Pharmacy & Therapeutics Committee Meeting
Private Dining Room
June 25, 2015 7:00 a.m.

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Next Meeting will be August 13, 2015 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: April 9, 2015 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

Members Present:			**Members Absent**:		**Guests**:
Richard Pesce, M.D.. David Dodson, M.D. Nathan Chamberlain, M.D. Samuel Currin, M.D.	Karen Babb, PharmD Michelle Denham, RN Patrick Ellis, PharmD Lila Heet, PharmD Karen Regal, Supply Chain Rhonda Poulson, CNO Scott Harbaugh, Finance	Melissa Roden, RN Sandy Vredeveld, DPh Hannah Walker, RN	Diona Brown, RN Vickie Burger, Lab William Oellerich, M.D. Michael Harper, M.D Allen Atchley, M.D Michael Stipanov, M.D. Mark Anderson, M.D Nathan Schatzman, M.D.	Rodney Elliott, PhT Brian Jones, RD Nan Payne, RN Shannon Harris, RN Kevin Lewis, M.D	Matthew Russell, PharmD Megan Whittier, PharmD Nick Martin, Student

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 12, 2015 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Anti-fungal Class Review** – The CHI antifungal class review was reviewed. CHI will be completing medication class reviews for the purpose of standardizing formularies across the various CHI hospitals. The CHI antifungal review is the first of these reviews and it is largely consistent with the existing Memorial formulary. The only necessary change to formulary is to transition to the use of Ambisome instead of Abelcet due to a recent contracting change which results in Ambisome being the most cost effective lipid based amphotericin product available at this time. Dr. Anderson is aware of this formulary change and is agreeable to this formulary modification. 2. **EpiPen (epinephrine auto-injector)** – The formulary status of EpiPen auto-injectors was discussed. Patrick recommended that these be removed from formulary now that a standardized anaphylaxis protocol is available for use throughout all clinical areas. The allergic reaction/anaphylaxis standing orders can be utilized in lieu of the use of EpiPen auto-injectors. 3. **Endothelin Receptor Antagonist Class Review** – Oral agents approved for treatment of patients with pulmonary arterial hypertension. Due to the REMS requirements for each medication, patients must be enrolled in the REMS program specific to each medication and thus patients must be maintained on their home therapy and not switched to alternate therapies while hospitalized. Due to the cost associated with these medications and their infrequent use it was recommended by Dr. Pesce for patients to utilize their own supply (dispensed by pharmacy) and for these to only be ordered in the event that a patient is not able to supply their own medications while hospitalized.	1. Approved 2. Information 3. Not approved for formulary addition	Complete Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	4. **Zerbaxa® (ceftolozane/tazobactam) –** New cephalosporin/beta-lactamase inhibitor combination approved for the treatment of cUTI and intra-abdominal infections. The available in-vitro susceptibility data shows that this antimicrobial may prove beneficial for the niche treatment of certain MDR *Pseudomonas* infections. It was recommended to approve for formulary addition with restriction to ID physicians or proven cases of susceptibility in the setting of multi-drug resistance on a case by case basis per Antimicrobial Stewardship Team.	4. Approved with restriction	Complete
	5. **Avycaz® (ceftazidime/avibactam) –** New cephalosporin/beta-lactamase inhibitor combination. Although only limited clinical data is available for this medication it was approved via an accelerated FDA approval pathway due to its unique ability to provide coverage for certain MDR organisms. The addition of avibactam allows this antimicrobial to inhibit most broad spectrum beta-lactamase enzymes including most carbapenemases. It was recommended to approve for formulary addition with restriction to ID physicians or proven cases of susceptibility in the setting of multi-drug resistance on a case by case basis per Antimicrobial Stewardship Team.	5. Approved with restrictions	Complete
	6. **Soliris® (eculizumab)** – Eculizumab is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. The cost of the drug is $6,086.66 per each 300 mg vial. Due to the cost and the need for appropriate lab tests for accurate diagnosis the development of a protocol was discussed. All physicians were in agreement that an order set/protocol is needed to ensure that appropriate diagnosis is made and that necessary lab tests are expedited to assist in diagnosis of aHUS. Patrick agreed to develop a draft protocol and it will be reviewed with the committee members at the next meeting.	6. Protocol to be developed	Pending
	7. **Toujeo® (U-300 insulin glargine) –** A concentrated 300 unit/ml formulation of insulin glargine (Lantus) only available in a pre-filled insulin pen. The Toujeo pen has been specially designed for Toujeo, therefore no dose conversion is required and it can be converted to Lantus or other long acting insulin as a 1:1 conversion. It has been recommended by CHI that all facilities designate this product as non-formulary and substitute Levemir for Toujeo. Dr. Dodson agreed that due to a lack of clear clinical benefit and risk of errors associated with concentrated insulin products to automatically interchange Levemir on a unit to unit basis in the event that Toujeo is ordered.	7. Formulary interchange approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Medication Use Evaluation	**1. Miacalcin Injection (calcitonin-salmon)** Pricing of injectable calcitonin recently increased by an extremely large amount and a medication use evaluation was conducted to determine calcitonin usage trends to determine if opportunities to decrease use exist. The MUE highlighted the need for physician education on the recent price increase and to recommend bisphosphonates as 1st line agents for treatment of mild to moderate hypercalcemia. The use as a pain control measure for compression fracture was also discussed. Due to the price increase the committee felt that education is necessary to discourage this practice and to encourage the use of nasal calcitonin for this indication. Patrick will follow up and coordinate education.	1. Information	Pending
	2. Timing of Antibiotic Administration-Sepsis – An evaluation of patients admitted to the ED with confirmed sepsis was conducted to evaluate the timing of antibiotic administration in relation to the recommendations from the *Surviving Sepsis Campaign* guidelines. The most recent guidelines also include a recommendation that IV antibiotic therapy should be started within the first hour of recognition of severe sepsis after initial cultures have been obtained. The sampling of data collected from patients in this review reveal that some opportunities for shortening the time to initial antibiotic administration do exist at both campuses. Overall (including both facilities), 78% of all patients received their first dose of any antibiotic greater than 60 minutes following their initial triage time. The initial antibiotic choice was also evaluated for appropriateness. In many situations the initial empiric antibiotic was appropriate based on the patient's suspected source of infection, however some patients were prescribed therapies that may not have been optimal based on local resistance patterns, etc. Rhonda explained that electronic prescribing of first dose antibiotics in the ED might enable quicker administration of the first dose antibiotic and this would be explored for feasibility. It was also recommended to standardize the initial antibiotic choices to mirror the Sepsis Admission Orders to provide a higher likelihood that the most optimal first dose antibiotic is ordered based on the suspected site of infection. Patrick will f/u with Rhonda and assess potential opportunities.	2. Information	Pending
	3. **Exparel Orthopedics Review –** Patrick reviewed a February memorandum from CHI Clinical Leadership Council that has "prohibited" Exparel in all procedures except for total knee replacements although details have yet to emerge on how this effects pre-existing use outside of knee surgeries. Patrick also shared Memorial's data related to TKA procedures and this information will also be shared with the surgeons. Recent data suggests that conventional local anesthetics (ropivacaine) may offer similar results to Exparel.	3. Information	Pending
Medication Safety/Quality	**ADR Review –** Karen reviewed ADR data from July-December 2015. One category 3 ADR was discussed and this will be reported to the FDA Medwatch program. A continued trend of opioid related ADRs was observed and a multidisciplinary group is evaluating the use of opioids and this work will be presented at the next meeting.	Information	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Policy, Procedure & Protocols	• **P&T Policy –** Edits to the existing P&T policy were presented. The content of the policy is largely unchanged but a few additions were made to conform to the standardized P&T policy. • **Prescription Pad Security –** Melissa initiated some discussion regarding the need for improved security measures to prevent theft and inappropriate use of hospital prescription pads. No clear recommendations were made but further discussion will continue and also via other multidisciplinary committees.	Approved Information	Complete Pending

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is June 25, 2015

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

GENERIC NAME: histidine-tryptophan-ketoglutarate crystalloid cardioplegia

PROPRIETARY NAME: *Custodial HTK* (Essential Pharmaceuticals)

*** Requested by Dr. Zellner for trial use in minimally invasive valve repairs ***

INDICATIONS: Custodial HTK is indicated for perfusion and flushing of donor kidneys, liver, and heart prior to removal from the donor or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation (not for continuous perfusion) to the recipient.

