Pharmacy and Therapeutics Committee Approvals, December 2008

P&T Date: December 2, 2008

AGENDA ITEM	P&T COMMITTEE DECISION	COMMENTS
• **HYDROXOCOBALAMIN KIT (CYANOKIT®)**	**ADDED TO FORMULARY**	• ***Indication:*** Treatment of known or suspected cyanide poisoning/toxicity • ***Mechanism of Action:*** 1:1 binding with cyanide, resulting in formation of cyanocobalamin, which is renally excreted • ***Adverse effects:*** increased blood pressure; red coloration of urine, skin, and mucous membranes; headaches; nausea. Potential allergic reactions • ***Contraindications:*** Previous hypersensitivity to either hydroxocobalamin or cyanocobalamin • ***Precautions:*** Safety of co-administration with other cyanide antidotes has not been established. As such, these agents should not be administered in the same IV line concurrently. Acneiform rash may appear 7 to 28 days following hydroxocobalamin administration. Patients should be advised to avoid direct sun exposure while/if their skin is discolored. Look-alike, sound-alike with cyanocobalamin, Cyanide Antidote Kit. Pregnancy category C; unknown if excreted into breast milk
• **LANREOTIDE (SOMATULINE DEPOT®)**	**ADDED TO FORMULARY FOR OUTPATIENT TREATMENT OF ACROMEGALY AND NEUROENDOCRINE TUMORS AFTER PRIOR AUTHORIZATION HAS BEEN OBTAINED**	• ***Indication:*** Long-term treatment of acromegaly when there is an inadequate response to surgery and/or radiotherapy, or when surgery and/or radiotherapy is not an option. It has also been used in the treatment of refractory neuroendocrine tumors. • ***Mechanism of Action:*** Sustained-release octapeptide somatostatin analog that inhibits Insulin-like growth factor-1 (IGF-1) and growth hormone (GH). • ***Adverse effects:*** Most common reactions in long-term clinical trials: diarrhea, abdominal pain, nausea, cholelithiasis, administration site reactions, arthralgias, and headache • ***Contraindications:*** None known • ***Precautions:*** Monitor periodically for gallstone formation, hypo- or hyperglycemia, sinus bradycardia. May decrease bioavailability of cyclosporine; may increase bioavailability of bromocriptine; potential additive heart rate decrease with beta-blockers; potential decreased clearance of other CYP-450_{3A4} metabolized medications. Look-alike, sound-alike with octreotide, lanthanum, Somatostatin. Pregnancy category C; unknown if excreted into human breast milk but serious reactions have resulted in animals, therefore consideration should be given to discontinuing nursing during lanreotide therapy

FORMULARY CHANGES	• **Diethylstilbestrol diphosphate (Stilbestrol®, DES) – REMOVED from formulary (no longer commercially available)**
• **AUTOMATIC SUBSTITUTIONS**	• **Calcium citrate (Citracal®) automatically substituted <u>TO</u> Calcium carbonate (Oscal-500®) as follows:** **<u>Medication Ordered</u>** Calcium acetate (Citracal®): 1 tablet (200-250 mg elemental Ca) 1 liquitab (500 mg elemental Ca) **<u>Automatic Substitution</u>** Calcium carbonate (Oscal-500®): ½ Oscal 500® tablet 1 Oscal 500® tablet • **Droperidol automatic substitutions for doses > 0.625 mg IVP every 6 hours:** **<u>Droperidol (Inapsine®) Q4H</u>** **<u>Droperidol (Inapsine®) Q6H</u>** • <u>Monitored bed:</u> 0.625 mg IVP Q6H PRN, MR x 1; Max: 5 mg/d • <u>Non-monitored bed</u>: 0.625 mg IVP Q6H PRN; Max: 2.5 mg/d • **Papain urea (Accuzyme®) automatically substituted <u>TO</u> Collagenase (Santyl®) at same dose** ***(all papain products "unapproved" by the FDA; must be discontinued by the manufacturer)*** ***** Substitution will begin once in-house supplies of Accuzyme have been exhausted***** • **Hetastarch in lactate electrolyte solution (Hextend®) automatically substituted <u>TO</u> Hetastarch in saline solution (Hespan®) at same dose, rate**
• **ANTICOAGULATION TASK FORCE –** **NPSG-3E**	Per National Patient Safety Goal requirements of The Joint Commission, new Cedars-Sinai anticoagulation protocols go into effect <u>Jan. 1, 2009</u>. These protocols will address the therapeutic/treatment uses of dalteparin, enoxaparin, heparin and warfarin, with the purpose to optimize and assure the safety of anticoagulation therapy for patients with respect to dosing, monitoring and education. The requirements of NPSG-3E, which the Anticoagulation Task Force has been addressing during the past year, follow the latest NPSG (3E). Among the regulations are: • All patients must have a current baseline lab of less than 24 hours and ongoing laboratory monitoring. • The care of patients on therapeutic anticoagulation should be managed per Cedars-Sinai regulations by a physician or pharmacist with deviations from protocols clearly noted in the Progress Notes. • Patients taking warfarin must have a nutrition consult. Specifics on the new protocols have been issued to physicians and links to the new order sets as well as TJC's goals for anticoagulation therapy have been added to the Clinical Workstation and Resources Intranet homepage. An issue of CSMC's new *Stop the Clot* newsletter is viewable via link in the December 12, 2008 issue of **<u>Medical Staff Pulse</u>**
• **LEPIRUDIN (REFLUDAN®) AND ARGATROBAN PROTOCOL (REVISED) – CHANGES TRACKED**	B5. DTIs Pharmacy Protocol 11.08.doc

• **DALTEPARIN (FRAGMIN®) FOR DVT PROPHYLAXIS**	B6. Fragmin Dosing chart 11.08.doc
• **RECOMMENDATIONS FOR ANTICOAGULANT/ ANTI-PLATELET/ THROMBOLYTIC REVERSAL**	B7. Reversal guideline - General 11
• **ANTIBIOTIC UTILIZATION REVIEW COMMITTEE**	• **ANTIBIOTIC DOSING PER PHARMACY (REVISED) – CHANGES TRACKED** B9B. Abx dosing per protocol 11.08.doc • **ATAZANAVIR (REYATAZ®) DEAR DOCTOR LETTER** B9C. Atazanavir DDL 11.08.pdf • **LINEZOLID (ZYVOX®) DEAR DOCTOR LETTER (REVISED) – CHANGES TRACKED** B9D. Linezolid DDL 11.08.pdf • **VANCOMYCIN PHARMACY PROTOCOL (REVISED) – CHANGES TRACKED** B9E. Vancomycin protocol 11.08.doc
• **FDA NEWS & WARNINGS SUMMARY**	B13A. Medwatch Alerts Summary Sep -

Requests for full monographs or questions regarding this listing may be addressed to the Drug Information Center at **(310) 423-3784**

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CEDARS-SINAI MEDICAL CENTER

Department of Pharmacy Services

Updated 11/19/08 (lepirudin: bolus dosing, goal aPTT, renal dosing, argatroban infusion for heart failure, severe anasarca or s/p cardiac surgery)

Lepirudin (Refludan®) & Argatroban per Pharmacy Protocol

FORMULARY STATUS

Lepirudin & Argatroban are ***non-formulary***, but available on a per-patient basis for patients with suspected HIT. Please follow the non-formulary approval process when processing orders for these agents.

PURPOSE

To establish guidelines for the management of lepirudin/argatroban therapy by pharmacists. The dosing of lepirudin/argatroban as specified in this protocol should be followed if the physician orders "lepirudin/argatroban per protocol", "lepirudin/argatroban per Pharmacy" or similar language.

