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SHANDS at the University of Florida

April 2005

Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 15, 2005. 2 drugs were added in the *Formulary* and no drugs were deleted. 1 drug was evaluated and not added. Criteria for use were changed for 1 drug. A drug was also added in the *Charity Care Formulary.*

◆ ADDED

Clofarabine
(Clolar® by Genzyme Corporation)*

**Restricted to pharmacy administrator approval.*

Meningococcal Vaccine
(Menomume® by Aventis Pasteur)

◆ DELETED

None

◆ EVALUATED, BUT NOT ADDED

Natalizumab
(Tysabri® by Biogen Idec)**

***Nonformulary and not available*

◆ CRITERIA FOR USE CHANGE

Bivalirudin
(Angiomax® by The Medicines Company)

◆ CHARITY CARE FORMULARY ADDITION

Clopidogrel
(Plavix® by Bristol Myers Squibb)

Clofarabine is a purine nucleoside anti-metabolite with a labeled indication for the treatment of acute lymphoblastic leukemia (ALL) in pediatric patients who have failed at least 2 prior regimens. It has also been studied for off-labeled use in pediatric patients with AML and-

(continued on next page)

FORMULARY PROPOSAL

Percocet instead of Tylox...

The P&T Committee is considering changing the oxycodone-acetaminophen combination listed in the *Formulary* from a generic version of Tylox® to a generic version of Percocet®. There are 2 reasons for re-evaluating the oxycodone-acetaminophen combination: medication safety and workload.

From a practical perspective, we are unable to purchase a "Tylox-generic" that will fit into the automatic dispensing machines (ie, SureMed®) used at Shands at UF. This requires many hours of manual trimming of the unit-dose packages in order for the product to fit in the SureMed® cabinets.

The P&T Committee is considering changing the oxycodone-acetaminophen combination listed in the *Formulary* from a generic version of Tylox® to a generic version of Percocet®.

More importantly, the higher amount of acetaminophen in Tylox® may result in patients exceeding the recommended daily amount of acetaminophen that patients should receive. Using Percocet® could help lower patients' daily exposure to acetaminophen, which often comes from various sources. Percocet-generics have 175 mg less acetaminophen per dose (ie, 325 mg per tablet versus 500 mg per capsule in Tylox-generics). Patients may also be prescribed acetaminophen for fever control, which adds to the daily acetaminophen exposure.

The maximum recommended daily dosage of acetaminophen is 4 grams per day. Chronic dosages over 4 grams per day may be associated with increased risk of adverse effects, particularly hepatoxicity. A patient who receives 8 Tylox® capsules in a day has reached their maximum dose of acetaminophen. If they get more than 8 doses or they receive plain acetaminophen for a fever (or both), they have exceeded the daily maximum dose for acetaminophen. Using an oxycodone-acetaminophen combination with less acetaminophen is 1 way to avoid this limit; using plain oxycodone is another.

Another issue that would be solved by switching to a Percocet-generic in the *Formulary* is the prescribing of "Tylox liquid." There is no commercially available Tylox® liquid, yet it is frequently ordered when patients taking oral Tylox® capsules cannot swallow an oral solid dosage form. The only oxycodone-acetaminophen liquid on the market contains 10 mg oxycodone and 325 mg acetaminophen per 5 mL. This product (ie, Roxicet) is a "Percocet liquid."

The P&T Committee is considering a proposal that would switch the oxycodone-acetaminophen combination product listed in the *Formulary* from a generic version of Tylox® to a generic version of Percocet®. However, unlike other therapeutic interchanges, the committee is recommending that orders for Tylox® be switched to a Percocet generic without changing the order in each patient's chart.

There is precedent for this type of interchange. For example, ferrous sulfate 300 mg is dispensed and administered when 325 mg is ordered. However, since this change is perceived as being more significant, this proposal is being announced in the *Bulletin* for comments. Please send any comments or concerns to Secretary, P&T Committee, Box 100316 JHMHSC or e-mail them to hatton@ufl.edu. Comments received by May 13, 2005 will be considered.

INSIDE THIS ISSUE

Formulary update, *from page 1*
in adult patients with refractory or relapsed acute leukemias.

In clinical studies, clofarabine has shown activity against refractory or relapsed acute leukemias. It has also been shown to have a favorable toxicity profile with the dose-limiting toxicity being reversible elevations in liver enzymes. However, studies assessing the long-term effects of therapy and survival benefit are lacking at this time.

