

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met May 17, 2011. 4 products were added in the *Formulary*; 2 were deleted and designated nonformulary and not available. 1 interchange was approved, while 3 criteria for uses were changed.

◆ ADDED

Acetaminophen IV
(Ofirmev® by Cadence Pharmaceuticals)*

*Restricted

Carglumic Acid
(Carbaglu® by Orphan Europe)

Mannitol Bronchial Challenge Test Kit (Aridol® by Pharmaxis)

Tobramycin-Dexamethasone Ophthalmic Suspension
(Tobradex® by Alcon)

◆ DELETED

Dextran 70 (Generic)†

Polysaccharide Iron Complex Liquid (Generic)†

†Nonformulary and not available

◆ INTERCHANGES

Digibind® for Digifab®‡

‡Once Digibind® supplies are exhausted, it will be interchanged to Digifab®

◆ CRITERIA-FOR-USE CHANGES

Epoprostenol
(Flolan® and Veletri®)*

*Restricted: Must use EPIC order set

Nicardipine IV (Cardene® IV)*

*Restricted use expanded to select adult uses

Treprostinil IV (Remodulin®)*

*Restricted: Must use EPIC order set

(continued on next page)

ADVERSE DRUG REACTIONS

The truth about drug fever

It is estimated that about 3–7% of febrile episodes are attributed to drug reactions; however, the true incidence is unknown due to underreporting and frequent misdiagnosis.¹ In the hospitalized patient, the most common presentation for drug fever is a patient with a resolving infection, on antimicrobial therapy, and after initial defervescence. Fever in this patient can result in the over-utilization of antimicrobials and the addition of agents to treat an infection that is not present. This could potentially cause more adverse effects and further contribute to antimicrobial resistance.

One study evaluating 51 episodes of drug fever in 2 Dallas hospitals from 1959 to 1986 found that episodes of drug fever resulted in a mean prolongation of hospital stay of 8.7 days, an average increase of 5 blood cultures, 2.85 more radiologic studies, and 0.53 more courses of antibiotics.² While no study evaluating another large group of patients has been performed since, procedures for ruling out infectious and other causes of fevers have not changed significantly and likely still reflect these findings.

Drug fever is difficult to diagnose because it is a diagnosis of exclusion.^{1,3} The febrile response should coincide temporally with the administration of a new drug and occur in the absence of underlying conditions that could contribute to the cause. Practitioners should always have drug fever on their differential, especially if the patient is receiving an agent that is frequently implicated with fever. These agents include antibiotics (especially beta-lactams and sulfonamides), antineoplastics, anti-convulsants (especially phenytoin and carbamazepine), antiarrhythmics (mainly quinidine and procainamide), and other cardiac medications (methyldopa).¹

Drug fever can occur at any point during a course of therapy with significant variation among patients.^{3,4} The median time to presentation of fever is 7 to 10 days, with a faster onset with antineoplastic agents (median 0.5 days) and

antimicrobials (median 6 days). Cardiac and central nervous system medications can induce fever at a much slower interval, median of 10 and 16 days after initiation, respectively.

Fever patterns may present as a continuous fever (temperature does not vary), remittent fever (where temperatures vary, but are consistently elevated), intermittent fever (with normal temperatures in between), or the most common: hectic fever (combination of remittent and intermittent).⁴ Degree of pyrexia tends to range from 38.8°C (102°F) to 40°C (104°F) but has been reported as high as 42.8°C (109°F).

Clinically, patients with drug fever look “inappropriately well” and are frequently unaware they are febrile. One of the most important clues to detection of drug fever is a relative bradycardia where the heart rate does not increase to the extent that would be expected given the temperature elevation. In general, a temperature greater than 39°C should elicit a heart rate greater than 110 beats per minute (assuming the patient is not on a beta-blocker and has no conduction abnormalities).⁴ Findings of leukocytosis, with or without a left shift, peripheral eosinophilia, and erythrocyte sedimentation rate of greater than 100 mm/hour complicate the diagnosis of drug fever and warrant further investigation of infection.³

In 18–29% of patients with drug fever, cutaneous manifestations of hypersensitivity are also present and allow for easier identification of a medication as the source of fever.³ Fever is most commonly caused by hypersensitivity to a drug and may precede more overt clinical manifestations of a drug reaction. Drug fever due to hypersensitivity may develop over several days to weeks; however, if the drug is discontinued and reintroduced days, months, or years later, fever will likely develop within hours of re-administration.