Although it is only indicated for the above clinical scenario it is widely used in other countries as a single dose cardioplegia and is claimed to offer myocardial protection for a period of up to 3 hours, allowing performance of complex procedures without interruption. Due to the single dose administration this is attractive for minimally invasive cardiac surgery (minimally invasive valve repairs, etc.).

CLINICAL PHARMACOLOGY: Custodial is an intracellular crystalloid cardioplegic solution used by some health systems for myocardial protection in complex cardiac surgery and for organ preservations in transplant surgery. It is considered an intracellular cardioplegia due to its low sodium and calcium content. Sodium depletion of the extracellular spaces causes a hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. This is a different mechanism of action from conventional extracellular cardioplegic solutions which are high in potassium content and cause arrest by membrane depolarization. The high histidine content buffers the acidosis caused by the accumulation of anaerobic metabolites during the long ischemic period. The ketoglutarate component improves ATP product during reperfusion, tryptophan stabilizes the cell membrane, and the mannitol decreases cellular edema and acts as a free-radical scavenger.

COMPARATIVE EFFICACY: Despite its widespread use in Europe, there is very little data comparing the efficacy of Custodial with conventional blood or crystalloid cardioplegia. A recent systematic review (14 randomized & non-randomized trials) suggests no significant difference between Custodial and conventional cardioplegia for the primary endpoint mortality, or the secondary endpoints used as surrogate markers of myocardial protection during cardiac surgery although data does indicate that the safety is similar. There was a trend for increased incidence of ventricular fibrillation in the Custodial group that did not reach statistical significance. Overall, the results of the available evidence suggest that Custodial offers myocardial protection that is equivalent to that of conventional cardioplegia, however the body of evidence available from which to draw conclusions is limited by the small number of randomized patients.

A single dose cardioplegia does however have some significant benefits for the performance of minimally invasive cardiac surgery and results summarized above support its ongoing trial use in this area. Re-administration of cardioplegia can disturb the technical flow of complex procedures such as minimally invasive surgeries.

ADVERSE REACTIONS: Custodial is a hypotonic solution (sodium 15 mmol/L) and some concerns have been raised about hyponatremia that follows rapid administration of the Custodial solution although none of the available data has specifically evaluated clinical hyponatremia as a data element.

PRODUCT AVAILABILITY & COST:
Product composition: Na – 15 mmol/L, K – 9 mmol/L, Mg – 4 mmol, Ca – 0.015 mmol/L, Histidine – 198 mmol/L, Tryptophan – 2 mmol/L, Ketoglutarate – 1 mmol/L, Mannitol – 30 mmol/L, pH – 7.02

Cost - $210 per 1 Liter (Standard cardioplegia - $84.60 - includes induction & maintenance solutions)

CONCLUSION: Based on the available data there is currently insufficient evidence to recommend the routine use of Custodial for use during coronary artery bypass grafting or other simple open cardiac surgical procedures. However, use as a single dose cardioplegia strategy may offer benefits in more complex minimally invasive cardiac surgeries.

DRUG CLASS REVIEW

Antitussives: Therapeutic Class: 48:08

AHFS Therapeutic Description: Antitussives
(Included: benzonatate, codeine, dextromethorphan, hydrocodone, diphenhydramine)

Background & Summary:
Strong evidence-based literature is lacking in regard to antitussive therapy despite the fact that many of the agents have been used in practice for a relatively long period of time. Many of the studies that exist to date are observational studies, have a small study population, and have questionable methods for measuring endpoints. Several studies assert that the available antitussive agents are not predictably efficacious, have undesirable side effects at antitussive dosages, and are at times no more effective than placebo. With this said, many clinical studies to date have demonstrated dextromethorphan, opioids (hydrocodone, codeine, etc.), benzonatate, and diphenhydramine to be effective in treating cough. Both opioids and benzonatate have evidence for use in chronic cough in cancer patients; hydrocodone may be associated with a better adverse reaction profile than some of the other opioids (such as morphine or hydromorphone). Hydrocodone possesses slightly better antitussive activity than codeine and is a much more potent analgesic than codeine. There is not sufficient evidence to highlight one agent as superior to the other agents overall. The choice of antitussive agent for empiric cough therapy should be based upon patient history, patient comorbidities, drug allergies, route of administration, and previous use of antitussives.

Formulary recommendations in the following table were made focusing on patient safety considerations, the reality of a current lack of strong evidence to support specific agents for empiric cough therapy, current product contract status and pricing and overall SKU reduction at the facility. For many of these medications, the more expensive unit dosed formulation was used for the pharmacoeconomic evaluation due to challenges with repackaging (benzonatate) and/or with work flow and monitoring issues created by drawing up liquid unit doses from bulk bottles, especially those containing codeine. Although Mucinex products may not appear to be contracted items, based on their comparable acquisition cost and less frequent dosing convenience they were added to the formulary.

FORMULARY AGENTS

Class	Formulary Generic Name	Common Brand Names	Cost per unit or 5ml
Antitussive	Benzonatate 100mg	Tessalon Perles	$0.29
Expectorant (liquid)	Guaifenesin 100mg/5ml or 200 mg/10ml*	Robitussin	$0.02 10ml $0.06 5ml
Expectorant (tablet)	Guaifenesin 600mg extended release	Mucinex	$0.21
Antitussive + Expectorant (tablet)	Guaifenesin 600mg + Dextromethorphan 30mg	Mucinex DM	$0.45
Antitussive + Expectorant liquid (opioid containing)	Guaifenesin + Codeine 100mg/10mg/5ml or 200mg/20mg/10ml*	Robitussin AC	$0.07 5ml $0.03 10ml
Antitussive + Expectorant liquid (non-opioid containing)	Guaifenesin + Dextromethorphan 100mg/10mg/5ml or 200mg/20mg/10ml*	Robitussin DM	$0.06 5ml $0.03 10ml

*For the products available as a 5 or 10 ml unit dose item, the 10 ml product is utilized in the below conversion table based on normal adult dosages. The 5 ml product may be considered for facilities with pediatric patients.

