

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 20, 2007. 3 drugs were added in the *Formulary*, and 4 drugs were deleted. 4 drugs were designated nonformulary and not available. The criteria-for-use were changed for 2 drugs, and interchanges were approved for 3 drugs.

◆ ADDED

Mycophenolate Delayed-Release
(Myfortic® by Novartis)

Ranolazine
(Ranexa® by CV Therapeutics)

Tranexamic Acid
(Cyklokapron® by Pfizer)

◆ NONFORMULARY AND NOT AVAILABLE

Aminoglutethimide
(Cytadren® by Novartis)*

Fluvastatin (Lescol® and Lescol® XL by Novartis)†

Lovastatin (Altopen® Extended-Release by Sciele and Generic Immediate-Release)†

Teniposide
(Vumon® by Mead Johnson)

*Nonformulary and not available, no longer marketed.

†Nonformulary and not available, automatically interchanged.

◆ CRITERIA-FOR-USE CHANGES

Ketorolac Injection (Generic)‡

Pegfilgrastim
(Neulasta® by Amgen)§

‡Automatic 5-day stop order.

§Nonformulary and not available for inpatient use, restricted to Bone Marrow Outpatient Clinic.

◆ INTERCHANGES

Pravastatin (Generic) **for Fluvas-tatin** (Lescol® and Lescol® XL)

Pravastatin (Generic) **for Rosuvastatin** (Crestor®)

Simvastatin (Generic) **for Lovas-tatin** (Altopen® and immediate-release generics)

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NEWS

Monitoring heparin with heparin levels: not aPTTs

Near the end of April, the Clinical Laboratory at Shands at UF will begin routinely reporting unfractionated heparin anti-Xa levels, which should be used instead of activated partial thromboplastin times (aPTTs) for monitoring the therapeutic anticoagulation effects of unfractionated heparin (UFH). The therapeutic range of these "unfractionated heparin levels" is 0.3 to 0.7 units/mL of anti-Xa activity.

The P&T Committee approved therapeutic anticoagulation protocol changes (ie, Deep Venous Thrombo-

among laboratories based on thrombo-plastin reagents and the coagulometers used.

When the Clinical Laboratory at Shands at UF needed to change its coagulometer that measures aPTTs, it was recognized that this was an opportunity to switch to heparin levels from using aPTTs. The new aPTT range will be changing from 57 to 85 (ie, the "old" aPTT therapeutic range) to 74 to 105 (ie, the "new" aPTT therapeutic range). If practitioners use the old range with the new monitoring system, patients

Therapeutic Unfractionated Heparin Levels	New aPTT Therapeutic Range*	Old aPTT Therapeutic Range
0.3 to 0.7 units/mL	74 to 105 seconds	57 to 85 seconds

*If the old therapeutic range is used for the new aPTT reagents and coagulometer, UFH will systematically be under-dosed by approximately 20%.

sis [DVT]/Pulmonary Embolism [PE] and Acute Coronary Syndrome [ACS] protocols) that use heparin levels to monitor UFH's effects and to adjust dosages based on these results, instead of aPTTs. The dosage adjustments are based on the relationship of the old aPTT therapeutic range, which is calibrated to heparin levels.

Unfractionated heparin has traditionally been monitored by aPTT ratios with values 1.5 to 2.5 times control considered "therapeutic." The advantages of aPTTs are that they are inexpensive, easy to perform, and the results are readily available. However, aPTT was never designed to monitor heparin therapy. It is an indirect measurement of heparin's therapeutic effect. There are many physiologic factors that can affect aPTTs, which leads to variability in this measurement of heparin's activity. There is also wide variability

will systematically be under-anticoagulated. The College of American Pathologists and the American College of Chest Physicians advocate that clinical laboratories calibrate their therapeutic ranges of aPTTs using unfractionated heparin levels from plasma samples from 30 to 40 patients on heparin therapy.

