Winter 2018, Issue 9

The Script

A Publication of the Department of Pharmacy, Norman Regional Health System

The 2017-2018 NRHS Pharmacy Residents

By Kim Whitley, BS, Pharm.D., BCPS

Norman Regional Health System offers a 12-month accredited Post Graduate Year 1 (PGY1) Pharmacy Residency that begins each year in July and ends in June of the following year. It allows pharmacists to accelerate their growth beyond entry-level competencies, to refine their clinical skills in a broad range of disease states and to provide evidence-based, patient-centered medication therapy. Residents are also cross-trained in distribution activities and can be found staffing at the Porter campus on Monday through Thursday evenings. In addition to clinical rotations, staffing, and other requirements, each resident undertakes a major project during their residency, in which they present their research at local and national pharmacy conferences throughout the year.

Mona Kamali grew up in Plano, TX and is a graduate from Texas Tech University Health Sciences Center School of Pharmacy. Her current areas of interest include cardiology, oncology, and internal medicine. Her major residency research project is titled "Impact of a Pharmacist-Driven Probiotic Protocol on the Incidence of Antibiotic- and *Clostridium difficile*-Associated Diarrhea in Hospitalized Patients Receiving Antibiotic Therapy." After completion of her residency, Mona plans to pursue a position as a clinical pharmacist and obtain certification as a Board Certified Pharmacotherapy Specialist (BCPS).

From left to right: Mona Kamali, Michael Wisner and Jaclyn Coffey

Michael Wisner is originally from North Alabama, but spent the last 9 years in Tennessee. He graduated from The University of Tennessee Health Science Center in Memphis. Michael's main area of interest is pharmacy informatics. His major research project is titled "Evaluating the Impact of Pharmacy Driven Hyperglycemia Interventions Identified by Real Time Clinical Surveillance Software." After his residency is complete, Michael plans on pursuing a PGY2 in pharmacy informatics.

Jaclyn Coffey was raised in Kearney, Missouri and graduated from the University of Missouri-Kansas City in 2017. Her current interests in pharmacy include internal medicine, emergency medicine, and infectious diseases. During the year, Jaclyn will be working on her research project titled "Impact of Skin Testing for Penicillin Allergy in Self-reported Penicillin Allergic Patients on the Use of Fluoroquinolones, Carbapenems, Aztreonam and Vancomycin in a Community Hospital." After completion of her residency, Jaclyn plans to pursue a career as a clinical pharmacist in an inpatient setting.

Please continue to make our residents feel welcome!

In This Issue:

We welcome your thoughts, comments and/or suggestions.

Do you have an idea for a story? Is there information we can provide you?

All correspondence concerning *The Script* should be sent to:

Lisa Mayer, Pharm.D., BCPS

3300 HealthPlex Pkwy

Norman, OK 73072

lmayer@nrh-ok.com

NORMAN REGIONAL Health System

Digoxin Toxicity

By Lauren May, Pharm.D.

Digoxin is a cardiac glycoside commonly used for cardiac conditions, including, atrial fibrillation, heart failure, and supraventricular tachycardia. It is considered a narrow therapeutic index drug and toxicity is a common adverse consequence of its use. Generally recognized therapeutic levels are 0.5-0.9 ng/mL for heart failure and 0.8-1.2 ng/mL for atrial fibrillation. Toxicity is usually associated with digoxin levels >2 ng/mL, but it is important to note that digoxin toxicity may occur in patients despite therapeutic digoxin concentrations.

In heart failure, digoxin works by inhibiting the sodium/potassium ATPase pump in myocytes which results in an increase in intracellular sodium. This in turn causes an ultimate increase in intracellular calcium which promotes increased myocardial contractility, known as positive inotropy. Increased contractility increases stroke volume to improve overall cardiac output, which is low in heart failure. Digoxin also acts by suppressing conduction through the AV node thereby exerting its effects in supraventricular arrhythmias (i.e. atrial fibrillation and supraventricular tachycardia). These pharmacologic effects are accountable for the cardiac toxicities seen with digoxin. Increased intracellular calcium may cause delayed after-depolarization, triggering arrhythmias and suppressed conduction through the AV node and may cause bradycardia.