FORMULARY INTERCHANGE TABLE

Class	Formulary Generic Name	Common Brand Names & Adult Dose
Antitussive	Benzonatate 100mg	Tessalon Perles 100-200mg TID PRN Cough
Antitussive + Decongestant	Benzonatate 100 mg + Decongestant#	Tessalon Perles 100-200mg TID PRN Cough + Decongestant#
Antitussive + Expectorant	(Guaifenesin + Dextromethorphan 200mg/20mg/10ml) OR OR (Guaifenesin ER + Dextromethorphan 600mg/30mg)	Robitussin DM 200-400mg Q4hrs PRN Mucinex DM 600-1200mg Q 12hrs
Antitussive + Expectorant + Decongestant (opioid containing)	(Guaifenesin + Codeine 200mg/20mg/10ml + Decongestant#)	Robitussin AC 100-200mg Q4hrs PRN + Decongestant#
Antitussive + Expectorant + Decongestant (non-opioid containing)	(Guaifenesin + Dextromethorphan 200mg/20mg/10ml + Decongestant#) OR (Guaifenesin ER + Dextromethorphan 600mg/30mg + Decongestant#)	Robitussin DM 200-400mg Q4hrs PRN + Decongestant# Mucinex DM 600-1200mg Q12hr + Decongestant#
Antitussive + Antihistamine	Benzonatate 100 mg + antihistamine* OR (Guaifenesin + Dextromethorphan 200mg/20mg/10ml + Antihistamine*)	Tessalon Perles 100-200mg TID PRN Cough + Antihistamine* Robitussin DM 200-400mg Q4hrs PRN + Antihistamine*
Antitussive + Antihistamine + Decongestant	No triple agent available. Consider alternative combination product +/- individual formulary agents (example: Benzonatate + Decongestant# + Antihistamine*)	
Expectorant	Guaifenesin 200mg/10ml OR Guaifenesin 600mg extended release tablet	Robitussin 200-400mg Q4hrs PRN Mucinex 600-1200mg Q12hrs PRN
Expectorant + Decongestant	Guaifenesin 200 mg/10ml + Decongestant# OR Guaifenesin 600 mg extended release tablet + Decongestant#	Robitussin 200-400mg Q4hrs PRN + Decongestant# Mucinex 600-1200 Q12hrs PRN

* Antihistamine – formulary non-sedating antihistamine

Decongestant – formulary short acting decongestant (phenylephrine, pseudoephedrine, etc.)

DRUG CLASS REVIEW

Vitamins: Therapeutic Class 88:00

Background: As part of CHI's national pharmacy formulary standardization process various classes of medications are being reviewed at a corporate level to evaluate opportunities to streamline formulary items and eliminate stock of certain products. The current hospital formulary regarding vitamins has been evaluated and we are largely compliant with CHI's recommendations. The below are formulary changes for CHI Memorial that are recommended in order to be in alignment with CHI as well as to eliminate some low use and/or high cost items from formulary.

Vitamin A products:

Aquasol A (injectable vitamin A)

- remove from formulary due to low cost & high cost ($1046 per vial)

Vitamin K products:

Mephyton 5 mg tab (phytonadione)

- remove from formulary and utilize pharmacy compounded 5 mg/5 ml liquid phytonadione solution due to cost (Mephyton 5 mg - $48.60 per tablet)

Vitamin C products:

Vitamin C 500 mg/50 ml injection

- remove from formulary due to low use

Vitamin D_2 products:

Calcidol drops 8000 units/ml (ergocalciferol)

- remove from formulary and utilize formulary tablets as alternative due to low product use.

Calcium products:

Calcium carbonate 1250 mg/5 ml liquid

- remove from formulary due to low use and utilize tablets as alternative (may be crushed)

Beta-carotene multivitamins:

Ocuvite (beta carotene containing multivitamin)

- remove from formulary and auto-substitute oral multi-vitamin as alternative.

RESPIRATORY FORMULARY INTERCHANGE- *product updates*

Beta-agonists	
ORDERED	**SUBSTITUTION**
Levalbuterol (Xopenex®)	Albuterol
Indacaterol (Arcapta® Neohaler) 1 inhalation (75 mcg) once daily	Formoterol (Foradil Aerolizer®) 1 inhalation (12 mcg) q 12 hours
Olodaterol (Striverdi Respimat®) 2 inhalations (5 mcg) once daily	Formoterol (Foradil Aerolizer®) 1 inhalation (12 mcg) q 12 hours
Formoterol (Perforomist®)	Arformoterol (Brovana®)

Inhaled Anticholinergics/Antimuscarinics	
ORDERED	**SUBSTITUTION**
Aclidinium (Tudorza®) 400 mcg twice daily via oral inhalation	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Tiotropium (Spiriva Respimat®) 5 mcg (2 puffs) via oral inhalation once daily	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Umeclidinium (Incruse Ellipta®) 62.5 mcg (1 puff) via oral inhalation once daily	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Tiotropium/Olodaterol (Stiolto Respimat®) 5 mcg/5 mcg (2 puffs) via oral inhalation once daily	Umeclidinium/Vilanterol (Anoro Ellipta®) 62.5 mcg/25 mcg (1 puff) via oral inhalation once daily
Note: When tiotropium (Spiriva®) is ordered for a patient currently on ipratropium (Atrovent®), the Atrovent® will automatically be discontinued per protocol.	

FORMULARY REVIEW

GENERIC NAME: IVABRADINE

PROPRIETARY NAME: CORLANOR (AMGEN)

INDICATIONS: Ivabradine is the first drug approved for systolic heart failure in a decade. It is indicated for reduction of hospitalization in patients with chronic heart failure, who have the following characteristics:

- Stable, symptomatic heart failure
- Left ventricular ejection fraction (LVEF) of <35%
- Sinus rhythm with resting heart rate of >70 beats per minute
- On maximum tolerated doses of beta-blockers or have a contraindication to beta-blockers

CLINICAL PHARMACOLOGY: Ivabradine selectively and specifically binds to channels in the SA node known as funny current (If) channels. This current was named "funny current" because of its unusual behavior of running inward and being activated by hyperpolarization during the resting phase of the cardiac action potential. It accelerates diastolic depolarization of the SA node, so inhibiting the current with Ivabradine slows this depolarization and therefore the spontaneous pacemaker activity of the SA node, reducing heart rate. In other words, it has been described as a pure heart-slowing agent in patients with heart failure.

PHARMACOKINETICS: Plasma protein binding is approximately 70%. Ivabradine undergoes extensive metabolism in the liver and intestines via CYP3A4-mediated oxidation. The effective half-life of ivabradine is approximately 6 hours. Approximately 4% of an oral dose is excreted unchanged in the urine; the metabolites are excreted to a similar extent in the feces and urine.

ADVERSE REACTIONS: Atrial fibrillation has been reported in just over 1% more patients. If atrial fibrillation occurs, discontinue the drug. The large SHIFT trial, done in patients with systolic heart failure, reports that approximately 100 patients would need to be treated with Ivabradine for two years in order to see one case of atrial fibrillation. In a meta-analysis that included a wider range of patients with heart failure and angina, the risk of atrial fibrillation was lower such that 208 patients would need to be treated with Ivabradine for one year in order to see one case of atrial fibrillation. In clinical trials, 1 in 50 patients experienced temporary brightness (luminous phenomena) in the field of vision and most cases resolved on their own even with continued use. Bradycardia and hypertension were also reported in about 1% of patients treated.

DRUG INTERACTIONS: Metabolized by CYP3A4. Use of strong CYP3A4 inhibitors such as itraconazole, clarithromycin, nelfinavir, and nefazodone, is contraindicated. Moderate inhibitors, such as diltiazem, verapamil, and grapefruit juice, should be avoided, as should CYP3A4 inducers, such as St. John's wort, rifampicin, barbiturates, and phenytoin. There is an increased risk of bradycardia in patients taking other heart rate lowering medications, such as digoxin, amiodarone, beta-blockers, etc. Patients with a pacemaker set to >60 beats per minute should not take Ivabradine since the goal with Ivabradine is to maintain a heart rate below this, at 50 to 60 beats per minute.

