

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 19, 2007. 4 drugs or dosage forms were added in the Formulary, and 3 drugs or dosage forms were deleted and designated nonformulary and not available. Criteria-for-use were changed for 2 drugs.

◆ ADDED

Conivaptan
(Vaprisol® by Astellas)*

*Restricted to approval by a clinical pharmacist

Esomeprazole IV (Nexium® IV by AstraZeneca)†

†Will switch to esomeprazole when our lansoprazole supplies are exhausted

Hydroxyzine Hydrochloride Syrup (generic)

Pioglitazone (Actos® by Pfizer)

◆ DELETED

Hydroxyzine Pamoate
(Vistaril® Suspension by Pfizer)†

†Nonformulary and not available (removed from the market)

Lansoprazole IV
(Prevacid® by TAP)†

*Will switch to esomeprazole when our lansoprazole supplies are exhausted

Zalcitabine (Hivid® by Roche)†

◆ CRITERIA-FOR-USE CHANGES

Infliximab (Remicade® by Centocor)§

§No longer restricted to approval by Gastroenterology

Tetanus Toxoid, Reduced Diphtheria Toxoid, & Acellular Pertussis Vaccine (Adacel® by Sanofi Pasteur)†

†No longer restricted to Occupational Health; post-partum use approved

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POLICIES AND PROCEDURES

Pneumococcal vaccine protocol should improve immunization rates

The P&T Committee approved a physician-approved protocol (PAP) that is intended to improve compliance with standards for pneumococcal vaccination of patients with community-acquired pneumonia (CAP). PAPs direct licensed health care providers to perform specific actions when clearly defined situations exist. Without a PAP, these actions would require a physician's order to initiate action. The Pneumococcal Vaccine PAP will allow pharmacists to assess patients and order a vaccine and/or document the patient's vaccine status in the chart.

Data show that pneumococcal vaccines prevent future pulmonary infections, even in patients who have been hospitalized for pneumonia.

Although this PAP was specifically designed to improve compliance with pneumococcal vaccinations in patients with CAP, it can be ordered for any patient admitted to Shands at UF. An order for the Pneumococcal Vaccine PAP will be part of the general medicine admission order set.

A public-private collaboration has established a method for public comparison of hospitals using national quality standards (www.hospitalcompare.hhs.gov). Currently, there are standards for 4 clinical situations (ie, myocardial infarction, heart failure, pneumonia, and surgical infection prevention). The standards for pneumonia include 4 process standards, including the percentage of pneumonia patients assessed and given a pneumococcal vaccine. This standard was established because data show that pneumococcal vaccines

prevent future pulmonary infections, even in patients who have been hospitalized for pneumonia.

The challenge for many practitioners is to time the administration of the pneumococcal vaccine so that the patient gets the most benefit, yet make sure they get the vaccine before the patient is discharged. When patients are admitted for pneumonia, it is not the optimum time to give a pneumococcal vaccine and get an immune response. Patients may be "vaccinated," but they may not be "immunized." Thus, orders often specify to delay the vaccine until the patient's condition has stabilized.

Conditional orders for pneumococcal vaccines are logistically difficult to carry out (ie, give pneumococcal vaccine when the patient is afebrile for 24 hours). This requires that the nursing staff monitor the patient's condition, then request the vaccine for administration. The new Pneumococcal Vaccine PAP will shift the monitoring of the patient's condition to a pharmacist, who will order the vaccine for immediate administration by a nurse when the patient is clinically stable.

It is hoped that this PAP will improve our compliance with the pneumococcal vaccine quality standard. Although administering the pneumococcal vaccine on admission for pneumonia could improve performance for the standard, it would not be the best immunization practice. The implementation of the Pneumococcal Vaccine PAP is designed to improve our performance with both vaccination and immunization rates.

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- ◆ High-dose vancomycin
- ◆ Standard IV calcium & phosphate doses

Formulary update, from page 1

Conivaptan is a parenteral vasopressin-receptor antagonist with a labeled indication for the treatment of euvolemic hyponatremia. Conivaptan promotes free water excretion, increases urine output, and decreases urine osmolality through antagonism of both V_{1A} and V_{2A} vasopressin receptors. This aids in normalization of plasma osmolality and serum sodium concentrations.

Hyponatremia is a serious disorder that can lead to various clinical manifestations, including rhabdomyolysis, seizures, respiratory arrest, and death. Therefore, intervention is often needed to correct this condition. Depending on fluid status and underlying pathophysiology, fluid restriction, exogenous sodium supplementation, and/or loop diuretic therapy are commonly utilized to treat hyponatremia.