There are many factors that may alter digoxin's effect in the body. Digoxin is renally eliminated and may accumulate in patients with acute kidney injury. A dose reduction is normally required in patients with renal dysfunction. It is also a substrate of p-glycoprotein, which works to lower serum drug concentrations by pumping drugs into the intestines and proximal renal tubule for elimination. Drugs that decrease the activity of p-glycoprotein (i.e. diltiazem, verapamil, amiodarone) can cause increased serum concentrations of digoxin. Digoxin is bound to plasma proteins, including albumin. Protein-bound digoxin is not recognized by serum drug assays, thus conditions that cause hypoalbuminemia can increase the free digoxin in the blood, effectively increasing serum digoxin concentrations.

Digoxin toxicity is a diagnosis based on clinical presentation. As mentioned earlier, a patient may present with signs and symptoms of toxicity despite having a digoxin serum concentration in therapeutic range. Patient presentation can differ based on whether the toxicity is due to acute or chronic poisoning. With acute ingestion, patients may appear asymptomatic for several hours and then develop gastrointestinal symptoms, including nausea, vomiting, and anorexia, and non-specific symptoms of lethargy and weakness. Hyperkalemia is also an important marker of acute digoxin toxicity. Chronic toxicity can be difficult to diagnose as symptoms can be more nonspecific and develop over days to months. Common signs of chronic toxicity include nausea, vomiting, anorexia, abdominal pain, cardiac arrhythmias, confusion, delirium, disorientation, headache, ocular disturbances (blurred or yellow-green vision) and electrolyte disturbances (hypokalemia, hypomagnesemia). While cardiac manifestations of toxicity are the most concerning for both acute and chronic toxicity, gastrointestinal and neurologic toxicities are most common. The most common rhythm disturbances for digoxin are bradycardia, atrioventricular junctional blocks, and ectopic ventricular rhythms.

DigiFab Dosing	
Acute Ingestion of Known Quantity	**Step 1: Calculate Total Body Load (mg):** Tablets: total body load (mg) = 0.8 x (amount in mg of digoxin tablets ingested) Capsules: total body load (mg) = amount in mg of digoxin capsules ingested **Step 2: Calculate DigiFab dose (vials):** DigiFab dose (vials) = total body load (mg) / 0.5
Acute Ingestion of Unknown Quantity	Administer 10 vials of DigiFab, with an additional 10 vials if necessary based upon symptoms
DigiFab Dose Based on Steady-state Serum Digoxin Concentration	DigiFab dose (vials) = (serum digoxin concentration [ng/mL] x weight [kg]) / 100

Table 1. Digoxin Immune Fab (DigiFab) Dosing

DigiFab is a digoxin-specific antibody fragment that binds digoxin to inhibit digoxin from binding to cardiac tissue to reduce myocardial toxicity. Each vial of digoxin immune Fab 40 mg will bind ~0.5 mg of digoxin. See Table 1 for the dose calculation of DigiFab. If the calculated dose based on the digoxin concentration differs from the estimated dose for a known ingestion amount, use the higher dose. The dose required should always be rounded up to the closest vial size. Partial vials should NEVER be dispensed due to the high cost of this medication.

The most important thing to know about DigiFab, is that it will falsely elevate serum digoxin levels after administration until it's completely eliminated from the body. DigiFab bound digoxin cannot cause toxicity so any digoxin level drawn after DigiFab administration has no clinical meaning. Repeat digoxin levels should be avoided in patients until DigiFab has cleared, which could take days to weeks in renally impaired patients. A repeat dose of DigiFab should only be given if the patient continues to have signs and symptoms of toxicity. Repeat DigiFab administration should never be given based on a total serum digoxin concentration. Only a free or unbound serum digoxin concentration would be of clinical significance, but this test is not performed at NRHS.

