Pharmacy & Therapeutics Committee Meeting
Private Dining Room
August 8, 2013 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Richard Pesce, MD
2. Approval of June, 2013 Minutes	Richard Pesce, MD
3. Therapeutic Interchanges and Formulary Decisions	Page
A. Injectable Iron (non-dextran) Formulary Review	Patrick Ellis, Pharm.D…....4-6
B. Rh(D) Immune Globulin Formulary Review	John Jantz, Pharm.D……...7
C. Adcirca® (tadalafil)	8
D. Edarbi® (azilsartan)	Patrick Ellis, Pharm.D…….....9
E. Cinryze® (C1 inhibitor) ….	Karen Babb, Pharm.D……..10
F. Rapaflo® (silodosin)	.....…11
G. Exparel® (liposomal bupivacaine)	Patrick Ellis, Pharm.D…12-13
4. Medication Safety	
A. Promethazine IV – update	Patrick Ellis, Pharm.D……
B. Medication Error Review	Lila Heet, Pharm.D…....14-16
C. Ketoconazole FDA Warning	Patrick Ellis, Pharm.D...…..17
5. MUE	
A. Fosfomycin	Patrick Ellis, Pharm.D....18-19
6. Policy, Procedure & Protocols	
A. Bivalirudin Weight Based Protocol (HIT)	Patrick Ellis, Pharm.D....20-23
B. Antimicrobial Surgical Prophylaxis Guidelines	Patrick Ellis, Pharm.D…24-26
C. Look-Alike, Sound-Alike Medications Policy...	Lila Heet, Pharm.D…..…...27
7. Nutrition Support Team	
A. Diet Order Policy – Dietician to Manage……	Dori Neufeld, RD.....28
8. Adjournment	

Next Meeting will be October 10, 2013 at 7:00am in the Private Dining Room

CATHOLIC HEALTH INITIATIVES

Memorial
Health Care System

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: June 13, 2013 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 7:56 A.M.

Members Present:		**Members Absent**:		**Guests**:
Richard Pesce, M.D.	Vickie Burger, Lab	Nathan Chamberlain, M.D.	Keith Lockwitz, RN	John Jantz, Pharm.D.
Mark Anderson, M.D.	Rodney Elliott, CPt	Samuel Currin, M.D.	Nan Payne, RN	
Allen Atchley, M.D.	Patrick Ellis, Pharm.D.	William Oellerich, M.D.	Melissa Roden, RN	
David Dodson, M.D.	Patrick Hagan, Finance	Karen Babb, Pharm.D.	Beverly Slate, Supply Chain	
Nathan Schatzman, M.D.	Lila Heet, Pharm.D.	Diona Brown, RN,C.N.O	Gwen Davis, RN	
Michael Stipanov, M.D	Brian Jones, RD, LDN	Deb Moore, RN, SVP		
	Elvie Smith, RN			
	Hannah Walker, RN			
	Sandy Vredeveld, DPh			

This meeting will be convened under the protection of the Tennessee Statute 63-6-219 and the Health Care Quality Improvement Act of 1986, Public Law 99-660. All information, case reviews, meeting minutes, statistics and correspondence are confidential and protected. Included in that protection are those that are involved in the review of the information. Any discussion of this information outside the realm of Peer Review constitutes a breach and violates the protection of the persons involved in the breach.

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Minutes	The February 14, 2013 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Invokana® (canagliflozin)** – New agent indicated for the treatment of type 2 diabetes mellitus utilizing a mechanism of action unique from other available agents (increases urinary glucose excretion). Committee recommended delaying formulary approval until more post-marketing data is available. Voted NOT to approve for formulary at this time. 2. **Mesalamine formulary review –** Asacol® has been removed from the market which has necessitated modifications to the formulary for this class of medications. It was recommended by Gastroenterology to add Lialda® and Delzicol® to formulary and designate Asacol HD® as non-formulary at this time. Pentasa® will remain on formulary and Apriso® will be substituted with Delzicol® per a therapeutic interchange. 3. **Topical Anti-virals Formulary Review** – Due to recent price increases and limited clinical benefit of the topical anti-virals, it was recommended to designate topical Zovirax® and Denavir® as non-formulary agents. Abreva® will be substituted via a therapeutic interchange when the non-formulary topical agents are ordered. 4. **Neupro® (rotigotine)** – A topical dopamine receptor agonist used for the treatment of Parkinson's disease (PD). Formulary addition requested by Dr. Freedman as an alternative for patients unable to take conventional oral PD drugs. 5. **Viibryd® (vilazodone)** – New oral treatment for major depressive depressive disorder utilizing a unique mechanism of action (SSRI/5-HT1A partial agonist). It was recommended to add to formulary due to its unique mechanism of action to provide continuity of therapy for patients admitted on this treatment as a home medication. 6. **Anti-fibrinolytics – Orthopedic surgery** – Dr. Bernard is interested in the potential peri-operative use of antifibrinolytics (tranexamic acid, aminocaproic acid) to minimize blood loss associated with total joint replacement surgery. The committee discussed this potential use and was supportive of a trial to examine the potential benefit of decreased blood loss and subsequent post-operative blood transfusions. Dr. Atchley recommended	1. Not approved. 2. Approved 3. Approved 4. Approved 5. Approved 6. Approved for trial	Complete Complete Complete Complete Complete Pending

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	that if a trial is ultimately pursued then a list of potential patients to exclude (history of VTE, recent cardiac stents, etc.) to help minimize the risk of thrombosis will need to be developed. This will be further discussed with Dr. Bernard and the committee will assist in developing exclusion criteria to optimize patient safety and pharmacy to assist in data collection if Dr. Bernard wishes to proceed with a trial.		
Medication Safety	♦ **Promethazine IV – Infusion Site reactions –** Beena from IV Team presented data on promethazine associated phlebitis. The data suggests that patients with repeated dosing are those at most risk for developing phlebitis. The committee discussed potential alternatives (prochlorperazine, limiting duration of promethazine). It was recommended to limit the duration of IV promethazine to 48 hours on all standing orders and post-operative order sets and utilize prochlorperazine as an alternative. Patrick will confirm availability of IV prochlorperazine.	Patrick to follow up	Pending
	♦ **ADR Review –** Patrick reviewed findings from October, 2012 – March, 2013.	Information	Complete
	♦ **Anti-thrombotic Reversal/Surgical Mgmt. Recommendations –** Surgery CQI committee requested a pocket card be developed to assist with the surgical management and bleeding complications associated with anti-thrombotic medications. The draft document was reviewed and no additions/edits were suggested.	Approved	Complete
Medication Use Evaluation	♦ **Procalcitonin – Antimicrobial use reduction –** An evaluation was performed to examine the utility of procalcitonin assays to reduce antimicrobial exposure in patients with lower respiratory tract infections (LRTI) and sepsis. The data suggests that when used in conjunction with clinical judgment, procalcitonin can be beneficial to reduce antibiotic utilization. The results will be presented to the hospitalist group to provide feedback on how this test can potentially be utilized to aid them in the treatment of patients with LRTI.	Information	Complete
Policy, Procedure & Protocols	♦ **Prothrombin Complex Concentrate – warfarin reversal –** Kcentra® (4 factor PCC) was reviewed and recommended that this be used for intracranial hemorrhage (ICH) and life threatening bleeds only.	Approved, with restrictions	Complete
	♦ **Renal Dosing Adjustments Policy –** Policy was created to clearly define the pharmacy process for dose adjusting certain renally eliminated medications as approved per the P&T committee after evaluation of a patient's renal function.	Approved	Complete
	♦ **Pharmacist Ordering of Lab Values –** It was approved to add vancomycin levels, phenytoin levels, and serum creatinine (to assess appropriate dosing of renally eliminated medications with narrow therapeutic windows) to those tests previously approved by P&T that may be ordered by pharmacy. Dr. Atchley recommended that digoxin levels no longer be included as part of this policy/procedure due to limited usefulness of this test once ordered. All of the above were approved.	Approved	Complete

There being no further business, the meeting was adjourned at 7:51 A.M. The next P&T meeting is August 8, 2013.

Respectfully submitted,

Sandy Vredeveld, D.Ph. Director of Pharmacy
Patrick Ellis, Pharm.D Pharmacy Clinical Coordinator

Approved by,

Richard Pesce, M.D. Chairman

Formulary Review & Therapeutic Interchange

Intravenous Iron (Non-dextran)

MEDICATIONS FOR REVIEW: **Sodium Ferric Gluconate, Iron Sucrose, Ferumoxytol**

DRUG CATEGORY: **Hematological Agents, Hematinics, Nutritional Supplements**

GENERAL PHARMACOLOGY

Intravenous iron therapy is as effective but somewhat more hazardous and considerably more expensive than oral therapy.

