Pharmacy News

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Special Points of Interest:

- P&T Update-Formulary Additions/ Deletions
- Policy and Procedure Update
- Naloxone: FDA Drug Safety Communication Update and the Role of Pharmacists
- Pharmacologic Prevention of Contrast-Induced Nephropathy
- The Effect of Genetic Testing on Cancer Treatment

P&T Update

Formulary Additions

- **Brolucizumab Safety follow up**
  Members discussed that there are 3 medications on formulary with the same indication and there was discussion of whether the existing formulation alternatives (aflibercept, ranibizumab) can be deleted from formulary.

  Requestor explained that the need for the redundancy of having on formulary because there is a niche for each of the drugs. The physicians cannot get rid of current approved medications because they are used for diabetic retinopathy (brolucizumab is not approved for this). They also have ambiguity of durability of one vs the other and are both considered standard of care. Approved with re-evaluation of use in 6 months.

- **Ceftolozane Tazobactam (Zerbaxa®)**
  Ceftolozane Tazobactam belongs to the cephalosporin class of antibacterial drugs. The bactericidal action of Ceftolozane results from inhibition of cell wall biosynthesis, and is mediated through binding to Penicillin-binding proteins (pbps). – Approved for Formulary Addition with restriction for use to the Infectious Disease Service and Antimicrobial Stewardship Team Evaluation.

- **Dofetilide (Tikosyn®)**
  Dofetilide is a class III antiarrhythmic that blocks the delayed rectifier cardiac potassium channel and increases the late sodium current, both actions that prolong repolarization. - Approved for Formulary Addition with restriction to Clinical Cardiac Electrophysiology Specialist (MD & ANP) for In-Patient use (Unrestricted if continue as home meds).

- **Ibutilide (Corvert®)**
  Ibutilide is a class III antiarrhythmic agent that blocks Ikr, the rapid component of the cardiac delayed rectifier potassium current. – Approved for Formulary Addition with restriction to Clinical Cardiac Electrophysiology Specialist (MD & ANP) for In-Patient use.

Formulary Deletions

- **Ranitidine**
  Contaminant has been found, and increases in concentration with storage time. Pharmacy has returned all stock and communicated with divisions. – Approved

- **Quinidine Gluconate 80mg/mL IV**
  Quinidine Gluconate IV is no longer manufactured in U.S. A Quinidine Gluconate IV deletion. – Approved

- **Evotaz (Atazanavir/cobicistat)**
  Item is being requested for deletion due to lack of use for 1+ years.
  UH Formulary also includes individual formulations of atazanavir and cobicistat
  Deletion from UH Formulary due to lack of use (> 1 year). – Approved

- **Gaviscon (Magnesium/Aluminum Hydroxide) tablets**
  Item is being requested for deletion due to lack of use for 1+ years
  Deletion from UH Formulary due to lack of use (> 1 year). – Approved

P&T Update

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Formulary Restriction Modification

- **Rifaximin**
  Reviewed rifaximin orders and found delays in profiling medication (~6 hours). Previously restricted to be reviewed by attending hepatologist for utilization. Orders reviewed showed that it was only used for hepatic encephalopathy refractory to lactulose. No value in delaying or restricting medication since it is being used appropriately. – Approved