How to Evaluate Heparin-Induced Thrombocytopenia

By Jacqueline Medina, Pharm.D.

Heparin induced thrombocytopenia (HIT) is an adverse effect that can occur in patients receiving heparin products, such as heparin flushes, heparin IV or SC, and enoxaparin. However, HIT is 10 times as likely with unfractionated heparin than low molecular weight heparins. Type I HIT is a non-immunologic response caused by the interaction of heparin with the platelet membrane, leading to enhanced platelet activation. A decreased platelet count usually occurs within the first few days of treatment and gradually rises to normal levels after several days, even if heparin therapy is continued.

Type II HIT is a life-threatening immune-mediated adverse effect which can occur in up to 5% of patients receiving heparin products and is the type of HIT that will be discussed in the rest of this article. HIT is caused by the formation of IgG antibodies to platelet-factor-4 (PF4) complexed with heparin. These antibodies bind to heparin-PF4 complex, which leads to platelet activation and a paradoxical pro-thrombotic state. Thromboembolic complications occur in about 50% of patients with confirmed HIT. This type of HIT is usually characterized by a decrease of more than 50% in the platelet count beginning 5 to 10 days after the start of heparin. Platelets usually increase within 2 to 5 days after the start of an alternative anticoagulant.

A widely validated scoring system to evaluate the probability of HIT is the 4T score (see Figure 2 on page 4), which evaluates four indicators: (1) the relevant platelet count fall, (2) the timing of the onset of the platelet count fall, (3) the presence or absence of thrombosis, and (4) the likelihood of another cause of thrombocytopenia. The scores for each component range from 0-2, with higher total scores indicating a higher likelihood of HIT. A low 4T score (≤ 3) indicates a very low probability of HIT of 0-3%. For patients whose score is intermediate (4-5) or high (≥6), laboratory assays are needed to rule out HIT.

There are two main types of laboratory tests used to diagnose HIT, antigen tests and functional tests, which are summarized in Table 1. Per NRHS policy, a positive antigen test automatically reflexes to a functional assay, the serotonin release assay (SRA). SRA is considered the gold standard because it only detects antibodies capable of activating platelets resulting in very high sensitivity and specificity. Diagnostic accuracy for HIT is improved with the use of both an antigen test and a functional test. **HIT assays should not be used to screen asymptomatic patients and should be interpreted only in the context of the pretest probability of HIT.**

	Antigen Tests		Functional Tests
Types	PF4-heparin antibody test	Heparin-induced platelet antibody	Serotonin Release Assay (SRA)
Advantages	• Results in less than 2 hours	• Results within minutes • Quantitative results	• The "gold standard" • Very sensitive and specific • False positives are rare
Disadvantages	• False positives • Qualitative Results • Reflex to SRA	• False positives – although fewer than with the PF4 • Requires dedicated instrumentation • Reflex to SRA	• Results take ≥5 days since it has to be sent to a specialized laboratory

Table 1. HIT Laboratory Tests

Currently we have two types of antigen tests at NRHS. The old test is labeled "heparin-PF4 Ab screen" and the new test is labeled "heparin-induced plt ab rapid" in the EMR. The new test uses HIT-mimicking anti-PF4/heparin murine monoclonal antibody (KKO) to determine if IgG antibodies are present (HIT positive). If antibodies are present, then KKO will not be able to bind to PF4 resulting in little or no agglutination and a positive result. If antibodies are not present, then KKO will be able to bind to PF4 causing agglutination and a negative result. **This increases its specificity,** because less reactivity correlates with greater likelihood of HIT. It provides a numerical value with pre-specified cutoffs, which will determine if it is positive or negative.