This P&T proposal reviews the clinical comparison of the non-dextran presentations of IV iron: sodium ferric gluconate complex in sucrose (Ferrlecit®, Nulecit®), polynuclear iron (III) hydroxide in sucrose (Venofer®), and superparamagnetic iron oxide coated with a polyglucose sorbitol carboxymethylether shell, or ferumoxytol (Feraheme®). The iron content of all products is dissociated from the parent compound when it enters the reticuloendothelial system. There it is incorporated into either ferritin or hemosiderin to replenish iron stores or into transferrin to be used for hemoglobin synthesis.

Non-Dextran IV Iron Formulations

Medication Name	**Sodium Ferric Gluconate Complex in Sucrose (Ferrlecit®, Nulecit®)**	**Iron Sucrose (Venofer®)**	**Ferumoxytol (Feraheme®)**
Dosage Forms/ Available Strengths	Injection: 12.5 mg elemental iron per ml; 5 ml ampules	Injection: 20 mg elemental iron per ml; 5 and 10 ml single dose vials	Injection: 30 mg elemental iron per ml; 17 ml single dose vials

PHARMACOKINETICS

The intravenous non-dextran iron products differ in their half-lives, and they are taken up at different rates by the reticuloendothelial system; **however the clinical relevance of these pharmacokinetic differences is insignificant.** Once bound to proteins in the body, iron is conserved with only a small amount lost daily through desquamation of cells of the skin, gastrointestinal mucosa, hair, and nails. Iron is not removed by hemodialysis. There is no need to adjust dosages of iron products in patients with renal impairment. Iron products should be used with caution in patients with hepatic impairment, who may have increased iron stores.

EFFICACY COMPARISON

IV iron products are expected to be similar in efficacy as long as similar doses of elemental iron are administered.
Most head-to-head studies of intravenous iron products focus on safety rather than efficacy. Comparative studies have found similar efficacy and safety profiles for iron sucrose and sodium ferric gluconate complex and lower rates of serious adverse events with iron sucrose and sodium ferric gluconate complex compared to iron dextran. Prospective determination of the relative safety of the intravenous iron products is challenging due to the low rate of serious adverse events and the nature of intravenous iron-related adverse events (nonspecific and overlap with dialysis-related effects).

Neither the National Kidney Foundation's KDOQI Guidelines for Anemia in Chronic Kidney Disease nor the National Comprehensive Cancer Network's Guidelines for Cancer- and Chemotherapy-Induced Anemia recommend the use of one non-dextran agent over another.

INDICATIONS AND DOSING

A series of summary tables for the comparative indications and dosing for pediatric and adult patients requiring intravenous iron are provided on the following pages.

Common Indications and Conventional Adult Dosing Table for IV Iron

	Dosing	Administration	Max Infusion Rate	Special Instructions
Sodium Ferric Gluconate	125 mg at each dialysis session until target monitoring parameters achieved, then minimum dose required to maintain target parameters	May be given undiluted as slow IV injection or diluted in 100 ml 0.9% sodium chloride (NS) and infused over 1 hr	125 mg over 10 minutes	Use immediately after dilution in saline
Iron Sucrose	Hemodialysis-dependent CKD: 100 mg at each dialysis session for total cumulative dose of 1000 mg	Hemodialysis-dependent CKD: given by slow IV injection over 2-5 minutes, or diluted in a maximum of 100 ml NS given over at least 15 min	100 mg of undiluted solution over 2 minutes	Continue therapy at lowest dose necessary to maintain monitoring parameter targets
	Non-dialysis dependent CKD: 200 mg on 5 different occasions within 14 day period	Non-dialysis dependent CKD: given by slow IV injection over 2-5 minutes, or by IV infusion over at least 15 minutes		
	Peritoneal dialysis-dependent CKD: 2 doses of 300 mg given 14 days apart, 400 mg 14 days after second dose	Peritoneal dialysis-dependent CKD: diluted in a maximum of 250 mL NS & given by slow IV infusion over 1.5 hours		
Ferumoxytol	510 mg followed by 510 mg 3-8 days later	Given by rapid IV injection (at least 17 seconds) In hemodialysis, wait at least one hour into dialysis session & until blood pressure stable to administer	30 mg (1 ml) per second	Monitor for hypotension, signs & symptoms of hypersensitivity reactions for 1 hour post-dose

SAFETY COMPARISON

Use of any intravenous iron preparation is accompanied by a small risk of serious hypersensitivity reactions including anaphylactic/anaphylactoid reactions, as well as hypotension caused by rapid infusions. Other adverse reactions associated with IV iron include musculoskeletal, cardiac, gastrointestinal, nervous system, hematologic, renal and electrolyte, and injection-site adverse effects. **Currently, no data suggests a statistically significant difference in safety outcomes between sodium ferric gluconate and iron sucrose**. A summation of safety outcomes from clinical trials, as well as contraindications and precautions for IV iron use, are provided in the following tables.

Contraindications, Warnings, & Precautions for the IV Iron Class of Agents

	Evidence of Iron Overload	Anemia Not Caused by Iron Deficiency	Hyper-sensitivity to Product Component	Iron Overload	Anaphylaxis/ Hyper-sensitivity	Magnetic Resonance Imaging	Hypo-tension	Pregnancy Category
Sodium Ferric Gluconate	**X**	**X**	**X**	**X**	**X***			**B**
Iron Sucrose	**X**	**X**	**X**	**X**	**X**			**B**
Ferumoxytol	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**C**

**ACE inhibitors may increase the risk for anaphylactic-type reactions associated with sodium ferric gluconate.*

Cost Analysis

IV Iron, Non-Dextran	Milligrams/Day of therapy	Cost/Day of therapy
Iron Sucrose (*Venofer®*)	100 mg	***$29.72***
Sodium Ferric Gluconate (Ferrlecit®*)*	125 mg	***$25.88***
Ferumoxytol (*Feraheme®*)	510 mg	***$297.67***

Comparative financial impact shows Ferrlecit® patient day of therapy as the most cost effective IV iron non-dextran therapy within this class of agents.

PHARMACY RECOMMENDATION: Due to the robust data across all indications for sodium ferric gluconate; and due to sodium ferric gluconate's comparable safety data to other IV iron (non-dextran) agents; and due to the superior cost-effectiveness of sodium ferric gluconate to other IV iron (non-dextran) agents; **it is then recommended in consideration of all these factors that sodium ferric gluconate be the sole inpatient IV iron (non-dextran) agent on formulary, and that all other non-dextran IV iron agents be designated non-formulary in the inpatient setting and automatically interchanged accordingly. An evaluation of the best product to use in the outpatient setting will be evaluated based on potential re-imbursement of each agent. Due to the therapeutic equivalence of all the available products the most cost effective agent will be used for outpatients requiring IV oral therapy.**

FORMULARY REVIEW
Rh(D) Immune Globulin (Anti-D)

BACKGROUND: IV anti-D has been shown to be an effective treatment for RhD-positive nonsplenectomized adults with both classic and HIV-related idiopathic thrombocytopenic purpura (ITP) as well as for obstetric use in Rh negative women for the indication indicated below. Anti-D is advantageous for ITP treatment due to shorter infusion time than IVIg and more favorable toxicity profile than corticosteroids. The first FDA approved anti-D agent and current formulary agent is WinRho® SDF. However, in 2007 the FDA approved Rhophylac®, the second anti-D agent for ITP and obstetric use and it is currently non-formulary. The following table outlines the two agents:

