

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 21, 2005. 4 drugs were added in the *Formulary* and 1 drug was deleted. 1 drug was evaluated, but not added in the *Formulary*. The criteria for use of 2 drugs were modified.

◆ ADDED

Arsenic Trioxide
(Trisenox® by Cell Therapeutics, Inc.)*

*Restricted to chemotherapy prescribers.

Fluvoxamine (Generic)

Lanthanum Carbonate
(Fosrenol® by Shire, Inc.)

Pentafluoropropane-Tetrafluoroethane
(Pain Ease® by Gebauer)

◆ DELETED

Dichlorotetrafluoroethane
(Fluro-Ethyl® by Gebauer)

◆ EVALUATED, BUT NOT ADDED

Morphine Epidural ER Liposomal
(DepoDur® by Endo)**

**Nonformulary and not available.

◆ CRITERIA FOR USE CHANGED

Factor VIIa, Recombinant
(NovoSeven® by Novo Nordisk)

Nesiritide (Natrecor® by Scios)

Arsenic trioxide has a labeled indication for the induction of remission and consolidation of acute promyelocytic leukemia (APL) in patients who are refractory or who have relapsed from retinoid and anthracycline chemotherapy and whose APL is characterized by the presence of the t(15:17) translocation on the PML/RAR-alpha gene
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NEWS

CA-MRSA: A new bug on the block

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first reported more than 30 years ago and, within a decade, was recognized as an important nosocomial pathogen.^{1,2} Several risk factors for acquiring MRSA have been identified, such as hospitalization in intensive care units, prolonged hospitalization, severe underlying illness, invasive procedures, indwelling devices, and prolonged or recurrent exposure to antibiotics.²

In the early 1980s, the first reports of community-acquired MRSA (CA-MRSA) in adults emerged.^{1,2} These isolates were found initially in intravenous drug users and members of other high-risk groups with frequent contact with the health care system.

In recent years, CA-MRSA has emerged as a pathogen in adults and children without traditional risk factors for MRSA acquisition.³ Reports have suggested that other risk factors may also exist, such as household contacts with risk factors for MRSA and child-care attendance.² Clusters of patients with CA-MRSA infections have been described, and some communities have reported that CA-MRSA infections are increasing in frequency.¹ Noticeably, the CA-MRSA isolates described in recent years differ significantly from previous strains of MRSA in that they lack multi-drug resistance.

Staphylococci have developed various mechanisms of resistance to antibiotics. One important mechanism of resistance to a specific class of antibiotics — the macrolides — involves modification of the drug-binding site. This results in resistance to macrolides (ie, azithromycin, erythromycin, clarithromycin), lincosamides (ie, clindamycin), and type B streptogramins (ie, quinupristin), and is commonly referred to as “MLS_B resistance.” Resistance can be expressed constitutively, (the MLS_Bc

phenotype), or only when induced into production (MLS_Bi phenotype). Although MLS_Bi strains are clearly resistant to erythromycin, they appear to be susceptible to clindamycin. However, it is possible for mutations to occur spontaneously that will transform MLS_Bi strains to the MLS_Bc phenotype. The concern is that this change in expression might occur in the midst of therapy with clindamycin.^{4,5,6}

Standard broth microdilution testing, automated susceptibility testing devices, or standard disk diffusion tests do not detect inducible clindamycin resistance. Uncertainty about the reliability of susceptibility reports for clindamycin, as well as confusion over the clinical importance of this inducible resistance, have lead some clinicians to avoid the use of clindamycin for staphylococcal infections whenever erythromycin resistance is noted.

Since the majority of reported CA-MRSA infections are skin and soft-tissue infections, clindamycin represents an attractive treatment option for several reasons. Clindamycin is available as both an intravenous and an oral formulation (with 90% oral bioavailability). It distributes well into skin and skin structures. Clindamycin is also less costly than some newer agents that might be considered for these infections. Finally, clindamycin may be able to inhibit production of endotoxins and virulence factors produced by staphylococci.