Initial evaluation of HIT practices at NRHS showed the use of HIT testing in patients without exposure to heparin on their current admission. Over-diagnosis and over-treatment of HIT are more common than under-recognition, given the high frequency of thrombocytopenia among early postoperative and critically ill patients and the low specificity of readily available antigen assays. Platelet factor 4–heparin antibody tests should be ordered only if clinical features are suggestive of HIT and the patient has an intermediate or high 4T score. Key interventions in patients with a high suspicion of HIT include the prompt cessation of heparin and the initiation of an alternative anticoagulant such as argatroban, bivalirudin, or fondaparinux. With high cost and mortality, it is imperative to use clinical judgement and available resources, such as the 4T score, to quickly and accurately treat patients with higher probabilities of HIT, while using sensitive antigen assays to rule out HIT.

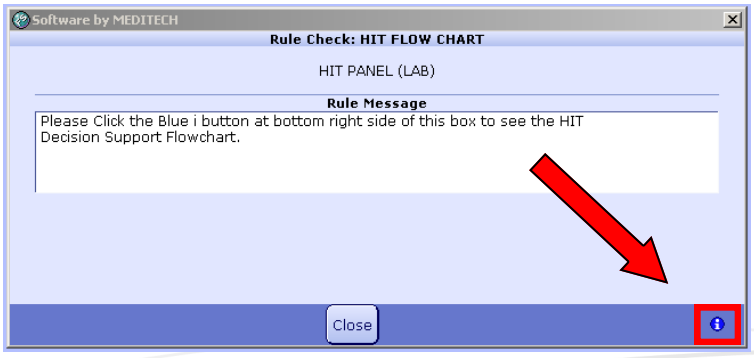
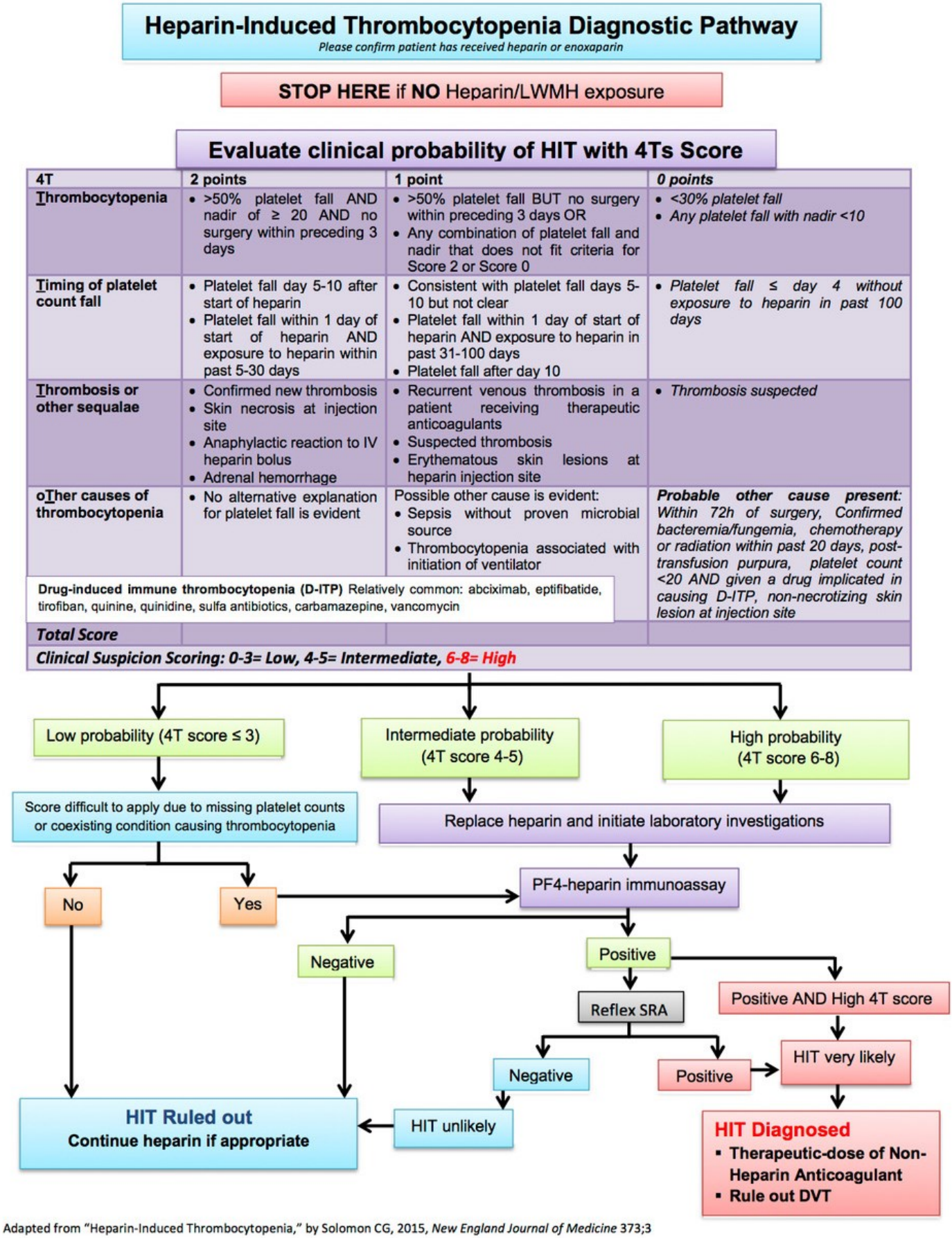