The therapeutic range for reagent-based monitoring of UFH will always be 0.3 to 0.7 units/mL of anti-Xa activity, regardless of the equipment or reagents used. Until unfractionated

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Formulary update, from page 1

Myfortic® enteric-coated delayed-release tablets were added in the *Formulary* for patients admitted on this dosage form or for patients who are intolerant to mycophenolate mofetil (CellCept®) capsules. Mycophenolate is an immunosuppressant most often used in a triple-drug regimen in combination with cyclosporine or tacrolimus and corticosteroids for the prevention of acute cellular rejection after organ transplantation.

Myfortic® was developed with the hopes that slower and more distal absorption from the gastrointestinal (GI) tract would decrease the occurrence of adverse effects (eg, diarrhea). Randomized controlled trials have not shown this, however. Observational switch studies have suggested better GI tolerability in patients who did not tolerate CellCept®, however, these studies are flawed (ie, use of a subjective response variable in a study with no blinded "switch" back to CellCept®).

Myfortic® does have slightly different pharmacokinetic characteristics; thus, converting to CellCept® is not as straightforward as using the same dosage. Keeping patients on Myfortic® during their admission eliminates the possible need for dosage adjustments and/or additional monitoring.

Ranolazine is the first drug in a new category of drugs for the treatment of angina and has occasionally been used nonformulary at Shands at UF. Unlike other drugs used to treat angina (eg, beta-blockers, calcium channel blockers, or nitrates), ranolazine does not depend on decreasing heart rate, blood pressure, or vascular resistance to improve angina symptoms. Although its exact mechanism of action is not known, it is thought to inhibit the late inward sodium current in myocardial cells, which reduces intracellular calcium concentrations and improves left ventricular function.

Ranolazine has a labeled indication for the treatment of chronic angina. However, because ranolazine prolongs the QT interval, it is reserved for patients who have not achieved an adequate response with other antianginal drugs. Thus, it is an add-on therapy for use in combination with amlodipine, beta-blockers, or nitrates in patients who have not achieved an adequate response.

Because ranolazine has a short half-life (ie, less than 2 hr), it is available as an extended-release tablet that is given twice a day.

There are 3 randomized controlled trials that compare extended-release ranolazine to placebo that have been published (CARISA, ERICA, and MARISA). These studies show a modest decrease in the number of angina episodes per week, decrease in the number of nitroglycerin tablets used per week, and an increase in exercise duration at the end of the dosage interval (ie, trough). Data on true outcomes are pending an ongoing trial (MERLIN TIMI 36).

The most common adverse drug reactions associated with ranolazine use are

dizziness, headache, constipation, and nausea. The most serious adverse effect is QTc prolongation. All adverse effects are dose-related. Ranolazine use is contraindicated in patients with pre-existing QTc prolongation, patients taking other drugs that prolong the QT interval, patients with liver impairment (because it is primarily metabolized by the CYP 3A isoenzyme system), and patients receiving other drugs that moderately inhibit the CYP 3A isoenzymes in the liver (eg, diltiazem).

Since ranolazine is an add-on drug for treatment-resistant angina, there is no comparable drug listed in the *Formulary*. It costs between \$5 and \$10 per day.

Ranolazine was added in the *Formulary* for use in patients with resistant angina who are admitted on the drugs, and for patients started on ranolazine at Shands at UF. With its addition in the *Formulary*, appropriate education, alerts, and monitoring can be implemented to help minimize the risk of QT prolongation with ranolazine.

Tranexamic acid is a lysine analogue antifibrinolytic acid that is used off-label to decrease the risk of bleeding and the need for transfusions after cardiothoracic bypass surgery. It was added in the *Formulary* as an alternative to aprotinin (Trasylol®), which has been associated with an increased risk of renal failure and mortality in observational studies.