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Formulary update, from page 1

Intravenous (IV) acetaminophen is an antipyretic and analgesic with FDA-labeled indications for use in adults and children (greater than 2 years old) for management of pain and fever. Formulation issues previously limited acetaminophen's IV stability and its use as an injectable agent. IV acetaminophen has fewer local adverse events and similar efficacy to propacetamol, the intravenous prodrug of acetaminophen that has been used in Europe.

IV acetaminophen works centrally to inhibit cyclooxygenase (COX) enzymes to disrupt prostaglandin synthesis. The onset of action for analgesia and antipyretic effects is expected to occur within 15 and 30 minutes, respectively, of the start of the infusion. Prescribers should remember, however, that it is just an intravenous dosage form of acetaminophen and works just like oral and rectal acetaminophen.

IV acetaminophen is supplied as a 100-mL, single-use vial of 10 mg/mL and is administered as a 15-minute infusion. The labeled dose for adults and adolescents greater than 50 kg is 1000 mg every 6 hours or 650 mg every 4 hours. Children 2 to 12 years of age and adolescents less than 50 kg should receive 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours. There is no advantage for the 4-hour dosage interval, which is more expensive because it uses more product and increases waste.

In studies evaluating IV acetaminophen's use in adults, it was effective when compared to placebo for post-operative analgesia. Studies show a decrease in opioid use in the first 24 hours when IV acetaminophen is used.

There are no published studies comparing oral or rectal acetaminophen to the IV route, and the suggestion that IV acetaminophen is less hepatotoxic or more effective is not supported by evidence.

The cost of a vial of IV acetaminophen is more than 170 times more expensive than oral acetaminophen and more than 40 times more expensive than acetaminophen suppositories. Small IV doses used in children waste most of a vial because it is a single-dose vial (ie, once a vial is opened, it cannot be stored and used later). Therefore, this agent could have a significant impact on pharmaceutical expenditures, which will be closely monitored.

IV acetaminophen was restricted to post-operative use up to 24 hours and as a single dose in the ED. Further restrictions include no PRN orders, no inclusion in EPIC order sets (except in the PACU), and only dosage regimens for every-6-hour intervals in adults and children (ie, no every-4-hour regimens). Also, it was added in the IV-to-PO policy permitting conversion to an oral

or enteral dosage form when other medications are being given orally or enterally. Rectal acetaminophen is an alternative to IV acetaminophen that should always be considered.

Since, IV acetaminophen should be used only when patients cannot take other oral medications, using more than 4 grams per day of acetaminophen should not be a concern with IV acetaminophen. Overdose remains a concern with oral acetaminophen and acetaminophen combinations like Percocet®, and prescribers should monitor the total dose of acetaminophen (eg, do not exceed 4 grams per day in adults).

Carglumic acid is a carbamoyl phosphatase synthetase 1 (CPS1) activator with labeled indications for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) and for maintenance therapy of chronic hyperammonemia due to the deficiency of NAGS. NAGS deficiency is a rare disorder, and, therefore, its safety and efficacy was evaluated in only 23 patients before it was approved by the FDA. Few cases of NAGS deficiency have been reported and the overall incidence is unknown. NAGS deficiency is one of several urea cycle disorders.

In February, the P&T Committee designated carginic acid a high-priority nonformulary drug with instructions in our computer systems on how to obtain it. Carginic acid is available from Accredo, and we have already purchased it twice when a patient was admitted and could not provide their own supply.

The original assumption for designating this product a high-priority nonformulary drug was that it would rarely be used. It is very expensive and has a short shelf life. A 5-tablet bottle costs \$685 (\$137 per tablet), while a 60-tablet bottle costs \$8220. Bottles must be discarded 1 month after opening. The 60-tablet bottle will not be purchased for inpatient use.