PROTOCOL INDEX

I. BACKGROUND

- **a. HIT: H**eparin **I**nduced **T**hrombocytopenia
- **b. HITTS: H**eparin **I**nduced **T**hrombocytopenia **T**hrombotic **S**yndrome
- **c. HAT: H**eparin **A**ssociated **T**hrombocytopenia – ***benign drop in platelets***
- **d.** Clinical Symptoms of HIT/HITT
  1. Decrease in platelets within 5 – 10 days of heparin exposure
  2. > 50% from baseline or < 100,000/ul or ≤ 50,000/uL ± thrombosis in presence of heparin or LMWH
  3. Thrombosis, inflammation at site of SQ injection

II. ORDER PROCESSING

- **a.** Upon receipt of order, get non-formulary approval and/or notify Sylvia Martin Stone (x32890) or DI (x33784) of case
  1. Upon approval, order 'HIT Panel' (includes PF4, SRA and pathology consult if necessary) and appropriate labs (see III. below)
- **b.** Leave message with case specifics at x32890 (Sylvia) or x 33784 (DI)

III. LABORATORY TESTS – WITHIN 24 HOURS PRIOR TO STARTING LEPIRUDIN/ARGATROBAN *(if > 24 hours, reorder STAT)*

- **a.** CBC & Scr
- **b.** aPTT/PT/INR – if not within normal range at baseline, please call DI (x33784) or Clinical Coordinator (pager 3092) for recommendations prior to starting therapy; do not start if aPTT ratio is **≥ 2.5 x** baseline
  1. aPTT ratio: patient's current aPTT/baseline aPTT
- **c. Argatroban only:** LFT panel (AST/ALT/Alk Phos/total bilirubin/albumin) if not done in last **48 hours.**

*****Report newly abnormal values to physician prior to starting lepirudin/argatroban*****

IV. DETERMINE TARGET aPTT

- **a.** Use **patient** baseline aPTT (if patient baseline not available, lab baseline can be used – see monitoring sheet)

INDICATION	LEPIRUDIN	ARGATROBAN
	GOAL	
HIT w/o thrombosis (i.e. isolated HIT)	1.5 - 2. x aPTT	1.5 – 3. x aPTT
HITTS w/ thrombosis	1.5 - 2. x aPTT	
Thrombosis prophylaxis in patient with +PF4 within 3 months	1.5 - 2. x aPTT	

V. INITIATION OF LEPIRUDIN

a. 1ST STEPS

1. If patient is on **warfarin** at initiation of lepirudin, **DC warfarin** (unless patient is on 'bridge therapy') until platelet counts recover & **ORDER Vitamin K 5mg PO STAT**
2. If not already done by MD, **DISCONTINUE** heparin in any form and by any route (LMWH, intravenous, subcutaneous, flushes, dialysis anticoagulation, TPN).
3. For ASA >162 mg/day, **call MD** for order to reduce dose to 162mg or DC (except in cardiac cases).
4. aPTT should be monitored **every 4 hours** until therapeutic x 2, especially at initiation of therapy
5. Write order for 'No IM injections while on lepirudin'
6. Infusion should be prepared as a **standard concentration (50mg/250ml NS = 0.2mg/ml)**
7. If patient on heparin infusion, wait **3 hours** prior to initiating lepirudin; if on LMWH, wait **8 hours**
8. Dosing: use ***actual body weight***, maximum dosing to 110 kg

b. LEPIRUDIN DOSING PROTOCOL BY INDICATION & RENAL FUNCTION (CRCL<15ML/MIN, USE ARGATROBAN)

Indication	Goal aPTT *(seconds)*	Bolus Dose *(max initial bolus = 44mg)*		Initial Infusion Dose *(max infusion rate = 16.5mg/hour)*			
		CrCl > 60ml/min *(Scr ≤1.5mg/dL)*	CrCl ≤ 60ml/min *(Scr >1.5mg/dL)*	CrCl > 60ml/min *(Scr ≤1.5mg/dL)*	CrCl ≤ 60ml/min *(Scr 1.5mg/dL)*		
					45-60 (1.6-2.0) ↓ 50%	30-44 (2.1-3.0) ↓ 70%	15-29 (3.1-6.0) ↓ 85%
HIT: *without* thrombosis *(aka isolated HIT)*	1.5-2 x baseline	None	None	0.1mg/kg/hr	0.05 mg/kg/hr	0.01 mg/kg/hr	0.01 mg/kg/hr
HITTS: *with* thrombosis *(DVT, PE, Stroke, MI, skin lesions)*	1.5-2 x baseline	0.2mg/kg	None	0.1mg/kg/hr	0.05 mg/kg/hr	0.01 mg/kg/hr	0.01 mg/kg/hr
Thrombosis prophylaxis (*in patients with history of HIT <3months ago and PF4+)*	1.5-2 x baseline	None	None	0.1mg/kg/hr	0.05 mg/kg/hr	0.01 mg/kg/hr	0.01 mg/kg/hr

c. MONITORING PARAMETERS & DOSE ADJUSTMENT

aPTT	Change Rate of Infusion	Next aPTT
< 1.5 x baseline	↑ infusion rate by 20%*	4 hours
1.5 – 2 x baseline (HIT/HITTS)	None	**Next AM** ***(at initiation of therapy, every 4 hours until ratio therapeutic x 2)***
> 2.5 x baseline (or greater than patient's goal)	Hold x 2 hours, then restart at 50% of previous rate	4 hours

***Do not exceed 0.21mg/kg/hr without checking for coagulopathies.**

d. CONVERSION OF LEPIRUDIN TO WARFARIN

1. Initiation of warfarin anticoagulation should not occur until platelets have recovered substantially
   - ≥ 150,000/ml **OR**
   - Return to baseline
2. Prior to initiation of warfarin, decrease lepirudin by 20% increments until aPTT is just above 1.5 x baseline
3. Warfarin per Pharmacy Protocol should be used for dosing in these patients
   - 'Loading' dose is not recommended
   - Initiate with previous daily maintenance dose (if known) or conservative initial dose (2.5mg - **no more** than 5mg)
4. Coadministration of lepirudin and warfarin (combined therapy) may result in increased PT/INR in some patients, although rarely
5. Lepirudin and warfarin therapy should overlap for **at least 4-5 days and until the INR is at the higher end of the patient specific therapeutic range for 2 consecutive days**

e. DISCONTINUATION OF LEPIRUDIN

1. Following discontinuation of lepirudin, recheck INR 4-6 hours later to assure it remains therapeutic
2. Taper lepirudin at 50% increments over 8 hours (i.e., decrease 50% for 4 hours, then decrease 50% for another 4 hours, then DC.)
3. In case of emergent situation (i.e., surgery, procedure), lepirudin can be discontinued more quickly.

VI. INITIATION OF ARGATROBAN

a. 1ST STEPS

1. If patient is on **warfarin** at initiation of argatroban, **DC warfarin** (unless patient is on 'bridge therapy') until platelet counts recover & **ORDER vitamin K 5mg PO STAT**
2. If not already done by MD, **DISCONTINUE** heparin in any form and by any route (LMWH, intravenous, subcutaneous, flushes, dialysis anticoagulation, TPN)
3. For ASA >162 mg/day, **call MD** for order to reduce dose to 162mg or DC (except in cardiac cases).
4. aPTT should be monitored **every 2 hours** until therapeutic x 2 especially at initiation of therapy
5. Write order for 'No IM injections while on argatroban'
6. If patient on heparin infusion, wait **3 hours** prior to initiating argatroban; if on LMWH, wait **8 hours**
7. Infusion should be prepared as **a standard concentration (250mg/250ml NS = 1mg/ml)**
8. Dosing: use ***actual body weight***

b. ARGATROBAN DOSING PROTOCOL FOR NORMAL & IMPAIRED HEPATIC FUNCTION (TOTAL BILIRUBIN ≥1.5MG/DL)/HEPATIC-RENAL IMPAIRMENT (TOTAL BILIRUBIN ≥1.5MG/DL & SCR ≥ 2.5 MG/DL)

1. Dosing does not differ between HIT/HITTS
2. Goal aPTT – 1.5-3.0 x baseline
3. **Normal Hepatic Function:** 2 mcg/kg/**min** (not to exceed 10 mcg/kg/min) or 120 mcg/kg/**hour** (not to exceed 600 mcg/kg/hour)
4. **Impaired Hepatic Function,hepto-renal insufficiency*, heart failure, severe anasarca, or s/p cardiac surgery:** 0.5 mcg/kg/**min** (not to exceed 10 mcg/kg/min) or 30 mcg/kg/**hour** (not to exceed 600 mcg/kg/hour)
5. **Critically Ill Patients* (MSOF, sepsis, respiratory failure, pressor support, CRRT)**
   - Initiate with 0.2 mcg/kg/min; adjust per table below

c. MONITORING PARAMETERS & DOSE ADJUSTMENTS

aPTT	Change Rate of Infusion		Next aPTT	
	Normal Hepatic Function	**Impaired Hepatic Function/Critically Ill*** *Total Bilirubin ≥1.5mg/dL*	**Normal Hepatic Function**	**Impaired Hepatic Function/Critically Ill*** *Total Bilirubin ≥1.5mg/dL*
1.0 – 1.2 x baseline	+ 1.0 mcg/kg/min *(+ 60 mcg/kg/hour)*	+ 0.2 mcg/kg/min *(+ 12 mcg/kg/hour)*	2 hours	4 hours
1.3 – 1.4 x baseline	+ 0.5 mcg/kg/min *(+ 30 mcg/kg/hour)*	+ 0.1 mcg/kg/min *(+ 6 mcg/kg/hour)*	2 hours	4 hours
1.5 – 3.0 x baseline**	None	None	**Next AM** ***(at initiation of therapy, every 2 hours until ratio therapeutic x 2)***	**Next AM** ***(at initiation of therapy, every 4 hours until ratio therapeutic x 2)***
3.1 – 3.5 x baseline	- 0.5 mcg/kg/min *(- 30 mcg/kg/hour)*	- 0.1 mcg/kg/min *(- 6 mcg/kg/hour)*	2 hours	4 hours
> 3.5 x baseline	- 1.0 mcg/kg/min *(- 60mcg/kg/hour)*	- 0.2 mcg/kg/min *(- 12 mcg/kg/hour)*	2 hours	4 hours