	WinRho® SDF	**Rhophylac®**
Indications	**ITP:** Non-splenectomized, Rh(D)-positive - Adults with chronic ITP - Children with chronic or acute ITP - Children and adults with ITP secondary to HIV **Suppression of Rh isoimmunization:** - Rh incompatible pregnancy - Threatened abortion at any time - Amniocentesis and chorionic villus sampling before 34 weeks	**ITP:** Non-splenectomized, Rh(D)-positive adult patients with chronic ITP to raise platelet counts **Suppression of Rh isoimmunization:** - Rh incompatible pregnancy - Obstetric complications/invasive procedures - Excessive fetomaternal hemorrhage
Contraindications	- Individuals with known anaphylactic reactions to human immune globulin products - IgA-deficient patients with antibodies against IgA - Patients with a history of autoimmune hemolytic anemia	- Individuals with known anaphylactic reactions to human immune globulin products - IgA-deficient patients with antibodies against IgA
Warnings	- Contains human plasma and therefore has the potential of transmitting infectious agents - If transfusion is necessary, use only Rh(D) negative blood products to prevent exacerbation of ongoing hemolysis	- Contains human plasma and therefore has the potential of transmitting infectious agents - If transfusion is necessary, use only Rh(D) negative blood products to prevent exacerbation of ongoing hemolysis
Adverse events	Common: - Headache, chills, fever, and nausea Severe: - Intravascular hemolysis - Clinically compromising anemia - Acute renal insufficiency - Rarely DIC and death	Common: - Fever, chills, and headache Severe: - Intravascular hemolysis - Clinically compromising anemia - Acute renal insufficiency - Rarely DIC and death
Dosing	**ITP:** - 50 mcg/kg (250 IU/kg) **IV** x 1 dose over 3-5 minutes **Suppression of Rh isoimmunization:** - Incompatible pregnancy: 300 mcg at 28 weeks followed by 120 mcg within 72 hrs of delivery - Threatened abortion, amniocentesis: 300 mcg x 1 dose	**ITP:** - 50 mcg/kg (250 IU/kg) **IV** x 1 dose (administer at rate of 2mL per 15-60 seconds **Suppression of Rh isoimmunization:** - Incompatible pregnancy: 300 mcg at 28 weeks followed by 300 mcg within 72 hrs of delivery - Obstetric complications, etc: 300 mcg within 72 hrs
Cost (per 70kg patient)	$352.63 – per 300 mcg dose $4,114.02 – ITP treatment	$71.49 – per 300 mcg dose $834.05 – ITP treatment

PROPOSAL: Add Rhophylac® as the formulary Anti-D and create a formulary substitution from WinRho® to Rhophylac® when it is ordered. This interchange has a potential annual cost savings of $3,000.

FORMULARY REVIEW

GENERIC NAME: TADALAFIL

PROPRIETARY NAME: *Adcirca* (Lilly)

INDICATIONS: Tadalafil is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability in patients with WHO group 1 pulmonary hypertension.

CLINICAL PHARMACOLOGY: Tadalafil is a selective inhibitor of phosphodiesterase type 5 (PDE5). PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentration of cyclic guanosine monophosphate (cGMP), resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

PHARMACOKINETICS: Following oral administration, peak plasma concentrations are reached within 2 to 8 hours (median, 4 hours). The rate and extent of absorption are not influenced by administration with food. Tadalafil is primarily metabolized hepatically by CYP3A4. The mean terminal half-life is 15 hours in healthy subjects and 35 hours in patients with PAH. It is excreted primarily as metabolites in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose). In patients with mild to moderate renal impairment (creatinine clearance [CrCl], 31 to 80 mL/min), the area under the curve (AUC) for tadalafil was doubled and greater than a 2 fold increase in peak concentrations was also observed in patients with ESRD. In patients with mild to moderate hepatic impairment, the tadalafil AUC was comparable with healthy subjects following a single 10 mg doses. No data are available from patients with severe hepatic impairment.

ADVERSE REACTIONS: The most common adverse effect is headache.

DRUG INTERACTIONS: Tadalafil is contraindicated in patients using any form of organic nitrates. Tadalafil potentiates the hypotensive effects of nitrates. At steady state of ritonavir, tadalafil exposure is similar as in the absence of ritonavir. Use of potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole) and CYP3A4 inducers (eg, rifampin) should be avoided with tadalafil.

DOSING: In the treatment of PAH, the recommended dosage of tadalafil is 40 mg (two 20 mg tablets) taken once daily with or without food. In comparison, the sildenafil dosage is 20 mg 3 times daily given approximately 4 to 6 hours apart. In patients with mild (CrCl, 51 to 80 mL/min) or moderate (31 to 50 mL/min) renal impairment, therapy should be initiated with a dosage of 20 mg once daily. The dosage may be increased to 40 mg once daily if tolerated. Dosage adjustments are not necessary with sildenafil in patients with mild, moderate, or severe renal impairment. In patients with mild to moderate hepatic impairment, consider a starting dosage of 20 mg once daily. Use is not recommended in patients with severe hepatic impairment (Child Pugh class C).

PRODUCT AVAILABILITY and COST: It is available as a 20 mg tablet supplied in bottles of 60.
Cost - $56 per day of therapy
Cost comparison to Revatio (sildenafil) - $1.26 per day of therapy

CLINICAL COMPARISON & CONCLUSION: Tadalafil appears to improve exercise ability in patients with PAH based on the results of available clinical studies. Additionally, tadalafil has demonstrated similar efficacy as compared to sildenafil although direct comparison studies are lacking. Per the most recent treatment guidelines, sildenafil and tadalafil are recommended as first-line therapy (Grade A and B, respectively) for Class II PAH over prostacyclins and are also options as first-line therapy in Class III patients. Both agents are FDA approved for the treatment of PAH without respect to functional class. Based on similar efficacy and similar levels of evidence to support the use of either agent with respect to the most recent treatment guidelines, these agents can be considered interchangeable at comparable dosing regimens (sildenafil 20 mg TID vs. tadalafil 40 mg Daily). Despite the advantage of once daily dosing for tadalafil, sildenafil offers a significant cost benefit ($54.74 per day of therapy) when comparing current acquisition costs. Due to the similar efficacy and decreased cost associated with sildenafil, it is recommend to substitute all tadalafil orders to a therapeutically equivalent dose of sildenafil as outlined below.

Tadalafil 40 mg Daily → Sildenafil 20 mg TID

FORMULARY REVIEW

GENERIC NAME: AZILSARTAN MEDOXOMIL

PROPRIETARY NAME: *Edarbi* (Takeda Pharmaceuticals)

INDICATIONS: Azilsartan is approved for the treatment of hypertension, alone or in combination with other antihypertensive agents.

CLINICAL PHARMACOLOGY: In the treatment of hypertension, azilsartan's beneficial pharmacologic effects were associated with its ability to block the binding of angiotensin II to the AT1 receptor in various tissues, resulting in decreased vasoconstriction and aldosterone secretion. All of the angiotensin II receptor blockers (ARBs) have this type of activity, but there are differences in their binding affinity and duration to the AT1 angiotensin II receptor. ARBs can be classified as surmountable or insurmountable antagonists. The surmountable antagonists (eg, losartan) produce a right-shift in the dose-response curve of angiotensin II and have no effect on the maximal response. While some of the insurmountable ARBs (eg, telmisartan, irbesartan, valsartan) are able to reduce the maximal response to angiotensin II, others (eg, azilsartan, candesartan, olmesartan) are able to completely suppress the response. The difference in activity is probably related to the drugs' affinity for the receptor site and the rate of dissolution from the AT1 receptor.

PHARMACOKINETICS: Azilsartan medoxomil is a prodrug that is structurally related to candesartan. Azilsartan medoxomil is rapidly hydrolyzed to azilsartan in the GI tract. Food has no effect on absorption. More than 40% is recovered in the urine. No dose adjustments are required for elderly patients or patients with renal or hepatic impairment.

ADVERSE REACTIONS: Azilsartan therapy is well tolerated. There were no adverse reactions that occurred with an incidence of more than 5% and at a rate higher than placebo. Diarrhea was the most frequently reported adverse reaction with an incidence rate of 2% with azilsartan and 0.5% with placebo. The various ARBs appear to have similar adverse reactions profiles.

DRUG INTERACTIONS: Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause a deterioration in renal function in patients who are elderly, are volume-depleted, or have preexisting compromised renal function.

DOSING: The recommended oral dosage for the treatment of hypertension in adults, alone or in combination with other antihypertensive agents, is 80 mg once daily with or without food. Patients receiving high doses of diuretics may need to be started on a lower dosage (40 mg once daily). No adjustments in dosage are required for elderly patients or patients with renal or hepatic impairment.