A Cochrane systematic review found that tranexamic acid was as effective as aprotinin in preventing blood loss post CT surgery. Although there are limited data on the safety of tranexamic acid in this patient population, thromboembolic events are a concern, including postoperative myocardial infarction, deep venous thrombosis, pulmonary embolus, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction. Most of these data come from use in patients with hemophilia. When tranexamic acid was evaluated in a large retrospective study in cardiac surgical patients, it was found to have a similar incidence of renal dysfunction, myocardial infarction, and cerebrovascular events to aminocaproic acid and placebo. Aprotinin was found to have a higher rate of these adverse effects.

Tranexamic acid costs less than 1/10th the cost of aprotinin.

Aminoglutethimide was deleted from the *Formulary* because it is no longer marketed. Aminoglutethimide was an oral adrenal steroid inhibitor used off-label in the treatment of breast and prostate cancers. It was also used to treat Cushing's syndrome, its labeled indication.

There are now more widely used aromatase inhibitors used in the treatment of cancers (eg, anastrozole or exemestane). Also, other drugs that decrease cortisol synthesis (eg, ketoconazole or metyrapone) are used for Cushing's syndrome.

Fluvastatin and **lovastatin** join **rosuvastatin** as HMG-CoA reductase inhibitors (or statins) that are nonformulary and not available for inpatient use at Shands at UF. These drugs will be interchanged to either **simvastatin** (lovastatin) or **pravastatin** (fluvastatin)

and rosuvastatin), which are available as generics. Equivalent doses for pravastatin and fluvastatin will be used; however, maximum doses of pravastatin (80 mg per day) will be used for rosuvastatin although the relative lowering of LDL is less. Equivalent doses of simvastatin will be used in place of lovastatin.

Pravastatin was selected as the alternative for fluvastatin and rosuvastatin because there is less concern about interactions with drugs like transplant drugs and drugs used to treat HIV. Simvastatin was selected as the alternative to atorvastatin because it is potent and widely used. Patients who use their own supply from home may continue to use these "not available" statins upon the order of the prescriber once they have been verified by a pharmacist for inpatient use.

Atorvastatin remains listed in the *Formulary*, not based on therapeutic superiority, but based on workload concerns. Atorvastatin is so prevalent in patients admitted, it would be difficult to switch these patients to an alternative, like simvastatin. Atorvastatin was the top drug prescribed based on the number of prescriptions filled in the US in 2006.

Patients should be switched back to the statin that they were admitted on as part of the medication reconciliation process. Patient choice of HMG-CoA reductase inhibitor is often driven by their third-party payor, who sets their outpatient co-pays. Expensive co-pays may affect patients' compliance, which is important for a chronic drug that does not alter symptoms.

Teniposide was deleted from the *Formulary* because of lack of use. Teniposide is a cytotoxic chemotherapeutic drug that has been used for a variety of cancers, but most specifically pediatric acute lymphocytic leukemia. It is also known as VM-26.

Etoposide (VePesid® or VP-16), which is similar to teniposide, is listed in the *Formulary*. Etoposide is more commonly used than teniposide. Teniposide has not been used at Shands at UF in the last year, but still would be obtained via a nonformulary request, if deemed necessary.

Ketorolac injection has a black-box warning stating that "the combined duration of ketorolac IV/IM and ketorolac oral is not to exceed 5 days because of the increased risk of serious adverse events." Ketorolac injection is a nonsteroidal anti-inflammatory (NSAID) that only has the advantage of being available in an injectable form. Oral ketorolac is nonformulary and not available.

The "adverse events" in the ketorolac labeling are increased risks of gastrointestinal ulceration, renal toxicity, and bleeding, which led to the 5-day prescribing limit. Ketorolac has been added in the Automatic Stop Order Policy, which will limit therapy to 5 days. The P&T Committee also authorized the automatic changing of any preprinted order to be consistent with the 5-day maximum limit.

Antimicrobial management makes progress

The Antimicrobial Management Program (AMP) has been making progress in improving the use of anti-infective agents, while improving outcomes. The accomplishments in 2006 and the goals for 2007 were recently reviewed.