Not knowing whether the in vitro susceptibility results generated for clindamycin are trustworthy is the
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INSIDE THIS ISSUE

◆ IV PPI use audited

Formulary update, from page 1 expression. APL is a subset of acute myelocytic leukemia with this specific chromosomal abnormality.

Treatment for newly diagnosed APL includes all-trans retinoic acid (ATRA) in combination with anthracyclines for consolidation, then ATRA for maintenance therapy. Although most patients respond to standard therapy, about a third of patients that achieve remission will relapse. Patients with APL who relapse are treated with stem cell transplantation (SCT), when an HLA-compatible donor is available. Arsenic trioxide offers an alternative to SCT. The response rate depends on the patient's previous treatment status.

Arsenic trioxide was originally added in the *Formulary* in May 2002. Arsenic trioxide was deleted from the *Formulary* in November 2003 because it was rarely used. In order to assure availability when it is needed, it was re-listed in the *Formulary*. Like all other cytotoxic chemotherapy, arsenic trioxide is restricted to credentialed chemotherapy prescribers.

Fluvoxamine was evaluated for addition in the *Formulary* because it is a frequently prescribed nonformulary drug.

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI). It has the shortest half-life of all the SSRIs, which is not a desirable feature. SSRIs with short half-lives are associated with more withdrawal symptoms.

Fluvoxamine has a labeled indication for use in obsessive-compulsive disorder (OCD) and was the first SSRI approved for use in children. It is still used preferentially by some prescribers for OCD. Fluvoxamine has also been used in the treatment of major depression and other SSRI indications.

Although there does not appear to be any obvious therapeutic advantage for fluvoxamine, there is no justification for switching patients admitted on this drug to another SSRI. If fluvoxamine is inadvertently stopped, patients could experience withdrawal symptoms.

Also, fluvoxamine is very inexpensive since it is available as a generic.

Lanthanum carbonate is an alternative phosphate binder to calcium-based phosphate binders or sevelamer (RenaGel®). Lanthanum carbonate is approximately as effective as aluminum salts, which are no longer routinely used as phosphate binders because of toxicities (ie, bone disease, anemia, and dementias).

Lanthanum carbonate dissociates at acid pH to bind phosphate in the gut when it is taken with or immediately after meals. Lanthanum combines with phosphate to form

an insoluble complex that is excreted in the stool. Only a small amount of lanthanum is absorbed systemically. Although serum concentrations of lanthanum are extremely low, lanthanum has been measured in body tissues of humans and animals taking the drug. The long-term toxicities of this chronic low exposure to lanthanum may not be known for many years.

Clinical trials comparing lanthanum carbonate to placebo show that most patients achieve adequate lowering of serum phosphorus and the calcium times phosphorus (Ca x P) product with a dosage between 1500 and 3000 mg per day (ie, 1 or 2 500-mg tablet(s) with each meal). Within a week, serum phosphorus levels decrease significantly, and most patients meet the goals for serum phosphorus and Ca x P product.

Current guidelines recommend a Ca x P product of less than 55 mg/dL for patients with a glomerular filtration rate (GFR) less than 60 mL/min. This aggressive goal is difficult to attain in patients with low GFRs using other phosphate binders. Also, calcium-based phosphate binders (ie, calcium carbonate and calcium acetate) can cause hypercalcemia.

Common adverse effects for lanthanum carbonate are gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain). Whether there are any rare, but serious, adverse effects associated with low systemic exposure to lanthanum is unknown.

There are no data on the efficacy or safety of lanthanum in children. The concern about long-term toxicities is greater in this population.

Lanthanum is expensive compared with calcium-based phosphate binders, but the cost is similar to sevelamer. It may be less expensive than sevelamer in some patients who require large doses of sevelamer. Sevelamer is a non-absorbed polymer that does not cause hypercalcemia, but may require large doses (ie, high pill burden) to lower serum phosphorus. Calcium-based phosphate binders will remain first-line treatments, but lanthanum is an alternative to sevelamer in patients who do not meet the target Ca x P product.