CONTRAINDICATIONS: Use of Ivabradine in patients with any of the following conditions is contraindicated:

- Acute decompensated heart failure
- Hypotension <90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block in patients without pacemakers
- Resting HR <60
- Severe hepatic impairment
- Heart rate completely maintained by pacemaker
- Patients taking a strong CYP3A4 inhibitor

DOSING: The recommended dose is 5mg PO BID with meals. After 2 weeks, if the heart rate is greater than 60 beats per minute, the dose should be increased to 7.5mg PO BID. If the heart rate is less than 50 beats per minute, the dose should be decreased to 2.5mg PO BID. Patients at risk of hemodynamic compromise, such as those with a history of heart conduction defects, sinus node dysfunction, or ventricular dyssynchrony, should be started at a dose of 2.5 mg twice daily.

PRODUCT AVAILABILITY: Ivabradine is supplied as 5mg and 7.5mg tablets.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is required but a Med Guide is required to be dispensed.

CLINICAL TRIALS: There have been two large, multi-center, double-blind, randomized, placebo-controlled trials evaluating ivabradine for the treatment of heart failure, SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) and BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction).
SHIFT looked at over 6000 patients in sinus rhythm with symptomatic heart failure who were on standard therapy. These patients had an LVEF of <35%, an elevated initial heart rate of >70 beats per minute, and had been admitted to the hospital for treatment of heart failure within the previous year. Ivabradine was given over two years as an addition to standard heart failure therapy. Compared to placebo, patients treated with ivabradine reported a 2% reduction in all-cause hospitalizations (1356 vs 1231, p value = 0.003), but there was no significant difference in all-cause mortality. For the primary endpoint (composite cardiovascular deaths or hospital admissions for worsening HF) patients treated with ivabradine demonstrated a statistically significant reduction in the primary endpoint as compared to placebo (placebo – 937/3264 (29%); ivabradine – 793/3241 (24%)).

The BEAUTIFUL trial enrolled 10,917 patients in sinus rhythm with stable coronary artery disease, a heart rate of >60 beats per minute, and an LVEF of <40%. Patients were stable on conventional cardiovascular medications, including beta-blockers, ACEIs or ARBs, aldosterone antagonists, aspirin, lipid-lowering agents, etc. Results showed an average heart rate reduction of six beats per minute from the baseline rate of 71.9 +/- 9.9 beats per minute. There were no significant effects found for the primary endpoints of cardiovascular death or hospitalization due to either heart failure or acute myocardial infarction. This trial differed from the SHIFT trial in that it included patients with lower initial heart rates and only heart failure patients with coronary artery disease.
As seen in the SHIFT study, many heart failure patients are not being treated with optimal doses of beta-blockers. The reasons for this are varied, but side effects often limit the dose of beta-blockers a patient can tolerate, and therefore limit the heart rate lowering actions.

Ivabradine is well tolerated, in large part due to its selective action. It has fewer reported side effects compared to beta-blockers, as it has no reported effects on atrioventricular conduction or myocardial contractility. However, ivabradine does not have the proven beneficial effects in heart failure patients that have been found with beta-blockers. Also, it is not clear if the benefits seen in SHIFT would be reproduced in a patient population being treated with optimal doses of beta-blockers.
The data suggests that Ivabradine prevents 1 in 25 patients from being hospitalized over 2 years when added to an ACEI or ARB, beta-blocker, and aldosterone antagonist, but it does not reduce overall mortality.

COST: Approximately $5.70 per 5mg and 7.5mg tablets = $11.40/day

CONCLUSION: Heart failure patients should first be optimized on standard therapy of a beta-blocker, an ACEI or ARB, and an aldosterone antagonist. If despite optimized therapy, a patient remains symptomatic with a heart rate above 70 beats per minute, Ivabradine may be considered as add-on therapy. Patients who are truly intolerant of maximum doses of beta-blockers may benefit from the addition of Ivabradine. Although statistically significant, the benefits of ivabradine have only been demonstrated in its ability to reduce heart failure readmissions with no significant differences in mortality or HF/CV death. Due to the data only showing a reduction in heart failure readmissions and no decrease in mortality, we recommend this agent be reserved for patients who are already stabilized on chronic therapy and it likely has little utility for new starts in hospitalized patients.

FORMULARY REVIEW

GENERIC NAME: NIVOLUMAB

PROPRIETARY NAME: OPDIVO (Britol-Myers Squibb)

INDICATIONS: Advanced melanoma and squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy.

Possible indications in the pipe-line: Renal-cell Carcinoma, acute myeloid leukemia, pancreatic cancer, metastatic breast cancer, Hodgkin Lymphoma, sarcomas, advanced solid tumors, and cervical cancers. Likely more to come.

CLINICAL PHARMACOLOGY: Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Up-regulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

PHARMACOKINETICS:
Steady-state: Reached by 12 weeks @ 3 mg/kg q2wks
Exposure (AUC): Increased dose proportionally over the dose range of 0.1-10 mg/kg q2wks
Renal impairment, mild hepatic impairment, gender, age, baseline LDH, PD-L1 expression, tumor type, and tumor size created no clinically relevant differences in the PK. Clearance of Opdivo did increase with increased weight, so weight based dosing is appropriate.

No dose adjustment is recommended for patients with mild hepatic impairment or renal impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment.

Safety based study:
The most common drug-related adverse events occurred in 91% (188) of patients: fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritus, and headache. Serious adverse events that investigators considered to be related to treatment occurred in 5% (11/207) of patients: adrenal insufficiency, endophthalmitis, pancreatitis, vomiting, sarcoidosis, and myasthenia gravis. Of note, 7/11 of the serious adverse events occurred at the 10 mg/kg dose, with only 3/11 of the serious adverse events occurring at the 3 mg/kg dose, 1/11 occurring in the 1 mg/kg dose, and none occurring in the 0.3 mg/kg dose.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:
- Immune-mediated reactions: Administer corticosteroids based on the severity of the reaction.
- Immune-mediated pneumonitis: Withhold for moderate and permanently D/C for severe or life-threatening pneumonitis.
- Immune-mediated hepatitis: Monitor for change in liver function.
- Immune mediated nephritis: Monitor for change in renal function.
- Immune-mediated hypothyroidism/hyperthyroidism: Monitor for changes in thyroid function.
- Embryo-fetal toxicity: Can cause fetal harm. Ad vise of potential risk to a fetus and use of effective contraception.

DRUG INTERACTIONS: No formal PK DDI studies have been conducted with Opdivo.

DOSING: Administer 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

COST AND COMPARISON: Nivolumab

3 mg/kg q2weeks in 70 kg patient = 210 mg q2weeks = $5,035.80 q2weeks

CONCLUSION: Over-all-survival as well as progression-free-survival showed statistical differences in favor of nivolumab over comparative treatment regimens currently being used. Also, studies did show objective decreases in tumor sizes compared to other chemotherapy regimens.

FORMULARY REVIEW

GENERIC NAME: HPβCD-DICLOFENAC INJECTABLE

PROPRIETARY NAME: DYLOJECT (HOSPIRA)

INDICATIONS: Hydroxypropyl betadex, sometimes referred to as hydroxypropyl beta-cyclodextrin, diclofenac sodium (referred to as diclofenac unless otherwise specified) is indicated for the management of mild to moderate pain alone or moderate to severe pain in combination with opioid analgesics in adult patients.