Figure 1. HIT Panel Rule Message

When ordering the "HIT PANEL" in Meditech, a pop-up will display that will allow you to view the HIT Decision Support Flowchart (Figure 2) on page 4 if you click on the blue "i' button as shown in Figure 1 .

Figure 2. 4T Score



Adapted from "Heparin-Induced Thrombocytopenia," by Solomon CG, 2015, *New England Journal of Medicine* 373;3

Critical Medication Shortages

By Donna Wilk, CPhT

Medication	Action Plan
Atenolol Tablets	Unavailable with an ETA of January to March 2018. We are managing at this time for our inpatient population.
Bupivacaine w/ EPINEPHrine IV	All preparations remain unavailable with an ETA of January 2018 to March 2019. We have a decent supply of the 0.5% without EPI 30 mL and 50 mL vials on hand as an alternative.
Ciprofloxacin IV	The SDVs were discontinued this year. Premix bags in dextrose remain unavailable with No ETA; however, we have a decent supply on hand.
Diazepam IV	Unavailable with an ETA of February 2018. We have a decent supply of the 10mg carpujects on hand.
Dobutamine IV	Due to the hurricane that hit Puerto Rico, all premix bags and vials are unavailable with No ETA. We have a great supply on hand of the 250 mg/200 mL premix bags.
Dopamine IV	Due to the hurricane that hit Puerto Rico, all premix bags and vials are unavailable with No ETA. We have a decent supply of the 800 mg/500 mL premix bags (1,600 mcg/mL).
Fentanyl/Ropivacaine Epidurals	Premix bags are currently unavailable with No ETA. Once we run out, they will have to be compounded by CRNAs for each patient as follows: Fentanyl 200 mcg in 100 mL bag of 0.2% Ropivacaine, which can be found in the labor and delivery pyxis (H2WCP).
Heparin Premix Bags	1,000 unit /500 mL NS bags remain unavailable due to the hurricane in Puerto Rico. We are managing stock at this time. 25,000 unit/500 mL D5W bags are on tight allocation. We have a decent supply on hand.
Hepatitis B Vaccine	We are out of stock of Recombivax and have converted to Engerix B. Product is expected to release sometime in 2018.
Hydromorphone Injection	Stock is intermittently available in small quantities with an ETA of January 2018 to June 2019. We have a decent supply and mixture of 1 mg and 2 mg vials/carpujects/ampules.
IV Fluids – Large Volume Bags	Due to the hurricane that hit Puerto Rico, all presentations of IV fluids are on nationwide shortage with No ETA. As a health-system we had been managing our supply, but we are getting closer to changing our primary work horse fluid – Sodium Chloride – to Lactated Ringers for hydration and in certain cases compounding medications. Communication will be sent out to Medical Staff when we are closer to that point. In surgery, the conversion to using Lactated Ringers for Irrigation in place of Sodium Chloride for Irrigation has begun.
IV Fluids – Small Volume Bags	Due to the hurricane that hit Puerto Rico, all presentations of IV fluids are on nationwide shortage with No ETA. As you have noticed, more medications are now required to be compounded by pharmacy for each patient as they are needed rather than being found in your Pyxis Med Station or patient cubby as a kit. **Please convert patients to PO medications whenever possible.**