Policies & Procedures/Floorstocks

- **Malignant Hyperthermia**
  Policy reviewed – combined policy from pharmacy, anesthesia, and PCS. Discusses how to manage crisis with updated formulation of dantrolene (higher concentration). – Approved
- **Multi-dose vial policy**
  Policy reviewed – update to the policy pertains to multi-dose eye drops. Can be used up to 5 days if not contaminated. For high risk procedures, eye drops become single use. – Approved
- **Resuscitation equipment checks policy**
  Policy reviewed – oversees the control of equipment, storage and security. Updated policy to add anaphylaxis kit. – Approved
- **Pediatric/Neonatal code cart status update**
  Policy reviewed – revised contents, supplies, and dosing booklets. – Approved
- **Standard Medication Infusion Concentration**
  Policy reviewed – vasopressin 20/50 mL to 40/100 mL concentration during the COVID crisis to decrease the amount of times nurses need to enter the room. For neonates/pediatrics, an additional concentration was added to meet the needs: 2.5 units/50 mL, 0.5 units/50 mL, 10 units/50 mL. – Approved
- **Alaris Drug Library Approval**
  Alaris IV pump drug library modification presented for approval. Delayed start function was re-activated with alarm turned on for before and after delay start function used. Discussion with Patient Care Services indicated inactivating this function is impacting patient bedside care. – Approved
- **707-700-101: Administering and Charting Medications to Patients (UPDATE)**
  Committee members discussed presented updates to this policy. – Approved
- **707-400-108: Resuscitation Equipment/ Emergency Boxes (UPDATE)**
  Committee members discussed presented updates to this policy. – Approved
- **Pharmacy Pandemic Response Policy (NEW)**
  Committee members discussed presented updates to this policy. – Approved
- **707-700-105 Administration of Intravenous Medication (UPDATE)**
  Committee members discussed presented updates to this policy. – Approved
- **Intravenous Hypertonic Sodium Chloride Administration Policy (NEW)**
  POLICY: Intravenous hypertonic saline containing greater than 1.5% w/v of sodium can be used for treatment of cerebral edema in (1) neurologically injured patients or (2) patients with symptomatic hyponatremia. The decision to start the treatment is based on serum sodium concentration, clinical presentation, as well as overall cardiovascular/ fluid status of individual patient. Adjustments will be made based on the observed response to treatment. – Approved

Medication/Clinical Guidelines:

- **ED Empiric Antibiotic Guideline**
  Updated Empiric Antibiotic Guideline reviewed. Major changes include changing empiric gram negative therapy from pip/tazo to cefepime +/- metronidazole. – Approved
- **Alaris Drug Library Approval**
  Policy of standard drug concentration in line with IV pump drug library. Deleted: Reopro, allopurinol, dantrolene; Added: Alteplase for catheter directed thrombolysis, chemo drug was added based on formulary addition, vasopressin new concentrations, ketamine as IVPB for pain. Delayed start function was inactivated due to Alaris pump recall. – Approved
- **IV medication Administration Guideline P&P Revision**
  Added medications that were added on to the formulary. Changes are in red in the Document. – Approved
- **Perioperative/procedure anticoagulant management**
  Guideline stratifies procedure based on high and low risk of bleed and how long you should wait before and after procedure. Most recommendations based on kinetics of medication and risk of bleeding. Approved by safe anticoagulation committee. – Approved

Naloxone: FDA Drug Safety Communication Update and the Role of Pharmacists

Millions of Americans suffer from pain and are often prescribed opioids to treat their conditions.[1] With the increase in opioid prescriptions to patients since the 1990s, from 1990 to 2018, more than 232,000 people in the United States have lost their lives from prescription opioid overdoses.[1] During the opioid crisis, in 2017, the U.S. Department of Health and Human Services launched the 5-point Strategy to prevent and respond to drug overdoses.[2] One of the strategies of this program involved increasing patient access to naloxone. This expansion of naloxone access was one of the contributing factors to the decrease in prescription opioid-involved overdose death rates by 13.5% in 2017 to 2018.[3] Despite recent progress in naloxone dispensing, naloxone remains under-prescribed and underused.