Although the primary dose-limiting toxicity associated with clofarabine use is reversible elevations in liver enzymes, the most common adverse events are gastrointestinal (ie, nausea, vomiting, and diarrhea), hematologic (ie, anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia), and infection.

Systemic inflammatory response syndrome (SIRS) or capillary leak syndrome is another adverse event associated with the administration of clofarabine in pediatric patients. Prophylactic administration of corticosteroids may minimize the incidence of this reaction.

Cardiovascular toxicities, including tachycardia, pericardial infusion, and left ventricular systolic dysfunction associated with clofarabine administration have also been noted. Precautions include insuring adequate hydration of patients receiving clofarabine to prevent dehydration that may occur due to vomiting and diarrhea as well as to reduce the effects of tumor lysis syndrome. Concomitant medications that are nephro- or hepatotoxic should be avoided due to the renal elimination of the drug and the increased incidence of hepatotoxicity associated with it.

The cost of one 5-day cycle of clofarabine for a child (0.7 m^2) would be approximately $22,500. It would cost considerably more for larger child or an adult. If clofarabine is used according to the labeled indication, this would be an added expense. It does not replace any specific therapy. However, if clofarabine is used as a first-line agent, the costs would be considerably more than current first-line therapy.

The available data support the use of clofarabine as salvage therapy in pediatric patients with acute leukemias. The data for other indications is insufficient.

Clofarabine will be restricted to pediatric patients with acute leukemias (ALL and AML) who have failed at least 2 prior regimens. A pharmacy administrator will have to approve each use based on this criterion before clofarabine will be dispensed.

Adult use of clofarabine may be considered as more data become available. This will require additional P&T Committee action.

Meningococcal vaccine was evaluated for formulary addition because there has been an increased use of this product. Increased use has been associated with more splenectomized patients on the new Shands at UF Trauma Service.

Meningococcal vaccine is a quadravalent polysaccharide vaccine that contains antigens for the serogroups A, C, Y, and W-135. The current Centers for Disease Control (CDC) guidelines recommend administration of meningococcal vaccines in (planned or emergent) splenectomized patients.

Splenectomized patients receive pneumococcal vaccine, *Haemophilus influenza* vaccine, and meningococcal vaccines (at the same time) to prevent infections caused by encapsulated organisms. If a splenectomy is planned, a patient should receive their vaccine 2 to 3 weeks before the spleen is removed to maximize the antigenic response. After the spleen is removed, patients have a limited response to vaccines for encapsulated organisms.

Whether meningococcal vaccine needs to be re-administered every 5 years is not explicitly stated in the CDC guidelines, but this practice has been implied by other references. Also, the guidelines do not differentiate between the unconjugated meningococcal vaccine (Menomune®) and a recently approved conjugated vaccine (Menactra®).

Menactra® is also a quadravalent vaccine with the same serotypes as Menomune®. It is conjugated with diphtheria toxoid to increase the immune response to the meningococcal antigens.

The CDC's Advisory Committee on Immunization Practices has formed a working group to update the recommendations for the prevention of meningococcal disease. The results of this group are expected soon. These recommendations may lead to additional formulary changes.

Natalizumab is a humanized monoclonal antibody with a labeled indication for the treatment of relapsing remitting multiple sclerosis (MS). The P&T Committee evaluated natalizumab because it is expensive and nonformulary inpatient use was a concern. However, recently identified adverse effects caused the manufacturer to voluntarily withdraw natalizumab from the market. Therefore, it is currently nonformulary and not available.

Natalizumab binds to alpha-4 subunit of integrin receptors on the surface of leukocytes (except neutrophils). This prevents the attachment of leukocytes to counter-receptors on vascular endothelium and inhibits the passage of leukocytes across the endothelium into inflamed tissues. By blocking these receptors on the blood-brain barrier, natalizumab is thought to prevent the passage of inflammatory mediators into the central nervous system. Although the exact mechanism of action is unknown, it is presumed that decreased transmigration of leukocytes across the blood brain barrier is responsible for the beneficial effects in multiple sclerosis.

The FDA approved natalizumab for the treatment of relapsing remitting multiple sclerosis on November 23, 2004 via the accelerated approval process. Approval was based on 1-year data from 2 Phase III trials that were planned for 2 years. These preliminary data showed relative decreases in relapse rates of 50% to 66%. These efficacy results were much greater than any other marketed product for the treatment of multiple sclerosis.