Hepato-Renal Impairment: total bilirubin *≥ 1.5 g/ dL & SCr ≥ 2.5 mg/dL

****Unless thrombosis is present, aim for lower end of target aPTT ratio.**

d. CONVERSION TO WARFARIN WHILE ON ARGATROBAN

1. Administration of warfarin and argatroban (cotherapy) produces synergistic increase in INR
   - INR **≥ 4** is due to lab interference and is not usually associated with increased risk of bleeding
2. Initiation of warfarin anticoagulation should not occur until platelets have recovered substantially
   - ≥ 150,000/ml **OR**
   - Return to baseline
3. Warfarin per Pharmacy Protocol should be used for dosing in these patients
   - 'Loading' dose is not recommended
   - Initiate with previous daily maintenance dose (if known) or conservative initial dose (2.5 - **no more** than 5mg)
4. **Cotherapy** (warfarin & argatroban) should continue for **at least 4-5 days <u>and</u> until the INR is ≥ 4 for 2 consecutive days.**
   - If argatroban dose is **≤ 2 mcg/kg/min and #4 above has occurred:**
     - HOLD argatroban and measure INR in 6 hours (this value is INR on warfarin 'alone')
     - Restart argatroban immediately after INR is drawn
     - If INR in desired range, continue argatroban/warfarin cotherapy **until the INR on warfarin alone is therapeutic for 2 consecutive days**
     - If INR < desired range, continue argatroban/warfarin cotherapy and repeat INR daily as outlined above
   - If argatroban dose is **≥ 2 mcg/kg/min**
     - Decrease dose to **≤ 2 mcg/kg/min**
     - Measure INR 4-6 hours later and follow steps above

e. DISCONTINUING ARGATROBAN

1. Following discontinuation of argatroban, recheck INR 4-6 hours later to assure it remains therapeutic
2. Taper argatroban at 50% increments over 8 hours (i.e., decrease 50% for 4 hours, then decrease 50% for another 4 hours, then DC.)
3. In case of emergent situation (i.e., surgery, procedure), argatroban can be discontinued more quickly, but anticoagulant effect may be prolonged to 4-5 hours in setting of impaired hepatic function.

VII. PHARMACIST ORDERS

Upon receipt of an order for DTI therapy:

a) ORDER:

i) 'HIT Panel' (includes PF4, SRA and pathologists consult if needed)
   (1) If PF4 already ordered by MD, DC PF4 order and order ***"HIT Panel"***

ii) CBC & SCr – if not yet drawn or values are >24 hours ago

iii) aPTT/PT/INR – if not yet drawn or values are >24 hours ago

iv) ***Argatroban only***: LFT panel (AST/ALT/Alk Phos/total bilirubin/albumin) if available values are >48 hours ago.

b) DISCONTINUE:

i) Heparin in any form and by any route (LMWH, intravenous, subcutaneous, flushes, dialysis anticoagulation, TPN)

ii) For **non-cardiac** cases on ASA >162 mg/day, call MD for order to **either** DC or **decrease** dose of ASA to 162mg/day (except in cardiac cases).

c) If patient is on **WARFARIN** at initiation of lepirudin OR argatroban and it is NOT for 'bridge therapy' (patient with recent hx of HIT on warfarin being bridged with DTI instead of heparin):

i) **DC** warfarin

ii) **ORDER** Vitamin K 5mg PO STAT

Please contact Sylvia Martin Stone (x32890)/DI (x33784)/AOD with any DTI orders.

VIII. REFERENCES

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Fragmin® Dosing Chart for Formulary Indications *(Updated 11/12/08)*	
	Dalteparin (Fragmin®)[1]
Hip replacement surgery prophylaxis [2]	5000 International Units sq Daily
Knee Replacement surgery prophylaxis[2]	5000 International Units sq Daily
Hip fracture surgery [2]	5000 International Units sq Daily
VTE treatment [2] (DVT or PE)	200 International Units /kg sq Daily* 100 International Units/kg SQ Q12H: obese (BMI ≥30 or >98 kg)
Prophylaxis of ischemic complications associated with UA/NQWMI [3]	**Fragmin® NOT recommended** **DO NOT AUTO-SUB FOR LOVENOX®** **Lovenox® 1 mg/kg SQ Q12H****
Neurosurgery [2]	5000 International Units sq Daily
Trauma [2]	5000 International Units sq Daily Start ASAP, preferably within 48hours of admission. Patients with intracranial hemorrhage can be started when sequential head CT scans show cessation of active bleeding.
"Bridge therapy" of warfarin pts hospitalized for invasive procedures or surgery [2]	200 International Units /kg sq Daily 100 International Units/kg SQ Q12H: obese (BMI ≥30 or >98 kg)
Neuraxial anesthesia [4]	Please refer to neuraxial anesthesia guidelines http://www.asra.com/consensus-statements/RAPM-Anticoagulation.pdf

*Evidence does not support superiority of LMWH over unfractionated heparin for these indications

**Clinical data currently favors enoxaparin over dalteparin for ACS. Enoxaparin recommended by ACC/AHA[3].

References: (1) Fragmin® package insert April 2007 (2) Chest guidelines 2008. (3) ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction. J Am Coll Cardiol. 2007 Aug 14;50(7):e1-e157.(4) Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med.* 2003;28(3):172-97.

GUIDELINES FOR ANTICOAGULATION/ANTI-PLATELET/THROMBOLYTIC REVERSAL (UPDATED 11 13 08)

Agent	Reversal agent	Reversal Guideline
Warfarin (Coumadin®) or elevated PT in the absence of warfarin **NO hemorrhage**	Vitamin K	• INR > therapeutic range but < 5.0: Lower the dose or omit the next dose and resume therapy at a lower dose when the INR is within therapeutic range. If the INR is only slightly above the desired range or associated with a transient causative factor, dose reduction may not be necessary. • INR 5.0 – 9.0 and/or no predisposing risk factors: o Option 1: Omit the next 1-2 doses, and resume therapy at a lower dose when the INR is within the desired range o Option 2: Omit a dose and give vitamin K_1 (1-2.5 mg PO), especially if the patient is at increased risk for bleeding. For patients requiring more rapid reversal before urgent surgery, give vitamin K_1 2 to 4 mg PO (INR reduction will occur in 24 hours). If INR is still high, an additional dose of vitamin K_1 1- 2 mg may be given. • INR > 9.0: Hold warfarin therapy and resume therapy at a lower dose **AND** Give vitamin K_1 2.5 to 5 mg PO (INR can be expected to reduce substantially in 24 to 48 hours). Monitor INR and administer additional vitamin K_1 if necessary.
Warfarin (Coumadin®) or elevated PT in the absence of warfarin **Active hemorrhage**	Vitamin K and FFP[1-6]	Order 2 to 4 units FFP (and begin thawing) • 10-20 mL/kg over 90 minutes (Each unit of FFP contains ~ 200 mL) o Administration of FFP @ 10 mL/kg is rarely associated with a risk of volume overload and congestive heart failure, but higher doses may lead to volume overload. Administer Vitamin K (10mg IV) and give with FFP, for prolonged correction of anticoagulation • When administered intravenously, the rate should not exceed 1mg/minute. o http://web.csmc.edu/resources/policies/iv/P/Phytonadione_(Vitamin%20K)$P-220.PDF o Intravenous vitamin K is associated with a small risk of severe allergic reaction.
	Platelet transfusion and DDAVP	• Consider platelet transfusion or DDAVP or platelet function assay (PFA-100) for those patients on concomitant antiplatelet therapy (see below)
	Follow up therapy	• STAT PT/INR q 4 hrs x 24; then q 6 hrs x 36; then as needed. • If the INR is > 1.3 at 4 hours after FFP administration, administer second dose of Vitamin K 10 mg IV and infuse a second dose of FFP (10 ml/kg over 90 minutes) • If the INR is > 1.3 at 8 hours, evaluate the patient for disseminated intravascular coagulation (repeat D-dimer, fibrinogen) or liver failure. • Vitamin K 10mg SQ daily for 3 days
	Factor IX Complex (Profilnine®)[1-6]	• Factor IX should be considered as a first line agent for INR >20 with serious hemorrhage, intracerebral or other life threatening hemorrhage • Obtain baseline coagulation profile and blood type & screen • Consent is required as Factor IX is considered a blood product • Thrombotic risk should be discussed with the patient's family • Administer 2000 units (2 vials) of Factor IX Complex (Profilnine®) immediately (1 vial = 1000 units) o Administer 3000 units (3 vials) of Factor IX Complex if patient weight > 90 kg o **NOTE: SOME VIALS VARY IN THE NUMBER OF UNITS PER VIAL SO USE AS MANY VIALS AS WILL APPROXIMATE THE TOTAL DOSE ORDERED** o Do not exceed administration rate of 10 ml/minute. • Alert Blood Bank that Factor IX Complex is being utilized (Phone: 310-423-5411) • **Guidelines continue on the next page**