CLINICAL PHARMACOLOGY: Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). It works through inhibition of the cyclooxygenase (COX-1 and COX-2) pathways leading to reduced prostaglandin synthesis. Injectable diclofenac sodium is formulated in a hydroxypropyl beta-cyclodextrin solubilizer that allows for rapid infusion and reduces complications from propylene glycol and benzyl alcohol solvents used in previous formulations approved outside of the United States.

PHARMACOKINETICS: After intravenous (IV) administration, the time to maximum concentration (T_{max}) ranges from 3 to 5 minutes. Intramuscular (IM) and subcutaneous administration results in delayed T_{max} to 34 to 39 minutes and 41 minutes, respectively. Total exposure (area under the curve [AUC]) and maximum concentration of diclofenac are dose-dependent from 18.75 to 75 mg with IV administration; oral dosing of diclofenac potassium 50 mg yields AUC between the IV 18.75 and 37.5 mg dose. With repeated dosing every 6 hours, accumulation was not seen and is not expected. Diclofenac is more than 99% bound to serum proteins, primarily albumin. The mean half-life of diclofenac ranges from 1.4 to 1.7 hours after a single dose, but increases to 2.3 hours with 4 repeated doses. Metabolism is by primarily by cytochrome P450 (CYP-450) 2C9 to a weakly active metabolite, and to a lesser extent by UDP-glucuronosltransferase-2B7 and CYP2C8/3A4 enzymes. Excretion is primarily renal (65%) as metabolites, with less than 1% excreted as the unchanged drug.

ADVERSE REACTIONS: The most commonly reported adverse reactions in patients treated with diclofenac include nausea, constipation, headache, infusion-site pain, and dizziness. In clinical trials, diclofenac was combined with rescue morphine and compared with either ketorolac injection plus rescue morphine or placebo injection plus rescue morphine. The combination of either diclofenac or ketorolac with morphine reduced the average dose of rescue morphine required for pain control.

DRUG INTERACTIONS: Drug-drug interactions are summarized in the complete *Formulary Monograph*.

DOSING: The recommended dose is diclofenac 37.5 mg every 6 hours as needed, given by IV push over 15 seconds. The maximum recommended dose is 150 mg per day.

PRODUCT AVAILABILITY: Diclofenac injectable was approved by the Food and Drug Administration on December 23, 2014. It is supplied as a 25-pack of 1 mL vials containing 37.5 mg/mL clear, colorless solution for injection.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is required.

Phase III Clinical Trial: Dyloject vs Ketorolac or Placebo for Acute Moderate-to-Severe Pain after Abdominal or Pelvic Surgery

- Primary Endpoint: Sum of Pain Intensity (SPID) differences over 48 hours (compared to placebo)

Dyloject 18.5mg	Dyloject 37.5mg (approved dose)	Ketorolac 30mg
P = 0.032	P = 0.0001	P = <0.0001

- Safety: The incidence of bleeding-related AEs was 6.6% in placebo group, 6.1% in ketorolac, 5.7% in diclofenac 37.5 mg (approved dose) and 2.3% in 18.75 mg. There were no declines in hemoglobin or platelets between baseline and follow up in any treatment group.

Phase III Clinical Trial: Dyloject vs Ketorolac or Placebo for Acute Moderate-to-Severe Pain after Orthopedic Surgery

- Primary Endpoint: SPID over 5 intervals (0-24, 0-48, 0-72, 0-96, and 0-129 hours) compared to placebo

Dyloject 18.5 mg	Dyloject 37.5 mg	Dyloject 50 mg	Ketorolac 30 mg	Ketorolac 15 mg
P <0.0001	P <0.0001	P <0.0001	P <0.0001	P <0.0001

- Safety: The incidence of bleeding-related adverse events was 16% in the Dyloject group (all strengths combined) and 16% in the ketorolac group (all strengths combined), and was not significantly greater than in the placebo group for either. In the subset of patients that received anticoagulants, there was no clinically meaningful difference in bleeding-related adverse events across treatment groups.

COST AND COMPARISON:

Diclofenac - 37.5mg $11.30 per dose

Ketorolac - 30 mg is 0.71 cents per dose

CONCLUSION: Based on the available data, diclofenac should not be used in place of ketorolac for the management acute moderate to severe pain in adults. Both treatments were found to be efficacious compared to placebo in clinical trials, and have a similar safety profile. Additionally, the cost of diclofenac is significantly more than ketorolac and it is recommended to not add to formulary.

SOLIRIS (eculizumab) – Inpatient Protocol & Orders

Indication for use: treatment of patients with atypical hemolytic-uremic syndrome (aHUS)
Prescribers must be registered with the Soliris REMS program in order to prescribe Soliris

Laboratory tests (if not already ordered): ADAMTS13 (notify lab to send to Vanderbilt laboratory), SHIGA-toxin

Clinical criteria for use – prescriber must check the appropriate boxes below:

Laboratory findings consistent with thrombotic microangiopathy (both of the below boxes should be checked)

- □ Thrombocytopenia (platelet count < 150,000 *OR* > 25% decrease from baseline) **AND**
- □ Hemolysis (schistocytes *and/or* elevated LDH *and/or* decreased hemoglobin)

Evidence of organ damage (one of the below boxes should be checked)

- □ Evidence of renal injury
- □ Neurological abnormalities

Evaluation of ADAMTS13 activity (one of the below boxes should be checked)

- □ ADAMTS13 activity > 10%
- □ Results not available but the patient's presentation is highly suggestive of a diagnosis of aHUS pending ADAMTS13 results.

Response to plasma exchange therapy (one of the below boxes should be checked)

- □ Patient not completely responding to PEX **OR** positive hematologic response but with progressive renal injury despite PEX therapy
- □ Patient is not a candidate for PEX therapy

Soliris Dosing (aHUS):

- 900 mg IV x 1 dose infused over 35 minutes (total volume 180 ml – diluted in normal saline)
  Subsequent weekly doses of Soliris must be ordered by the prescriber after further clinical evaluation, review of ADAMTS13 results and other appropriate laboratory data.

Meningococcal Vaccine (meningococcal disease prophylaxis):

- Quadrivalent meningococcal vaccine x 1 dose now prior to Soliris.

FORMULARY REVIEW

GENERIC NAME: C1 ESTERASE INHIBITOR (Human)

PROPRIETARY NAME: *Berinert* (CSL Behring)

Requested by Anesthesia (Dr. Schatzman) for treatment of ACE inhibitor induced angioedema

INDICATIONS: C1 esterase inhibitor (*Berinert*) is indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adults and adolescents. C1 esterase inhibitor (*Cinryze*) is indicated for routine prophylaxis of HAE attacks in adults and adolescents.

CLINICAL PHARMACOLOGY: C1 esterase inhibitor (human) (*Berinert*) is a plasma-derived, purified, pasteurized preparation of C1 esterase inhibitor made from plasma collected in the United States and processed with a variety of 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 esterase inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact-system) pathway and also regulates the fibrinolytic system. Patients with HAE have a low baseline C1 inhibitor concentration and activation of any protease that is inactivated by C1 inhibitor leads to consumption of the C1 inhibitor to the extent that activation of the complement and contact systems becomes completely unregulated. During HAE attacks, contact system activation leads to bradykinin generation which mediates an increase in vascular permeability. Administration of C1 inhibitor suppresses contact system activation by inactivating plasma kallikrein and factor XIIa, which may modulate vascular permeability by preventing bradykinin generation.