On February 28, 2005, Biogen Idec announced the suspension of marketing of Tysabri® because of reports of 2 serious adverse events that occurred in clinical trial patients treated with natalizumab in combination with interferon beta-1a (Avonex®). 1 patient receiving natalizumab in a long-term study died of progressive multifocal leukoencephalopathy (PML). After a second patient was diagnosed with PML, the drug was removed from the market. Neither patient had risk factors for PML, which is normally only seen in severely immunocompromised patients.

All clinical trials of natalizumab for MS and other indications (Crohn's disease) are currently on hold. The manufacturer is reviewing data for all patients who have received natalizumab and is doing MRIs and physicals to assess the risk for PML. A goal is to develop methods of differentiating between PML and MS.

The manufacturer plans to reintroduce natalizumab to the market as soon as the third quarter of this year. If necessary, the inpatient use of natalizumab will be re-evaluated by the P&T Committee.

Bivalirudin is a direct thrombin inhibitor. It has an FDA-labeled indication for use an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). A year ago, the Shands at UF criteria for use for bivalirudin were modified to include general use in PTCA.

(continued on next page)

Formulary update, *from page 2*
It was already listed in the *Formulary* for therapeutic anticoagulation in patients with a history of heparin-induced thrombocytopenia-thrombosis (HITT).

The additional criterion for use change was limited to a 1-year evaluation period. After reviewing the available evidence, the general use in PTCA was made permanent.

Data show that abciximab use is trending downward and bivalirudin use has been modest. The recently published evidence-based guidelines published in *Chest* for the use of anticoagulants for PTCA now recommend bivalirudin.

Clopidogrel is an oral antiplatelet agent with the labeled indication for the reduction of thrombotic events in patients with recent MI, stroke, or established peripheral artery disease. It is also used to reduce cardiac events in acute coronary syndrome (unstable angina/non-Q-wave MI) for patients treated medically and for the prevention of complications in patients receiving percutaneous coronary interventions (PCI) or coronary artery bypass grafts (CABG).

While aspirin is the traditional and most cost-effective therapy used in many of these clinical situations, there are instances where aspirin is not tolerated or the development of a coronary event while taking aspirin justifies changing to or adding clopidogrel. Current literature also supports the use of the combination clopidogrel and aspirin in coronary stenting, which is commonly performed on charity care patients at Shands at UF.

While the Department of Pharmacy has acknowledged the utility of clopidogrel for several years, the cost to charity care patients has often been prohibitive. Charity care patients could purchase clopidogrel from the Outpatient Pharmacy at hospital cost plus $5. While this cost was 30% to 40% less than other pharmacies, some patients opted to go without their clopidogrel because of their inability to pay.

Recently, Bristol-Myers Squibb Company, the manufacturer of Plavix®, has accepted Shands at UF's Outpatient Pharmacies into a program that provides replacement drug for all qualified patients. Patients who qualify for the *Charity Care Formulary* will now receive clopidogrel for a $5 copay.

ANTI-INFECTIVE STEWARDSHIP

Cefepime use audited

Cefepime is a fourth-generation cephalosporin with a spectrum of activity including both gram-negative and gram-positive aerobic organisms. Unlike other commercially available cephalosporins, cefepime has *in vitro* inhibitory activity against beta-lactamase producing organisms resistant to third-generation cephalosporins. Cefepime is active against *Pseudomonas aeruginosa, Acinetobacter baumanii,* and Enterobacter species.

A medication use evaluation (MUE) was done to determine current prescribing practices for cefepime because of its high-volume use. Appropriateness of prescribing was assessed using indication, clinical signs and symptoms, offending pathogen, sensitivity data, and dose. Additionally, opportunities for streamlining therapy to more appropriate agents were evaluated.

New cefepime orders from October 11, 2004, to October 26, 2004, were evaluated. Patients under 18 years old and 1-time doses were excluded. 73 orders were included in this audit.

Empiric use of cefepime was considered appropriate if a nosocomial infection or a resistant pathogen was suspected. Empiric therapy was considered appropriate in patients hospitalized for more than 48 hours, in patients who had a previous hospitalization in the last month, in nursing home or long-term-care residents, for chronic antibiotic therapy in previous hospital-acquired infection with new signs of infection, and in patients on chronic hemodialysis. Streamlining therapy was based on culture and sensitivity analysis, and therapy should have been discontinued when cultures were negative. However, continued empiric therapy was deemed appropriate if signs and symptoms persisted.

