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Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met August 18, 2004. 4 drugs were added in the *Formulary* and 2 drugs were deleted. 4 drugs were designated nonformulary and not available. 1 drug was evaluated and designated a high-priority nonformulary drug.

◆ ADDED

Azacitidine (Vidaza® by Pharmion)*

Bortezomib (Velcade® by Millennium Pharmaceuticals)*

Eplerenone (Inspra® by Pfizer)

Progesterone Suppositories (Compounded)

*Restricted to chemotherapy prescribers AND approval by an oncology pharmacist

◆ DELETED

Beef Lung Heparin (Beef Lung Heparin by Upjohn)**

Prochlorperazine Syrup (Compazine® Syrup by SmithKline Beecham)**

**Nonformulary and not available

◆ NONFORMULARY AND NOT AVAILABLE

Hydroxyprogesterone Caproate Injection (Compounded)

Venlafaxine Immediate-Release Tablets (Generic)

◆ EVALUATED, BUT NOT ADDED

Botulism Immune Globulin (BabyBIG® by California Department of Health Services)***

***Cannot be stocked, but designated a high-priority nonformulary drug

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PRESCRIBING

Acute otitis media — No antibiotics does *not* equal no treatment!

Acute otitis media (AOM) is the most commonly treated bacterial infection in children. Treatment accounts for greater than 50% of pediatric antibiotic prescriptions and as much as $5 billion annually.[1] Studies show that the spontaneous resolution rate of AOM is between 70-90%, and only 1 in 7-14 children with AOM benefits from treatment with antibiotics.[2]

In May of 2004, The American Academy of Pediatrics and the American Academy of Family Physicians published evidence-based clinical practice guidelines for the diagnosis and management of AOM in children between 2 months and 12 years of age with uncomplicated AOM. The guidelines recommend that observation without use of antibacterial agents in a child with uncomplicated acute otitis media is an option for selected children based on diagnostic certainty, age, illness, severity, and assurance of follow-up. This "observation option" refers to deferring antibacterial treatment of selected children for 48-72 hours and limiting management to symptomatic relief. Appropriate and adequate management of symptoms such as otalgia (ear pain) is essential during this time period.

Once AOM is diagnosed, the decision must be made to observe or treat the patient. Based on guideline recommendations, observation should be limited to otherwise healthy children 6 months to 2 years of age with non-severe illness at presentation and an uncertain diagnosis, and to children 2 years of age and older without severe symptoms at presentation or with an uncertain diagnosis. Observation allows the patient time to improve without instituting antibacterial therapy. If the patient does not improve within 48-72 hours, antibiotics should be instituted immediately.

Observation of AOM should not equal no treatment. All patients should receive adequate analgesics, especially during the first 24 hours after diagnosis.[3] Although various treatments for otalgia have been used, none are well studied.

Acetaminophen and ibuprofen are the mainstay of treatment for pain associated with AOM due to their effective analgesia for mild-to-moderate pain.[1] The usual dosage of ibuprofen in infants and children in 4-10 mg/kg/dose orally every 6-8 hours, not to exceed 30 mg/kg/day.[4] The usual dosage of acetaminophen is 10-15 mg/kg/dose orally given every 4-6 hours as needed for pain, with a maximum of 5 doses in 24 hours. Topical agents such as benzocaine (Auralgan® otic) have limited usefulness, as there is no evidence supporting their use over systemic analgesics. Other treatments for otalgia in AOM include narcotic analgesics, which are effective for moderate or severe pain. However, these agents may be more problematic than acetaminophen and ibuprofen due to their adverse effect profile, which includes respiratory depression, altered mental status, gastrointestinal upset, and constipation.[4]

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INSIDE THIS ISSUE

◆ P&T Actions

Formulary update, *from page 1*

Azacitidine is a pyrimidine nucleoside analog that is used in the treatment of myelodysplastic syndromes. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematological disorders characterized by cytopenia and death from bleeding, infection, or progression to acute myelogenous leukemia (AML).

There is no standard therapy for MDS and treatment options are determined by the patient's age and prognostic factors. Most patients with MDS receive supportive care (ie, hematopoietic growth factors and cytokines, transfusions, and antibiotics). The only curative therapy is stem cell transplantation and most patients do not qualify for this option.

Chemotherapy is an alternative to supportive therapy. Azacitidine is the only drug with a labeled indication for the treatment of MDS.

