

DRUG UPDATE

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FORMULARY UPDATE

The following is a summary of the business conducted at the last three P&T Committee meetings:

ADDED:

- ◆ Pioglitazone (Actos[®])
- ◆ Buprenorphine (Subutex[®]), Suboxone[®])
- ◆ Hydroxocobalamin (Cyanokit[®])
- ◆ Simvastatin (Zocor[®])

REVIEWED BUT NOT ADDED:

- ◆ Anidulafungin (Eraxis[™])
- ◆ Micafungin (Mycamine[®])

CRITERIA FOR USE:

- ◆ Bivalrudin (Angiomax[®])
- ◆ Omalizumab (Xolair[®])
- ◆ Rotavirus Vaccine (Rotateq[®])
- ◆ Hydroxocobalamin (Cyanokit[®])
- ◆ Linezolid (Zyvox[®])
- ◆ Tizanidine (Zanaflex[®])
- ◆ Ibuprofen Lysine (NeoProfen[®])

Pioglitazone (Actos[®]), an oral thiazolidinedione hypoglycemic medication, was added to the Shands Jacksonville *Formulary*. Pioglitazone is in the same class as the *Formulary* medication rosiglitazone (Avandia[®]). A recent meta-analysis published in the *New England Journal of Medicine* suggested a potential increased risk of myocardial infarction with the use of rosiglitazone. The design and analysis of this study has undergone much scrutiny and a true association has yet to be determined.

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Drug Safety

Methemoglobinemia and benzocaine spray (Hurricane[®], Cetacaine[®])

In the past 12 months, there have been 5 adverse events reported at Shands Jacksonville of methemoglobinemia associated with the use of benzocaine spray. Methemoglobinemia is a condition that reduces oxygen-carrying capacity of hemoglobin by oxidizing ferrous hemoglobin to its ferric state (methemoglobin). Early symptoms may include dizziness, nausea, headache, dyspnea, and confusion. Methemoglobin exists in the body and is produced by continuous oxidation of ferrous iron. Under normal conditions, methemoglobin concentrations are under 2% of the total hemoglobin due to intrinsic reducing systems and red cell turnover. Clinical cyanosis is typically observed with methemoglobin concentrations greater than 15%; however, with concentrations of 55 to 70%, the patient may develop circulatory failure, cardiac arrhythmias, seizures, and coma.¹

Causes of methemoglobinemia may result from exposure to drugs or chemicals and may rarely be due to heredity.¹ There are two hemoglobin forms that can increase the susceptibility to methemoglobinemia, hemo-

globin F and deoxyhemoglobin, typically found in higher concentrations in newborns and the elderly. More commonly seen is methemoglobinemia related to exposure to chemicals or medications that can accelerate hemoglobin oxidation. Medications associated with acute toxic methemoglobinemia include nitrates (i.e., amyl nitrate, sodium nitrite, isobutyl nitrite), nitroglycerin, dapsone, sulfonamides, metoclopramide, hydroquinone, local anesthetics (i.e., benzocaine, lidocaine, prilocaine), flutamide, phenazopyridine, and phenytoin. Also, substances such as aniline dyes, cobalt preparations, chlorates, crayon wax, menthol, diesel fuel additives, shoe polish, nitroethane (nail polish) have been associated with this condition.²

The key to treating methemoglobinemia is to restore the oxygen-carrying capacity of the blood, in addition to concurrent supportive therapy (i.e., airway patency, hemodynamic support, supplemental oxygen).¹ Severe methemoglobinemia requires administration of methylene blue, 1-2 mg/kg, over five to ten minutes. Methylene blue serves as a cofactor for transfer-

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Methemoglobinemia may be caused by multiple or longer duration of benzocaine sprays that exceed the labeled dosage recommendations.

(Nonformulary from page 1)

At this time, there is no information describing a similar link with the use of pioglitazone. Until more data is available, the P&T Committee added pioglitazone to the *Formulary* as an alternative to rosiglitazone for the inpatient and ambulatory areas. The automatic inpatient substitution of pioglitazone to rosiglitazone was also removed.

Buprenorphine +/- Naloxone
Buprenorphine (Subutex[®], Suboxone[®]) was added to the Inpatient *Formulary*. Its use is reserved for continuation of home therapy in patients admitted to the hospital. Buprenorphine is indicated for the treatment of opioid addiction, as is methadone. Unlike methadone, buprenorphine may be prescribed in the physician office setting, due to the approval of the Drug Addiction Treatment Act of 2000 (DATA 2000). Buprenorphine is a partial and not a full opioid agonist; therefore, its dose response curve plateaus, limiting the drug's ability to cause significant respiratory depression. Buprenorphine is considered a schedule III controlled substance (methadone is schedule II), and buprenorphine sublingual tablets are available in a fixed 4:1 dose combination with naloxone to prevent illicit injection of the agent.

Physicians are required to register to prescribe buprenorphine through the Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment (SAMHSA), which mandates education and registration of all buprenorphine prescribers. Registered practitioners may treat up to 100 patients. There are three Shands Jacksonville physicians authorized to prescribe buprenorphine.