PRODUCT AVAILABILITY and COST: Azilsartan is available as a 40 or 80 mg tablet in 30- and 90-tablet bottle sizes. It was approved in February 2011 for the treatment of hypertension.
Cost – $3.02 per dose

CONCLUSION: Azilsartan medoxomil is effective in lowering blood pressure (BP), alone or in combination with other antihypertensive agents, in patients with hypertension. The contraindications, warnings, precautions, and adverse effects associated with azilsartan therapy are similar to those reported with other ARBs. In the clinical trials, azilsartan 80 mg was able to produce a greater reduction in 24-hour mean systolic BP than olmesartan 40 mg and valsartan 320 mg; whether this effect will result in improvements in morbidity or mortality compared with other ARBs remains to be proven.

It is recommended to add azilsartan to formulary at this time to provide continuity of care for those patients admitted to the hospital who take this medication as a home therapy. However, with several recent generic approvals for the ARBs a formulary interchange may later be evaluated if cost savings are a possibility.

FORMULARY REVIEW

GENERIC NAME: C1 INHIBITOR (Human)

PROPRIETARY NAME: *Cinryze* (Lev Pharmaceuticals / ViroPharma)

INDICATIONS: C1 inhibitor is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). The new drug application (NDA) also included information on the use of C1 inhibitor in the acute treatment of HAE attacks, but this portion of the NDA was withdrawn by the sponsor and this remains an off label indication.

HAE is an autosomal dominant disease caused by a functional C1 inhibitor deficiency. Laboratory testing can confirm or rule out the diagnosis. Almost all patients with HAE have persistently low antigenic C4 level with normal antigenic C1 and C3 levels. Measurement of C4 levels is often used as a screening test to rule out HAE; subsequent measurement of antigenic and functional C1 inhibitor levels confirms the diagnosis.

CLINICAL PHARMACOLOGY: C1 inhibitor (human) is a plasma-derived preparation of C1 inhibitor made from plasma collected in the United States and processed with a variety of filtration, chromatographic, and viral-reduction procedures. C1 inhibitor is a normal constituent of human blood, and is one of the serine proteinase inhibitors. The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system.

PHARMACOKINETICS: Following intravenous (IV) administration of C1 inhibitor (*Cinryze*), functional C1 inhibitor levels peak within 2 to 4 hours. The half-life of C1 inhibitor (*Cinryze*) is about 60 hours which explains the rationale behind the every 3-4 day re-dosing schedule.

ADVERSE REACTIONS: The most common adverse reactions observed in clinical trials, occurring in at least 5% of patients treated with C1 inhibitor, were upper respiratory tract infection, sinusitis, rash, and headache.

DRUG INTERACTIONS: No drug interaction studies have been conducted.

DOSING: C1 inhibitor is approved for IV administration only. The recommended dosage is 1,000 units (reconstituted in 10 mL) IV every 3 or 4 days. It should be administered at an injection rate of 1 mL/min over 10 minutes. IV self-administration, both in the treatment of acute attacks and as prophylaxis, has been demonstrated in several reports, including 1 report describing the use of the *Cetor* C1 inhibitor product (Sanquin, Netherlands) as on-demand treatment in 31 patients and prophylaxis in 12 patients over a mean follow-up period of 3.5 years. Current guidelines recommend home-care C1-inhibitor therapy be offered to patients. The prepared solution must be administered within 3 hours of reconstitution.

PRODUCT AVAILABILITY and COST: It is available as a lyophilized powder containing C1 inhibitor 500 units in an 8 mL single-use vial.

Cost per dose: $4,886.96
Annual cost per patient: $596,209.12

CONCLUSION: C1 inhibitor does provide an alternative for long-term prophylaxis for patients in whom long-term use of androgens is ineffective, poorly tolerated, or inappropriate (eg, pregnant women, children, etc.). although the cost of this medication will limit its use at MHCS. **Due to the extreme annual cost of therapy it is recommended to designate Cinryze non-formulary for inpatient use and for use in an outpatient basis on a case by case basis ONLY pursuant to insurance pre-approval and finance review to ensure reimbursement available.**

FORMULARY REVIEW

GENERIC NAME: SILODOSIN

PROPRIETARY NAME: *Rapaflo* (Watson)

INDICATIONS: Silodosin is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

CLINICAL PHARMACOLOGY: Silodosin is a selective postsynaptic alpha-1 adrenoreceptor antagonist. Receptor blockade results in smooth muscle relaxation in these tissues, resulting in improvement in urine flow and a reduction in BPH symptoms. Silodosin is a selective antagonist of both alpha-1A and alpha-1L adrenoreceptors, the receptor subtypes primarily expressed in the human prostate. It has low affinity for alpha-1B and alpha-1D.

Like silodosin, alfuzosin, doxazosin, and terazosin are all selective alpha-1 adrenoreceptor antagonists. Tamsulosin is a selective alpha-1A adrenoreceptor antagonist. Silodosin, tamsulosin, and terazosin all exhibited similar extent and duration of alpha-1 adrenoreceptor occupancy in human prostate. Silodosin exhibited greater selectivity for the prostate than for the carotid artery when compared with tamsulosin.

Both tamsulosin and silodosin are selective alpha-1 receptor antagonists and both are known to cause less hypotension than other alpha blockers due to enhanced specificity of the alpha receptors on the prostate. Tamsulosin has 7-38 fold greater affinity for alpha 1a receptors than for alpha 1b receptors whereas silodosin has a 538 fold greater affinity for alpha 1a receptors than for alpha 1b receptors.

PHARMACOKINETICS: In the clinical trials, silodosin was always administered with food. Silodosin is approximately 97% protein bound. The silodosin elimination half-life is 13.3 hours. The primary metabolite is active, has an area under the curve (AUC) approximately 4 times greater than that of silodosin, and has a longer half-life (approximately 24 hours). In patients with moderate renal function impairment, the AUC was increased 3.2-fold, the peak concentration was increased 3.1-fold, and the elimination half-life was increased 2-fold compared with subjects with healthy renal function.

ADVERSE REACTIONS: Adverse reactions observed in at least 2% of patients treated with silodosin in clinical trials included retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion. Administration with a meal is advised to reduce the risk of adverse reactions.

DRUG INTERACTIONS: Silodosin is a substrate of CYP3A4 and does not inhibit or induce the cytochrome P450 system. Concomitant use of silodosin with other alpha blockers is not recommended.

DOSING: The recommended dose of silodosin is 8 mg once daily with a meal. A 4 mg once-daily dose is recommended for patients with moderate renal function impairment (creatinine clearance [CrCl] of 30 to 50 mL/min).

PRODUCT AVAILABILITY and COST: It is available as 4 and 8 mg hard gelatin capsules.
Cost: Rapaflo (silodosin) - $4.37 per dose; Flomax (tamsulosin) - $0.29 per dose

CONCLUSION: Silodosin offers another alpha blocker alternative for the treatment of BPH. Both tamsulosin and silodosin are selective alpha 1a antagonists with silodosin being the more selective of the two agents. Limited clinical comparison data is available directly comparing the two agents although the data that is available suggests similar clinical response and adverse effect profiles between the two agents. Based on the cost difference between these two agents and similar clinical efficacy, it is recommended to substitute a therapeutically equivalent dose of Flomax (tamsulosin) for all Rapaflo (silodosin) orders as indicated below.

Silodosin 4 mg ONCE daily → Tamsulosin 0.4 mg ONCE daily
Silodosin 8 mg ONCE daily → Tamsulosin 0.4 mg ONCE daily

FORMULARY REVIEW

GENERIC NAME: Bupivacaine Liposomal

PROPRIETARY NAME: Exparel (Pacira)

INDICATIONS: Exparel is a liposome injection of bupivicaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia.

CLINICAL PHARMACOLOGY: Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers.

PHARMACOKINETICS: Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site. Systemic plasma levels of bupivacaine following administration are not correlated with local efficacy. The difference in pain intensity when compared to placebo occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo on mean pain intensity.

ADVERSE REACTIONS: Nausea, Constipation, and Vomiting were reported in greater than or equal to 10% of the patients.

DRUG INTERACTIONS: Do not admix with lidocaine or other non-bupivacaine-based local anestheics.

DOSING: Is intended for single-dose administration only. The recommended dose is based on the surgical site and the volume required to cover that area:

Surgery	**Dose of EXPAREL**	**Volume of EXPAREL**
Bunionectomy	106 mg	8 mL
Hemorrhoidectomy	266 mg	20 mL

PRODUCT AVAILABILITY and STORAGE: This medication was approved by the U.S. FDA on October 28, 2011. It is available in 20ml single use vials at 13.3mg/ml. The vials should be stored in the refrigerator (2-8 degrees C) in the original carton to protect from light. The vials may be held at a controlled room temperature of 20-25 degrees C for up to one month in sealed, unopened vials. Vials should not be re-refrigerated. Do not freeze.