GUIDELINES FOR ANTICOAGULATION/ANTI-PLATELET/THROMBOLYTIC REVERSAL (UPDATED 11 13 08)

Active hemorrhage (Con't)	Factor IX Complex (Profilnine®)[1-6] (con't)	• Recheck PT 10 minutes after infusion of Factor IX Complex to verify effect. o This must be a new blood draw o Repeat Factor IX Complex at 2000 units (2 vials) if repeat INR ≥ 3 o Repeat Factor IX Complex at 1000 units (1 vial) if repeat INR <3 for a desired INR goal of 1.3-1.4 • **Warning:** Be aware that rapid reversal of anticoagulation could lead to thrombosis or DIC, confounding the initial reason that the patient was on Coumadin. This concern is increased in patients with liver failure.
Oral Anti-platelet agents	**Reversal agent**	**Reversal Guideline**
• Aspirin • Aspirin/dipyridamole (Aggrenox®)	Platelet transfusions[7]	• There is no specific antidote for these agents, thus efficacy of the agents below remains uncertain • Platelet transfusion is the optimal approach for reversal, however the optimal # of platelets to be transfused in uncertain • Consider ordering platelet function assay (PFA-100)
• Clopidogrel (Plavix®) • Ticlopidine (Ticlid®)	Platelet transfusions and DDAVP[7-10]	• There is no specific antidote for this agent, thus efficacy of the agents below remains uncertain • Platelet transfusion is the optimal approach for reversal, however the optimal # of platelets to be transfused in uncertain o In a study of 11 healthy subjects, patients loaded (300-600 mg) with clopidogrel, followed by ASA 325 mg and clopidogrel 75 mg daily X 2 days 10-12.5 platelet concentrate units were needed for complete reversal of platelet function[8] • Consider ordering platelet function assay (PFA-100) • Consider administering DDAVP (0.3 microgram per kg[9-10]) over 30 minutes and 1 platelet pheresis concentrate (equivalent to 6-10 individual platelet packs) o An additional dose of DDAVP or an additional platelet transfusion may be required o Caution: Serial doses are associated with tachyphylaxis, hyponatremia and seizures[24] o IV policy: http://web.csmc.edu/resources/policies/iv/D/Desmopressin_(DDAVP)$D-110.PDF • Clopidogrel is ***not*** removed by dialysis[7]
IIb/IIIa inhibitors	**Reversal agent**	**Reversal Guideline**
• Abciximab (Reopro®)	Platelet transfusions[7,11-13]	• There is no specific antidote for this agent, thus efficacy of the agents below remains uncertain • Abciximab (Reopro®) o Platelet transfusion is the optimal approach for reversal, however the optimal # of platelets to be transfused in uncertain[7,11-13] ▪ In 1 clinical trial of 12 patients undergoing emergency CABG, average transfusion requirements were as follows: RBC (3.6 units), apheresis platelets (1.4 units), FFP (1.5 units) [12] o Without treatment platelet function generally returns to ~50% of baseline w/in 48 hours of discontinuation o Abciximab is ***not*** removed by dialysis

• Eptifibatide (Integrellin®) • Tirofiban (Aggrastat®)	Platelet and FFP/ cryoprecipitate transfusions[7, 14-15]	• There is <u>no specific antidote</u> for this agent, thus efficacy of the agents below remains uncertain • Eptifibatide (Integrellin®) and Tirofiban (Aggrastat®) o Platelet transfusions alone may not be adequate, FFP/cryoprecipitate may be needed[15] o ***The studies below suggests that up to 8 units FFP and 2 units of single-donor platelets may be required:*** ▪ In 24 healthy volunteers: platelet aggregation was inhibited by 40-50%, but reversal was achieved with fibrinogen in a concentration-dependent manner. ▪ In vitro experiments: recovery of platelet aggregation to ≥ 50% was achieved after the addition of fibrinogen (0.76-0.80 g/L), platelets (2.4×10^{11}/L), or their combination. Inverse relationship bet. baseline fibrinogen and amount of supplemental fibrinogen to restore platelet aggregability (r = -0.60;*P* <.01). o Without treatment platelet function generally returns to normal within 4-8 hours o Eptifibatide/tirofiban are removed by dialysis
Heparin, Low molecular weight heparin, Direct Xa inhibitor	**Reversal agent**	**Reversal Guideline**
• Unfractionated Heparin (UFH)	Protamine[16,20]	• 1mg protamine neutralizes 100 units UFH (based on the dose given over last 4 hours) [16,20] o Undiluted solution given IV push slowly ▪ Not exceed (NTE) 5 mg / minute (bradycardia and hypotensive risk) o IV policy: http://web.csmc.edu/resources/policies/iv/P/Protamine$P-300.PDF • Follow up PTT monitoring: o STAT PTT q1 hour for the next 4 hours o Then Q4H X 12 hours o Then Q24H X 3 days
• Dalteparin (Fragmin®) • Tinzaparin (Innohep®)	Protamine[16-17]	• 1 mg protamine to neutralize 100 anti-Xa units dalteparin o Undiluted solution given IV push slowly over 1-3 minutes NTE 5 mg / minute • May repeat in 2-4 hours after checking aPTT o 0.5 mg/100 anti-Xa units if aPTT continues to be prolonged • **Caution:** Even with higher doses of protamine the aPTT may remain more prolonged vs heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum 60%) • Dalteparin/tinzaparin are ***not*** removed by dialysis[7]
• Enoxaparin (Lovenox®)	Protamine[16, 18]	• <u>If given < 8 hours after last dose</u>: 1 mg protamine to neutralize 1 mg enoxaparin • <u>If given > 8 hours after last dose or if readministration is necessary</u>: 0.5 mg protamine to neutralize 1 mg enoxaparin o Undiluted solution given IV push slowly over 1-3 minutes NTE 5 mg / minute • **Caution:** Even with higher doses of protamine the aPTT may remain more prolonged vs heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum 60%) • Enoxaparin is ***not*** removed by dialysis[7]
• Fondaparinux (Arixtra®)	Factor VIIa[19-21]	• There is <u>no specific antidote</u> for this agent, thus efficacy of the agents below remains uncertain • Factor VIIa has only been studied in healthy patients[20-21] and case reports o 90 mcg/kg has been utilized • Fondaparinux is removed by dialysis and may increase clearance by ~20%[19]

GUIDELINES FOR ANTICOAGULATION/ANTI-PLATELET/THROMBOLYTIC REVERSAL (UPDATED 11 13 08)

Direct Thrombin Inhibitors	Reversal agent	Reversal Guideline

• Argatroban®
• Lepirudin (Refludan®)
• Bivalirudin (Angiomax®)
	DDAVP
	Cryoprecipitate
	FFP
	Aminocaproic acid (Amicar®) or Tranexamic acid (Cykolkapron®) [23-27]
		• There is <u>no specific antidote</u> for these agents, thus efficacy of the agents below remains uncertain
		• DDAVP: 0.3 mcg/kg IV, may repeat if necessary in 8-12 hours[23-26]
		  o Caution: Serial doses are associated with tachyphylaxis, hyponatremia and seizures
		• The optimal amounts of cryo and FFP to be transfused remains uncertain
		  o Cryoprecipitate: ≥ 10 units[23]
		  o FFP: 2 units (limited efficacy)[23]
		• Antifibinolytic therapy (Caution in patients being treated for HIT: increased risk for thrombosis):
		  o Aminocaproic acid (Amicar®)[23]:
		  ▪ Bolus: 0.1-0.15 gm/kg IV over 30 minutes
		  ▪ Continuous infusion: 0.5-1 gm/h until bleeding ceases
		  o Tranexamic acid (Cyklokapron®)[23]:
		  ▪ 10 mg/kg Q6H-Q8H until bleeding subsides
		• Dialysis, hemofiltration, plasmapheresis
		  o Lepirudin is optimally removed by the use of high-flux dialyzers with polysulfone membranes [26-30]
		  ▪ Hemofiltration and plasmapheresis also appear to be effective[27]
		  o Bivalirudin is removed by hemofiltration (in vitro[32], 1 case report[31]) (~65% removed) or plasmapheresis filter (~69% removed)
		  ▪ Hemofilteration may be preferred b/c it does not remove coagulation factors
		  o Argatroban® is ***not*** removed by dialysis[34-35]