Shands Jacksonville does not have a drug addiction treatment clinic nor does it have a methadone treatment center. The current policy for methadone allows patients ad-

mitted to the hospital who are currently in a treatment program to continue the use of methadone as an inpatient for opioid addiction treatment. Methadone can also be used in the hospital and in the clinic setting for pain. Buprenorphine was added to the Inpatient *Formulary* for continuation of therapy in patients in a treatment program. Buprenorphine was not added to the Ambulatory *Formulary*.

Hydroxocobalamin (Cyanokit[®]) was added to the *Formulary* for the treatment of known or suspected cyanide poisoning. Hydroxocobalamin is an alternative treatment of cyanide toxicity/ smoke inhalation. This agent rapidly binds with cyanide to form cyanocobalamin (Vitamin B12), a relatively non-toxic agent, excreted in the urine. The current *Formulary* alternative, Cyanide Antidote Kit (e.g., Taylor kit), consists of three components: amyl nitrite, sodium nitrite, and sodium thiosulfate. Concerns have been raised about the safety of the Taylor kit such as the need for rapid dose calculations, risk of additive nitrite-induced vasodilation, and occurrence methemoglobinemia, especially in the setting of smoke inhalation where carboxyhemoglobin is formed following exposure to carbon monoxide. Cyanokit is easier to administer and lacks effect on the oxygen-binding capacity of blood. This agent has been more commonly associated with hypertension; however, significance may be offset by the hypotension commonly associated with cyanide toxicity. Other potential disadvantages of hydroxocobalamin include cosmetic alterations of urine (red-colored) and skin (redness) that may persist from 1-5 weeks. This agent is also associated with transient, self-limiting alterations of hemodynamic parameters (e.g., blood pressure and heart rate) that appear to be associated with increased dose. Due to the deep red color of this agent, hydroxocobalamin may interfere with colorimetric determination of labora-

tory tests (e.g., clinical chemistry, hematology, coagulation, CKMB, and urine parameters).

The HMG Co-A reductase inhibitor, **simvastatin (Zocor[®])**, was added to the Shands Jacksonville Ambulatory and Inpatient Formularies. Simvastatin is also available in the Community Care Rx- Medicare Part D *Formulary*. The generic form of simvastatin will join the other statins in the *Formulary*, atorvastatin (*Lipitor[®]*) and pravastatin (*Pravachol[®]*).

The echinocandins, **micafungin Mycamine[®]**, **anidulafungin (Eraxis[™])**, and **Caspofungin (Cancidas[®])** were reviewed as a class to determine the best agent for Shands Jacksonville. Caspofungin (Cancidas[®]) is currently in the Shands Jacksonville *Formulary*. The three echinocandins share the same mechanism of action as they all inhibit the synthesis of $\beta(1,3)$ -D-glucan synthesis, a major component of the fungal cell wall. Caspofungin has the advantages of greater clinical trial data to support its place in therapy and greater clinical experience. Caspofungin carries all of the same FDA-approved indications as the other agents with the exception the indication for prophylaxis during hematopoietic stem cell transplantation (HSCT). Micafungin is the only agent with the HSCT indication. Micafungin and anidulafungin have the advantage of not requiring a dosage adjustment for hepatic impairment. All echinocandins can be dosed without regard to renal function. Additionally, micafungin and anidulafungin have a decreased propensity for drug interactions. Caspofungin has documented drug interactions with the immunosuppressants tacrolimus, sirolimus, and cyclosporine as well as the anti-infectives nevirapine, nelfinavir, efavirenz, rifampin, and rifabutin. Anidulafungin has no clinical evidence to support use in invasive aspergillosis, and the evidence to support the effectiveness of micafungin in invasive candidiasis and

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(*Methemoglobinemia from page 1*)

ring an electron from the NADPH to the ferric heme ion. The reduction of the methemoglobin concentration is usually seen in 30 to 60 minutes following parenteral administration. However, caution is advised in using higher doses due to potential toxic effects (dyspnea, tremors, precordial pain); ironically, methylene blue may produce methemoglobinemia at higher doses.¹

The Institute for Safe Medication Practices (ISMP) and the FDA have implicated benzocaine-containing topical sprays in cases of methemoglobinemia.³ The FDA MED-WATCH database contains about 100 reports of methemoglobinemia related to the use of benzocaine. Additionally, it has been estimated that methemoglobinemia occurs in one out of every 7,000 bronchoscopies. These cases may be caused by multiple or longer duration of benzocaine sprays that exceed the labeled dosage recommendations.⁴

The FDA recommends the following actions to help minimize the risk:⁵

- Use only the minimum amount of spray to produce required anesthetic effect. The duration for benzocaine spray should not exceed 2 seconds.
- Carefully observe patients treated with benzocaine sprays for signs of methemoglobinemia.
- Promptly treat patients suspected of having high levels of methemoglobinemia.
- Analyze blood samples with a co-oximeter to detect hypoxia.
- Infants less than 4 months and patients with certain hemoglobin and enzyme abnormalities are at increased risk for developing toxic levels of methemoglobinemia.