As a part of the U.S. Food and Drug Administration's (FDA) continuous efforts to address the opioid crisis even during the global pandemic, on July 23, 2020, FDA announced that it is required for manufacturers of opioids and medicines to treat opioid use disorder (OUD) to update the prescribing information section of the labeling to recommend naloxone as a routine part of prescribing these medicines.[4] These required labeling changes were announced in a Drug Safety Communication, which also recommended that health care professionals discuss naloxone with all patients when prescribing opioid pain relievers or medicine to treat OUD.[5] The FDA Commissioner Stephen M. Hahn, M.D said, "Today's action can help further raise awareness about this potentially life-saving treatment for individuals that may be at greater risk of an overdose and those in the community most likely to observe an overdose."[4]

The drug safety communication was intended to reduce the risk of death from an opioid overdose. For all patients who are prescribed opioid pain relievers or medicines to treat OUD, healthcare professionals (HCPs) are now recommended to discuss the availability of naloxone and consider prescribing it to patients who are at increased risk of opioid overdose, including those taking benzodiazepines or CNS depressants, history of OUD, or history of an opioid overdose.[5] For other patients at increased risk of opioid overdose, the HCPs should consider

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Naloxone: FDA Drug Safety Communication Update and the Role of Pharmacists

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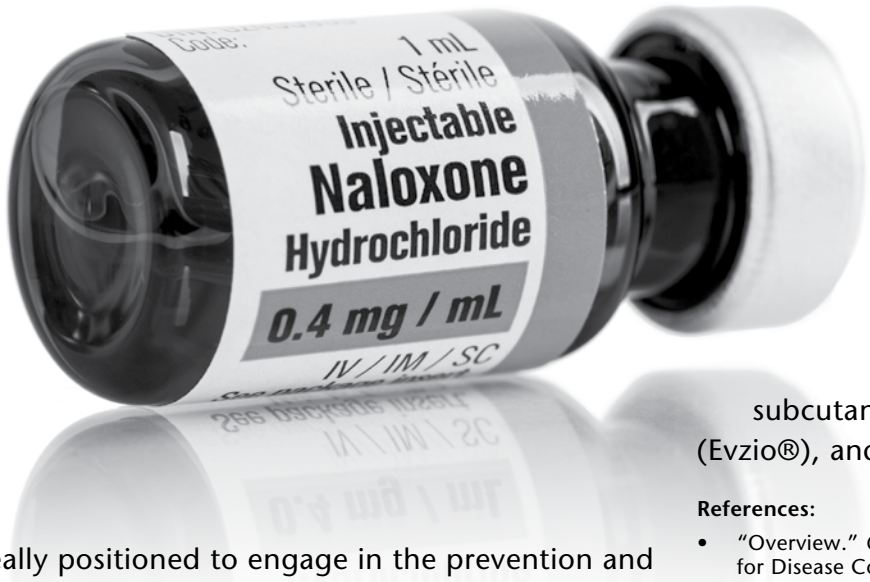
prescribing naloxone, even if the patient is not receiving a prescription for an opioid pain reliever or medicine to treat OUD. HCPs should also consider prescribing naloxone to patients with household members, such as children or other close contacts who are at risk for accidental ingestion or opioid overdose.[5]

Pharmacists, being on the frontlines of dispensing opioids and medicines to treat OUD and of providing medication-related services, are ideally positioned to engage in the prevention and treatment of opioid overdose and OUD. They can play a vital role in the routine discussion of the availability of naloxone while counseling patients on the safe use of opioid medications. Forty-eight states (including New York and New Jersey) and Washington, DC, allow pharmacists to dispense naloxone without a physician's prescription.[6] To do so, some states require pharmacists to enter into collaborative practice agreements and some also require them to undergo specific training.[6]



This drug safety communication not only promotes patient well-being but also gives pharmacists a unique opportunity to aid in battling the opioid crisis while taking steps towards prescriber status.

What is Naloxone?

Naloxone is an FDA approved life-saving medication that can temporarily stop or reverse the effects of an opioid or heroin overdose.[7] It is a pure, competitive opioid antagonist with a high affinity for the mu-opioid receptor, allowing for reversal of the effects of opioids. The onset of action varies depending on the route of administration but can be as fast as one minute.[8] Upon rapid reversal, patients may experience body aches, diarrhea, tachycardia, vomiting, dysphoria, nervousness, and agitation. Although these symptoms are unpleasant, they are not life-threatening and are typically of little clinical consequence.[9, 10]