Thrombolytics	**Reversal agent**	**Reversal Guideline**

• tPA (Alteplase/Activase®)
• Reteplase (Retavase®)
• Streptokinase (Streptase®)
• Tenecteplase (TNKase®)
• Urokinase (Kinlytic®)
	Platelet transfusion
	Cryoprecipitate
	FFP
		• There is <u>no specific antidote</u> for these agents, thus efficacy of the agents below remains uncertain
		• STAT head CT, if ICH suspected and consult Neurosurgery for ICH
		• Check CBC, PT, PTT, platelets, fibrinogen and D-dimer. Repeat q 2 h until bleeding is controlled
		• Institute frequent neurochecks and therapy of acutely elevated ICP, as needed
		• If patient received concomitant heparin (see protamine reversal above)
		• The optimal amounts of platelets, cryo and FFP to be transfused remains uncertain[7,23]:
		  o Cryoprecipitate 10-20 units
		  ▪ If fibrinogen level < 200 mg/dL at 1 hr, repeat cryoprecipitate dose.
		  o Platelet transfusion: 10 Units
		  ▪ Especially useful if patient is thrombocytopenic[23]
		  ▪ Repletes factor V, which may be depleted[23]
		  o FFP: 2 units, every 6 hours for 24 hours after dose
		  ▪ Repletes factor V, which may be depleted[23]
		• Thrombolytic removal by dialysis has not been studied[7]

GUIDELINES FOR ANTICOAGULATION/ANTI-PLATELET/THROMBOLYTIC REVERSAL (UPDATED 11 13 08)

Platelet disorders	Reversal agent	Reversal Guideline
Thrombocytopenia (platelet count < 100,000/uL)	Platelet transfusion	• Transfuse with platelets until platelet count exceeds 100,000/uL.
Von Willebrand syndrome	Von Willebrand Factor DDAVP	▪ Recommendations from the NHBLI/NIH Management of Von Willebrand disease management of major bleeding episodes[37] (1) Order a loading dosing: 40-60 VWF:RCo international units/dL /kg X 1 (2) Phone consult with a staff member of hematology or transfusion medicine for further doses of VWF factor concentrate • Usual maintenance dose: 20-40 units/kg Q8H to Q24H • Monitoring: VWF:RCo and Factor VIII trough and peak at least daily o Therapeutic goal: ▪ Initial goal: VWF:RCo and factor VIII > 100 international units/dL ▪ Trough VWF:RCo and factor VIII > 50 international units/dL for 7-10 days o Safety: Do not exceed VWF:RCo 200 international units/dL or factor VIII > 250-300 international units/dL ▪ May alternate with DDAVP for the later part of treatment • DDAVP 0.3 mcg/kg DDAVP given IV over 30 minutes
Uremic platelet dysfunction Congenital platelet function disorders	DDAVP	▪ DDAVP 0.3 mcg/kg DDAVP given IV over 30 minutes

Protocol for Dosing Antimicrobials ("Per Pharmacist") in Adults

Inclusion: **Physician order for Pharmacist to dose any of the antibiotics below**
Exclusions: **Meningitis (except if outlined below), Endocarditis, Osteomyelitis**
(The Pharmacist must contact the Physician to discuss alternative dosing**.** The order must be written as a telephone order)

Procedure:

1. Determine the correct dose from the table below (requires calculation of creatinine clearance)
2. Write the appropriate order in the chart.
3. No ongoing patient monitoring is required. To assure the prescriber is aware the order must state the following: "*Please contact the Department of Pharmacy if additional dosage adjustment is needed"*

Agent	Route	Usual Adult Dose	ClCr (mL/min)	Suggested Dosage Regimen for Renal Impairment	HEMO-Dialysis Dosing	Suggested Dosing in Obesity (where obesity is >140% IBW) (Adjust interval accordingly for creatinine clearance) *Note: "corrected weight" different for each drug*
Acyclovir (Zovirax®)	PO	**Varicella zoster and immunocompromised:** 800 mg q4h (Max dose/day: 4 gm)	10-25 <10	800 mg q8h 800 mg q12h	Give dose immediately after HD[b] and re-adjust q12h admin time in the MAR	No change
	IV	**Herpes simplex mucocutaneous infxns: 5 mg/kg IBW q8h** **Varicella zoster in immunocompromised:** 10 mg/kg IBW q8h **Encephalitis:** 12.5 mg/kg IBW q8h	25-50 10-24 <10	q12h q24h 50% of dose q24h	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR	Same doses as listed in "Usual Adult Dose" column EXCEPT: For encephalitis: 15 mg/kg IBW q8h
Ampicillin (Omnipen®, Polycillin®)	IV	1 gm q6h 2 gm q4h for meningitis	10-50 <10	q8h (2 gm q6h-q8h meningitis) q12h (2 gm q12h meningitis)	Give dose immediately after HD[b] and re-adjust q12h admin time in the MAR	***Non CNS infections***: 2 gm q6h ***Meningitis and <200% IBW***: 2gm q4h ***Meningitis and > or = 200% IBW***: 170 mg/kg *corrected weight*/day in 6 divided doses (where *corrected weight* = IBW + (0.3 X TBW-IBW in kg)) ***Round final dose to nearest 250 mg increment*** *****Must contact prescriber to discuss dose correction in meningitis AND TBW >200% *****
Cefazolin (Ancef®, Kefzol®)	**IV**	1 gm q8h (2 gm for SSTI[a])	10-30 <10	q12h q24h	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR	2 gm q8h
Cefotaxime (Claforan®)	**IV**	1 gm q8h (2 gm for SSTI[a]) 2gm q4h for meningitis	10-50 <10	q12h (2 gm q6h-q8h for meningitis) q24h (2gm q12h for meningitis)	Give dose immediately after HD[b] and	***Non CNS infections***: 2 gm q6h ***Meningitis and <200% IBW***: 2 gm q4h ***Meningitis and > or = 200% IBW***: 170 mg/kg *corrected weight*/day in 6 divided doses

Agent	Route	Usual Adult Dose	ClCr (mL/min)	Suggested Dosage Regimen for Renal Impairment	HEMO-Dialysis Dosing	Suggested Dosing in Obesity (where obesity is >140% IBW) (Adjust interval accordingly for creatinine clearance) *Note: "corrected weight" different for each drug*
					re-adjust q24h (q12h for meningitis) admin time in the MAR	(where *corrected weight* = IBW + (0.3 X TBW-IBW in kg)) ***Round final dose to nearest 250mg increment***
Cefepime (Maxipime®)	**IV**	1 gm Q12H (2 gm for non-ICU F/N and SSTI[a]) 2 gm Q8H for F/N in ICU or meningitis	30-59 10-29 <10	1 -2 gm q24h (2 gm q12 F/N in ICU, SSTI[a] or meningitis) 500 mg-1 gm q24h (1 gm q12h F/N in , SSTI[a] or meningitis) 250-500 mg q24h (1 gm q24h F/N in ICU, SSTI[a] or meningitis)	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR	***Non CNS infection***: 2 gm q12h ***Meningitis or non-ICU F/N AND <200% IBW***: 2 gm q8h ***Meningitis or F/N in ICU AND > or = 200% IBW***: 170 mg/kg *corrected weight*/day in 6 divided doses (where *corrected weight* = IBW + (0.3 X TBW-IBW in kg)) ***Round final dose to nearest 250 mg increment*** *****Must contact prescriber to discuss dose correction in meningitis AND TBW ≥200% *****
Cefuroxime (Zinecef®, Ceftin®)	**IV**	750 mg q8h	10-20 <10	q12h q24h	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR	1.5 gm q8h
	PO	500 mg q12h	<10	q24h	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR	750 mg q12h
Cefotetan (Cefotan®)	**IV**	1g q12h (2 gm for SSTI[a])	<30 <10	q24h q48h	Give 1/4 dose on non-HD[b] days; Give 1/2 dose after HD[b] on HD days and readjust q24h admin time	2 gm q12h
Colistin	**IV**	Serious gram negative infxn: 5 mg/kg IBW in 2 divided doses	10-50 <10	2.5mg/kg IBW q24h 1.25mg/kg IBW q24h	Give dose immediately after HD[b] and re-adjust q24h admin time in the MAR CRRT[c]: 2 mg/kg IBW q12h	Same dose as listed in "Usual Adult Dose" column EXCEPT: If TBW ≥ 150% IBW then use *corrected weight* (where *corrected weight* = IBW + 0.2(TBW – IBW)) **** Must contact prescriber to discuss dose in patients ≥ 150% IBW ****
Fluconazole (Diflucan®)	PO or **IV**	**Systemic candida:** 400 mg q24h **Systemic Cryptococcus induction:** 400 mg q24h **UTI:** 100 mg q24h	<50	Half of normal dose q24h	Give full dose after HD[b] on HD days ONLY	6mg/kg/day based on *corrected weight* (where *corrected weight* = IBW + 0.3(TBW-IBW)) *Round final dose to nearest 200mg increment* *****Must contact prescriber to discuss doses greater than 800mg based on *corrected weight******