Clinicians and patients should be aware of proper dosing of topical anesthetics as well as the possibility of methemoglobinemia occurring with these products.⁶ A complete medical history should be obtained for patients who will receive topical anesthetics to

assess for predisposing risk factors which include:

- age (infants less than six months and elderly with cardiac problems)
- area of administration (if inflamed, greater absorption may occur)
- concomitant use of drugs associated with methemoglobinemia
- genetics (altered hemoglobin, glucose-6-phosphate dehydrogenase deficiency, methemoglobin reductase enzyme deficiency).⁶

As a result of these adverse events, new safeguards are in place. A warning label is affixed to each spray can of benzocaine that reads, "Maximum dose = 2 second spray. Do not keep at bedside." A reminder is in the pharmacy computer system to remind the pharmacists to label all spray cans with the warning, and the

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departments where these adverse events occurred have received insertives regarding the prevention and potential causes of this adverse event.

In summary, benzocaine spray use can result in potentially dangerous levels of methemoglobinemia, and patients with breathing problems (asthma, bronchitis, emphysema), heart disease, and smokers are at greater risk for complications. The smallest effective dose of benzocaine spray should be used to decrease the risks associated with methemoglobinemia, and patients should be carefully observed for signs of methemoglobinemia (e.g., pale, gray, or blue colored skin, headache, lightheadedness, shortness of breath, anxiety, fatigue, and tachycardia). A late and dangerous sign of methemoglobinemia is chocolate-brown color of blood; however, patients should be treated promptly when methemoglo-

binemia is first suspected.⁴

Although lidocaine is an alternative topical anesthetic; it has also been associated with methemoglobinemia following intravenous and topical administration.⁷ Most cases have been mild and resolved spontaneously, but some required treatment with oxygen and/or methylene blue.⁸ Since methemoglobinemia may occur with either lidocaine or benzocaine-containing products, proper screening of patients and appropriate doses should be used.

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aspergillosis is limited. Additionally, anidulafungin administration requires an infusion of 250 to 500 ml of fluid, compared to 100 to 250 ml of fluid for caspofungin and micafungin. The volume may become an issue in patients with fluid restrictions. Based on the clinical trial data, caspofungin was retained as the echinocandin of choice in the Shands Jacksonville *Formulary*.

The Shands Jacksonville Criteria for **Bivalirudin (Angiomax®)** were drafted in collaboration with the Division of Cardiology. Bivalirudin should be used as an alternative to heparin anticoagulation during percutaneous coronary intervention (PCI), with provisional use of a glycoprotein IIb/IIIa inhibitor in patients who cannot receive heparin due to documented or suspected heparin-induced thrombocytopenia or hypersensitivity to heparin.

The Criteria for **Omalizumab (Xolair®)** were revised to include the new FDA MedWatch warning of anaphylaxis occurring 24 hours or longer following administration of the drug. Patients will be observed for at least two hours following administration to assess for injection site reactions or rare anaphylaxis.

The Criteria for **Rotavirus Vaccine (Rotateq®)** were revised to include the FDA MedWatch alert of

intussusception in infants who received the vaccine. The Criteria state the causality of the event is unknown, but patients should be monitored as recommended in the FDA alert.

The Criteria for Use for **Intravenous Immunoglobulin (IVIG, Carimune™, Gamunex®)** indicate its use should be reserved for patients with Kawasaki disease, idiopathic thrombocytopenia purpura (not qualified for WinRho®), primary immunodeficiency syndromes, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis (unlabeled use), multiple sclerosis (unlabeled use), Guillain-Barre syndrome (unlabeled use), and hyperbilirubinemia in hemolytic disease of the newborn. IVIG has been in short supply and should be reserved for the most critical patients.

The Criteria for **Linezolid (Zyvox®)** was revised to include the FDA MedWatch warning that linezolid is not-approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or infections caused by gram-negative bacteria. Also, that it should only be used for the treatment of "concurrent" bacteremia, complicated skin/skin structure infection, or pneumonia caused by documented, "susceptible" VRE and use as 2nd line therapy for the same infections caused by documented, "susceptible" MRSA or coagulase-negative staphylococci.

New FDA MedWatch warnings were added in the Criteria for Use for **Tizanidine (Zanaflex®)** regarding drug interactions with CYP1A2 inhibitors/ inducers (e.g., fluvoxamine, fluoroquinolones, some antiarrhythmics, cimetidine, famotidine, oral contraceptives, acyclovir, and ticlopidine). These interactions may increase serum concentrations of tizanidine and potentiate sedative and hypotensive effects.

The criteria for **bevacizumab (Avastin®)** were revised to include a new FDA MedWatch warning of gastrointestinal/esophageal fistula formation. Bevacizumab can result in the development of gastrointestinal perforation and intra-abdominal abscess, in some cases resulting in fatality.

Ibuprofen Lysine Injection (Neoprofen®) is a new injectable formulation, restricted to the Department of Pediatrics as an alternative to indomethacin for treatment of patent ductus arteriosus (PDA) in premature infants weighing less than 2500 grams, who are 32 to 34 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) are ineffective. Advantages over indomethacin include less adverse effects on cerebral and renal blood flow.