CONTRAINDICATIONS: Do not use in obstetrical paracervical block anesthesia.

WARNINGS AND PRECAUTIONS: Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection. It is metabolized by the liver, so use with caution in patients with hepatic disease. It is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Other formulations of bupivacaine should not be administered within 96 hours following administration of Exparel.

STUDY RESULTS: One hundred eighty-nine patients were randomly assigned and treated; 186 completed the study. Pain intensity scores were significantly lower in the bupivacaine extended-release group in comparison with the group receiving placebo (141.8 vs 202.5, $P< 0001$). More patients in the

bupivacaine extended-release group remained opioid free from 12 hours (59%) to 72 hours (28%) after surgery compared with patients receiving placebo (14% and 10%; *P*<.0008 through 72 h). The mean total amount of opioids consumed through 72 hours was 22.3 mg and 29.1 mg in the bupivacaine extended-release and placebo groups (*P*<.0006). The median time to first opioid use was 14.3 hours in the bupivacaine extended release group vs 1.2 hours in the placebo group (*P*<.0001). A greater proportion of patients in the bupivacaine extended-release group were satisfied with their postsurgical analgesia (95% vs 73%, *P*<.0007) than in the placebo group.

It is important to note that for both the FDA approved indications (bunionectomy & hemmorhoidectomy) that liposomal bupivacaine demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo treatments on mean pain intensity.

COMPARISON TO CONVENTIONAL BUPIVACAINE: The FDA approval for liposomal bupivacaine was based on a comparison to placebo therapy for determining superiority based on the primary efficacy endpoint of the area under the curve (AUC) of the numerical rating scale pain scores as compared to placebo. The formal FDA review does however also have unpublished information related to the comparison of conventional bupivacaine to the liposomal formulation. It is important to note that for both soft tissue infiltration following bunionectomy and hemorrhoidectomy that the liposomal formulation failed to demonstrate superiority when actively compared to the conventional buipivacaine formulation and actually performed worse than conventional bupivacaine for hemorrhoidectomy.

CONCLUSION & RECOMMENDATION: Based on the study results above, Exparel demonstrated a statistically significant reduction in pain through 72 hours, decreased opioid requirements, delayed time to first opioid use, and improved patient satisfaction compared with placebo after hemorrhoidectomy when compared to placebo. Although, the primary efficacy end point of pain intensity scores through 72 hours did show superiority as compared to placebo, the difference in pain intensity compared to placebo was only observed during the first 24 hours following drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo treatments on mean pain intensity. Based on the pharmacokinetics of liposomal bupivacaine, local infilatration results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. Based on the trial results, the systemic plasma levels of bupivacaine are clearly not correlated with local efficacy as indicated by no difference being observed between 24 and 72 hours after drug administration when compared to placebo. Additionally, when compared to conventional bupivacaine for soft tissue infiltration no difference in pain intensity scores were observed.

Based on the available data, it is recommended to designate liposomal bupivacaine non-formulary for soft tissue infiltration use following surgical procedures. Use for other indications (nerve blocks, etc.) will need to be assessed by the committee on a case by case basis when requested. No data is currently available for the use as post surgical nerve blocks (intercostal nerve blocks, etc.).

COST: $285/20 ml

Medication Error Workgroup
Summary
1st and 2nd Quarter 2013
(January through June)

Interpretation

- 332 Errors reported
- 187 Reached Patient
- 1 Serious Safety Event involving Phenytoin (Medication Reconciliation)
  (800 mg TID – should have been 100 mg TID)
- 74 % (138/187) Did not Cause Harm or Additional Monitoring
- Top three medication errors: Insulin, Heparin and Vancomycin
- Top therapeutic class: Anticoagulants, Opiate Agonists, Antimicrobials, Insulins

Action Plan

- Insulin, Heparin and Vancomycin errors divided by team to investigate and develop an action plan. Follow up in September.

Completed Action Plans/Improvements

- Pneumococcal and Influenza Vaccine Compliance improvement post pharmacist involvement
- Medication Reconciliation: Medication Errors identified need for medication history technicians in ED. New ED Medication History team approved and under implementation phase
- To prevent errors with administration surrounding trough levels, Pharmacy has begun keying a "pending" order 30 minutes prior to the dosage being due
- Wrong patient errors are reviewed/investigated in Clinical Oversight Committee

Generic Name	
VANCOMYCIN HCL	20
HEPARIN SOD,PORK IN 0.45% NACL	18
INSULIN	16
OXYCODONE HCL	12
HYDROMORPHONE HCL	11
MORPHINE SULFATE	10
WARFARIN SODIUM	10

Drug Class	
ANTICOAGULANTS	39
OPIATE AGONISTS	38
ANTIBACTERIALS, MISCELLANEOUS	21
INSULINS	16

Anticoagulants:

Heparin

- 5 - Delay in Initiation of weight based drip (1 due to not being connected to IV site)
- 3 – DVT prophylaxis delay (order not scanned to pharmacy)
- 4 – Wrong rate
- 1 – Med Reconciliation (restarted by Radiologist post procedure)
- 1 - Administration route given SQ versus IV
- 1 – Wrong Protocol entered
- 1 - Started inappropriately (order to start if CT negative)
- 1 - Heparin flush used for saline flush per protocol
- 1 – Given incorrectly by administering piggyback with IV

Warfarin

- 1 Should have not been restarted (Med Rec)
- 1 Not Held- Given
- 1 Wrong Dosage (Med Rec- should have been on 0.5 mg versus 1.0 mg)

Enoxaparin

- Wrong Drug (Lovenox given instead of Heparin), Not held, Wrong dosage (should have been q24 versus q12), 2 DVT prohylaxis order not sent to Pharmacy- 1 without DVT Prophylaxis for 8 days

Fondiparinux

- Wrong Dosage (illegible handwriting- should have given 2.5 mg versus 7.5 mg)

Opiate Agonists:

Hydromorphone

- 2 Underdosage
- 2 Discrepancies
- 1 Overdosage
- 1 Pump Programming error
- 1 Wrong Patient
- 1 Omission
- 1 Wrong Route
- 1 Allergic
- 1 Medication Left Unsecured

Morphine

- 2 Allergic

- 2 Overdosage
- 1 Underodsage
- 1 Unsecured medication
- 1 Pump programming error (wrong rate)

Oxycodone

- 3 Discrepancy
- 4 Wrong patient
- 4 Overdosage
- 1 Wrong schedule (should be routine not prn)

Others: 2 Hydrocodone (1 Wrong patient; 1 Overdosage); 1 Narcan given (for oversedation)

Antibacterials:

Vancomycin

- 10 - Omissions (1 caused an inappropriate surgery proph. Time, 2 consult to pharmacy delay in scanning (12 hr and 5 hr delay), 3 due to not being reconstituted, 1 one time ordered and not given, 1 -16.5 hour delay, 1- 24 hour delay due to patient being off floor- noted to have MRSA Cellulitis)
- 3 - Inappropriate timing for surgery prophylaxis (2 MDs said to roll, 1 MD originally wanted cultures drawn- then opted not to and gave intraop)
- 2 - Extra Dosages
- 1–Wrong Med (Zithromax sent- near miss)
- 1 - Infiltration
- 1 - Allergy and given
- 1 - Wrong Patient

Others: Levaquin (Wrong Patient), Clindamycin (Wrong Route), Metrogel (Medication rec.- Should not have been ordered), and Zyvox (Wrong Route)

Insulin

- 7 – Overdosage (Illegible handwriting caused Lantus 100 units versus 10 units- received 2 dosages)
- 2 – Wrong patient (1 near miss)
- 2 – Wrong route
- 2 – Wrong insulin types
- 1 – Omission
- 1 - Wrong timing
- 1 – Under dosage

FDA Drug Safety Communication (7/26/2013)
Nizoral (ketoconazole): Drug Safety Communication - Potentially Fatal Liver Injury, Risk of Drug Interactions and Adrenal Gland Problems

[Posted 07/26/2013]

AUDIENCE: Internal Medicine, Infectious Disease

ISSUE: FDA is taking several actions related to Nizoral (ketoconazole) oral tablets, including limiting the drug's use, warning that it can cause severe liver injuries and adrenal gland problems, and advising that it can lead to harmful drug interactions with other medications. FDA has approved label changes and added a new Medication Guide to address these safety issues. As a result, Nizoral oral tablets should not be a first-line treatment for any fungal infection. Nizoral should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

Liver Injury (Hepatotoxicity)

Nizoral tablets can cause liver injury, which may potentially result in liver transplantation or death. FDA has revised the Boxed Warning, added a strong recommendation against its use (contraindication) in patients with liver disease, and included new recommendations for assessing and monitoring patients for liver toxicity.