Pain Ease® is a topical skin refrigerant used to anesthetize the skin for minor procedures (eg, starting IVs and venipunctures). Pain Ease® was added in the *Formulary* as an alternative to **Fluro-Ethyl®**, which was deleted because of reports of adverse effects.

In February 2005, ethyl chloride was deleted from the *Formulary* because it is flammable and the proper storage requirements made continued use of this product impractical. Fluro-Ethyl®, a skin refrigerant containing dichlorotetrafluoroethane, was selected as an alternative because it has similar indications as

ethyl chloride, but is nonflammable.

After being distributed to a few locations, 2 incidences of skin "burning" upon administration of Fluro-Ethyl® were reported. One patient experienced blistering (ie, frostbite). Upon further investigation it was determined that the burning was associated with improper administration technique. Fluro-Ethyl® is a colder product than ethyl chloride and a shorter spray duration must be used to avoid adverse effects. Rather than focus on administration technique, it was decided that a product similar to ethyl chloride was needed.

Pain Ease® is a combination of pentafluoropropane and tetrafluoroethane. It is an over-the-counter product that is not flammable. It has the extra advantage of not depleting ozone. Pain Ease® has similar indications and coolant properties to ethyl chloride and should be administered in a manner similar to ethyl chloride.

DepoDur® is a single-dose, extended-release, injectable form of morphine intended for epidural use only after surgical procedures. DepoDur® has a labeled indication for single-dose administration by the epidural route, at the lumbar level, for the treatment of pain following major surgery. Although specific surgeries are not listed in the labeled indications, dosages are given for lower abdominal surgeries, major orthopedic surgeries of the lower extremities, and Cesarean sections. DepoDur® is administered 30 minutes before surgery or after clamping the umbilical cord during a Cesarean section.

There are 3 recently published clinical trials examining DepoDur® compared with placebo or standard, preservative-free epidural morphine. There are no published comparisons with scheduled doses of opioids (injection and/or oral). None of the published studies directly compared among the various DepoDur® doses, but there was a trend that low doses were ineffective and there appeared to be little difference among dosages between 15 mg and 25 mg. Although some patients were able to go without any supplemental analgesic after a dose of DepoDur®, most patients did require supplemental analgesia. Like most early clinical trials, the limited published data for DepoDur® is in relatively healthy patients. All patients were monitored by pulse oximetry.

Adverse effects of DepoDur® are as expected for morphine. Nausea, vomiting, constipation, pruritus, and respiratory depression are reported, and the epidural route of administration did not decrease the frequency of these reactions. Of the patients

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Formulary update, from page 2 treated in clinical trials, 4% exhibited signs of respiratory depression requiring treatment with narcotic antagonists. Approximately 90% of the incidences of respiratory depression occurred within 24 hours of DepoDur® administration; however, 0.6% occurred after 48 hours (ie, 10% occurred after 24 hours).

Medication safety concerns include persistent respiratory depression in overdoses and persistent symptoms of anaphylactoid or allergic reactions. There could also be name confusion with other “Depo” drugs (eg, Depo Medrol®). Monitoring for respiratory depression is an important concern. Prescribers who do not recognize that a long-acting opioid has been given may order additional opioids or other central nervous system depressants, which may cause respiratory complications.

Although a formal cost-benefit assessment for DepoDur® has not been done, it may help decrease the use of continuous epidural infusions. It could, however, increase the use of PCA. Overall, the benefits of DepoDur® do not outweigh the increased risks. Safety is the major reason that Depo-

Dur® was designated nonformulary and not available.

Recombinant factor VIIa functions like endogenous activated factor VII in the body. It is a vitamin K-dependent clotting factor that results in fibrin clots by activation of factors IX and X. It also can improve platelet function. The result is decreased bleeding. Although NovoSeven® was developed for the treatment of hemophilia in patients with inhibitors to factors VIII or IX, it has been used off-label extensively for various types of uncontrolled bleeding.

NovoSeven® is extremely expensive and appropriate off-label use is crucial. Criteria for NovoSeven®, recombinant factor VIIa, were reviewed to promote responsible use.