Consumption of key antimicrobials is described as changes in the defined daily dose (DDD) of anti-infective agents consumed per 1000 patient days. The DDD is a measurement determined by the World Health Organization based on the assumed average maintenance dose per day for a drug when used for its main indication in adults. The DDD does not necessarily reflect the recommended or prescribed daily dose. DDDs provide a fixed unit of measurement independent of price and formulation enabling an assessment of trends in drug consumption and comparisons between population groups.

Antibiotic consumption changes of note at Shands at UF include reductions in both imipenem (Primaxin®) and the fluoroquinolone class by 41% and 26%, respectively. Appropriate use of these antibiotics is important as overuse has been associated with the development of resistance among certain pathogens as well as superinfections such as *Clostridium difficile*-associated diarrhea and candidiasis.

Increased consumption of agents used to target resistant gram-positive infections has occurred. Vancomycin is the most widely used agent to treat infections involving hospital-acquired MRSA. Vancomycin consumption increased by 18% in calendar year 2006. It is hypothesized that overall consumption has increased due to changes in prescribing patterns to achieve higher target trough concentra-

tions. Nationally published guidelines for certain infections advocate the use of high doses of vancomycin in order to achieve higher target trough concentrations (ie, 15-20 mcg/mL) despite little clinical evidence to support these recommendations. An audit is currently being conducted to compare the average per patient dose used in early 2004 with late 2006. In 2007, these data will be used to identify potential areas where high dosing of vancomycin may be occurring so that steps can be taken to ensure that high dose therapy is used appropriately.

Linezolid consumption also increased in 2006. Linezolid is primarily used to treat resistant enterococcal infections and methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients that are either intolerant or refractory to vancomycin therapy. Use of this agent increases as the number of resistant gram-positive infections increases. Linezolid use will continue to be monitored very carefully as it is one of the few "last-line" antibiotics available to treat resistant gram-positive infections.

There have been reductions in antifungal use noted at Shands at UF. Caspofungin use decreased significantly in 2006. The combined efforts of the Infectious Diseases Division, the AMP, and the Microbiology Laboratory to both rapidly identify yeast species in bloodstream infections and use high dose fluconazole when appropriate in place of caspofungin resulted in a 53% reduction in overall consumption as compared to 2005. Prudent use of caspofungin is warranted as it is one of only a few agents with activity against resistant candida species and must be

preserved for use in severe infections due to these resistant fungi.

Susceptibility trends as reported in the published hospital antibiogram show that resistance rates among important nosocomial gram-negative pathogens appear to be stabilizing. There may be a slight downward trend, although it is too early to conclude that an actual decrease is occurring. The stabilization of gram-negative resistance rates is a positive sign, and it is hoped that further reductions will be realized as global antimicrobial use is improved.

Unfortunately, this trend is not echoed among the gram-positive pathogens, including vancomycin-resistant enterococci (VRE) and MRSA. Slight increases in resistance rates were reported in 2006 in both of these pathogens, consistent with the upward trend seen throughout North America. In response to these and other resistance issues, a resistant pathogens task force combining members from multiple fields including infectious diseases, infection control, microbiology, and antimicrobial management has been formed. Reducing infections due to both MRSA and VRE is a key goal of this committee.

Prudent antimicrobial use has not only been associated with stabilizing resistance and improving patient care, but it also has resulted in cost reduction. These cost benefits help offset the costs associated with the AMP. It is the hope of the AMP that cost benefits will continue to be realized as part of the overall benefit from continued appropriate use of antimicrobials within Shands at UF.

By Ben Staley, PharmD

DRUG INFORMATION FORUM

How do patients dispose of drugs?

Patients or their family member may wonder how best to dispose of outdated, unwanted, or unneeded prescription and nonprescription drugs. Unfortunately, there is no mechanism for oral dosage forms (eg, tablets, liquids) that have been given to patients as prescriptions to be legitimately recycled for use in patients who cannot afford their prescription. Physicians and pharmacists should not have these drugs returned to them. Since drugs cannot be recycled, they have to be discarded.