Various studies show that conivaptan increases serum sodium concentrations. Although studies document conivaptan's efficacy for the treatment of euvolemic hyponatremia, trials that compare conivaptan therapy to more commonly used therapies, such as exogenous sodium supplementation and diuretics, need to be conducted.

Conivaptan is associated with significant injection site reactions (eg, pain and erythema), including phlebitis in more than 50% of patients. Therefore, infusion sites should be switched every 24 hours to minimize this risk. Conivaptan is best administered in a large vessel.

Published studies have suggested that the rise in serum sodium can be rather rapid (ie, greater than 12 mEq/L over 24 hours), which could put patients at risk for osmotic demyelination syndrome (eg, central pontine myelinolysis).

Conivaptan is also associated with many drug interactions. It is both a substrate and inhibitor of CYP3A4.

A 4-day regimen of the recommended starting conivaptan dose (ie, 20 mg IV load followed by 20 mg over 24 hours as a continuous infusion) is estimated to cost the hospital \$1200. Although combination hypertonic saline and loop diuretic therapies can be used, fluid restriction is more commonly used to manage euvolemic hyponatremia. Hypertonic saline and loop diuretic therapy cost the hospital and patient a fraction of conivaptan therapy.

Due to the lack of data demonstrating a benefit of conivaptan therapy over other existing therapies, and due to conivaptan's potential adverse effects, drug interactions, and cost, there does not appear to be a reason to use conivaptan for its labeled indi-

cation. However, there may be patients in the ICU setting who would benefit from off-labeled use of conivaptan. For example, ICU patients with low sodium values, who need to go to the operating room for a procedure (eg, CABG or LVAD), may benefit from conivaptan therapy when all other measures have failed to sufficiently raise their serum sodium levels.

Therefore, a clinical pharmacist will have to approve conivaptan use. If there is controversy regarding the lack of approval by a clinical pharmacist, the pharmacist will consult with Nephrology, Cardiology, or Endocrinology, depending on the indication for conivaptan use. Data on this restriction process will be reported to the P&T Committee in 12 months.

Esomeprazole IV will be the intravenous proton-pump inhibitor (PPI) listed in the *Formulary* when the supplies of **lansoprazole IV** have been exhausted. Lansoprazole will be nonformulary and not available because it has been discontinued by its manufacturer. Orders for an intravenous PPI other than esomeprazole (ie, lansoprazole or pantoprazole) will automatically be interchanged to esomeprazole (see *Table*). Esomeprazole will be given as an intermittent infusion (slow push) over no less than 3 minutes or as a constant infusion that will require the bag to be changed every 12 hours. Research is ongoing that may show more prolonged stability.

DRUG ORDERED	DOSAGE	DRUG DISPENSED	DOSAGE DISPENSED
Lansoprazole	30 mg IVPB daily	Esomeprazole	20 mg IVPB daily
	60 mg IVPB daily	Esomeprazole	40 mg IVPB daily
	60 mg load, then 6 mg/hr infusion	Esomeprazole	80 mg load, then 8 mg/hr infusion
Pantoprazole	40 mg IVPB daily	Esomeprazole	20 mg IVPB daily
	80 mg load, then 8 mg/hr infusion	Esomeprazole	80 mg load, then 8 mg/hr infusion

Esomeprazole was selected over pantoprazole because there have been chronic supply problems (ie, shortages) with pantoprazole, and esomeprazole is slightly less expensive. There are also better data for intravenous esomeprazole compared with intravenous pantoprazole use in children.

Lansoprazole will remain the oral PPI listed in the *Formulary*. Oral lansoprazole has the best data regarding use in children.

Hydroxyzine pamoate suspension has been removed from the market and was designated nonformulary and not available. It has been replaced by **hydroxyzine hydrochloride syrup**. This should not result in a difference for most patients; however, this change could cause problems if the different strengths are not appreciated.

Hydroxyzine pamoate suspension was available as a 5 mg/mL concentration, while the syrup is 2 mg/mL. Therefore, the same dose will require a larger volume. Also, the syrup will expose patients to sucrose, which could be a problem in some conditions (ie, diabetics or patients on the ketogenic diet).

Pioglitazone is a thiazolidinedione oral hypoglycemic agent usually used in combination with other hypoglycemic agents to treat type 2 diabetes. It was added in the *Formulary* as an alternative to **rosiglitazone**, the "glitazone" that had been the only formulary choice. Also, the automatic interchange from pioglitazone to rosiglitazone was suspended.

The P&T Committee decided to take these actions after a recent meta-analysis published in the *New England Journal of Medicine* questioned the cardiovascular safety of rosiglitazone. This publication has received considerable attention in the lay media. The analysis is controversial and there are many unanswered questions. For example, is the increased risk of myocardial infarction and death specific to rosiglitazone or is it a class effect (ie, also associated with pioglitazone).