The courier service that delivers this product charges over \$500 for delivery. This high cost of delivery, the fact we anticipate using this product, and its unique therapeutic niche made addition in the *Formulary* the preferred option.

Inhaled mannitol powder is an alternative to methacholine for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma. It is in a ready-to-use form and eliminates the need to make dilutions of methacholine in the IV Center.

Bronchoprovocation tests are used to assess, quantify, and establish airway hyperresponsiveness associated with asthma. Bronchoprovocation tests serve as an objective tool for establishing a diagnosis of asthma. The 2 classes of bronchoprovocation tests used are direct (methacholine and histamine) and indirect challenges (mannitol). The available data are conflicting in terms of which is the better diagnostic tool, but the general

consensus is that the mannitol test is a more specific but less sensitive test than the methacholine challenge test.

Many trials have examined the diagnostic properties of both the mannitol and methacholine challenge tests. One of the main limitations seen across all studies is the fact there is no "gold-standard" definition for asthma diagnosis to compare the challenge test results. Consequently, the definition for asthma diagnosis is highly variable across studies. This affects overall generalizability of study results since it is possible that diagnoses of asthma will vary from physician to physician. Other limitations of these trials include possible sampling bias and the utilization of younger population samples.

Although most studies indicated that mannitol is a more specific test than methacholine, 1 study found that the sensitivity and specificity for both mannitol and methacholine to identify exercise-induced bronchospasm and a clinician diagnosis of asthma were equivalent. Unlike populations in other studies, the population evaluated in this study consisted of subjects with normal FEV₁, mild symptoms, and mild airway hyperresponsiveness. Essentially, these subjects did not have a confirmed diagnosis of asthma; they only had symptoms suggestive of asthma. This population is, therefore, more analogous to populations in which these challenge tests would actually be utilized.

The mannitol challenge test was added in the *Formulary* as an alternative to the methacholine challenge test. It should be used as part of a clinician's overall evaluation of asthma and should not serve as the sole criterion for diagnosis or as a screening test for asthma. Patients must not have a past medical history significant for aortic or cerebral aneurysm, uncontrolled hypertension, recent myocardial infarction, or cerebral vascular accident. Patients must have an FEV₁ greater than 70% of the predicted value in order to qualify for administration of the mannitol bronchoprovocation tests. The challenge test must be stopped if after administration of the 0-mg dose (control), the patient's FEV₁ drops 10% or more from the pre-challenge value.

Tobradex® is an ophthalmic mixture of the aminoglycoside antibiotic tobramycin and the corticosteroid dexamethasone. Both individual ingredients are listed in the *Formulary*. The addition of this dosage form in the *Formulary* was based on the volume of nonformulary requests.

Dextran 70 is a colloid volume expander. It was an alternative to albumin or crystalloids like saline. All dextran 70 products are now off the market; therefore, it was deleted from the *Formulary* and designated nonformulary and not available.

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Formulary update, from page 2

Polysaccharide-iron complex is intended to provide an oral iron supplement with less gastrointestinal adverse effects. These products were added in the *Formulary* in 1992 without evidence to support superiority over ferrous sulfate.

Since the **liquid** version of this product is no longer on the market, it was deleted from the *Formulary* and designated nonformulary and not available. Ferrous sulfate drops are the liquid alternative to polysaccharide-iron complex liquid listed in the *Formulary*. Polysaccharide iron-complex capsules remain in the *Formulary*.

Digibind® and **Digifab®** are both **digoxin immune fab** products. There are no clinically relevant differences reported in administration, storage, dosing, efficacy, and safety of Digibind® and Digifab®.

Digibind® is being discontinued from the market. Once supplies of Digibind® are exhausted, Digibind® will be deleted from the *Formulary* and designated nonformulary and not available. Digifab® will then be stocked. Because the use of these products is not predictable, it is not clear when this will occur; however, the Digibind® in stock will expire in 2013.

Digoxin immune fab is a protein that consists of antibody fragments that are used as an antidote for digitalis toxicity. Digibind® is produced by immunizing a sheep with digoxin coupled to human albumin, then isolating immunoglobulins from the sheep serum and then obtaining specific antibody fragments from the immunoglobulins. Digifab® is produced in a similar manner except that digoxindicarboxymethylamine (a digoxin derivative) is used instead of digoxin coupled to human albumin.