Lidocaine IV	Unavailable with an ETA of December 2017 to February 2018. We have a decent mixture on hand of the 10mL and 50mL vials.
Lidocaine w/ EPINEPHrine IV	Unavailable with an ETA of September 2017 through 2nd Quarter 2018. We have a decent supply of the 1% 50mL vials on hand.
Metoclopramide IV	Unavailable with an ETA of January 2018. We have a decent supply on hand.
Morphine IV	Unavailable with an ETA of January to February 2018. We have a decent supply at this time of 2mg and 10mg injection.
OnQ Pumps	Premix are currently unavailable with No ETA. Surgery Satellite pharmacists are compounding each pump at this time.
Sincalide IV	Unavailable with No ETA. Nuclear Medicine is aware of the situation and is working on an alternative option for HIDA Scans: Ensure.
Sterile Talc	Unavailable with no release date.
Total Parenteral Nutrition (TPN) Components	The shortage of dextrose 70% and sterile water used to compound TPNs is improving. We are also experiencing intermittent supply issues with electrolytes. At this time, we will continue to use premix formulations of Clinimix 5/15 and Clinimix 5/15 + electrolytes for adult TPNs which were also affected by the hurricane that hit Puerto Rico. Neonatal TPNs remain unaffected.

**This table is not inclusive. If you wish to see all reported nationwide shortages please refer to https://www.ashp.org/Drug-Shortages/Current-Shortages.

Pharmacy and Therapeutics Committee Update

Drug	Indication	Usual Dose	Dosage and Strength	P&T Action
Benzylpenicilloyl polylysine (PRE-PEN®)	Used to determine if a patient will have an IgE mediated allergic reaction to antibiotics in the penicillin class	0.25 mL total for scratch and intradermal test	6×10^5 M (0.25 mL) ampule	Added to formulary with restrictions
Fat emulsion-fish oil and plant based (Smoflipid®)	Caloric/fatty acid source containing soybean oil, fish oil, olive oil and medium-chain triglycerides for patients on parenteral nutrition	1-2 grams/kg/day IV infused over 12-24 hours	20 g/100 mL 50 g/250 mL	Added to formulary with restrictions
Lactobacillus acidophilus CL 1285®, *L. casei* LBC80R®, *L. rhamnosus CLR2*® (Bio-K Plus®)	Dietary supplement used to help maintain a healthy intestinal flora and support intestinal functions. It also has data to support reduction of antibiotic- and *Clostridium difficile* -associated diarrhea	1 capsule orally twice daily	50 billion CFU per capsule	Added to formulary
Patiromer (Veltassa®)	Hyperkalemia	8.4 grams PO daily Max of 25.2 grams daily	8.4 gram oral powder	Added to formulary with restrictions
Telavancin (Vibativ®)	Complicated skin and skin structure infection and hospital -acquired and ventilator–associated bacterial pneumonia caused by susceptible gram-positive organisms	10 mg/kg IV over 60 minutes every 24 hours	750 mg/50 mL	Added to formulary with restrictions

Antimicrobial Stewardship (AMS) Q and A

By Fran Esfahani, Pharm.D., BCPS

Question: WHAT IS ANTIMICROBIAL STEWARDSHIP?