ACE Inhibitor Angioedema: ACE inhibitor induced angioedema occurs in approximately 0.1 - 0.7% of patients taking these medications. ACE inhibitors block the effects of the enzyme ACE (kininase II) and impacts both the renin-angiotensin-aldosterone pathway and the degradation of bradykinin. In some patients the ACE blockade can result in elevated levels of bradykinin. Bradykinin is an inflammatory vasoactive peptide which can result in vasodilation of blood vessels and in some cases angioedema. The C1 inhibitors have been shown to be effective for ACE inhibitor-induced angioedema in case reports. One of the functions of C1 inhibitors is the inhibition of kallikrein which facilitates the production of the active form of bradykinin.

ACE INHIBITOR ANGIOEDEMA TREATMENT: Antihistamines, glucocorticoids, and epinephrine are commonly used to treat angioedema but these medications are not known to alter levels of bradykinin and are usually considered ineffective or minimally effective in treating ACE inhibitor induced angioedema. Additional therapies to speed the resolution of ACE inhibitor-induced angioedema should be considered if the swelling is threatening the patient's airway and does not appear to be stabilizing or improving, such that intubation seems imminent. These other therapies are agents approved for use in HAE. Of these therapies the only agent that is available for purchase by a health system is *Berinert.* Case reports do exist which have shown that C1 inhibitors can be effective for ACE inhibitor-induced angioedema.

PHARMACOKINETICS: Following intravenous (IV) administration, peak plasma concentration of C1 inhibitor was reached in 0.5 to 2.9 hours. In adults, the mean elimination half-life is 16.7 to 43.9 hours.

ADVERSE REACTIONS: The most common adverse reactions observed in clinical trials with *Berinert* were headache, nausea, diarrhea, abdominal pain, muscle spasms, pain, and vomiting. Adverse events occurred with equal or less frequency in the C1 esterase inhibitor 20 units/kg group than in the placebo group. The most serious adverse reaction reported in patients treated with *Berinert* was an increase in the severity of pain associated with HAE.

DRUG INTERACTIONS: No drug interaction studies have been conducted.

DOSING: C1 esterase inhibitor is approved for IV administration only. It should be administered by slow IV injection, at a rate of approximately 4 mL/min, and not in combination with other medicinal products or solutions. The recommended dose is 20 units/kg. It should be administered at room temperature within 8 hours of reconstitution. Dosing for treatment of ACE inhibitor induced angioedema is not defined.

COST: $1,945 per 500 units (20 unit/kg dose: $5,835 – 3 vials total, based on 75 kg patient)

CONCLUSION: Berinert is the only C1 inhibitor approved for treatment of acute attacks and is the drug of choice for treatment of an acute attack of hereditary angioedema. The use of C1 inhibitors for treatment of ACE inhibitor induced angioedema is limited to case report data to demonstrate its usefulness for this indication. Case reports mention other therapies such as bradykinin receptor antagonists (icatibant) these are not available for purchase by health systems which leaves Berinert as the only therapy available for this off label indication. Although expensive, Berinert does provide a potential therapy for patients experiencing a severe angioedema episode with airway compromise. If approved, Berinert should be reserved for severe cases of ACE inhibitor angioedema.

FORMULARY REVIEW

VITAMIN D ANALOGUES – ORAL & INJECTABLE

BACKGROUND: Currently there are three commercially available vitamin D agents available and all three are currently on formulary – Calcitriol, doxercalciferol, paricalcitol. These agents are all used for the treatment Vitamin D deficiency (secondary hyperparathyroidism) in patients with chronic kidney disease. In general, calcitriol is the least expensive oral or injectable product currently available and is the same as endogenous vitamin D_3. Doxercalciferol and paracalcitol are vitamin D analogs that have less affinity for both intestinal and parathyroid gland vitamin D receptors and therefore have been shown to cause a lower incidence of hypercalcemia.

USAGE: The injectable formulations of each the available agents are rarely utilized and calcitriol is the most commonly utilized injectable agent with the other two agents very rarely utilized in the IV formulation. Oral calcitriol is by far the most commonly utilized oral medication with very low usage of both doxercalciferol and paracalcitol.

RECOMMENDATION: It is recommended that due to low use that only one of the Vitamin D analogues be carried on formulary. Paracalcitol (Zemplar) is currently the most cost effective of these agents and it is recommended that oral paracalcitol be designated as the oral vitamin D analog formulary agent and orders for doxercalciferol (Hectorol) be automatically converted to a therapeutically equivalent dose of paracalcitol as designated below. Also, due to extremely low use of the injectable formulations of doxercalciferol and paracalcitol it is recommended that neither medication be carried on formulary and if ordered the physician will be notified and the order either converted to an equivalent oral dose or calcitriol injectable will be recommended as an alternative if an injectable formulation is required.

Doxercalciferol (Hectorol) 0.5 mcg → Paracalcitol (Zemplar) 1 mcg

FORMULARY INTERCHANGE

SYMBYAX (olanzapine/fluoxetine)

Background: Symbyax is a combination atypical antipsychotic and SSRI that is FDA approved for treatment of depressive episodes associated with bipolar I disorder and for acute and maintenance treatment of treatment-resistant depression.

The available strengths of Symbyax (3/25, 6/25, 12/25, 6/50, 12/50) are formulated as strengths that are not available in the same strengths as the individually available products – olanzapine (2.5, 5, 12.5) & fluoxetine (25, 50). However, when using individual components of fluoxetine with olanzapine rather than a fixed dose combination product (Symbyax), approximate dosage correspondence is available in drug information references to aid in conversions (see below). Acquisition cost comparison between Symbyax and the individual component products varies greatly (Symbyax cost: $9 - $20 per dose; Individual components: ~ < $1 per dose).

Recommendations: Due to the cost difference between products and to eliminate the need to carry multiple strengths of Symbyax it is recommended to automatically substitute the individual drug components as outlined below.

Olanzapine 2.5 mg + fluoxetine 20 mg = Symbyax® 3/25

Olanzapine 5 mg + fluoxetine 20 mg = Symbyax® 6/25

Olanzapine 12.5 mg + fluoxetine 20 mg = Symbyax® 12/25

Olanzapine 5 mg + fluoxetine 50 mg = Symbyax® 6/50

Olanzapine 12.5 mg + fluoxetine 50 mg = Symbyax® 12/50

Naloxone (Narcan) Medication Use Evaluation
Memorial Health System

A medication use evaluation was conducted to determine naloxone usage trends at Memorial Hospital. The purpose of this evaluation was to determine when and why naloxone is being used and to identify opportunities for preventing over sedation secondary to inpatient opioid use. Data from 94 instances of naloxone use from January 2014 through March 2015 were evaluated.

Background:
Opioid safety is an ongoing concern as healthcare practitioners attempt to balance the need for adequate pain control with reducing the risk of over sedation. Among the drugs most frequently associated with adverse drug events, the Joint Commission published a Sentinel Event Alert in 2012 regarding the safe use of opioids in hospitals.