A phase III trial has shown that azacitidine had significantly higher response rates, improved quality of life, reduced risk of leukemia transformation, and improved survival compared with supportive care. Response rates of 60% (7% complete) were dramatically better than with supportive care (ie, 5% response rate and 0% complete response). The time to transformation to leukemia or death occurred in a median of 21 months versus 12 months for supportive care. These results were apparent despite 53% of the supportive care arm crossing-over to the treatment arm because of lack of effect.

Myelosuppression is the most common toxicity seen with azacitidine. Toxicity is difficult to assess, however, because of the underlying cytopenias associated with MDS.

Azacitidine is expensive. A typical 7-day course will cost over $11,000. Usually this drug will be administered as an outpatient; however, there will be instances when patients will be admitted for complications of their disease and require their scheduled treatment. In order to avoid cost shifting to the inpatient setting, an oncology pharmacist must approve the inpatient use of azacitidine.

Bortezomib is the first proteasome inhibitor. It is a cytotoxic drug with a labeled indication for the treatment of multiple myeloma in patients who have failed at least 2 prior therapies and demonstrated disease progression.

Bortezomib received accelerated approval from the FDA based on the favorable results found in 2 Phase II trials; however, only 1 of these trials has been published. These data suggest that bortezomib is a possible option for the outpatient management of refractory multiple myeloma. Bortezomib plus dexamethasone may offer benefit to patients who are refractory to dexamethasone alone.

The most serious adverse reactions associated with bortezomib include thrombocytopenia, asthenia, peripheral neuropathy, neutropenia, anemia, nausea, vomiting, and diarrhea. Asthenia (fatigue, malaise, weakness) occurs in most patients. Over 40% of patients experience thrombocytopenia.

A typical course of therapy will cost approximately $20,000. In August 2003, bortezomib was reviewed by the P&T Committee and designated nonformulary and not available for inpatient and outpatient use because it was expensive and both inpatient and outpatient reimbursements did not cover this added expense.

Bortezomib was a reason for a change in federal reimbursement rules. The FDA approved bortezomib, yet reimbursement was not provided for its labeled indication. Regulations now require that all drugs, including bortezomib, be a covered expense for its labeled indication in the outpatient setting.

In the inpatient setting, however, reimbursement is "covered" by fixed reimbursement. Therefore, use should be outpatient or in rare instances when a patient is hospitalized and requires continuation of therapy. Since patients must pay a co-pay in the outpatient setting, there is potential for patients to be inappropriately admitted to avoid this expenditure. Thus, an oncology pharmacy specialist must approve inpatient use of bortezomib.

Eplerenone is a selective aldosterone receptor blocker with labeled indications for hypertension and heart failure post myocardial infarction (MI). It is similar to spironolactone, but pharmacologically it is more specific for aldosterone receptors and has less effect on progesterone and androgen receptors. This may result in fewer adverse effects.

There is 1 large randomized trial (EPHESUS) that shows a reduction in mortality in post-MI patients with congestive heart failure compared with placebo (when added to traditional therapy). This study showed an absolute risk reduction of 2.3% (ie, number needed to treat [NNT] of 43). There is no direct comparison between spironolactone and eplerenone in the heart failure population.

The absolute benefit in the RALES trial, which compared spironolactone to placebo in a population of patients with severe congestive heart failure receiving standard therapy (eg, ACE inhibitors, loop diuretics, and digoxin), showed a larger absolute risk reduction of 11% (NNT= 9). Although approximately 50% of the patients in the RALES trial had ischemic heart failure, these patients were not in the immediate post-MI setting, like the eplerenone trial.

Spironolactone use in males with congestive heart failure is associated with gynecomastia in about 10% of patients. It is also associated with impotence and menstrual irregularities in women. These may be less problematic with eplerenone because of less affinity for progesterone and androgen receptors, but this has not been proven in a head-to-head study.

Hyperkalemia is the most troublesome adverse effect associated with the use of eplerenone. Excessive dosages or use with drugs that inhibit the metabolism of eplerenone may increase the risk of hyperkalemia. Some diseases and drugs (eg, ACE inhibitors) may independently increase the risk of hyperkalemia. A recent time series analysis showed increased morbidity and mortality associated with hyperkalemia in patients treated with spironolactone for heart failure. Similar problems are expected with eplerenone unless appropriate monitoring is done.

Serum potassium should be measured before the institution of eplerenone, within the first week of therapy, and after 1 month after the start of therapy. Serum potassium should be measured "periodically" thereafter. It should be re-measured within 1 week and at 1 month after a dosage change (or the addition of a mediation that may decrease the metabolism of eplerenone). Eplerenone is contraindicated in patients with a creatinine clearance less than 30 mL/min and patients with a serum potassium greater than 5.5 mEq/mL at initiation of therapy.