Digibind® and Digifab® come as sterile lyophilized powders that are reconstituted with 4 mL of sterile water. Each vial of Digibind® contains 38 mg of digoxin immune fab, while each vial of Digifab® contains 40 mg of digoxin immune fab. Each vial of Digibind® or Digifab® binds approximately 0.5 mg of digoxin. Digibind® and Digifab® must be stored in the refrigerator and, once reconstituted, must be used within 4 hours. Both Digibind® and Digifab® can be diluted with sterile isotonic saline to a convenient concentration. Both should be administered by intravenous infusion for at least 30 minutes, but they can be given as a bolus in case of imminent cardiac arrest. All calculations and formulas used in the treatment of digoxin toxicity with Digibind® also apply to Digifab®, so no adjustments in dosing will be necessary due to the transition from Digibind® to Digifab®.

A study done in healthy patients to compare the pharmacokinetics of Digifab® and Digibind® shows that Digifab® binds and neutralizes digoxin in a man-

ner equivalent to Digibind®. Both Digifab® and Digibind® effectively lowered the levels of free digoxin to below detectable in all subjects studied.

Therefore, the therapeutic interchange of Digifab® and Digibind® was approved by the P&T Committee. **Epoprostenol** and **treprostinil** are prostaglandins used intravenously for the treatment of pulmonary arterial hypertension. These agents are difficult to use correctly and there can be confusion between different brands of the same product (eg, Flolan® and Veletri®), which may be dosed and administered differently.

Restricting these agents to EPIC order sets was intended to encourage the safe use of these products. The order set guides prescribers, particularly prescribers who do not specialize in the use of these agents, by using standardized concentrations, dosages, monitoring, and administration. In addition, they recommend additional drugs to support the use of these agents. This should improve safety for these high-risk, rarely used drugs.

Nicardipine IV has been listed in the *Formulary* but restricted to PICU for use in patients with renal failure who have failed initial hypertension management with a labetalol infusion. It was reviewed because of concerns about toxicity and adverse events that have occurred with formulary alternatives for IV nicardipine in adults. These adverse events include cyanide toxicity (associated with the use of sodium nitroprusside) and difficult-to-reverse hypotension upon anesthesia induction (which has been associated with labetalol use in patients undergoing neurosurgery).

Nicardipine is a dihydropyridine calcium channel blocker approved for management of hypertension when oral therapy is not feasible or desirable. It has also been shown to be safe and effective for blood pressure control in the setting of neurological injury and perioperative hypertension in both cardiac and non-cardiac surgeries. It is as effective as sodium nitroprusside in the reduction of blood pressure. Nicardipine's advantages include a relatively fast onset and offset, a lack of association with the accumulation of toxic metabolites like sodium nitroprusside, and a lack of association with an increase in intracranial pressure (ICP). Nicardipine has a faster onset of action than sodium nitroprusside, is associated with fewer adverse events than sodium nitroprusside, requires fewer dosage adjustments than sodium nitroprusside or labetalol, and may confer in-hospital mortality benefit compared to sodium nitroprusside in patients with intracerebral hemorrhage (ICH). Nicardipine can be administered in large peripheral veins; however, the peripheral infusion site must be changed every 12 hours to avoid adverse administration reactions. Disadvantages to nicardipine include cost, contraindication in aortic stenosis, and the potential for interaction with anesthetics.

Studies have shown the safety and efficacy of nicardipine in acute stroke patients when compared to sodium nitroprusside and to IV labetalol with fewer adverse events seen with nicardipine. Guidelines recommend the use of nicardipine for blood pressure management in stroke patients and that sodium nitroprusside should be avoided due to its ability to increase ICP. Additionally, nicardipine has been proven safe and effective for the management of hypertensive emergency and perioperative hypertension and is recommended in guidelines for these indications.