Ganciclovir (Cytovene®)	**IV**	**Induction:** 5 mg/kg IBW q12h x 7-21 days **Maintenance:** 5 mg/kg IBW q24h	50-69 25-49 10-24 <10	**Induction:** / **Maintenance:** 2.5 mg/kg IBW q12h / 2.5 mg/kg IBW q24h 2.5 mg/kg IBW q24h / 1.25 mg/kg IBW q24h 1.25 mg/kg IBW q24h / 0.625 mg/kg IBW q24h See HD dosing / See HD dosing	**Induction:** 1.25 mg/kg IBW TIW after HD[b] **Maintenance:** 0.625 mg/kg IBW TIW after HD[b]	**No recommendation**
Imipenem / Cilastatin (Primaxin®)	**IV**	500 mg q6h	41-70 21-40 6-20	500 mg q8h 250 mg q6h 250 mg q12h	Give dose immediately after HD[b] and re-adjust q12h admin time in the MAR	***** Do NOT use imipenem ***** Contact prescriber to change order to meropenem 2 gm q8h
Levofloxacin (Levaquin®)	**IV or PO**	500-750 mg q24h (750 mg dose ONLY for community and nosocomial pneumonia)	20-49 10-19	750 mg 1st dose, then 750 mg q48 (pneumonia/SSTI[a]) 500 mg 1st dose, then 250 mg q24h 750 mg 1st dose, then 500 mg q48h (pneumonia/SSTI[a]) 500 mg 1st dose, then 250 mg q48h	**Due to q48h dosing**, IF given on HD[b] day, give immediately after HD[b] and re-adjust q48h admin time; NO dose needed if not scheduled to be given on HD[b] day	750 mg q24h **If TBW ≥ 200% IBW, use ciprofloxacin[7] (exception: CAP)** Intravenous ciprofloxacin: 11mg/kg *corrected weight* in 2-3 divided doses (where *corrected weight* = IBW + 0.45(TBW-IBW)
Metronidazole (Flagyl®)	**IV**	500 mg q8h	NA	No dosage adjustment for renal impairment	N/A	500 mg q6h
	PO				N/A	
Piperacillin / Tazobactam (Zosyn®)	**IV**	3.375 gm q6h (4.5 gm q6h for neutropenic fever)	20-40 <20	2.25 gm q6h (3.375 gm for F/N) 2.25 gm q8h (3.375 gm for F/N)	2.25 gm immediately after dialysis on HD[b] days and re-adjust q8h admin times	3.375 gm q4h
Trimethoprim-Sulfamethoxazole (Bactrim®, Septra®)	**PO**	1 DS tab q12h	15-30 <15	1 DS tab q24h or 1 SS tab q12h Not recommended	Not recommended	Same doses as listed in "Usual Adult Dose" column
	IV	***** Doses listed below as TMP component ***** **PCP:** 15-20 mg/kg/day IBW in 3-4 divided doses Meningitis: 20 mg/kg/day IBW/day in 4 divided doses **Systemic bacterial infxn or stenotrophomonas:**10 mg/kg/day IBW in 2-4 divided doses	15-30 <15	PCP 10 mg/kg/day IBW divided q8h Bacterial infection, stenotrophomonas or meningitis: decrease dose by 50% PCP treatment: 8mg/kg/day IBW divided q12h Stenotrophomonas: same as 15 to 30 ml/min Not recommended for other infections	PCP treatment Only: 8 mg/kg IBW after dialysis on HD **days only**	

[a] SSTI (skin and soft tissue infections) include: cellulitis, erysipelas, furuncle/carbuncle, decubitis ulcers, r/o osteomyelitis, animal/human bite, abscess, and necrotizing infections
[b] HD = hemodialysis
[c] CRRT = Continuous renal replacement therapy

1. Micromedex and AHFS 2006; Mendell, Douglas, Bennett's Principles and Practices of infectious diseases: 6th edition
2. Tunkel A. et al. Practice Guidelines for the Management of Bacterial Meningitis CID 2004;39:1267-1284.
3. Cheymol G. Effect of Obesity on Pharmacokinetics. Clinical Pharmacokinetics 2000;39:215-231
4. Wurtz, R. Antimicrobial Dosing in Obese Patients CID 1997;25:112-118.
5. Manufacturer's Product Information. Various drugs
6. More data with ciprofloxacin in dosing patients with extreme obesity in comparison to levofloxacin. Ciprofloxacin should not be used for CAP
7. Mofenson LM, Oleske J, Serchuck L, et al: Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004; 53(RR-14):1-92.

CEDARS-SINAI MEDICAL CENTER

DEPARTMENT OF PHARMACY SERVICES

TO DOCTOR		ID #
FROM CLINICAL PHARMACIST		
PAGER #	EXT.	DATE

This is **a permanent** part of the patient's medical record.

Addressograph

ATAZANAVIR (REYATAZ®) DRUG INTERACTION WITH ACID SUPPRESSING AGENTS

To Doctor_____ ID#: _____

Your patient was prescribed:

Atazanavir and ☐ **esomeprazole ____mg IV/PO q_____** **OR**

☐ **ranitidine ____mg IV/PO q____**

This combination will lead to decreased Atazanavir levels and potential treatment failure.
~~See b~~Below is Department of Health and Human Services' ~~for specific~~ recommendations:

Esomeprazole
Do not use esomeprazole in treatment experienced patients (alternatively consider ranitidine). Treatment naïve patients should not receive doses exceeding 40mg daily of esomeprazole.

Ranitidine
Use ranitidine 150mg PO BID or 50mg IV q8hours with boosted atazanavir to increase antiviral levels (Atazanavir 300mg + Ritonavir 100mg daily). IF unable to use ritonavir, then a dose of atazanavir 400mg is recommended.

Clinical Pharmacist: _____ Pager#:_____ Ext: _____

For more information:
Department of Health and Human Services: http://aidsinfo.nih.gov/contentfiles/AA_Tables.pdf (see Table 15a)

CEDARS-SINAI MEDICAL CENTER

DEPARTMENT OF PHARMACY SERVICES

TO DOCTOR		ID #
FROM CLINICAL PHARMACIST		
PAGER #	EXT.	DATE

Addressograph

This is a *permanent* part of the patient's medical record.

LINEZOLID (ZYVOX®) DRUG INTERACTIONS

Your patient was prescribed linezolid and is receiving one of the agents in the table below

Linezolid is a weak reversible non-selective monoamine oxidase inhibitor, which may lead to the development of serotonin syndrome when co-administered with serotonergic agents or hypertension when co-administered with adrenergic agents. Serotonin syndrome often occurs within 24 to 48 hours of co-administration. Symptoms include **tachycardia, tremor, hypertension, agitation, diaphoresis, confusion, clonus, and hyper-reflexia**. A recent retrospective study reported an incidence of 3%[1]. Hypertension can occur immediately with the co-administration of linezolid and adrenergic agents, amphetamines and OTC cold preparations.

Medication category	Some Specific Drugs			Possible consequence
Anti-depressants ***(MAOIs are CONTRAINDICATED – alternative antibiotic therapy is necessary)***	***MAOIs (Contraindicated)*** • Isocarboxazid • Phenelzine • Selegiline • Tranylcypromine	***TCAs*** • Amytriptiline • Amoxapine • Clomipramine • Desipramine • Doxepine • Imipramine • Maprotiline • Nortriptyline • Protriptyline • Trimipramine	***SSRIs*** • Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline ***Other*** • Bupropion • Desvenlafaxine • Duloxetine • Mirtazapine • Trazodone • Venlafaxine	Serotonin syndrome
Other serotonergic agents	• Dextromethorphan • Meperidine	• Tramadol • 5-HT_1 agonists		Serotonin syndrome
Alpha agonists	• Dopamine • Norepinephrine	• Phenylephrine • Phentermine • Amphetamines		Accentuated pressor response (hypertension)

Recommendations:

1. Linezolid is the drug of choice for infections caused by vancomycin-resistant enterococci (VRE). Alternatives are considered inferior.
2. Consider decreasing antidepressant dose to help lower risk of serotonin syndrome (except fluoxetine)
3. If serotonin syndrome is suspected, consider discontinuing **one or both agents**
4. Cautiously titrate pressor drugs and discontinue decongestants

This letter has also been faxed to your office at _____

Clinical Pharmacist: _____ _____ Pager#: _____ Ext: _____

[1]Clinical Infectious Diseases 2006;43:180-7
http://www.fda.gov/medwatch/safety/2008/jun08.htm#Zyvox

CEDARS-SINAI MEDICAL CENTER
DEPARTMENT OF PHARMACY
VANCOMYCIN PROTOCOL
(Revised 10/24/08)

The dosing of vancomycin as specified in this policy should be followed if the physician orders "vancomycin per protocol", "vancomycin per Pharmacy", or similar language. **This protocol covers orders for prophylaxis and treatment of infection.**

A. PROPHYLAXIS DOSING (PERIOPERATIVE) AS ORDERED BY SURGEON/PHYSICIAN

Definition: Duration of antibiotic use is determined from time of pre-op/pre-incisional dose (time charted in nursing intra-op record through WebVS system or anesthesia record).