Criteria were based on a comprehensive review of the literature and other published criteria. These criteria were then reviewed and approved by all of the affected medical services. These criteria will now be used as a resource and to prospectively monitor factor VIIa use — not for restriction.

Nesiritide is a recombinant form of human (B-type) natriuretic peptide. It has a labeled indication for acute decompensated fluid-overloaded heart failure.

However, it has been used off-label and the P&T Committee continues ongoing monitoring of nesiritide to promote responsible use.

The criteria for nesiritide have been altered based upon data from an unpublished observational study done here at Shands at UF and a recently published study of atrial natriuretic peptide (ANP) that showed benefit in post-cardiothoracic surgery patients. These studies suggest a decrease in renal dysfunction when nesiritide is used.

These favorable findings are balanced with new data associating the use of nesiritide for heart failure with a higher incidence of acute renal failure and death in patients treated with nesiritide compared with vasodilators and diuretics.

The new order form for nesiritide now has fixed durations of therapy (ie, 48 hours for severe volume overloaded heart failure and 5 days for post-CT surgery). Durations longer than these require re-evaluation, and nesiritide must be re-ordered. Exclusion criteria now include dialysis. The new order form can be found on the Shands at UF intranet at <http://intranet.shands.org/pharm/>.

MEDICATION USE EVALUATION

Improving intravenous PPI use

Intravenous pantoprazole is a proton-pump inhibitor (PPI) with a labeled indication for short-term treatment (7–10 days) of gastroesophageal reflux disease (GERD) or Zollinger-Ellison Syndrome in patients who are unable to take oral medications. It has also been used for stress ulcer prophylaxis in high-risk patients, although there is no evidence that PPIs are superior to H2-blockers. Continuous infusions of pantoprazole are often used for acute GI bleeds.

In late 2004, there was a shortage of IV pantoprazole caused by manufacturing problems. During the shortage, many patients were shifted to an oral PPI (pantoprazole tablets or lansoprazole liquid) or an injectable H2-blocker (ranitidine) without any noticeable impact on patient care.

Therefore, an audit of the use of IV pantoprazole was done in April and May 2005 to describe the current use and determine whether there are possible areas for improvement. This audit identified when the use of IV pantoprazole could be avoided.

A convenience sample of 40 patients was reviewed. An equal number of ICU and general ward patients were evaluated. Over 40% of the IV use of pantoprazole in this audit was for stress ulcer prophylaxis. Many of these patients were located on general wards and did not have an indication for stress ulcer prophylaxis.

Important risk factors for stress ulcers include mechanical ventilation for greater than 48 hours, patients with coagulopathies (ie, INR greater than 1.5, platelets less than 50,000 per mm³, or a partial thromboplastin 2 times greater than control), renal failure, hepatic failure, burns, organ transplant recipients, shock, sepsis, multiple trauma, or head-spinal cord injuries. Most patients who were candidates for stress ulcer prophylaxis should be treated with IV or oral ranitidine. There currently is insufficient evidence that IV PPIs are superior to IV H2-blockers for stress ulcer prophylaxis.

The potential benefit of preventing bleeding must be balanced against potential increased risk of pneumonia. One recent observational study showed an 89% higher risk of pneumonia in patients taking PPIs and a 63% higher risk with H2-blockers in a community setting.

Over 40% of the IV pantoprazole used during the audit was used for GI bleeds. An upper GI bleed is an appropriate use for an IV PPI; however, it is not for a lower GI bleed. Only half of the patients who received IV pantoprazole had a diagnostic or therapeutic endoscopy. The American Society for Gastrointestinal Endoscopy recommends upper endoscopy for patients with an upper GI bleed once patients are stabilized.

Some patients received prolonged therapy on IV pantoprazole, which could

have been converted to oral therapy once the acute bleeding stopped. A cost-effectiveness study found that an IV PPI in combination with diagnostic or therapeutic endoscopy demonstrated superior effectiveness and lower costs.