Until FDA provides addition guidance, the P&T Committee decided that the automatic interchange from pioglitazone to rosiglitazone should be stopped. The formulary status of

rosiglitazone and pioglitazone will continue to be monitored as additional information becomes available.

Zalcitabine was one of the first nucleoside reverse transcriptase inhibitors (NRTIs) used for the treatment of patients infected with HIV. It has been on the market since 1992. In June 2006, the manufacturer of Hivid[®] announced that it would no longer be available after December 2006.

Current HIV treatment guidelines do not recommend zalcitabine and several discourage consideration of its use in favor of newer NRTIs. Therefore, zalcitabine was deleted from the *Formulary* and has been designated nonformulary and not available.

(continued on page 3)

High-dose vancomycin for MRSA infections

Since its introduction into clinical practice in 1958, vancomycin has been used extensively for the treatment of infections caused by multiple gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA infections are associated with increased morbidity and mortality, as well as increased healthcare costs. Recently, nationally published treatment guidelines for certain MRSA infections have changed vancomycin dosing recommendations due to reports of clinical failures associated with infections caused by isolates with increased minimum inhibitory concentrations (MIC) to vancomycin.¹

Recommended vancomycin goal trough serum concentrations have been increased for infections such as pneumonia and endocarditis in an effort to achieve concentrations 4 to 5 times the MIC at the site of infection. These recommendations have resulted in routine use of larger doses of vancomycin. In vitro studies showing a correlation between increased MICs and treatment failure have driven this change; however, the efficacy and safety of these recommendations have not been clinically proven in controlled studies.^{2,3}

Vancomycin was discovered in the 1950s and was found to be active against a variety of gram-positive bacteria.⁴ Its early use was limited as antistaphylococcal penicillins displayed increased activity against similar organisms without the associated toxicity seen with early formulations of vancomycin.¹ Today, vancomycin is used extensively to combat resistant gram-positive infections. The percentage of *S. aureus* isolates resistant to methicillin has increased to greater than 50% in most US hospitals, and MRSA has become a leading cause of hospital-acquired infections.

Recently, a growing amount of microbiological and clinical data indicates that isolates of *S. aureus* are less likely to respond to vancomycin therapy when the vancomycin MICs are ≥ 4 mcg/mL. In 2006, the Clinical Laboratory Standards Institute (CLSI) lowered the vancomycin MIC "susceptible" breakpoint for *S. aureus* from 4 mcg/mL to 2 mcg/mL to increase detection of heterogeneously resistant isolates of *S. aureus*. In response, several clinical guidelines have changed the recommended goal vancomycin serum trough concentrations. Previous goal trough concentrations of 5 to 10 mcg/mL were considered to be appropriate for most infections caused by MRSA. Guidelines for pneumonia and endocarditis now recommend higher trough levels of 15 to 20 mcg/mL² and 10 to 15 mcg/mL,

respectively.³ The intent of vancomycin therapy is to achieve unbound serum concentrations of vancomycin 4 to 5 times the MIC at the site of infection. It has been shown that approximately 20% to 30% of the serum concentration is achieved in the lung tissue; therefore, trough concentrations of 15-20 mcg/mL would be required for adequate free drug concentrations at the site of infection.² Similarly, drug levels necessary for penetration into vegetations in endocarditis may be increased.

The efficacy and safety of higher doses of vancomycin have been questioned; however, well-designed clinical studies are lacking. A recently published, retrospective cohort study evaluated the safety and efficacy of various doses of vancomycin for the treatment of MRSA infections.² 86 patients were compared by MIC of infecting strain and by target trough attainment. Patients infected with strains with vancomycin MICs of 1.5 or 2 mcg/mL and those with MICs of 0.5, 0.75, or 1 mcg/mL were placed into high- and low-MIC groups, respectively. Target trough attainment was defined as trough concentrations ≥ 4 times the MIC of the infecting isolate. There was no difference in overall treatment response between patients that did and did not achieve target trough concentrations (76 vs 73%, respectively); however, end-of-treatment response rate was lower for the group infected with higher MIC isolates (62% with high MIC vs. 85% with low MIC; $p=0.02$). Of the 65% of the patients that attained trough concentrations within the desired range, 11 patients (12%) developed nephrotoxicity, 10 of which were receiving concomitant nephrotoxic agents. A longer duration of vancomycin therapy was also a predictor of nephrotoxicity. Vancomycin trough levels of 15 to 20 mcg/mL for ≥ 14 days correlated with an increase in serum creatinine in 30% of the patients.