Results:

Specialty	Count
Ortho	34
Hospitalist	21
EM	8
CTVS	5
GS	4
Anesthesia	4
Intensivist	4
IM	3
FP	3
Oncology	2
Colorectal	2
Cardiology	2
Renal	2
Grand Total	**94**

Primary Cause	Count
Polypharmacy	34
Single Drug	30
PCA	12
LA + PCA	8
LA	6
Epidural	3
Cause Unclear	1
Grand Total	**94**

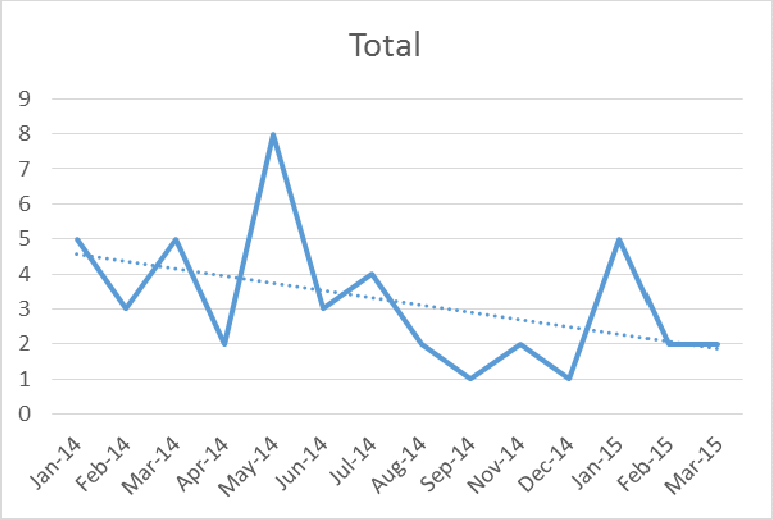
Hospitalist Orders 21 total patients (10 opioid naïve) 5 instances that led to LOC increase		
Causative agent	**Instances**	**Comments**
Hydromorphone IV	9	6 instances as single agent All doses 0.5-1 mg
PCA	3	2 non-standard PCA orders
Long-acting PO	3	
Duragesic	2	1 patient opioid naïve

Hospitalist Order Sources	
Written	14
PSO	4
Home meds	3

Ortho Orders 34 total patients (18 opioid naïve) 6 instances that led to LOC increase		
Causative agent	**Instances**	**Comments**
Long-acting PO	12	6 patients opioid naïve
PCA	15	
Duragesic	1	

Ortho Order Sources	
Written	7
PSO	26
Intraop	1

Naloxone Usage by Month – 3 South		
Jan 2014	5	Average 4/month
Feb 2014	3	
Mar 2014	5	
Apr 2014	2	
May 2014	8	
June 2014	3	
Jul 2014	4	
Aug 2014	2	
Sep 2014	1	Average 2.2/month
Nov 2014	2	
Dec 2014	1	
Jan 2015	5	
Feb 2015	2	
Mar 2015	2	



Summary & Conclusion:

Overall data summary:

An initial analysis of the 94 instances of naloxone usage showed a variety of primary causes for its use, with the majority simply being related to polypharmacy or various single causative agents. Of the 94 instances, 55 were related to orders from either the hospitalist or ortho groups. This was to be expected given the volume of patients treated by each of these groups, and the relatively large amounts of narcotics required by ortho patients. Focusing further on these groups independently allowed specific trends to become more evident.

Within the instances of naloxone use related to hospitalist orders, hydromorphone IV was the most prevalent causative agent. Hydromorphone was involved in 9 of the 21 instances of naloxone use, and in 6 of those cases it appeared to have been the single causative agent. All doses of hydromorphone were in the range of 0.5 to 1 mg. Other causative agents from this group included PCAs (3), long-acting PO narcotics (3), and Duragesic patches (2).

Within the instances of naloxone use related to ortho orders, specific trends were less evident. In the majority of instances, long-acting PO narcotics and/or PCAs appeared to have been involved as causative agents. In 1 case, a Duragesic patch appeared to have been a causative agent. Overall naloxone usage on 3-South was also evaluated over this time period to determine the general trend in naloxone usage in this patient population. Prior to September 2014, the average instance of naloxone use in this patient population was 4 per month. Since September 2014 this average is 2.2 per month. This reduction in naloxone use coincides with widespread use of

intra-operative peri-articular infiltration use of local anesthetics which has demonstrated an approximate 100 mg reduction of oral morphine equivalent usage per patient admission.

Conclusion:

Given the high instance of hydromorphone as a causative agent in the hospitalist group of orders, it appears that doses of even 0.5-1 mg may be too much for some patients. It is possible that there is also still some confusion related to the equipotency of morphine vs hydromorphone.

In the ortho group, trends were less evident. Many of the patients who received naloxone were on PCAs or long-acting narcotics, but due to the similarity in treatment regimen for this group of patients, it is difficult to identify any noteworthy causes. The reduction in average naloxone use, however, is an encouraging sign that the reduction in narcotic use in this patient population due to local anesthetic peri-articular injections appears to be increasing opioid safety in this group.

Of note, there were 2 instances of possible inappropriate Duragesic use in the hospitalist and ortho groups. Duragesic carries black box warnings for its use in opioid naïve patients and in the management of acute pain.

Adverse Drug Reaction (ADR) Summary
FY15 January-April 2015

Category 1: Commonly recognized ADR's which are expected and do not result in serious medical consequences or extended hospitalization (e.g. antibiotic rash, nausea, mild hypokalemia).

Category 2: Significant ADR's which extend hospitalization and/or require extensive therapeutic measures (e.g. gastrointestinal bleed secondary to NSAIDs, Aminoglycoside nephrotoxicity.

Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse Event Reporting System).

Inpatient: 207 (36%)
Prior to hospitalization: 365 (63%)
Total: 572

Category 1: 423
Category 2: 146 (1 severe)
Category 3: 0

Severe Category 2 to discuss: LS was an 83 yo male transferred from NH where he was recovering from a small bowel surgery. Prior to arrival, NH called to report an INR of 9.6 and said patient was coughing up blood. EMS responded. Upon being loaded into ambulance, patient coded. ACLS protocol was started. Upon arrival to the ED, patient was found to have copious amounts of coffee-ground emesis/blood in his oropharynx. After 60 minutes of resuscitation efforts, the patient was in asystole as well as without pulse. MD's assessment says probably aspiration of hemoptysis. Of note, patient has a history of dysfibrinogenemia, so the warfarin could have contributed, but it is difficult to say the warfarin was the cause of death.

Narcotics continue to be a major contributor to inpatient ADRs. Leading reactions include altered mental status changes, nausea, constipation, and respiratory distress. A work group is still reviewing Narcan and opioid usage with data to be shared soon.

(Order Set: 2355) Revised: (6/16/2015)

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

IV IRON REPLACEMENT - INPATIENT PROTOCOL

Medication (CHECK ONE):

☐ Iron Dextran (InFed) - pharmacy to calculate dose using formula below (single dose replacement).

1. Total dose in ml = [0.0442 x (desired Hb - observed Hb) x LBW] + (0.26 x LBW)
   - InFed concentration = 50mg/ml
   - Use actual body weight if < lean body weight (LBW)
   - Desired Hb = 14.8 unless otherwise specified by physician
2. Give test dose = 25 mg (0.5 ml)
   - Monitor patient for 1 hour for s/s of infusion/anaphylactic reaction
   - If an allergic reaction occurs, initiate the Allergic Reactions/ Anaphylaxis Orders (PSO#2039)
3. Once test dose completed, give remaining amount as infusion over 4-6 hours

☐ Sodium Ferric Gluconate (Nulecit) - pharmacy to calculate dose using formula below (multiple dose replacement)

1. Total dose in mg = total body weight x (15 - current Hb) x 2.4 + 500
   - Use adjusted body weight for patients with BMI > 25
   - Round total dose to the closest 250 mg
   - Divide rounded total dose by 250 mg to calculate number of doses needed
   - Order will read: Give 250 mg in 100 ml NS over 2 hours every 12 hours x _____ doses until total dose completed or patient discharged

Physician Signature:_____ Date:_____ Time:_____

Title: DRUG AND FOOD INTERACTION / EDUCATION			
Page 1 of 2			
Policy Number: MM-05450		Date Last Revised: 1/13	Valid Until: 1/16
Department(s) Affected: Nutrition Services, Nursing, Pharmacy		Review Period: every 3 years	

OUTCOME:

Patient education will be provided to patients receiving medications determined to have potential drug-food interactions prior to discharge.