Many of the patients who received IV pantoprazole had enteral access via a nasogastric tube or by mouth. These patients could have received lansoprazole liquid rather than IV pantoprazole. Studies have shown that oral liquid PPIs increase gastric pH greater than an equivalent IV dose. Further, IV pantoprazole is 22 times more expensive than an equivalent oral dose.

Although not the main purpose of this audit, it was noted that patients are often discharged on a PPI when they received treatment as an inpatient. In many cases, the continued need for the PPI is questionable. When writing discharge prescriptions, please determine whether continued outpatient therapy with a PPI is necessary.

This audit suggests that there is room for improvement in the overall use of IV pantoprazole. IV pantoprazole should be limited to acute upper GI bleeds or patients requiring a PPI who cannot take oral therapy. In all other situations, ranitidine 50 mg IV every 8 hours, ranitidine 150 mg PO every 12 hours, pantoprazole tablets 40 mg PO daily, or lansoprazole suspension 30 mg daily should be ordered.

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**EDITOR,
DRUGS & THERAPY BULLETIN**

Randy C. Hatton, PharmD

**DIRECTOR,
PHARMACY SERVICES**

Alan Knudsen, MS, RPh

**CHAIRMAN,
PHARMACY & THERAPEUTICS
COMMITTEE**

Ricardo Gonzalez-Rothi, MD

EDITING, DESIGN, & PRODUCTION

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problem created by MLS_Bi resistance in staphylococci. Because of this concern, most microbiology laboratories, including Shands at UF, routinely report clindamycin resistance if an MRSA isolate is erythromycin-resistant, unless additional testing is performed.

A relatively simple means to induce phenotypic resistance to clindamycin in MLS_Bi strains is to place an erythromycin susceptibility testing disk in close proximity to a clindamycin disk on an agar growth medium. With MLS_Bi strains, this results in a blunting of the clindamycin zone of inhibition on the zone margin closest to the erythromycin disk. The truncated or blunted clindamycin zone of inhibition may resemble the shape of the letter D. Therefore, this type of disk induction testing is often referred to as a "D test." Organisms that do not display a blunting of the clindamycin zone of inhibition on the edge closest to the erythromycin zone of inhibition (a negative D test result) can be safely reported as susceptible to clindamycin.^{4,5,6} Isolates that demonstrate an inducible clindamycin resistance (a positive D test result) should be reported as clindamycin-resistant.

Due to the increasing prevalence of CA-MRSA, our microbiology laboratory

routinely performs the D test on any MRSA cultures isolated from patients less than 18 years of age that demonstrate erythromycin resistance with clindamycin susceptibility during initial testing. The results of the D test are reported in the microbiology section of laboratory results, but usually takes slightly longer than the initial susceptibility report to be available.

The emergence of CA-MRSA has led to a resurgence of interest in therapy options for *S. aureus* infections. MRSA isolates circulating in the community have antibiotic susceptibility profiles that differ from that of nosocomial MRSA infections. Clindamycin represents a useful option for therapy for various CA-MRSA infections that are D test-negative, including musculoskeletal infections and skin and soft-tissue infections.

In addition to the potential use of clindamycin for CA-MRSA infections, trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim[®], Septra[®]) may also be an option for empiric therapy for mild to moderate infections. Based on the MRSA isolates identified at our institution, there is a 99% susceptibility rate to TMP-SMX. Although few adequately randomized controlled trials have documented the efficacy of TMP-SMX against MRSA infections, a large body

of anecdotal data supports its use. The excellent oral bioavailability, low cost, and good tissue penetration of TMP-SMX make it a desirable option for treatment of skin and soft-tissue infections due to susceptible strains of MRSA and for transitioning patients to oral therapy.

CA-MRSA will be increasingly prevalent. While vancomycin is often selected as presumptive therapy for MRSA infections, the community-acquired strains of MRSA tend to be susceptible to a wide variety of antibiotics. Both clindamycin and TMP-SMX represent viable alternatives for the treatment of CA-MRSA. Testing for the prevalence of the inducible resistance to clindamycin helps avoid therapeutic failures.

by Jennifer Norberg, PharmD

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