

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 17, 2006. 2 drugs were added in the *Formulary*, and 1 was deleted. 2 drugs were designated nonformulary and not available. There was 1 criteria-for-use change and 3 interchanges approved.

◆ ADDED

Methoxsalen
(UVADEX® by Therakos)

Varenicline (Chantix® by Pfizer)

◆ DELETED

Mivacurium
(Mivacron® by Abbott)*

*Nonformulary and not available

◆ CRITERIA-FOR-USE CHANGES

Clonidine Injection (Duraclon®
by Xanodyne Pharmaceuticals)

◆ INTERCHANGES

Bupropion SR for Wellbutrin® XL

Guaifenesin Liquid for Mucinex®*

*Mucinex® designated nonformulary
and not available

Paroxetine IR for Paxil® CR†

†1 mg = 1.25 mg (eg, 20 mg = 25 mg)

Methoxsalen is a naturally occurring photoactive agent. It is in a class of compounds known as psoralens. Psoralens react upon activation to ultraviolet (UV) light in the 315-400 nm wavelengths (ie, UVA). Although their exact mechanism of action is unknown, psoralens covalently bond to DNA and inhibit cellular replication.

In extracorporeal photopheresis (ECP), white blood cells (WBCs) are separated from the patient's whole
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PRESCRIBING

Collect before you treat: obtaining cultures before antibiotic treatment

When treating infections, health-care providers realize the importance of initiating antibiotic therapy as soon as possible. It is also recognized that tailoring pharmacologic therapy to the organism(s) responsible for the infection is equally important. When initiating therapy, standard of care calls for the use of broad-spectrum antibiotics to cover the organisms usually associated with the infection being treated.

Therapy is streamlined after cultures and sensitivities are available. Delaying therapy when infectious processes are suspected is not an option, but similarly, obtaining adequate cultures before administering antibiotics is equally important. In these situations, timing is key. Obtaining appropriate cultures before initiating antimicrobial therapy plays an important role in patient care.

Why is this so important? The prompt identification of offending organisms will influence diagnosis, therapy, and prognosis. This will not only benefit the patient by providing more appropriate and definitive treatment, but will also help control the emergence of antibiotic resistance by minimizing the use of broad-spectrum agents, when possible.

Obtaining cultures before antibiotic use improves the chances of identifying the offending microorganism, which improves patient care. Inappropriate antibiotic use can result in prolonged hospital stays and increased costs, but it can also have adverse consequences on the patient's prognosis.

The Surviving Sepsis Campaign Guidelines state that antibiotic therapy should be initiated within 1 hour of recognition of severe sepsis.¹ These guidelines state that appropriate cultures should be obtained in order to identify causative organisms before starting therapy. The guidelines reiter-

ate that antimicrobial therapy should be reassessed once these organisms have been identified in order to more accurately direct therapy.¹

Obtaining cultures after antimicrobial therapy has been started can cause inconclusive results because organisms that would otherwise be detected may not necessarily grow after exposure to an antibiotic agent. The administration of antimicrobials before the collection of samples may decrease blood culture yields.

The American Heart Association encourages acquiring blood cultures promptly when diagnosing infective endocarditis.² In fact, a positive blood culture is a major diagnostic criterion for infective endocarditis. Most patients with infective endocarditis will yield a positive culture. However, low-grade bacteremia (less than 50 colony-forming units per milliliter of blood) is a common occurrence.² In these cases of low-grade bacteremia, the administration of antibiotics before obtaining blood cultures may affect bacterial growth in the sample and hinder the ability to appropriately tailor therapy to the offending pathogen.

Appropriate antibiotic therapy plays an important role in the prevention of antibiotic resistance. The Centers for Disease Control and Prevention (CDC) outlines that in order to help control antibiotic resistance and effectively diagnose and treat infections, it is very important to obtain cultures in order to target antimicrobial therapy to suscep-

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Formulary update, from page 1 blood. The WBCs are placed in the photoactivation bag along with normal saline and plasma, and methoxsalen is added to the bag before being exposed to UVA irradiation. ECP is performed using either the UVAR® Photopheresis System, or the UVAR® XTS™ System. The manufacturer outlines the dosage as 200 mcg if the UVAR® Photopheresis System is used, or a prescribed dosage specific to treatment volume with the UVAR® XTS™ System. The photoactivated WBCs are then re-administered to the patient. The net effect is a modulation of the patient's cellular immune system.

The current labeled indication for ECP using UVADEX® sterile solution is for the palliative treatment of cutaneous T-cell lymphoma. At Shands at UF, the primary use will be off-label for the treatment of graft-versus-host disease (GVHD).

Several publications report the benefits of ECP in patients with treatment-refractory acute and chronic GVHD. Some of the benefits described in these reports include complete and partial resolution of cutaneous and visceral manifestations of GVHD. In addition they also demonstrate improved survival rates in patients who respond to ECP, compared to non-responders. An additional advantage of ECP is that when clinical response is obtained, other immunosuppressive therapies can be reduced or even discontinued, thereby reducing their potential for toxicity with chronic use. In addition, ECP is reported as being well tolerated by patients.