1. LOADING DOSE (pre-op/pre-incisional dose):

a. If written as "Per Pharmacy" on pre-op orders, use 15 mg/kg based on total body weight (generally written by physician as "Vancomycin 1 gram IVPB pre-op").

b. IF the administered loading dose ordered by a physician was much greater than 15 mg/kg, use clinical judgment for timing of maintenance dose. Be sure that the last dose is not given outside of the 24 or 48 window for prophylaxis.

2. MAINTENANCE DOSE

a. CABG or Cardiac Surgery (48 hour prophylaxis)

i. Calculate CrCl and determine dose, frequency and number of doses from the table below

ii . Order Serum Creatinine if not available in previous 48 hours

a) If order received 12 hours after pre-op/pre-incisional dose, give next dose now and base subsequent doses on CrCl

b) If order received within 8 hours of pre-op/pre-incisional dose, hold further dosing until serum creatinine available, then base number of doses on CrCl and table below.

b. Other surgeries (24 hour prophylaxis)

i. If serum creatinine available and calculated CrCl > 40 ml/min, give one dose per table below

ii. If NO serum creatinine available, give one 12 mg/kg dose 12 hours after pre-op/pre-incisional dose unless patient is known to be on hemodialysis, then no more doses

MAINTENANCE DOSE AND DURATION FOR SURGICAL PROPHYLAXIS

For Joint Commission core measure* compliance, be certain the timing of the last dose is not administered 24 or 48 hours beyond the dose given pre-op

Surgery Type	Duration of Prophylaxis (beginning w/ pre-op dose)	# of Doses post surgery CrCl > 70	# of Doses post surgery CrCl 40-69	# of Doses post surgery CrCl 20-39	# of Doses post surgery CrCl < 19
CABG, Cardiac Surgery	**48 hrs**	**15 mg/kg q8hrs x 5**	**12 mg/kg q12hrs x 3**	**12 mg/kg q24hrs x 1**	**Zero**
All other	**24 hrs**	**15 mg/kg q12hrs x 1**	**12 mg/kg q12hrs x 1**	**Zero**	**Zero**

* Core measure surgical procedures include CABG, other cardiac, Colon, Hip, Knee, Abdominal or Vaginal hysterectomy, and Colorectal surgeries.

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- Post-op orders state duration of prophylaxis (24 or 48 hrs); however, post-op ICU transfer orders do not state the duration needed, therefore reference table above
- For CABG and cardiac surgery patients with a CrCl greater than 70 ml/min: give only 4 post-op doses IF first post-op dose is given more than 15 hours after pre-op/pre-incisional dose
- e.g:
  65 kg patient with estimated CrCl of 89 ml/min S/P cardiac surgery
  Pre-op dose given at 0753 on 10/21/08
  First post-op dose of 1 gram IVPB Q8H due @1600 on 10/21/08
  5th (final) dose @2400 on 10/22/08 to complete 48 hours of prophylaxis

3. Monitoring and Documentation

a. No ongoing monitoring necessary (no monitoring form to be filled out)
b. No documentation in progress notes necessary
c. Write order for dose, number of doses, and time of next dose

B. TREATMENT DOSING

1. LOADING DOSE: 15 mg/kg (all patients, **exception for hemodialysis in section 6**), based on total body weight

2. MAINTENANCE DOSE NOMOGRAM (hemodialysis is addressed in section 6 and 7): Initial maintenance dose is based on estimated creatinine clearance for all indications excluding pulmonary and meningeal infections. The monogram below is intended to achieve a steady state trough level of 10-15mcg/ml. Use total body weight (TBW).

All indications EXCLUDING pulmonary, meningeal and parameningeal* infections:

calculated CrCl (mL/min)	Dosing regimen (rounded to the nearest 250mg)
> 70	15 mg/kg every 8 hours
40-69	12 mg/kg every 12 hours
20-39	12 mg/kg every 24 to 36 hours
10-19	12 mg/kg every 48 to 72 hours

**Parameningeal infections include brain abscess, epidural/paraspinal abscess, etc.*

For pulmonary infections, meningitis, parameningeal infections:
Use the CSMC approved PK calculator to determine initial dose to achieve a steady state trough level of >15-20mcg/ml. This will require a dosing interval of at least 8 hours in patients with normal renal function. Careful manipulation of dose and interval will be necessary to determine desired trough.

3. ORDERING A SERUM TROUGH LEVEL:
Order a steady state trough level for **ALL** patients. The level must be drawn one hour or less before the subsequent dose (true trough). Order the trough level before the 4th dose (includes loading dose) since steady state is achieved after 3.3 half lives. For patients who are on q6h or q8h interval, steady state may not be achieved before dose #5 or #6. The trough levels for these patients should be ordered with dose #5 or #6. Peak levels are not indicated in this protocol. The table below shows the target trough level to be obtained based on type of infection.

Indication	Target Serum Trough Range
All infections except those listed below	10-15mcg/ml
Pulmonary infections, parameningeal infections meningitis	>15-20mcg/ml

4. DOSAGE ADJUSTMENT AFTER RECEIPT OF STEADY STATE "TRUE" TROUGH LEVEL

a. Calculate Vd (as above): Vd = 0.17(age in years) + 0.22 (TBW in kg) + 15

b. Calculate Cmax: C_{max} = observed trough + (dose/Vd)

c. Calculate Ke: $\ln$ (Cmax/observed trough)/ τ
(Where τ is dose interval or Tau)

d. Calculate new maintenance dose (MD):
Dose = (desired trough) X Vd X $(1-e^{-K\tau})/ e^{-Ke\tau}$
(Where τ is desired interval or Tau)

e. The interval selected should extend long enough to include one half-life.
(Where $t_{½}$ = 0.693/ Ke)

f. A follow up trough level to confirm target range was achieved is not necessary if renal function is stable.

5. MONITORING & DOCUMENTATION:

a. **Monitoring form:** Protocol patients require daily follow up on the approved monitoring form. Documentation of all findings is critical for communication between shifts AND necessary for internal quality assurance measurements

b. **Progress notes:** Notes should be written in the chart at initiation of therapy, receipt of a vancomycin level, and when there is a dosage change. Notes must include dose and treatment plan. Additional notes may be written when deemed necessary by Pharmacist.

c. **Interdisciplinary Plan of Care:** check off date initiation for infection, drug level goal range and Vancomycin per Rx protocol box

d. **Serum creatinine values:** Order at least every other day. Order for every day if the patient is receiving concomitant nephrotoxins (cyclosporine, tacrolimus, cisplatin, carboplatin, ifosphamide, methotrexate, amphotericin, foscarnet, aminoglycosides, pentamidine, contrast media, high-dose loop diuretics, NSAIDs, or COX2s) or for any special concern about renal function (e.g., if unstable), etc.

e. **Laboratory:** Follow cultures and susceptibilities (day 1, 3, 5 and as needed); WBC counts with differentials, vital signs, and clinical status daily.

f. **Serum levels should be (re)ordered and dosage adjustment made for:**

- **i.** Patients dosed to trough of >15-20mcg/ml must have a trough level drawn <u>every 3 days</u>.
- **ii.** Patients dosed to a trough level of 10-15mcg/ml should have a trough level drawn every 3 days if there are risk factors present for renal insufficiency (e.g., concomitant nephrotoxins, disease states, sepsis, volume depletion, etc.)
- **iii.** ALL patients should have a level drawn at least weekly following the required initial serum level.
- **iv.** Patient is not responding to therapy ie: (↑ WBC, Bandemia, febrile etc.)
- **v.** Changing renal function: Non-steady state conditions require several serum levels to determine when to re-dose the patient. Remember that the above calculations in section 4 do not apply when renal function is changing.