An additional retrospective study designed to determine the relationship between mortality and vancomycin trough levels or area under the curve (AUC) included patients diagnosed with MRSA pneumonia.⁵ Results revealed no correlation between trough concentrations or AUC values and mortality. MICs for the isolates, time to reach target vancomycin trough, and nephrotoxicity were not evaluated in this study.

Vancomycin continues to be the cornerstone of therapy for severe infections caused by MRSA. The utility of targeting higher vancomycin trough concentrations and the associated risks remain unresolved issues. At this time,

aggressive vancomycin therapy is warranted for certain infections (ie, pneumonia) caused by MRSA isolates with high MICs. Until further safety and efficacy data are known, careful monitoring of clinical status and adverse events is essential. Further evaluations of high-dose vancomycin therapy are needed to identify the most appropriate doses and durations of therapy in this era of increasingly resistant *S. aureus*.

by Laura Smith, PharmD

References available upon request to the editor.

Formulary update, from page 2

Infliximab is a monoclonal antibody against tumor necrosis factor alpha. It was the first monoclonal antibody approved with a labeled indication for the treatment of moderate to severe Crohn's disease. When it was added in the *Formulary* in 2001, data were only available for use in Crohn's disease. It was restricted to use in patients that had been approved by the Gastroenterology Service.

Infliximab is now prescribed for several labeled (eg, rheumatoid arthritis) and off-labeled uses. It is no longer rational to limit its approval to the Gastroenterology Service. Therefore, this restriction has been lifted.

A medication use evaluation is planned to determine what inpatient uses are occurring. The evidence for these uses will be reviewed to determine whether another form of restriction needs to be implemented.

Adacel[®] is the first tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and was added in the *Formulary* in November 2006. It was restricted to use by Occupational Health for employees at risk for pertussis exposure. This restriction was driven by a shortage that resulted in a limitation on the number of vials that could be purchased each month.

Since the shortage has been resolved and current guidelines recommend routine use in post-partum women, the restriction on Adacel[®] has been lifted. The most recent Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) guideline recommends that pregnant women, who have not received a dose of Adacel[®] (including women who are breastfeeding), receive Adacel[®] after delivery and before discharge from the hospital, if 2 years or more have elapsed since their last tetanus and diphtheria immunization.

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POLICIES AND PROCEDURES

Standard doses for calcium chloride & gluconate and sodium phosphate

Similar to the policy passed last fall for magnesium, there will now be standardized doses for intermittent intravenous infusions of calcium chloride, calcium gluconate, and sodium phosphate in adult patients. This policy was passed to improve medication safety.

By establishing standard doses, these products will be purchased commercially, which will decrease the chances of a compounding error. This will also prevent preparing these IV infusions by nursing staff in the patient care area. Standardization of IV doses decreases the chances of incorrect dosages.

grams (ie, rounded down for amounts less than 0.5 gram and rounded up to the next gram for orders of 0.5 gram or more). Larger doses require separate doses (eg, separated by approximately 20 minutes or more).

For calcium gluconate, the starting intermittent infusion is 2 grams or multiples of 2 grams up to a maximum of 6 grams. Rounding will occur (*see Table*). If amounts greater than 6 grams are deemed appropriate, separate doses (eg, at least 20 minutes later) will be needed.

For all adult intravenous calcium chloride doses, the starting intermittent infusion dose is 1 gram or multiples of 1 gram. Doses will be rounded (*see Table*) up to a maximum of 3

For sodium phosphate, the recommended standard intermittent infusion doses are 9, 15, and 24 mmoles of phosphate. Rounding of orders will occur. No single dose greater than 24 mmoles can be given and separate doses are needed for higher doses.

The P&T Committee also authorized the automatic changing of pre-printed orders to be consistent with these changes. However, the Continuous Renal Replacement Therapy Order Form will not be changed to these standards (ie, smaller doses of calcium gluconate will be allowed).

ELECTROLYTE	DOSE ORDERED	DOSE ADMINISTERED
Calcium Chloride	< 1 gram	1 gram
	< 1.5 gram	1 gram
	1.5 – < 2.5 gram	2 gram
Calcium Gluconate	≥ 2.5 gram	3 gram*
	< 2 gram	2 gram
	< 3 gram	2 gram
Sodium Phosphate	3 – < 5 gram	4 gram
	≥ 5 gram	6 gram*
	< 9 mmoles	9 mmoles
	< 12 mmoles	9 mmoles
	12 – < 21 mmoles	15 mmoles
	≥ 21 mmoles	24 mmoles*

*Maximum dose that may be given at one time. Larger doses require a separate order for the additional amount required.