This guideline addresses issues related to warfarin dosing in the pediatric population. The Seventh ACCP Conference on Antithrombotic and Thrombotic Therapy Evidence-Based Guidelines published in Chest in 2004 defines the pediatric population as 28 days old to 16 years.

THE FOLLOWING GUIDELINES ARE NOT MEANT TO REPLACE GOOD SOUND CLINICAL JUDGMENT

Warfarin

DESCRIPTION/MECHANISM:
Warfarin works by inhibiting the cyclic interconversion of vitamin K and vitamin K 2, 3 epoxide, which are essential cofactors in the synthesis of blood coagulation factors II, VII, IX, X, as well as, Protein C and S. Warfarin is a mixture of S and R enantiomers, with each being metabolized by different cytrochrome (CYP) P450 enzymes. The more potent S isomer (5 x more potent) is metabolized by CYP 2C9. Recent studies have shown that patients with variant types of CYP 2C9 and/or VKORC1 (vitamin K epoxide reductase) are more sensitive to warfarin. However, there is no widely accessible test to identify these patients in a timely fashion when initiating therapy. Current pharmacogenetic testing for these genetic variations take several days for results to be available.

PHARMACOKINETICS:

Half-Life	36-42 hrs
Absorption	Rapid and complete
Time to Initial Effects	Within 24 hrs due to inhibition of Factor VIII (half-life 6 hrs)
Peak Effects	Delayed for 3-4 days due to longer half life of Factor II (60-72 hrs)

Therefore, due to the aforementioned pharmacokinetic and pharmacodynamic profile of warfarin, when bridging patients from systemic anticoagulation to warfarin, it is recommended to overlap therapy for at least 4 to 5 days to ensure adequate anticoagulant protection.

GENERAL MONITIORING (SEE TABLE 2 IN DOSING SELECTION FOR SPECIFIC GOALS):
The prothrombin time (PT) is the most commonly used test to monitor warfarin. It should be reported as International Normalized Ratio (INR), for which the therapeutic range is standardized irrespective of the thromboplastin reagent used. In contrast to adults, only about 10 to 20% of children can safely be monitored on a monthly basis, for the following reasons:

1. There are very limited data evaluating the dosing of warfarin in the pediatric population.
2. Most studies suggest that oral anticoagulation therapy in pediatric patients is complicated and variable.
3. Age-related dosing curves have been characterized, with an increased dose requirement in younger individuals.
4. Infant formulas are supplemented with Vitamin K, which make formula fed infants more resistant to warfarin and, therefore breast-fed infants more sensitive.
5. Physiological changes in production of vitamin K clotting factors make frequent monitoring and dosage adjustments required in younger children.

ADVERSE EFFECTS:
Common: Major and minor bleeding and bruising:

Minor bleeds are defined as requiring no treatment, referrals, additional test or visits, such as epistaxis, hematuria, skin hematomas, gingival bleeding, mild vaginal bleeding, and mild hemorrhoidal bleeding.

Major bleeds are defined as requiring treatment, medical evaluation, or a defined drop in hemoglobin leading to transfusion, and/or leading to hospitalization. Major bleeds also include fatal and life-threatening events (leading to cardiac arrest, surgical/angiographic intervention, or irreversible sequelae).

The risk of bleeding is directly related to the intensity and duration of therapy. Known risk factors for bleeding include a history of GI/GU bleed, uncontrolled hypertension, advanced age, low platelets (< 75K), metastatic cancer, anemia, hepatic/renal disease, drugs affecting platelet function, and any disease that increase the risk of falls.

Rare: Rare side effects are skin necrosis, cholestatic hepatic injury, alopecia, N/V, diarrhea, urticaria, and purple toe syndrome. Recently, two cohort studies have described reduced bone density in children who have received warfarin for > 1 year. Skin necrosis and purple toe syndrome is primarily associated with use in patients with a deficiency in protein C and S. In these patients, overlapping therapy with unfractionated

heparin or LMWH prior to initiating warfarin therapy, and using small initial warfarin doses is required, since a hyperthrombotic state is initially created during the beginning of warfarin therapy due to rapid decreases in protein C and S levels (natural anticoagulants).

RELATIVE CONTRAINDICATIONS TO WARFARIN USE:

NOTE: THERE ARE NO SAFETY AND EFFICACY DATA IN THE NEONATAL POPULATION, SO WARFARIN IS NOT RECOMMENDED IN THOSE < 3 months of age.