g. **Document specific clinical reason/justification for any deviation from the protocol**

6. HEMODIALYSIS (PolyFlux 140H – a high-flux dialyzer):

Indication	Target trough range	Loading Dose	Maintenance Dose
All infections except those listed below	**10-15 mcg/ml**	**15mg/kg TBW**	**7mg/kg TBW post dialysis**
Pulmonary infections, meningitis and parameningeal infections	**>15-20mcg/ml**	**20mg/kg TBW**	**7mg/kg TBW post dialysis**

a. **Calculation:** After calculating the dose round up to next 50mg increment

b. **Dosage adjustment:** Dosage adjustment is simplified for patients on dialysis. In general the dose is adjusted and the interval remains post dialysis. The following equation below should be used to determine an increase or decrease in the dose.

$$\text{Revised Dose} = \text{Current Dose} \times (C_{\text{desired}} / C_{\text{observed}})$$

c. **Monitoring:** Generally same as section 5 above except draw first level prior to **2nd** dialysis to confirm therapeutic range and every **3rd** dialysis thereafter. Ordering serum creatinine is not necessary for patients with chronic renal failure on dialysis

7. ACUTE DAILY OR IRREGULAR HEMODIALYSIS AND PERITONEAL DIALYSIS

	Acute RF- Hemodialysis (Where dialysis is irregular)	Peritoneal dialysis (PD) (IV therapy only)
Loading dose	15mg/kg TBW	15mg/kg TBW
First serum level (following loading dose)	Before 2nd or 3rd dialysis	48-72 hours (72 hours if no residual RF)
Maintenance dose	[(LD/Vd) – $trough_{measured}$][Vd]* (where Vd = 0.7L/kg X TBW)	[(LD/Vd) – $trough_{measured}$][Vd]** (Where Vd = 0.7L/kg X TBW)
Serum level monitoring	Every 3-4 days	Every 3-4 days
Maintenance interval	Redose as needed to maintain target serum level range	Give every 48-72 hours

* The dose (and renal function) will be more variable in acute hemodialysis versus PD

** A maintenance dose of approximately 8mg/kg is generally expected

8. CONTINUOUS VENOVENOUS HEMODIALYSIS (CVVHD) OR CONTINUOUS VENOVENOUS HEMODIAFILTRATION (CVVHDF) IN THE INTENSIVE CARE UNIT:

Vancomycin clearance while on CVVHDF is measured at 1.8 ± 0.4 liter/hr (30 ± 6.7 ml/min) and half-life is measured at 15.6 ± 8.7 hr.

a. Initial Loading Dose: 15mg/kg TBW
b. Initial Maintenance Dose: 15mg/kg TBW Q24hr
   - If dose exceeds 1750mg, consider dividing total daily dose in 2 and administer Q12hrs
   - Monitor and adjust dose as prescribed in section 3 and 4 of protocol

9. CONTINUOUS VENOVENOUS HEMOFILTRATION IN THE INTENSIVE CARE UNIT:

a. Initial Loading Dose: 15mg/kg TBW
b. Maintenance Dose based on vancomycin random level 36-48 hours after load dose

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FDA News & Warnings*

September – November 2008

* For more information please visit: http://www.fda.gov/medwatch/index.html

Raptiva (efalizumab): Boxed Warning describes risk for life-threatening infections

There has been extensive labeling changes with the use of Raptiva, including a Boxed Warning, to highlight the risks of life-threatening infections, including bacterial sepsis, viral meningitis, invasive fungal disease, progressive multifocal leukoencephalopathy and other opportunistic infections. In addition, the prescribing information will be updated to describe a potential risk for the permanent suppression of the immune system with repeat administration of Raptiva in children. Raptiva is not approved for children under 18 years of age. Prescribers need to evaluate and weigh the risk/benefit profile of Raptiva for patients who would be more susceptible to these risks and monitor carefully. Completion of all vaccinations prior to initiation therapy is important.

Tarceva (erlotinib) - **Cases of hepatic failure and hepatorenal syndrome, including fatalities**

Cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported during use of Tarceva, particularly in patients with baseline hepatic impairment. Patients with hepatic impairment receiving Tarceva should be closely monitored during therapy and the product should be used with extra caution in patients with total bilirubin >3x ULN. Dosing should be interrupted or discontinued if changes in liver function are severe, such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside the normal range. New information from a pharmacokinetic study in patients with moderate hepatic impairment associated with significant liver tumor burden has been provided in the revised package insert.

Epoetin alfa- Preliminary safety findings show more deaths in patients given epoetin-alpha vs placebo

FDA has been made aware of preliminary safety findings from a clinical trial conducted in Germany investigating the use of epoetin alfa to treat acute ischemic stroke. The clinical trial utilized doses of epoetin alfa that were considerably higher than the doses recommended for the treatment of anemia as described in the FDA-approved labeling for the product. Over a period of 90 days after the start of the trial, there were more deaths in the group of patients who received epoetin alfa compared to patients who received the placebo (16% versus 9%). Roughly half of all deaths in both groups occurred within the first seven days after starting the drug, with death from intracranial hemorrhage occurring among approximately 4% of patients who received epoetin alfa compared to 1% of patients in the placebo group.

FDA anticipates the receipt of additional data within the next several weeks. As soon as the review of these data is complete, FDA will communicate our conclusions and recommendations to the public.

Statin drugs and amyotrophic lateral sclerosis (ALS)

An FDA analysis provides new evidence that the use of statins does not increase incidence of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease often referred to as "Lou Gehrig's Disease." The FDA analysis, undertaken after the agency received a higher than expected number of reports of ALS in patients on statins, is based on data from 41 long-term controlled clinical trials. The results showed no increased incidence of the disease in patients treated with a statin compared with placebo.

The FDA is anticipating the completion of a case-control or epidemiological study of ALS and statin use. Results from this study should be available within 6-9 months. FDA is also examining the feasibility of conducting additional epidemiologic studies to examine the incidence and clinical course of ALS in patients taking statins. Based on currently available information, health care professionals should not change their prescribing practices for statins and patients should not change their use of statins.

Rituzan (rituximab)- Safety Information Regarding Progressive Multifocal Leukoencephalopathy

Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study. The patient developed a JC virus infection with resultant PML and death 18 months after taking the last dose of Rituxan. Healthcare professionals treating patients with Rituxan should consider PML in any patient presenting with new onset neurologic manifestations. Additionally, consultation with a neurologist, brain MRI and lumbar puncture should be considered as clinically indicated.

Tiotropium (Spiriva HandiHaler) – No Increase Risk of Stroke

The preliminary results of a review from UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) reported by Boehringer Ingelheim to the FDA showed that there was no increased risk of stroke with tiotropium bromide compared to placebo (4 year, placebo controlled, approximately 6000 patients with COPD). Two recent publications reported increased risk for mortality and/or cardiovascular events in patients who received tiotropium or inhaled anticholinergics. Both studies examined cardiovascular outcomes.

FDA expects to receive the complete report for UPLIFT in November 2008. Results from this trial will also help to address some issues raised about tiotropium in the two recent publications. Due to the amount of data collected in UPLIFT, a complete review of the results could take several months, at which time FDA will update this communication with the final results of the UPLIFT analysis, as well as all the available data regarding tiotropium and stroke risk.

Label of OTC Cough and Cold Medicines To Be Modified To State " Do Not Use" In Children Under 4 Years Of Age

The Consumer Healthcare Products Association (CHPA) is voluntarily modifying the product labels for consumers of over the counter (OTC) cough and cold medicines to state "do not use" in children under 4 years of age. FDA supports CHPA members to help prevent and reduce misuse and to better inform consumers about the safe and effective use of these products for children. FDA continues to assess the safety and efficacy of these products and to revise its OTC list of approved ingredients and amounts for these medicines. Parents and care givers should adhere to the dosage instructions and warnings on the label that accompanies OTC cough and cold medications before giving the product to children, and should consult their healthcare professionals if they have any questions or concerns.

Ammonul (sodium phenylacetate and sodium benzoate) Injection 10%/10% - Particulate matter detected in product

Ucyclyd Pharma, Inc. informed healthcare professionals of the detection of particulate matter in the Ammonul Injection product. This particulate matter may impact the safe use of Ammonul. To ensure optimal patient care, healthcare providers are being

instructed to use a MilIex Durapore GV 33 mm Sterile Syringe Filter (0.22 µm) during the admixture process when injecting Ammonul into the 10% Dextrose IV bag. Since this particulate matter may not be readily seen on visual inspection, a filter must be employed in all cases regardless of whether particulate matter is seen in the vial. Testing has confirmed the removal of this specific particulate when using this filter to admix Ammonul.