11 patients were started on cefepime based on culture and sensitivity data. Therapy was appropriate in 8 (72.7%) of these patients. 3 patients received cefepime when narrow-spectrum antimicrobial agents were indicated (eg, pan-sensitive *E. Coli* and Methicillin-Sensitive *S. Aureus*).

62 patients were started on empiric therapy. Cultures were obtained in 60 of these patients, but only 51 were obtained on day 1 of treatment. 8 of 9 cultures obtained after day 1 were negative. Overall, 35 patients had positive cultures and 25 patients were culture-negative. Initial empiric therapy was appropriately continued in 15 patients, appropriately streamlined in 25 patients, and inappropriately continued in 20 patients.

Cefepime was used primarily for empiric therapy of suspected nosocomial infections. It was appropriate 66% of the time for empiric therapy. In other words, a third of patients could have been treated with alternative agents.

There is room for improvement in ordering and collecting specimens for cultures and sensitivities. Physicians can specify that blood, urine, and sputum cultures be obtained before antibiotics are started. Promptly drawing specimens for culture and sensitivities provides information that can guide appropriate therapy. Specimens drawn after antibiotics have been started are not useful.

The results of this audit suggest that cefepime use can be significantly less. This is particularly important because there is a nationwide shortage of cefepime. Manufacturing problems at the production plant in Italy will make cefepime difficult to obtain for the next 2 months. Thus far, Shands has been able to continue to obtain drug. Prudent use of cefepime is recommended, especially during this time of short supply.

As shown by the MUE, most patients receive cefepime for empiric therapy, where alternative agents could often be used. Cefepime should be reserved for critical indications. Because of the results of this MUE, the Anti-Infective Stewardship (AIS) will be monitoring cefepime therapy and making recommendations regarding empiric therapy and opportunities for streamlining to alternative agents.

The following indications are recommended for cefepime: febrile neutropenia, known or suspected central nervous system infections with hospital-acquired gram-negative pathogens, and patients with a well-documented penicillin allergy with a known or suspected hospital-acquired infection with resistant gram-negative pathogens.

Alternative agents such as piperacillin, ceftazidime, or Timentin® can be used instead of cefepime for known or suspected pseudomonal infections. Specific recommendations can be obtained from the Infectious Diseases Service or the AIS.

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MEDICATION SAFETY

PRN orders must have indications

Pro re nata is a Latin phrase, abbreviated by "PRN," meaning "as required." PRN is commonly used to write medication orders and is interpreted to mean "as needed" or "when needed." Some "PRN orders" are based on symptoms (eg, pain) or measurements (ie, body temperature) and are given intermittently based on the indication for use. The Joint Commission mandates that all PRN orders must have an indication for use to be a valid order. The goal is to reduce medication errors.

Mixing Latin abbreviations and English words and symbols in prescription orders are carryovers from days gone by. Physicians scribbled prescriptions and pharmacists interpreted these instructions to compound remedies. These cryptic messages written by physicians and filled by pharmacists added to the mystic of each treatment. Emphasis was not on clarity. The patient was not intended to be able to read the ingredients or the instructions for use. Unfortunately, sometimes pharmacists also struggled to read the prescription.

Today, with the emphasis on medication error prevention, clarity is paramount. Misinterpretation of orders must be avoided. Instead of using PRN, writing "as needed for" makes more sense. However, the use of PRN as an abbreviation is still permitted…at least for now.

◆

The Joint Commission is mandating that all PRN orders must have an explicit indication to be a valid order. We must be compliant with this mandate for 12 months before our next Joint Commission survey.

The Joint Commission is, however, mandating that all PRN orders must have an explicit indication to be a valid order. We must be compliant with this mandate for 12 months before our next Joint Commission survey. An order for "Acetaminophen 650 mg PRN for a fever greater than 38°C" is acceptable. An order for "Acetaminophen 650 mg PRN" is incomplete. Is the acetaminophen for fever or pain? The indication must be explicit.

By not specifying the indication, the wrong symptom or measurement may be used to determine whether or not the patient is treated. The patient could get suboptimal treatment.

All PRN orders on pre-printed orders have already been screened for this standard. However, handwritten orders need improvement.

An audit done at Shands at UF in January and February revealed only 55% and 62% compliance with this standard. Based on the volume of PRN orders, refusing to process any written order that does not state an indication is being considered. Regardless, this practice will continue to be monitored. Prescribers should expect to write order clarifications when the indication for use is not specified for all PRN orders.