Pregnancy, lumbar block, cerebral aneurysms, dissecting aorta, bacterial endocarditis, bleeding tendencies (i.e PUD), hemorrhagic CVA, malignant hypertension, pericarditis/effusion, poor patient compliance, spinal puncture, recent surgery of central nervous system, and recent traumatic surgery with potential for hemorrhagic.

AVOID concurrent aspirin and NSAIDS use while on warfarin.

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Miller Children's Hospital Warfarin Dosing Guidelines

Initiation of therapy

1. Screen patients for appropriateness of warfarin therapy, and evaluate patient dosing based on sensitivity risk factors and INR goal. Refer to Tables 1 and 2.
    a. Determine and document the desired INR goal in the chart.
    b. Document that the patient and/or caregiver has been educated in chart with any special comments as need. (i.e. refused to talk). Education should include, but not be limited to indication for therapy, monitoring, goals, drug/food/herbal interactions, signs and symptoms of bleeding, contact information, administration parameters /missed dose information, and need for follow-up.
        i. Give Warfarin (Coumadin) brochure to patient/caregiver
    c. Attempt to switch any concomitant drugs to alternative agents that do not interact with warfarin.
    d. Avoid herbal medication use in hospital or as an outpatient.
    e. Avoid IM injections, if possible
    f. Discontinue any order for NSAID's or other antiplatelet drugs, if possible.

2. All patients should have baseline PT/INR, CBC and LFTs prior to therapy.
    a. Obtain the INR daily in hospitalized patients until the INR is consistently within the desired therapeutic range, then two or three times per week for 1 to 2 weeks, then less often depending on the INR results.
    b. Administer warfarin at a consistent time daily. The standard administration time at Miller Children's Hospital is 14:00. This allows the INR value from the morning lab draw to be more reflective of the previous dose due to the variable half-lifes of the affected clotting factors. If the warfarin is given at a different time, the INR should be checked at least 10 to 14 hrs after the last warfarin dose.
    c. CBC should be checked at least weekly in the hospital or more frequently as clinically indicated.

3. Maintain consistent intake of vitamin K
    a. Order a nutrition consult to review and educate the patient/caregiver on warfarin-diet interactions.
    b. Consider discontinuing vitamin K from parenteral nutrition solution and enteral multivitamin supplementation
    c. Consider holding continuous enteral feeds 1 hour prior and after warfarin administration.
    d. Closely monitor the patient's response to warfarin therapy when a tube feeding is started, stopped or altered.
    e. In breast fed infants only, consider one supplemental feeding of infant formula for more consistent intake of vitamin K if needed. More consistent vitamin K intake leads to less fluctuation in INR values.
    f. Consider alternatives to soy protein containing infant formulas and nutrition supplements.

Table 1: INR Goal Ranges for Specific Indications

Indications	INR Goal Range
Thrombotic Event (i.e. DVT/PE, catheter-related thrombosis)	2.0 to 3.0
Central Venous Line clot prophylaxis after document clot (if needed)	1.5 to 1.9
Primary prophylaxis post - Fontan procedure (if choosen)	2.0 to 3.0
Primary prophylaxis for dilated cardiomyopathy	2.0 to 3.0
Tissue Heart Valve	2.0 to 3.0
Mechanical Prosthetic Valve (mitral/tricuspid)	2.5 to 3.5
Bileaflet mechanical valve in aortic position	2.0 to 3.0
Kawasaki Disease with giant aneurysms	2.0 to 3.0
Sinovenous thrombosis in children	2.0 to 3.0

Arterial ischemic stroke, cardioembolic stroke, or vascular dissection	2.0 to 3.0

Table 2: Sensitivity Dosing Risk Factors

High Sensitivity	Moderate Sensitivity	Low Sensitivity
Baseline INR > 1.5 Significant hepatic disease Advanced cancer Decompensated CHF; Fontan procedure Malnourished/diarrhea/vomiting/malabsorption CYP 2C9/ VKORC1 variants Drug-drug interaction*	Baseline INR 1.3 to 1.5 Significant renal disease Drug-drug interaction* Hypermetabolic state	INR < 1.3 Drug-drug interaction*

* See Tables on specific drug sensitivity factor below

Warfarin Dosing Nomogram for INR Goal of 2.0 - 3.0

1. Dosing is highly variable and is based on laboratory data, known risk factors, and INR goal.
    a. Dosing should be based on an individual's response to subsequent dosing and may be adjusted based on clinical judgment, known risk factors including acute changes in clinical status, nutritional status, and/or new drug interaction(s), and INR goal.
2. If the etiology of clot is unknown, then protein C and S deficiency may be possible. Doses greater than 5 mg put these patients in a hypercoagulable state and bridge therapy with heparin or a low molecular weight heparin is warranted.