Adrenal Insufficiency

Nizoral tablets may cause adrenal insufficiency by decreasing the body's production of corticosteroids.

Drug Interactions

Nizoral tablets may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems.

See the FDA Drug Safety Communication for additional information, including a Data Summary.

BACKGROUND: Nizoral (ketoconazole) is indicated for the treatment of fungal infections when alternatives are not available or not tolerated. The topical formulations of Nizoral have not been associated with liver damage, adrenal problems, or drug interactions. These formulations include creams, shampoos, foams, and gels applied to the skin, unlike the Nizoral tablets, which are taken by mouth.

RECOMMENDATION: Nizoral tablets should be used only for the treatment of certain life-threatening mycoses when the potential benefits outweigh the risks and alternative therapeutic options are not available or tolerated. Healthcare professionals should assess the liver status of the patient before starting oral ketoconazole, and monitor serum ALT levels during treatment. Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.). Review all concomitant medications for the potential for drug interactions with Nizoral tablets.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

Medication Use Evaluation
Fosfomycin

From January 2012 to March 2013, the use of fosfomycin (Monurol®) in extended-spectrum β-lactamase (ESBL) cystitis was evaluated.

Methods:

1. Reviewed urine cultures from Memorial Hospital with ESBL isolates during 01/01/12 to 03/01/13 (14 months).
2. Classified patients as receiving fosfomycin, carbapenem, or "other" antimicrobial therapy.
3. Determined failure of carbapenem and fosfomycin therapy.
4. Prior to recommending fosfomycin, 20 fosfomycin E-tests were performed on hospital ESBL isolates to confirm sensitivity.
5. Pharmacists recommended fosfomycin 3 grams by mouth every 48 hours for 3 doses in patients with ESBL cystitis that did not exhibit any signs/symptoms of systemic involvement.

Data:

- All 20 fosfomycin E-tests initially performed tested sensitive with MICs ≤ 64.
- 104 ESBL urine isolates were reviewed and categorized.

Table 1. Antibiotic Therapy for Patients with urine ESBL isolates

Antibiotic Therapy	# of Patients
Fosfomycin	18*
Meropenem	39
Ertapenem	3**
Other	56

* 11 Patients received meropenem prior to receiving fosfomycin.
** 1 Patient received ertapenem prior to receiving meropenem.

Results:

"Therapy failure" was defined as an ESBL- positive urine culture within 30 days after receiving fosfomycin or a carbapenem.

- **4 of 18 patients (22.2%) failed fosfomycin therapy**
- **8 of 39 (20.5%) failed carbapenem therapy**

Table 2. Patients that Failed Fosfomycin Therapy

Patient	Organism	Hx of Organism	Indwelling Foley	Fosfomycin E-test	# of Fosfomycin Doses (Inpatient)	Eradication with Merrem
#1	E. Coli ESBL	No	No	Not Performed	1	Yes
#2	E. Coli ESBL	Yes	Yes	Sensitive (MIC = 2)	3	No
#3	E. Coli ESBL	Yes	No	Not Performed	2*	No
#4	E. Coli ESBL	Yes	No	Not Performed	1	Yes

*Discharged with 1 additional dose of Fosfomycin 3 gram PO.

Side Effects:

- Gastrointestinal upset was noted as the primary side effect.
- Either nausea, vomiting, or diarrhea was reported in 6 of 18 (33.3%) fosfomycin patients
- 4 patients were PCR tested for Clostridium difficile, and all were negative.

- 2 patients received anti-emetics during fosfomycin therapy.
- Candida species grew in 3 (16.6%) follow-up urine cultures .

Discussion:

- Overall, fosfomycin is less expensive than carbapenem therapy.
- Increasing fosfomycin use may lead to decreased resistance rates while lowering the use of broad spectrum antibiotics.
- Data regarding fosfomycin dosing when treating ESBLs is limited.
- Interpreting sensitivity to fosfomycin can be challenging. E-tests must be manually performed.
- GI upset is a consideration; however, it is the most common side effect for many antibiotics. Of note, all of the C. diff cultures were negative.

Study Limitations:

- Retrospective review – information bias
- Education barrier – time spent to educate physicians on fosfomycin and recommend it delayed initiation of fosfomycin therapy
- Confounder – 11 patients received meropenem prior to fosfomycin
- Patients were lost to follow-up

Conclusion:

According to this study, fosfomycin is a viable option for treating ESBL organisms in the urine with a comparable success rate to carbapenems. This study had similar results to other literature documenting around 80% resolution of ESBL infections with carbapenems. [Paterson CID 2004; Bhavnani DMID 2006;Zanetti AAC 2003]

Using the E-test method, 100% of the ESBL isolates (E. coli and Klebsiella) have been sensitive to fosfomycin. This finding is corroborated with other studies showing >90% susceptibility to fosfomycin in ESBL isolates. Since E. coli ESBL isolates are highly sensitive, E-tests are most likely not needed for this organism. However, fosfomycin E. tests are useful for other ESBL isolates, VRE, and MRSA in the urine.

Angiomax (Bivalirudin) Weight Based Protocol - *Proposal*

Bivalirudin (Angiomax) for treatment of suspected or confirmed heparin-induced thrombocytopenia

The most recent version of the American College of Chest Physicians guidelines recommends anticoagulation with a direct thrombin inhibitor for patients with heparin-induced thrombocytopenia (HIT).[1]Since publication of these guidelines, lepirudin has been removed from the market leaving argatroban and bivalirudin as the two parenteral direct thrombin inhibitors available in the United States.

For the treatment of HIT, the Chest guidelines recommend argatroban for patients with impaired renal function (Grade 2C). Bivalirudin is recommended as the anticoagulant of choice for patients with acute or subacute HIT requiring urgent cardiac surgery (Grade 2C), primarily due to a lack of data evaluating its use in HIT treatment.

Table 1. Comparison of parenteral direct thrombin inhibitor agents

Characteristic	Argatroban	Bivalirudin
Half-life	40-50 min	25 min
Elimination	Hepatobilliary	Enzymatic 80% Renal 20%
Effect on INR	+++	++
Immunologic features	None	Potentially cross-reactive with anti-lepirudin antibodies
Antidote available	No	No
Dialyzable	20%	25%

Bivalrudin is currently available at MHCS for use during percutaneous coronary intervention. This agent is an attractive option for anticoagulation management in HIT given its short half-life, primary enzymatic route of elimination, and minimal effect on INR. As neither of the direct thrombin inhibitor agents have available antidote or reversal agents, the benefit of the shortest half-life among the class may mean less risk for prolonged bleeding.[2]Although it currently lacks an FDA approval for treatment of HIT, case series have shown bivalirudin to be a safe and effective option.[3-8]

A recent study published by The Ohio State University Wexner Medical Center (OSUWMC) provides data on a nurse-driven sliding scale dosing nomogram that required fixed dose adjustments according to current activated partial thromboplastin time (aPTT) value relative to aPTT goals.[9] Overall the use of the nomogram resulted in adequate anticoagulation and bleeding rates consistent with other published literature. Nurse adherence to the nomogram was 100% with no dosing errors. Pharmacy was consulted for initial starting dose and goal aPTT based on indication.

Bivalirudin has been studied in patients with renal impairment as well as those requiring continuous and intermittent renal replacement therapies.[6,7] Because 20% of each dose is excreted unchanged in the urine, infusion rates of bivalirudin must be adjusted based on creatinine clearance. Based on available literature, a recommended dosing strategy has been created (Table 2). Bivalirudin does not require dose adjustment for hepatic impairment.

Table 2. Initial bivalirudin infusion rate based on renal function

Patient Characteristic	**Dosage (mg/kg/hr)**
Creatinine clearance (mL/min)	
> 60	0.08
30-60	0.05
≤29 or CRRT	0.03
Hemodialysis	0.02

Bivalirudin should be dosed on total body weight even in the obese population.[8]There is no recommendation to cap the infusion rate at a maximum dosage. Indeed, patients weighing up to 202 kg have been included in clinical trials without difference in rates of bleeding or thrombosis.