DEFINITION:

SIGNIFICANT DRUG-NUTRIENT INTERACTIONS: Those occurring with relative frequency or occurring less frequently, but with potentially grave consequences.

Medications determined by the Pharmacy and Therapeutics Committee to have clinically significant drug-nutrient interactions:

Generic Name	***Brand Names***
Warfarin	Coumadin, Jantoven
Metronidazole	Flagyl
Linezolid	Zyvox
Monoamine Oxidase *Inhibitors (MAOI's) such as:*	
Phenelizine	Nardil
Tranylcypromine	Parnate
Rasagiline	Azilect
Selegiline	Eldepryl, Zelapar

POLICY:

Patient and family education will be provided as outlined in *PATIENT-FAMILY EDUCATION PROGRAM (PC-07230)*.

1. Patients receiving the medications listed above will be provided information on clinically significant drug-nutrient interactions using approved resources as noted in *PATIENT-FAMILY EDUCATION PROGRAM (PC-07230)*.
    a. Nutrition clinical staff will provide patient education on Monoamine Oxidase Inhibitors and Linezolid (Zyvox)
    b. Nursing will provide patient education on Warfarin (Coumadin, Jantoven) and Metronidazole (Flagyl)
2. Inpatients receiving the medications listed above will be flagged daily in the Kardex file in Nutrition Services (Hixson) to prevent them from receiving foods that might result in a medication interaction. At the Memorial Glenwood campus this information will be entered into the CBORD System.
    a. Grapefruit juice is not available on the patient menu.
    b. Herbal supplements will be reviewed as part of the Registered Dietitian nutritional assessment as requested.
    c. Patients on Warfarin will be served no more than 1 serving of food HIGH in Vitamin K per day.
    d. Patients with a known reaction to aspartame (NutraSweet) will not be served products containing aspartame.
        i. Any patient with a known allergy or reaction to aspartame (trade name "Nutrasweet") should be so identified in order for Nutrition Services to make appropriate substitutions for products containing Nutrasweet.

ii. The allergy should be entered into the "Allergy" section of the patient profile in the computer.
iii. Nutrition Services will not serve food products containing Nutrasweet, including but not limited to Equal, diet soft drinks and other diet beverages, diet jellies/syrups, and diet Jello.

e. Clinical dietitians and dietetic technicians will provide counseling to patients on other drug / food interactions as requested.

3. Inpatient education documentation is recorded on the Intervention Education: Interdisciplinary as outlined in *PATIENT-FAMILY EDUCATION PROGRAM (PC-07230)*

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CHYLE DIET
(For Patients with Chylothorax)
Patient Education

What is Chyle?
Chyle is a milky white fluid containing fat, which is normally taken up by the lymph system during the digestion and is circulated to the rest of the body.

What is Chylothorax?
Chylothorax occurs when chyle gets into the chest cavity. Fat and protein often leaks into the rest of the body resulting in other problems. The cause may be unknown or may stem from other medical complications.

Helpful Hints:
- A no significant fat diet will help reduce the amount of chyle production.
- Fat free supplements may be helpful (Ensure Clear beverage).
- Fat soluble vitamins, essential fatty acids, and MCT oil supplements may be helpful.

Use of Diet Supplements:
- Fat –soluble and essential fatty acid supplements should be taken under a physician's care.
- MCT Oils (Medium Chain Triglyceride):

1. Are used directly by the body
2. Do not require the lymph system to be carried to the rest of the body.
3. Lower the risk of the chyle formation when they are used as the main source of fat.
4. Should be used in moderation, too much may cause diarrhea and GI distress.
5. Dosage is a 4-5 Tablespoons (60-70grams/day) –taken throughout the day.
6. Contains 8.3 calories/gram.

What does a "Fat Free" on a food label mean?
- Very low level of significant fat or saturated fat.
- The product contains less than 0.5 grams of fat per serving.

What does "Low Fat" on a food label mean?
- The product contains less than 3 grams of fat per serving.
- These foods should be limited on a chyle diet.

See the following sheet for foods that are allowed and those that need to be avoided on a Chyle Diet.

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CHYLE DIET

(For Patients with Chylothorax)

Foods Allowed and Foods to Avoid on a Very Low Fat Diet (20 grams fat)

Food Group	Food Allowed Fat Free	Foods to Avoid
Fruits	Fresh, frozen or canned fruit. Fruit juice, raisins, dried fruit, jelly, fruit spreads.	Canned fruit pie filling, coconut or avocado.
Vegetables	Plain fresh, frozen, canned vegetables. Vegetable or tomato juice. Pickles.	Olives, vegetables in butter, oil, cream sauce, fried, sautéed with fat or topped with nuts/seeds/bacon.
Breads, Cereals, Rice, Pasta & other grains	Plain rice, couscous, potatoes, pasta, Plain bread or toast **(1 piece/day)**, plain grits, cream of wheat, pita bread, english muffin, fat free saltine crackers, pretzels, rice cakes, melba toast, or bread crumbs.	Bread with nuts or seeds, biscuits, muffins, bagels, cold cereal, egg or chow mein noodles, Fried rice/potatoes/hash browns/Tater tots.
Meats & other Protein Choices	98% extra lean or FF Luncheon meat. Chicken or turkey breast without skin. Pork tenderloin. Haddock/cod/pollock/flounder Shrimp/scallops (grilled/baked/broiled). Canned tuna or crab in water. 98% extra lean ground beef, turkey or chicken. ***(The above meats or fish must be baked/broiled/grilled with no butter, oil, margarine or animal fat. Total daily intake limited to 9oz.)*** Legumes, lentils or FF refried beans. Egg substitute or egg whites.	Fish or meat not on the "food allowed" list. Whole eggs, bacon, sausage, fried meats or fish. Meats or fish cooked with oil, butter, margarine or animal fat. Peanut or other nut butters. Garbanzo beans, soybeans or other beans cooked with bacon, salt pork or other fat.
Dairy	Fat free milk, fat free milk powder, fat free yogurt, fat free cream cheese, fat free cottage cheese	Milk, cheese, sour cream, cream cheese, ice-cream or yogurt that contain fat (this includes low fat).
Beverages	Fruit Juices, lemonade, soda, Gatorade and other sports drinks, tea, black coffee.	Beverages which contain cream or icecream.
Desserts	Fresh, frozen or canned fruit or gelatin. Chewing gum, hard or gummy candy, licorice, frozen 100% juice bars, popsicles, or sorbet.	Candy bars. Pies, cakes, cookies and other desserts made with butter, milk, cream, margarine, oil, or lard.
Fats	Fat free mayonnaise or fat free salad dressing.	Butter, cream, lard, oils, fat back, salt pork, margarine, salad dressing or mayonnaise with fat.
Miscellaneous	Ketchup, BBQ sauce, hot sauce, salsa, mustard, teriyaki sauce, soy sauce, cocktail sauce, relish, syrup, sugar.	Tartar sauce.