Days	INR and Risk Factors	Dosing
1	< 1.3	0.2 mg/kg (max 10 mg)
	≥ 1.3 or post Fontan, and/or significant risk factors (esp. liver dysfunction, drug-drug interaction, protein C or S deficiency)	0.1 mg/kg (max 5 mg)
2 thru 4	1.1 to 1.3	Repeat initial dose
	1.4 to 1.9	50% of day 1 dose
	2.0 to 3.0	50% of day 1 dose
	3.1 to 3.5	25% of day 1 dose
	> 3.5	Hold dose until < 3.5, and restart at 50% of previous dose
5 and beyond (maintenance)*		
	1.1 to 1.4	Increase by 20% of dose
	1.5 to 1.9	Increase by 10% of dose
	2.0 to 3.0	No change
	3.1 to 3.5	Decrease by 10% of dose
	> 3.5	Hold dosing until INR < 3.5, then restart with a reduced dose (decrease last dose by 20% to 40%)

* If the INR is not greater than 1.5 on day 5, the patient should be reassessed and dosed based on individual response.

FOR INR GOAL of 2.5 TO 3.5 - Refer to above nomogram for initial dosing, with the caveat that more aggressive dosing may be warranted for days 2 to 4. Remember dosing should be based on individual's response and INR goal.

Increase Sensitivity Drug Interaction Tables (Lower warfarin dosing requirement)

Level	Anti-infective	Cardiovascular Drugs	Analgesic, Anti-inflammatory , immunologic, other	CNS Drugs
Highly Probable	Ciprofloxacin Bactrim/Septra Erythromycin Fluconazole Isoniazid (600mg/day) Metronidazole Miconazole Voriconazole	Amiodarone Fenofibrate Propafenone Propranolol Heparin Fish oil	Piroxicam Cimetidine Omeprazole Etoposide Carboplatin Anabolic Steroids Zafirlukast Imatinib Dasatinib	Alcohol Sertraline Fluoxetine Quetiapine
Probable	Augmentin Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir/amprenavir Tetracycline 2nd and 3RD generation cephalosporins Beta-lactam combos (i.e. Zosyn) Terbinafine	Fluvastatin Simvastatin Lovastatin Quinidine Ropinirole	APAP (high dose) Celecoxib Interferon Tramadol Fluorouracil Tamoxifen Grapefruit juice Gemcitabine Dong Quai Trastuzumab Garlic/Gingko/Ginger Zileuton Vitamin E (high dose) Thryoid hormones Flu vaccine	Chloral Hydrate Fluvoxamine Phenytoin (biphasic) Tricyclic antidepressants
Possible	1st generation cephalosporins Penicillin Nitrofurantoin Chloramphenicol Daptomycin	Gemfibrozil Metolazone Disopyramide	Indomethacin Leflunomide Propoxyphene Sulindac Acarbose Cranberry Juice	Felbamate

* Drugs such as aspirin, clopidogrel, ticlopidene, pencillins, NSAIDs, increase risk for warfarin associated bleeding by inhibiting platelet function.

Decrease Sensitivity Drug Interaction Table. (Higher warfarin requirement likely)

Level	Anti-infective	Cardiovascular Drugs	Analgesic, Anti-inflammatory , immunologic, other	CNS Drugs
Highly Probable	Nafcillin Ribavirin Rifampin Griseofulvin	Cholestyramine	Mesalamine Green tea Mercaptopurine Sucralfate Large amounts of avocado High vitamin K content food	Barbiturates Carbamazepine Propofol
Probable	Dicloxacillin	Bosentan	Azathioprine Cyclosporine Sushi containing seaweed Chelation therapy Raloxifene	Chlordiazepoxide
Possible		Telmisartan	Sulfasalazine	

Reversal of Warfarin

The reversal of warfarin anticoagulation is dependent on the need for rapid reversal and presence of bleeding. The following data is based on adult ACCP guidelines for management of elevated INR or presence of bleeding.