An order set and weight based dosing protocol have been developed for the use of bivalirudin for treatment of suspected or proven HIT (see attached). Infusion rates will be initiated based on creatinine clearance

without use of a loading dose to target an aPTT range 55-75 which represents 1.5 – 2.5 times average population baseline values at MHCS. Due to the short 25 minute half-life of bivalirudin, aPTT values will be tested three hours after infusion initiation and any dose changes until two consecutive values are within the therapeutic range.

As recommended by Chest guidelines, warfarin should be held until the platelet count has recovered, usually to 150,000 to prevent the pro-coagulant effect of protein C and protein S depletion.[1]Bivalirudin should be continued with warfarin dosing until the INR reaches a value greater than 3.0 with an overlap of at least 5 days as it has demonstrated less of an effect on false INR test prolongation.[6]A recent study reported a median INR increase from 1.5 (IQR 1.3-1.7) to 1.9 (IQR 1.9-2.1) associated with bivalirudin in patients not receiving warfarin (p=0.002).

Assuming maximum dosing of each direct thrombin inhibitor in a patient weighing 100 kg gives a relative cost comparison among agents when rounded for vial size (Table 3). The cost for daily therapy in this scenario favor a decrease in cost associated with bivalirudin.

Table 3. Cost comparison of available direct thrombin inhibitor agents

Medication	Vial size	Cost per vial	Estimated daily dose (80 kg patient)	Estimated daily cost (rounded for vial size)
Argatroban	50 mg	$186	300 mg	$1100
Bivalirudin	250 mg	$762	240 mg	$762

Recommendation and Conclusion: Bivalirudin is a safe and effective parenteral anticoagulant option for the management of HIT. The initial dose should be adjusted based on estimated creatinine clearance with monitoring and subsequent dose adjustments to target aPTT values of 55 – 75 seconds (1.5 – 2.5 baseline aPTT). Dosing should be calculated based on total body weight.

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8. Tsu LV, Dager WE. Comparison of bivalirudin dosing strategies using total, adjusted, and ideal body weights in obese patients with heparin-induced thrombocytopenia. Pharmacotherapy. 2012:32(1):20-26.

9. Burcham PK, Abel EE, Gerlach AT, et al. Development and implementation of a nurse-driven, sliding-scale nomogram for bivalirudin in the management of heparin-induced thrombocytopenia. Amer J Health-System Pharmacy 2013. 70; 11 980-87.

ANGIOMAX (BIVALIRUDIN) WEIGHT BASED DOSING PROTOCOL

Criteria for use:

- Should be used for suspected or confirmed HIT or other intolerance to heparin in patients with indications for full anticoagulation (e.g., DVT, PE, atrial fibrillation, mechanical prosthetic valve)
- May be used in patients with renal and hepatic dysfunction
- If bleeding develops at any time, **IMMEDIATELY** notify Physician
- This dosing protocol is not intended for use in PCI or other invasive procedures (vascular surgery, cardiac surgery, etc.)

Baseline Labs: PTT, PT/INR, platelet count, serum creatinine, HIT assay (if not already done). All labs should be drawn after discontinuation of heparin products.
Available concentration: 250 mg in 250 mL normal saline (1 mg/1 mL)
Initial Adult Dosage:

Patient Characteristic	Dosage (mg/kg/hr)
Creatinine clearance (mL/min)	
> 60	0.08
30-60	0.05
≤29 or CRRT	0.03
Hemodialysis	0.02

Laboratory Monitoring:

- Check PTT 3 hours after start of infusion and adjust dose (see chart below)
- Check PTT 3 hours after each dose adjustment
- After two consecutive PTT readings in therapeutic range (55-75), may check PTT daily
- CBC daily
- INR daily (if on warfarin)

Infusion Rate Adjustments (Goal PTT 55-75 seconds):

PTT (sec)	Recommendation
< 40	Increase by 0.01 mg/kg/hr
40 – 54	Increase by 0.005 mg/kg/hr
55 – 75	No change – goal PTT
76 – 90	Decrease by 0.005 mg/kg/hr
91 – 105	Hold for 2 hr, then decrease by 0.01 mg/kg/hr
> 105	Hold for 2 hr, and recheck PTT every 3 hr until PTT in goal range, then decrease by 0.01 mg/kg/hr

Guidelines for administration with Warfarin: (Physician must order)

- Angiomax and warfarin should be overlapped for a minimum of 5 days.
- Do not start warfarin until the platelets reach at least 150,000.
- Starting warfarin dose recommended to be 5 mg per day. No loading dose recommended.
- Combination of Angiomax and warfarin results in "**false elevation**" of INR. This does not necessarily increase the risk of bleeding.
- Discontinue Angiomax when the INR is greater than 3.0. An INR should be drawn 3 hours after the infusion is stopped, to confirm that the INR is within desired therapeutic range. Notify prescriber.

- If the repeat INR is less than the desired therapeutic range, the most recent infusion rate should be restarted, INR drawn the next day, and this process repeated until the INR is within the desired therapeutic range.

Perioperative Hold Parameters

Patient Characteristic	Recommendation
Creatinine clearance (mL/min)	
> 60	Hold for 2 – 4 hr and recheck aPTT
≤ 60	Hold for 4 – 6 hr (may need to hold longer during off-dialysis period in patients receiving hemodialysis) and recheck aPTT until aPTT is back to baseline

ANTIMICROBIAL PROPHYLAXIS IN SURGERY
Summary of Guideline Changes

BACKGROUND: In February 2013, new clinical practice guidelines for antimicrobial prophylaxis in surgery were published. These guidelines reflect substantial changes from the previous guidelines published in 1999 and those changes are outlined below.

CHANGES:

Preoperative-dose timing: These guidelines outline a more specific time frame for administration than the previous recommendation time, which was "at induction of anesthesia." The optimal time for administration of preoperative doses is **within 60 minutes before surgical incision**. The administration of antimicrobials that require longer infusions (i.e. vancomycin) should begin within 120 minutes before surgical incision.

Dosing changes: The new guidelines place a larger emphasis on weight-based dosing than previous recommendations. This is attributable to obesity being linked to an increased risk for surgical site infections (SSI). Key dosing changes include:

- **Cefazolin (Ancef®)**: <80 kg = 1g; 80-120 = 2 g; >120 = 3 g
- **Vancomycin**: 15mg/kg (max. of 2 g)
- **Gentamicin**: 5mg/kg (based on dosing weight)
- **Cefoxitin**: 2 g
- **Clindamycin**: 900mg

Recommended redosing interval: Redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure. Key changes include:

- **Cefoxitin**: Q 2 hrs
- **Gentamicin**: No redosing (due to large single dose)

Duration of prophylaxis: The duration of antimicrobial prophylaxis should be **less than 24 hours for most procedures** and evidence is mounting that postoperative antimicrobial administration is not necessary for most procedures. Cardiothoracic procedures for which a prophylaxis duration of up to 48 hours has been accepted without evidence to support the practice is an area that remains controversial.

REFERENCE:

Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical Practice Guideline for Antimicrobial Prophylaxis in Surgery. *Am J Health-Syst Pharm*. 2013;70:195-283

***** If MRSA screen positive **ADD Vancomycin** to Cardiac, Vascular, Total joint, and Spine surgeries

****** If MRSA screen positive **AND** β-lactam allergy **ADD Gentamicin** 5 mg/kg based on dosing weight to Cardiac, Vascular, Total joint, and Spine surgeries

******* Patients receiving therapeutic antibiotics for an infection before surgery should be given an additional dose (if same antibiotic) or the recommended prophylatic regimen for the type of procedure they are undergoing. For patients with chronic renal failure receiving vancomycin, a pre-op dose of cefazolin should be considered instead of an extra dose of vancomycin, or clindamycin if β-lactam allergy.