There is insufficient evidence to support the use of eplerenone for the treatment of hypertension or heart failure in any other population except in the immediate post-MI setting. Eplerenone is 14 times more expensive than spironolactone.

Progesterone vaginal suppositories were added in the *Formulary* for the management of patients at risk of pre-term delivery when they are hospitalized. The American College of Obstetrics and Gynecology recommends that when progesterone is used to prevent preterm labor that it is restricted to women with a documented history of previous spontaneous birth at less than 37 weeks of gestation because "unresolved issues remain, such as optimal route of delivery and long-term safety of the drug."

(continued on next page)

Prescribing, *from page 1*

The impact of appropriate pain control on patients and their families was demonstrated in a prospective study conducted by Siegel and colleagues.[2] In this study, parents of children with uncomplicated AOM were given prescriptions for an appropriate "safety net antibiotic." Parents were asked to not fill the prescription unless symptoms worsened or did not improve after 48 hours. At the time of diagnosis, practitioners recommended appropriate pain control medications and dispensed samples of ibuprofen, acetaminophen, and antipyrine/benzocaine (Auralgan®) otic drops. Of the 175 families enrolled in the study, 120 (69%; 95% CI=61.7-75.5) families did not fill the antibiotic prescription. Of these 120 families, 117 (97.4%; 95% CI=94.4-100) said that they were willing to use pain medication without antibiotics in the future. Furthermore, the majority of parents or guardians believed that their children had adequate pain control and there was a significant lowering of antibiotic use compared with previous episodes. The 55 families that did fill the antibiotic prescription did so for the following reasons: continued pain (42, 24%), continued fever (19, 11%), sleep disruption (11, 6%), no reason (8, 5%), missed days of work (6, 3%), and missed days of child care (5, 3%).

Due to the growing rates of antimicrobial resistance and growing costs of antibiotic prescriptions, the judicious use of antimicrobials is strongly recommended. The American Academy of Pediatrics and American Academy of Family Physicians guidelines on the diagnosis and management of AOM emphasize the appropriate treatment of these patients. The observation period is recommended in certain patients with uncomplicated AOM. Depending on the patient and practitioner, a safety-net antibiotic prescription can be written and filled only if the patient does not improve after a defined period of time.

It is important to stress that during this observation period, and in any patient with AOM, appropriate pain control is necessary. Appropriate pain control not only eases the pain of the affected child, but the parents and families as well.

by Gina K. Soliman, PharmD

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Formulary update, *from page 2*

Progesterone suppositories have been shown to be effective at decreasing the incidence of preterm birth in a small, randomized placebo-controlled trial in women with at least 1 previous spontaneous preterm birth. Progesterone suppositories reduced the rate of preterm births by an absolute percentage of 15.6% (ie, NNT = 6.3). These favorable results and the availability of a formula to compound these suppositories at Shands at UF make this option more desirable than other dosage forms (ie, injectable hydroxyprogesterone).

Intramuscular progesterone as **hydroxyprogesterone caproate** has also been shown to decrease the incidence of preterm birth in a large randomized placebo controlled trial. Unfortunately, there is no commercially available hydroxyprogesterone injection.

Hydroxyprogesterone caproate is prepared by compounding pharmacies. The risk of complications from noncommercial products discourages its inpatient use at Shands a UF. Thus hydroxyprogesterone caproate was designated nonformulary and not available. Patients also may not use their own supply of this drug.

Beef lung heparin is no longer manufactured and was deleted from the *Formulary* and designated nonformulary and not available. For many years, unfractionated heparin came from 2 animal sources: beef lung (bovine heparin) and pork intestine (porcine heparin). The use of beef lung heparin has decreased over the last few years. Beef lung heparin was more expensive than pork heparin, and there were concerns about Mad Cow Disease. Beef lung heparin was no longer a financially viable product and was discontinued by manufacturers. The supply in the market has now been exhausted.

Beef lung heparin was restricted at Shands at UF. Restriction was done because of a higher incidence of thrombocytopenia associated with the use of beef lung heparin. It remained in the *Formulary,* but was limited to Hematology approval for use in patients with a true porcine heparin allergy or patients with a religious objection to the use of pork products.

Prescribers now must find alternatives to beef lung heparin. The appropriate alternative anticoagulant will depend on the indication. A Hematology Consult will be recommended to prescribers to determine the appropriate alternative.