Condition	Description
INR above therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose, monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR ≥ 5.0 but < 9.0; no significant bleeding	Omit next one to two doses, monitor more frequently and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give oral vitamin K, particularly if at increase risk of bleed, or if more rapid reversal is required.
INR ≥ 9; no significant bleeding	Hold warfarin therapy and give vitamin K. Monitor more frequently and use additional vitamin K if necessary.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K, supplement with FFP or prothrombin complex concentrate; recombinant factor VIIa may be considered as an alternative to prothrombin complex concentrate; intravenous vitamin K can be repeated every 12 hours.
Life-threatening bleeding	Hold warfarin therapy and give prothrombin complex concentrate or FFP, and supplement with vitamin K; recombinant factor VIIa may be considered as an alternative; repeat if necessary depending on INR

If continuing warfarin therapy is indicated after high doses of vitamin K, then heparin or LMWH can be given until the effects of vitamin K have diminished and the patient becomes responsive to warfarin therapy. It should be noted that INR values > 4.5 are less reliable than values in or near the therapeutic range.

Recommendations for Managing Anticoagulation Therapy in Patients Requiring Invasive Procedures from ACCP Guidelines.

Condition	Description
Low risk of thromboembolism	* Stop warfarin therapy approximately 4 days before surgery, allow the INR to return to near normal, briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with a low dose of UFH or a prophylactic dose of LMWH and simultaneously begin warfarin therapy; alternatively, a low dose of UFH or a prophylactic dose of LMWH can also be used preoperatively.
Intermediate risk of thromboembolism	Stop warfarin approximately 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH or a prophylactic dose of LMWH and then commence therapy with low-dose UFH (or LMWH) and warfarin postoperatively; some individuals would recommend a higher dose of UFH or a full-dose LMWH in this setting.
High risk of thromboembolism†	Stop warfarin approximately 4 days before surgery, allow the INR to return to normal; begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively); UFH can be given as a SC injection as an outpatient, and can then be given as a continuous IV infusion after hospital admission in preparation for surgery and discontinued approximately 5 hours before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery; it is also possible to continue with SC UFH or LMWH and to stop therapy 12–24 hours before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery.
Low risk of bleeding	Continue warfarin therapy at a lower dose and operate at an INR of 1.3–1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients; the dose of warfarin can be lowered 4 or 5 days before surgery; warfarin therapy can then be restarted postoperatively, supplemented with a low dose of UFH or a prophylactic dose of LMWH if necessary.
	In patients undergoing dental procedures with a need to control local bleeding, ACCP guidelines recommend the use of tranexamic acid mouthwash or epsilon aminocaproic acid mouthwash without interrupting anticoagulant therapy.

*Low risk of thromboembolism includes no recent (< 3 months) venous thromboembolism, atrial fibrillation without a history of stroke or other risk factors, and bileaflet mechanical cardiac valve in aortic position.
†Examples of high risk of thromboembolism include recent (< 3 months) history of venous thromboembolism, mechanical cardiac valve in mitral position, and old model of cardiac valve (ball/cage).

PHYTONADIONE (Vitamin K) Dosing for oral anticoagulant overdose:

NOTE: THERE IS A RISK OF ANAPHYLAXIS WITH THE USE OF IV VITAMIN K, SO ANY IV DOSES SHOULD BE INFUSED OVER 1 HOUR WITH MONITORING.

Intravenous vitamin K may not be given on the General Pediatrics Floor.

1. Do not give IM injection of vitamin K to patients on anticoagulants, due to the potential for hematoma formation.
2. Oral route is preferred when patients are not actively bleeding.
3. Subcutaneous administration is not recommended per ACCP guidelines, secondary to less predicatable effects

PHARMACOKINETICS:

	Oral	Intravenous
Onset	6 to 12 hrs	1 to 2 hrs
INR Reduction effect seen	24 hrs	3 to 6 hrs

Reduced oral absorption seen in patients with cholestasis.

ADVERSE REACTIONS:
Facial flushing, diaphoresis, chest pain, hypotension, or dyspnea associated with or without anaphylaxis. Tenderness at injection sites, dizziness, GI upset, and hyperbilirubinemia and hemolytic anemia in neonates when greater then recommended doses are given.

DOSING:
Infants and Children:
No bleeding, rapid reversal needed, patient will require further oral anticoagulant therapy:
I.V., oral, or SubQ: 0.5-2 mg
No bleeding, rapid reversal needed, patient will not require further oral anticoagulant therapy:
I.V., oral, or SubQ: 2-5 mg
Significant bleeding, not life-threatening: IV, SubQ: 0.5-2 mg
Significant bleeding, life-threatening: I.V.: 5 mg – higher doses may be warranted

Adolescents:
I.V., Oral, or SubQ: 2.5-10 mg/dose may repeat in 6-8 hours if given by SubQ, I.V. route; may repeat 12-48 hours after oral route

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