Currently, naloxone can be given by intravenous injection (requires professional training), subcutaneous or intramuscular injection (Evzio®), and intranasal spray (Narcan®).[11]

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Pharmacologic Prevention of Contrast-Induced Nephropathy

Contrast is a type of media or temporary dye used in patients to get a better picture of the inside of the body during scans such as x-rays, computed tomography (CT) scans, magnetic resonance (MR) images, and ultrasounds. Its main purpose is to aid medical professionals in distinguishing between normal and abnormal conditions of tissues within the body. Contrast materials can be administered to patients by a variety of routes including orally, rectally, or via injection either intravenously or intra-arterially and is absorbed by the body for imaging and then eliminated. The use of iodine-based contrast media for CT scans in patients with impaired renal function has been linked to the development of Contrast Induced Nephropathy (CIN)[1].

Contrast-induced nephropathy (CIN) is a worsening in renal function resulting in an increase in baseline serum creatinine within 48 to 72 hours following contrast administration. This occurs as a relative increase in serum creatinine of at least 25% above baseline without other probable causes.[2] While efforts have been made to make contrast media safer for use, CIN is still a common clinical problem that is continuing to grow in relevance due to an ever-increasing number of tests and procedures performed that require the use of contrast media as well as an increase in the number of patients with risk factors for CIN development.[1]

CIN likely develops due to acute tubular necrosis caused by ischemia and the cytotoxic properties of the contrast media. Renal free-radical production increases after the administration of a contrast medium, and reactive oxygen species have a role in CIN. An increase in hospital and long-term morbidity and mortality has been shown to be associated with CIN. For inpatients, CIN is the third leading cause of acute kidney injury (AKI). Incidence of CIN varies between 3% and 30% depending on contrast volume, concomitant risk factors, and whether the contrast is given intravenously or arterially. Lower incidences occur with venous administration.[3] Some risk factors for developing CIN include pre-existing renal function, diabetes mellitus, increasing age, heart failure, hypertension, low effective circulatory volume, myocardial infarction, and use of an intra-aortic balloon pump.[4] While development of CIN is rare and there is potential for reversal in most instances, prevention remains key and the benefits should outweigh the associated risks when considering use of contrast media in patients with impaired renal function and those at higher risk for development.

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Pharmacologic Prevention of Contrast-Induced Nephropathy

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Historically, the only widely accepted prophylaxis was appropriate hydration of the patient by administering normal saline prior to contrast administration.[5] However, this method of prophylaxis has proven to be of limited use due to the fact that not all patients have the ability to handle large volumes of fluid. Therefore, research has been ongoing to find alternative ways to limit or prevent the incidence of CIN. Multiple agents and combinations of agents have been studied for the prevention of CIN and there is considerable interest in antioxidant compounds, specifically N-Acetylcysteine. There has been a long-time debate over the effectiveness of N-Acetylcysteine in the prophylaxis of contrast induced nephropathy (CIN) due to its effectiveness as a kidney tissue protective agent for other indications.

N-Acetylcysteine (NAC) is an acetylated cysteine amino acid most commonly used as an antidote to acetaminophen overdose. Its usefulness in protection from hepatotoxicity can be attributed to the fact that it is a precursor to glutathione, working to increase the amount of available glutathione to conjugate toxins for renal excretion. Another major protective mechanism of N-Acetylcysteine is that as an antioxidant, it works to reduce reactive oxygen species and prevent direct oxidative tissue damage. It is available orally, intravenously, and via respiratory inhalation routes. In many studies this compound has been used in combination with the current standard of care (SOC) for CIN prophylaxis, namely hydration using isotonic fluids.