Nature of Operation	Common Pathogens	Recommended antimicrobials***	Alternatives for β-lactam allergy	Usual adult dosage	Redose interval
CARDIAC	*S. aureus, S. epidermis*	Cefazolin*****		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin******	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
THORACIC	*S. aureus, S. epidermis,* streptococci, enteric gram-negative bacilli	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
GASTRODUODENAL Bariatric surgery, gastrectomy, gastric carcinoma resection, gastric outlet stricture repair, pancreaticoduodenectomy (Whipple), PEG insertion	Enteric gram-negative bacilli, gram-positive cocci	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A
BILIARY TRACT **APPENDECTOMY** **SMALL INTESTINE** **COLORECTAL**	Enteric gram-negative bacilli, gram-positive cocci, enterococci, anaerobes	Cefoxitin		2 g IV	2 hours
			Clindamycin	900 mg IV	6 hours
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A
HERNIA REPAIR	Aerobic gram-positive organisms	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
HEAD AND NECK Clean		None			
Clean with placement of prosthesis	*S. aureus, S. epidermis,* streptococci	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
Clean-contaminated (Oropharyngeal mucosa is compromised) Excluding tonsillectomy or funtional edoscopic sinus	Anaerobes, enteric gram-negative bacilli, *S. aureus*	Cefazolin **+** metronidazole		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
				500 mg IV	N/A

			Clindamycin	900 mg IV	6 hours

NEUROSURGERY	*S. aureus, S. epidermidis*	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
GYNECOLOGIC	Enteric gram-negative bacilli, anaerobes, group B strep, enterococci	Cefoxitin		2 g IV	2 hours
			Clindamycin	900 mg IV	6 hours
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A
ORTHOPEDIC	*S. aureus, S. epidermidis*	Cefazolin*****		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin******	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
VASCULAR	*S. aureus, S. epidermidis*, enteric gram-negative bacilli, clostridia	Cefazolin*****		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin******	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
PLASTIC Surgery and BREAST Procedures Clean with risk factors or clean-contaminated Including axillary lymph node dissection and primary nonreconstructive surgery	*S. aureus, S. epidermidis*, streptococci	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Vancomycin	< 80 kg: 1g IV 80-120 kg: 1.5g IV > 120 kg: 2g IV	N/A
UROLOGIC Lower tract instrumentation with risk factors for infection (including prostate biopsy) or clean procedure with or without entry into the urinary tract	Enteric gram-negative bacilli, enterococci	Cefazolin		< 80 kg: 1 g IV 80-120 kg: 2 g IV > 120 kg: 3 g IV	4 hours
			Clindamycin	900 mg IV	N/A
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A
Involving implanted prosthesis		Cefazolin **±** Gentamicin		<120 kg: 2 g IV ≥120 kg: 3 g IV	4 hours
				5 mg/kg based on dosing weight	N/A
			Clindamycin	900 mg IV	N/A
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A
Clean-contaminated (Enters GI tract)		Cefoxitin		2 g IV	2 hours
			Clindamycin	900 mg IV	N/A
			PLUS		
			Gentamicin	5 mg/kg based on dosing weight	N/A

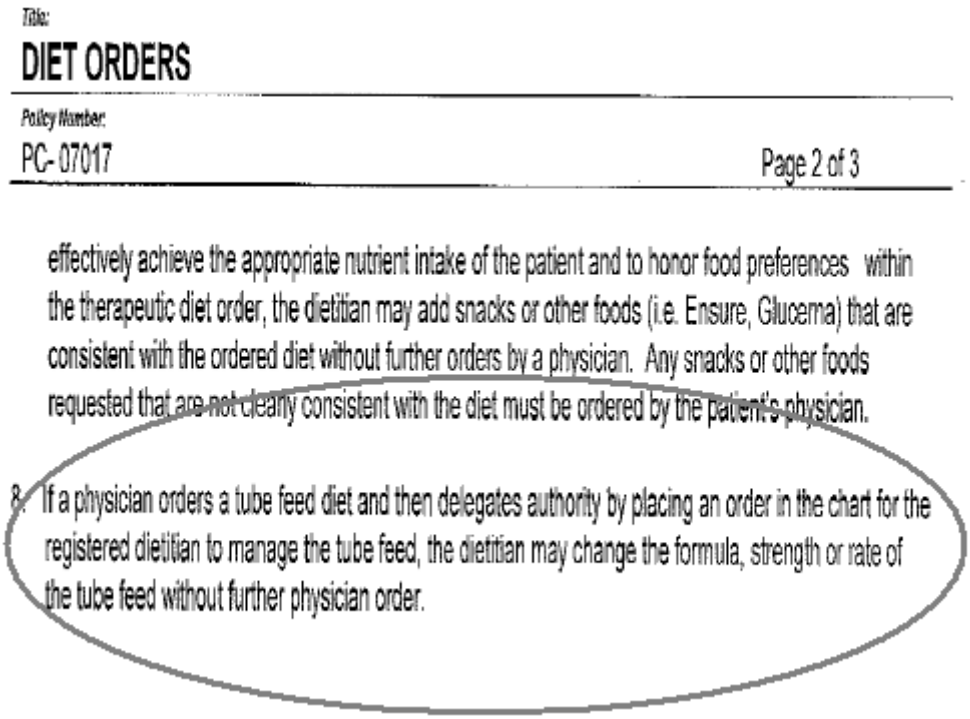
Look Alike/Sound Alike Drug List 2013

Drug Name	Drug Name	Potential Errors	Prevention Strategies
KETAmine	kePPRA	Similar names and strengths	1. Tall man lettering in Pyxis &Meditech 2. Pyxis pop-up warning 3. Witness required when KETamine removed from Pyxis to verify correct medication.
NovoLIN 70/30	NovoLOG MIX 70/30	Similar names and strengths	1. Tall man lettering in Pyxis &Meditech 2. Pyxis pop-up warning
hydrOXYzine	hydrALAzine	Similar names	1. Tall man lettering in Pyxis &Meditech 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR and indication.
DOXOrubicin *Liposomal*	DOXOrubicin *Conventional* and DAUNOrubicin	Similar names	1. Tall man lettering in Pyxis & Meditech. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
metroNIDAZOLE	metFORMIN	Similar names and strengths	1. Tall man lettering in Pyxis & Meditech 2. Pyxis pop-up warning 3. Do NOT store next to each other. 4. Name alert on MAR.
oxyCODONE controlled-release	oxyCODONE immediate-release	Similar names	1. Tall man lettering in Pyxis & Meditech 2. Pyxis pop-up warning. 3. Name alert on MAR.
CeleBREX®	CeleXA® and CereBYX®	Similar names	1. Tall man lettering in Pyxis & Meditech 2. Pyxis pop-up warning 3. Name alert on MAR. 4. Do NOT store next to each other.
cloniDINE	KlonoPIN®	Similar names	1. Tall man lettering in Pyxis & Meditech 2. Pyxis pop-up warning. 3. Name alert on MAR. 4. Do NOT store next to each other.
Wellbutrin SR®	Wellbutrin XL®	Similar names	1. Pyxis pop-up warning. 2. Name alert on MAR. 3. Do not store next to each other.
MuciNEX®	MucoMYST®	Similar names	1. Tall man lettering in Pyxis & Meditech 2. Pyxis pop-up warning. 3. Name alert on MAR. 4. Do not store next to each other.
Plavix®	Pradaxa®	Similar names and strengths	1. Pyxis pop-up warning 2. Name alert on MAR. 3. Do NOT store next to each other.

Revision to DIET ORDERS policy PC-07017

Proposal for Pharmacy and Therapeutics
8/8/2013

When speaking with physicians and educating on the TJC action plan for tube feeding orders, many voiced frustration. Physicians may intend for the RD to "manage" the TF but are not using the correct wording (per policy) in order to delegate the responsibility. The current policy states:



Title:
DIET ORDERS

Policy Number:
PC- 07017 Page 2 of 3

effectively achieve the appropriate nutrient intake of the patient and to honor food preferences within the therapeutic diet order, the dietitian may add snacks or other foods (i.e. Ensure, Glucerna) that are consistent with the ordered diet without further orders by a physician. Any snacks or other foods requested that are not clearly consistent with the diet must be ordered by the patient's physician.

8. If a physician orders a tube feed diet and then delegates authority by placing an order in the chart for the registered dietitian to manage the tube feed, the dietitian may change the formula, strength or rate of the tube feed without further physician order.

We propose the following change to the policy to streamline the process:

8. If a licensed independent practitioner orders a tube feed diet and then delegates authority by placing an order in the chart for the registered dietitian to "manage" the tube feed, the dietitian may change the formula, strength or rate of the tube feed without further physician order. Additionally, if the licensed independent practitioner orders "tube feeds per dietitian" or "dietitian for tube feeds" it will be interpreted as an order to manage the tube feeding unless otherwise specified.

9. If a licensed independent practitioner orders tube feeding goal per dietitian, the dietitian will write the order for the tube feeding goal, but not take over continued management of the feeding unless otherwise ordered.

Respectfully submitted,
Memorial Hospital Clinical Dietetics Team