The recommendations to "flush drugs down the toilet" or "toss them in the trash" are no longer optimal because of environmental concerns.

With controlled substances and other potentially harmful drugs, there is also the potential for diversion from the trash. There are guidelines for the disposal of drugs that can help protect the environment and/or decrease the risk of diversion.

Over the last few decades, there has been increasing evidence that discarded drugs are detectable in the environment, like the water supply. Although these are trace amounts, there is increasing concern about this trend. For example, the theoretical effect of disposed antibiotics on microbial resistance is a concern. Of course, the entire course of an antibiotic should be taken, and there should rarely be any "left-

overs." However, there are instances when patient intolerance results in unused antibiotics. Other drugs with possible toxic effects, such as hormones or drugs used to treat cancer, could also have health consequences. Thus, it is now recommended that drugs be disposed like other potentially hazardous waste.

Pharmacies and hospitals use commercial disposal services to take care of outdated pharmaceuticals to make sure that they are disposed of properly by following DEA, EPA, and state regulations. The appropriate documentation for controlled substances is meticulously maintained. Patients do not have

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Drug information forum, from page 3 access to these commercial services (ie, "reverse distributors"), but they have access to free services in many communities.

In Alachua County, the Environmental Protection Department provides a service for proper management of hazardous and toxic materials for county residents at the Alachua County Hazardous Waste Collection Center (HWCC). Various chemicals including pharmaceutical waste from households can be dropped off at the HWCC free of charge. The HWCC is located 2 miles north of the Gainesville Airport off Waldo Road at 5125 NE 63rd Avenue. They can be reached by phone at 334-0440.

If patients are not concerned about the environmental effects of drugs, they may be concerned about diversion or inadvertent misuse of discarded drugs. In February 2007, the Office of National Drug Control Policy provided new guidelines for the proper disposal of prescription drugs.

These federal guidelines suggest that patients take their unused, unneeded, or expired prescription drugs out of their original containers and throw them in the trash. Prior to disposal, the drugs should be mixed with an undesirable substance, such as used coffee grounds or kitty litter, and they should be put in an impermeable, non-descript container, such as an empty can or sealable bag. This further guards against the diversion

of these drugs. Drugs should only be flushed down the toilet only if the label or accompanying patient information specifically instructs doing so.

These new federal guidelines encourage patients to take advantage of community take-back programs that allow the public to bring unused drugs to a central location for proper disposal. Some communities have specific pharmaceutical take-back programs or solid-waste programs (ie, Alachua County), which allow the public to bring unused drugs to a central location for proper disposal. Where these central disposal programs exist, they are the best way to get rid of drugs. These programs address both diversion and environmental concerns.

News, from page 1

or reagents used. Until unfractionated heparin levels became readily available for clinical use, they were used to calibrate aPTTs and in specific patients with problems being adequately anticoagulated based on aPTTs. Now the turn-around time for reagent-based unfractionated heparin levels is the same as for aPTTs (ie, 24 hours a day, 7 days a week). Thus, the reliability of unfractionated heparin levels makes

it the preferred method for measuring anticoagulation from UFH.

Although unfractionated heparin levels cost more than twice that of aPTTs, cost savings and increased quality of care are expected. Based on published results, the number of measurements of anticoagulation and the number of dosage adjustments needed for UFH therapy are expected to decrease. An added benefit of using unfractionated heparin levels is that the monitoring range will not change with future

changes in reagents or equipment. The ultimate goal of adequate therapeutic anticoagulation with UFH while minimizing the risk of bleeding should be promoted by this change.

You can still order and get results for aPTTs, which may have some indications for use (eg, monitoring patients with hemophilia). However, unfractionated heparin levels should always be the preferred method of monitoring therapeutic anticoagulation with UFH.