These reports, however, have limitations. Randomized controlled clinical trials would help to define ECP's place in the treatment of treatment-refractory GVHD.

UVADEX® was added in the *Formulary* to provide patients with treatment-refractory GVHD an alternative therapy. The use of methoxsalen and ECP is reserved for patients who have not responded to first-line therapies for GVHD.

Varenicline is an alpha4/beta2 nicotinic receptor partial agonist, which is a new class of drugs for smoking cessation. By inhibiting smoking-induced dopaminergic activation and simultaneously providing a moderate increase in mesolimbic dopamine, varenicline may counteract the low dopamine levels that occur during smoking cessation attempts and, thereby, provide relief from the craving and withdrawal syndrome. Varenicline has a labeled indication as an aid to smoking cessation treatment. There are no known off-label uses.

Hospitalized patients are particularly good targets for smoking cessation efforts, since continued smoking could inhibit their recoveries. First-line agents for smoking cessation have been nicotine replacement therapies (NRTs) or bupropion in combination with behavioral modification therapy. Although quit rates with these treatments have been modest, any reduction in cigarette smoking is important because of the health consequences of continued smoking.

Evidence from published randomized controlled trials suggests that varenicline has equal or better efficacy than bupropion. It has a different adverse effect profile than bupropion (ie, more nausea versus less insomnia) and may be associated with more weight gain (ie, 2-3 pounds). Varenicline has not been directly compared with NRT or bupropion in combination with NRT.

Nausea is a common dose-dependent adverse effect, which may be reduced by gradually increasing the daily dosage (eg, taking 0.5 mg once daily for the first 3 days, 0.5 mg twice daily for the next 4 days, and then 1 mg twice daily). In addition, patients should be advised to take varenicline after eating and with a full glass of water to decrease the risk of developing nausea. Abnormal dreams, constipation, vomiting, flatulence, and xerostomia are also associated with varenicline use. Dosage reductions can be considered for patients unable to tolerate the adverse reactions. Using varenicline with NRT may increase adverse effects. Also, as with any new drug, whether there are any rare, but serious, adverse effects will be determined only with widespread use.

The typical dosage for varenicline is 1 mg twice a day. Lower dosages are used in severe renal dysfunction (CL_{cr} less than 30). Treatment is 12 weeks, which may be repeated once. Varenicline is roughly the same cost as nicotine patches, but is twice as expensive as bupropion.

Varenicline was added in the *Formulary* for use with behavioral modification for smoking cessation. There are behavior modification programs that are available in the outpatient setting when patients fill their prescriptions, but inpatient behavioral modification should be initiated with any pharmacological intervention to aid in smoking cessation. Behavioral modification in combination with drugs like varenicline is essential to improve "quit rates."

Mivacurium is a short-acting neuromuscular blocking agent (ie, onset 3 minutes, duration 15-20 minutes) used to facilitate intubation and relax skeletal muscles as an adjunct to general anesthesia. Abbott has stopped selling

mivacurium for marketing reasons and has no plans to resume marketing of mivacurium. There are no other manufacturers of mivacurium. Therefore, mivacurium was deleted from the *Formulary* and designated nonformulary and not available.

The neuromuscular blocking agent with the most similar onset of action and clinical duration of effect listed in the *Formulary* is vecuronium (ie, onset 2.5-3 minutes and duration 25-30 minutes).

Clonidine is a centrally acting alpha2 agonist that inhibits sympathetic outflow and decreases systemic vascular resistance. It was originally marketed with a labeled indication for hypertension, but the inhibition of sympathetic outflow led to various off-labeled uses (eg, hot flushes, alcohol withdrawal). It is available as an oral tablet and transdermal patch for these uses.

The only parenteral form of clonidine has a labeled indication for epidural administration for the treatment of pain. Clonidine's alpha2 agonist effects at the spinal level are thought to prevent transmission of pain signals to the brain.

Low doses (eg, 1 mcg/Kg) of **intravenous** clonidine have been used for several off-labeled indications including the treatment of post-operative shivering and with regional anesthesia to decrease general anesthesia requirements. There is a risk, however, for hemodynamic instability when intravenous clonidine is used for off-labeled uses; therefore, its use will be restricted to the OR, PACU, Florida Surgical Center, and to administration by an anesthesiologist.

When patients are receiving oral or transdermal clonidine for hypertension or other uses and patients cannot take medications by mouth, there have been instances when clonidine has been ordered intravenously. The above restrictions prevent this conversion.

Generic **bupropion SR** will be automatically interchanged for orders for **Wellbutrin® XL** giving the daily amount as 2 equally divided doses every 12 hours. Bupropion is a unique antidepressant that is used for labeled indication of depression and smoking cessation as well as various off-labeled uses (eg, post-herpetic neuralgia). It has been on the US market since 1985 and the patent for the "SR" extended-release dosage form has expired. Bupropion SR is given twice a day.

In 2003, the "XL" once-daily extended-release dosage form was marketed as the "SR" patent was

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Formulary update, from page 2 expiring. The main advantage of Wellbutrin® XL is that it can be given once daily compared with twice daily for bupropion SR. Since it is still a brand name dosage form, the “XL” bupropion is considerably more expensive than the generic SR product. Wellbutrin® XL has been nonformulary and not available since September 2003.