Answer: Antimicrobial stewardship (AMS) refers to coordinated interventions designed to promote and measure the appropriate use of antimicrobial agents. Specifically, AMS is defined as the optimal selection, dosage, & duration of antimicrobials with the goal of:

- Optimizing clinical outcomes for treatment & prevention of infections
- Minimizing toxicity to the patient (including *Clostridium difficile* diarrheal infections)
- Minimizing impact on subsequent bacterial resistance

Question: WHY IS ANTIMICROBIAL STEWARDSHIP IMPORTANT?

Answer: Tens of thousands of patients die each year from antibiotic-resistant infections. These infections are associated with higher mortality, prolonged hospitalization, and increased healthcare cost. Incorporating an antimicrobial stewardship program can slow organism resistance; optimize medication selection, dose, and duration; reduce adverse events; lower rates of morbidity/mortality; reduce hospital stay; and drive down costs.

Question: DOES NRHS HAVE AN AMS PROGRAM?

Answer: Yes, NRHS has an Antimicrobial Stewardship Program (ASP), comprised of members from multiple disciplines, including medical, pharmacy, nursing, microbiology, infection control, health information technology, and administration.

Question: WHAT ROLE CAN NURSES PLAY IN AN AMS PROGRAM?

ANSWER: As the discipline that has the most patient contact, nurses play an important and crucial role in success of any AMS program. As nurses, you've probably witnessed firsthand the consequence of inappropriate antibiotic use ranging from development of *C. difficile* to infections with multi-drug resistant pathogens. Here are five key ways to influence antibiotic management decisions and help prevent further emergence of antibiotic resistance:

1. Ensure pertinent information about antibiotics is available at the point of care. Know the indication, dosage, and likely duration of therapy for your patient's antibiotic therapy, so you would be more likely to inquire about stopping therapy when appropriate.
2. Question the antibiotic administration route. Every day, assess your patient's IV antibiotic therapy for the ability to switch to oral therapy to help shorten hospital stays and reduce the risks associated with IV catheter access. Discuss a switch to oral therapy with the physician and other care team member, i.e. your unit-based clinical pharmacist.
3. Reassess antibiotic therapy after 2 to 3 days for de-escalation or streamlining, when additional information on cultures and clinical status becomes available.
4. Review antibiotic therapy if your patient develops a new *C. difficile* infection. Discuss with the patient's physician and care team whether prescribed antibiotics are still indicated.
5. Evaluate the need for antibiotic therapy at each change-of-shift, upon patient transitioning within the facility, or discharge to an outpatient setting. Educate your patients and their families about AMS. Your patient should have received the AMS Patient/Family education brochure in their admission packet. You may provide them with additional copies if needed.

The Script The Newsletter of the Department of Pharmacy

Editor in Chief:
Jaclyn Coffey, Pharm.D.
PGY1 Pharmacy Resident

Contributors:
Lisa Mayer, Pharm.D., BCPS
Clinical Pharmacy Specialist
Kim Whitely, BS, Pharm.D., BCPS
Clinical Pharmacy Specialist
Fran Esfahani, Pharm.D., BCPS
Clinical Pharmacy Specialist
Lauren May, Pharm.D.
Clinical Pharmacy Specialist
Donna Wilk, CPhT
Clinical Pharmacy Technician
Michael Wisner, Pharm.D.
PGY1 Pharmacy Resident
Jacqueline Medina, Pharm.D.
Former PGY1 Pharmacy Resident
Christopher Brown, Pharm.D., BCPS
Clinical Pharmacy Specialist