The criteria for IV nicardipine were extended to include adult patients who require continuous infusion agents for blood pressure management. However, it should be used only when blood pressure is either poorly controlled with the formulary alternatives or when patients have experienced an adverse reaction or have a contraindication to formulary alternatives. The following will be used to determine whether a patient meets these criteria:

- Continuous infusion medication required for blood pressure control and 1 of the following:
 - Failure of combination sodium nitroprusside and labetalol defined as less than a 15% decrease in blood pressure after 1 hour OR not reaching blood pressure goal after 2 hours on sodium nitroprusside 3 mcg/kg/min and labetalol 120 mg/hr.
 - Failure of sodium nitroprusside in patients with contraindication/ADR to labetalol. Failure defined as less than a 15% decrease in blood pressure after 1 hour OR not reaching blood pressure goal after 2 hours on sodium nitroprusside 3 mcg/kg/min.
 - Contraindications/ADRs to labetalol defined as one of the following:
 - Heart rate less than 60 beats per minute
 - 2-3 degree heart block
 - Cardiogenic shock
 - Acute decompensated heart failure
 - Sick sinus syndrome
 - Failure of labetalol in patients with contraindication/ADR to sodium nitroprusside. Failure defined as less than a 15% decrease in blood pressure after 1 hour OR not reaching blood pressure goal after 2 hours on labetalol 120 mg/hr. Contraindications/ADRs to sodium nitroprusside defined as any one of the following:
 - Renal Failure defined as one of the following: requiring hemodialysis, anuric for 12 hours, tripling of serum creatinine (SCr) from baseline, SCr greater than 4, urine output less than 0.3 mL/kg/hr for 24 hours

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Adverse drug reactions, from page 1

A review of drug fever during antibiotic administration was performed in a University hospital in Japan during the late 1980s.⁵ In their study, they found that 13% of patients (51 of 390) being treated with antibiotics for respiratory infections for more than 7 days developed a fever of 37.5°C (99.5°F). It was found that 49 of the 56 episodes of fever were greater than or equal to 38°C (100.4°F) and they were all unrelated to a true infectious process. Beta-lactams were the agents primarily used in this study. The onset of drug fever ranged from 7 to 35 days and varied based on previous exposure to a beta-lactam. Fever patterns were most commonly described as low-grade at onset, followed by high and remittent fever. Eosinophilia was found in 25% of patients.

In the febrile patient completing antimicrobial therapy for a resolving infection, it is recommended to discontinue therapy if the infection is resolved and further infections have been ruled out.³ If the patient is stable but the infection is unresolved, the most likely offending agents should be removed and a modification should be made to the antimicrobial regimen so that further drug sensitization is avoided. Antibiotics with a lower association of fever include clindamycin, vancomycin (new formulations are not associated with fever),

chloramphenicol, aztreonam, tetracyclines, macrolides, imipenem, fluoroquinolones, and aminoglycosides.⁴

After discontinuing the offending agent, rapid defervescence should occur within 72 hours. Rechallenging the patient with the suspected drug is very controversial and should only be performed if the benefit of confirming the diagnosis of drug fever outweighs the risk of hypersensitivity.⁴ Additionally, testing for antidrug antibodies or histone antibodies does not confirm or rule out drug-induced fever and is, therefore, not recommended for evaluation of drug hypersensitivity as a cause of fever.

A patient with drug fever is likely to undergo a number of unnecessary

tests and exposure to antibiotics until infection is ruled out. Drug fever does not present in a classic manner and is a challenging diagnosis. It is appropriate to keep medications near the bottom of the differential for fever until more serious causes have been ruled out.

By Danielle Lazear, PharmD

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Formulary update, from page 3

- Lactate greater than 4 or 20% increase from baseline
- Methemoglobinemia
- Elevated ICP
- First line in patients with contraindication/ADR to labetalol AND sodium nitroprusside as described above.
- Neurosurgery/Neurology patients in the perioperative period (48 hours before and 24 hours after neurosurgical procedure)

Additionally, nicardipine IV was approved for the limited population of patients with an acute intracranial process in whom operative intervention is planned within 24 hours for use through the peri-operative period, followed by transition to a more cost-effective continuous infusion antihypertensive agent. IV nicardipine can be used in adults in the Emergency Department, Operating Room, Post Anesthesia Care Unit, and Intensive Care Units. A 6-month medication use evaluation is planned to assess compliance with these criteria.