Guaifenesin liquid will be automatically interchanged for **Mucinex® tablets** using the same equivalent dose given every 4 hours while awake, instead of every 12 hours. Guaifenesin is the most commonly used expectorant and the only nonprescription expectorant on the US market. Mucinex® is the only extended-release version of guaifenesin on the market.

Guaifenesin has always had questionable efficacy. The limited data that FDA used to approve the nonprescription use of guaifenesin

was based on the liquid dosage form. There is no available evidence to support the efficacy of extended-release guaifenesin.

The proposed mechanism of action for guaifenesin is by irritating the gastric mucosa, which subsequently increases respiratory tract secretions. In theory, sustained-release dosage forms would decrease the efficacy of guaifenesin by decreasing gastric irritation.

In the absence of evidence for effectiveness for extended-release guaifenesin and based on the limited efficacy data for liquid guaifenesin, the automatic interchange to liquid guaifenesin was approved. Mucinex® is nonformulary and not available. Liquid guaifenesin 200 mg every 4 hours while awake replaces Mucinex® 600 mg twice a day.

Generic **immediate-release paroxetine** will be interchanged for **Paxil® CR**. Paroxetine is a commonly used selective-serotonin reuptake inhibitor (SSRI) used for many labeled and off-labeled uses.

As the patent for Paxil® expired, Paxil® CR was marketed. Both are once-daily versions of paroxetine. Paxil® CR is marketed as having less gastrointestinal adverse effects than immediate-release (IR) generic paroxetine.

3 studies compare the tolerability of the “CR” formulation with the “IR” tablets. 1 study is an observational study published in a supplement. Another is a short-report of a retrospective observational study from a claims database. The third study is a combination of 2 randomized controlled trials that were pooled together. These studies show small differences in GI effects. In the pooled randomized controlled trials, diarrhea was higher in the CR-group.

The P&T Committee approved automatically changing Paxil® CR to paroxetine IR using 10 mg IR for each 12.5 mg of the CR dosage form. Paxil® CR has been nonformulary and not available since October 2003.

POLICIES AND PROCEDURES

Pharmacokinetics physician-approved protocol

At the October P&T Committee meeting, the Pharmacokinetics Physician-approved Protocol (PAP) was re-authorized. Improvements in the policy were made in the area of dosing and monitoring aminoglycosides and vancomycin in patients on hemodialysis and CVVH.

This PAP allows physicians to request pharmacokinetic consults for vancomycin or aminoglycosides. The clinical pharmacy specialists who staff this service order and monitor serum concentrations and write orders to adjust dosages.

PAPs allow licensed healthcare providers (eg, nurses, pharmacists) to perform specified actions when clearly defined situations exist. Without a PAP, the directed actions would require a physician's order to initiate “the order.”

Inherent in PAPs is that physician input and review is required before the protocol can be instituted. When PAPs involve drug therapy, the P&T Committee reviews the appropriateness of these activities. All PAPs must be re-authorized every 2 years.

When any PAP is instituted, a specific order for the protocol must be

documented in the patient's medical record: For example, *Pharmacokinetic Consult for Tobramycin to Treat Pneumonia per Protocol*.

After an order is written, the unit clerk faxes the order to the appropriate decentralized pharmacy. This service is covered 24 hours a day, 7 days a week. Appropriate dosage modifications and monitoring is instituted. Notes are written in the Progress Notes section of a patient's chart with the heading, *Pharmacokinetic Consult*.

Prescribing, from page 1 tibility results.³ The sepsis guidelines also stress the importance of initiating narrower-spectrum antibiotic therapies in order to minimize the development of resistant pathogens.¹ Obtaining samples before the administration of therapy is essential, so that while empiric therapy is being administered, culture and sensitivities are being done.

Whenever possible, healthcare providers should obtain appropriate blood cultures before initiating antimicrobials. Some other general considerations when obtaining cultures are: obtain at least 2 samples of blood (if the same pathogen is identified from both samples, it is more likely that the organism is the cause of the infection);¹ ensure that samples are obtained in a sterile man-

ner as to avoid contamination;⁴ collect an adequate volume of sample (at least 10 mL per sample);⁴ and, ensure that specimens are collected appropriately (eg, aerobic vs. anaerobic tubes).

It is important to note that although previously outlined examples refer to the collection of blood samples, the same principle of early detection applies to infections at other sites. It is equally important to culture other bodily fluids/sites before the initiation of antimicrobial therapy. Therefore, other specimens such as cerebrospinal fluid, respiratory secretions, urine, and wounds should be cultured whenever warranted by clinical presentation. Again, these cultures should be obtained prior to the initiation of antibiotic therapy.

To summarize, the prompt initiation of therapy is very important whenever

infections are suspected. It is also important to remember to obtain cultures from patients before administering antimicrobial agents so that more appropriate treatment strategies can be tailored based on culture and sensitivity results. So remember, collect before you treat to ensure optimal patient care. Do not delay therapy by delaying cultures. Get cultures immediately.

By Maria Rojo, PharmD

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