Low-molecular-weight heparins are generally not alternatives to unfractionated porcine heparin. Low-molecular-weight heparins are fragments of porcine heparin and would be objectionable to patients with religious concerns. Also, it is unpredictable whether a patient with a porcine heparin allergy will tolerate a low-molecular-weight heparin.

Prochlorperazine syrup has been discontinued by the manufacturer and has been deleted from the *Formulary.* This product has not been used recently at Shands at UF. If an alternative is needed, it will depend on the indication.

Venlafaxine immediate-release tablets were designated nonformulary and not available. Venlafaxine extended-release (ER) tablets remain in the *Formulary* and will be recommended as an alternative. The total daily dose of the immediate-release (IR) tablets should be given once daily as venlafaxine ER.

Venlafaxine is an antidepressant with a mechanism of action similar to SSRIs (ie, serotonin reuptake inhibition), but it also inhibits the reuptake of norepinephrine and dopamine. Venlafaxine is used for various off-label uses including neuropathic pain.

Botulism immune globulin is an orphan drug that is the only available treatment for infant botulism. Infant botulism is the infectious form of human botulism. It is recognized in only 80 to 100 patients per year in the United States. It is difficult to diagnose, and with symptomatic treatment patient are usually hospitalized for more than 5 weeks. Treatment with botulism immune globulin can cut the typical hospital course in half.

Botulism immune globulin cannot be stocked in the hospital and, therefore, cannot be listed in the *Formulary*. However, it was designated a high-priority nonformulary drug, which requires pharmacists to contact prescribers immediately to facilitate the procurement of this product.

Botulism immune globulin must be obtained from the California Department of Health Services. Information on how to acquire botulism immune globulin is available at www.infantbotulism.org. The treating physician must first contact the manufacturer to determine whether the patient qualifies for treatment before it can be obtained for nonformulary use.

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NEWS

P&T Commitee Action 2003–04

The P&T Committee's year goes from July to June. Thus, another productive year was just completed. The P&T Committee is the medical staff committee that is the formal line of communication between the medical staff and Shands at UF. Therefore, formulary activities, drug use polices, adverse drug reaction monitoring, and medication safety are most of the activities.

27 new drugs were added in the *Formulary* this year. There were only 9 new drugs requested, the rest of the additions were the result of reviewing nonformulary drugs, drug category reviews, and the proactive review of new products.

16 drugs were deleted from the *Formulary.* 33 drugs were designated nonformulary and not available. "Not available" drugs cannot be requested through the nonformulary process.

Several therapeutic interchanges were approved this year including rosiglitazone for pioglitazone, fenofibrate tablets for fenofibrate capsules, albuterol MDI for nebulizations, and ipratropium MDI for nebulizations. When these changes are made, a new order with "P&T Authorized Interchange" will be placed in the patient's chart.

Drugs that are being used nonformulary are reviewed. High volume nonformulary drugs are reviewed to determine whether they should be added in the *Formulary,* added with restriction, or designated "not available." High-priority nonformulary drugs are those drugs that a delay could result in patient harm, like antibiotics, pain medications, hypotensive agents, and ophthalmic agents. These agents are reviewed for formulary consideration.

As part of the normal function of the P&T Committee, several drug use policies were reviewed throughout the year. The following is a partial list of policy changes.

- Policy & Procedure for High-Cost, Problem-Prone Drugs: A detailed procedure was established to assure appropriate utilization of high-cost and problem-prone drugs. This procedure uses "expert panels" to give the P&T guidance in order to make the best "evidence-based" decisions.
- Ceftriaxone Automatic Dosage Interchange: An Infectious Diseases Clinical Pharmacist may automatically interchange ceftriaxone dosages based on P&T approved criteria.
- Strategic Plan for the Anti-Infective Stewardship Program: The strategic plan for the Anti-Infective Stewardship program and the rationale and proposed actions of the program were endorsed. The program will periodically report to the P&T Committee.
- Vancomycin Guidelines: Guidelines for the use of vancomycin were approved and a program for a clinical pharmacist (as part of the Anti-Infective Stewardship Program) to evaluate all use of vancomycin at 48-72 hours implemented. The pharmacist will assist in streamlining therapy based on culture and sensitivity reports.

The *Drugs & Therapy Bulletin* is the primary method for communicating P&T activities throughout the year. In most years the P&T Committee meets 10 times and a Bulletin is published after each meeting.

Dr. Gonzalez-Rothi chairs the P&T Committee. This is his 5th year leading this medical staff committee. If you have questions or comments about the activities of the committee, Dr. Gonzalez-Rothi can be reached by e-mail at RothiRJ@medicine.ufl.edu.