In 2006, a study was done to investigate the antioxidant N-acetylcysteine for the prevention of contrast induced nephropathy in patients undergoing primary angioplasty.[6] A total of 354 patients undergoing primary angioplasty were assigned to one of three groups, 116 patients were assigned to a standard dose of N-acetylcysteine (a 600-mg intravenous bolus before primary angioplasty and 600 mg orally twice daily for the 48 hours after angioplasty), 119 patients to a double dose of N-acetylcysteine (a 1200-mg intravenous bolus and 1200 mg orally twice daily for the 48 hours after intervention), and 119 patients to placebo. The primary end point of the study was the occurrence of contrast induced nephropathy, defined as an increase in the serum creatinine concentration of 25 percent or more from the baseline value within a 72-hour period after the primary angioplasty procedure. Overall, contrast induced nephropathy occurred in 66 (19 percent) of the 352 patients. The rate of contrast induced nephropathy was 33 percent in the control

group, 15 percent in the standard dose N-acetylcysteine group, and 8 percent in the high dose N-acetylcysteine group ($P < 0.001$). From the data of this study, high doses of N-acetylcysteine appeared to be more beneficial as a protective agent than standard doses, suggesting not only effectiveness but a dose-dependent effect. This study concluded that both intravenous and oral N-acetylcysteine may prevent contrast induced nephropathy with a dose-dependent effect in patients treated with primary angioplasty and may improve hospital outcomes on morbidity and mortality.

A more recent study showed results that were contradictory to the findings from earlier studies. It was found that administration of NAC actually proved to be an indication for the development of CIN.[7] While the authors hypothesized this may be due to the fact that NAC was shown to be administered to patients that appeared at higher risk, it is still worth noting as it warrants the need for further studies.

It would appear that past studies that may have shown positive, statistically significant results for the use of NAC in combination with appropriate hydration with isotonic fluids as prophylaxis for CIN have also shown major limitations, and systematic reviews have found high heterogeneity between studies so no universal recommendation can currently be made for the use of NAC for CIN. Further studies will be needed to determine whether a recommendation can be made either for or against routine use of NAC as a protective agent for patients at increased risk of CIN development. Although the use of NAC for the prevention of CIN remains undetermined, it is of utmost importance to continue studying the efficacy and safety of NAC and other pharmacologic prophylaxis for CIN in those who are critically ill and at an increased risk for CIN.

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The Effect of Genetic Testing on Cancer Treatment

Cancer is a disease that starts from an abnormal growth or behavior of a cell leading to unrestricted and continuous cell reproduction. The disease can start anywhere in the body and has the potential to spread all throughout, eventually leading to harmful consequences. Over the years, many studies have been done to understand cancer in an attempt to develop effective cancer treatments.[1,2] As a result, the survival prognosis of cancer has drastically improved over the years. One of the most important findings about cancer was the discovery of cancer genes, which paved the way for precision medicine.[2] The genetic and epigenetic changes that accumulate over time cause mutations in oncogenes and tumor suppressor genes, which leads to cancer.

Both genetic and epigenetic mutations must be present for a cell to become malicious, and certain individuals are born with one or several mutations that make them more susceptible to developing cancer in their later years. The genetic expression of cancer is a predictive marker for patient outcomes and the current course of medicinal development places it at the forefront of future research.[2] The discovery of cancer genes has revolutionized the way cancer is treated and has led to advancements in drug development and treatment.

The primary avenue in which discovery of cancer genes has changed cancer therapy is through the incorporation of genetic testing in treatment course decision making for each individual patient. Treatment for cancer, fundamentally, is to kill off the cancer cells or prevent the malignant cells from reproducing further through palliation.[2] This can be accomplished through surgical removal or cytotoxic chemotherapy, both of which carry unpleasant aftereffects and the possibility of damage in the course of treatment.

Surgical treatments are usually used against isolated solid cancer tumors though they are ineffective against metastasized or blood cancers.[2] As such, chemotherapy and radiation are used most often for cancer treatment. While effective at killing cancer cells, such treatments also come with side effects and many toxicities to the human body when used, including killing healthy cells along with malignant ones. As a result, major goals in the development of cancer treatments have been to reduce the toxic effects of chemotherapy and to target the malignant cells more than the healthy cells.[2] Many genes have been identified to be specific to certain cancer types, such as BCR-ABL for chronic myeloid leukemias, HER2 and BRCA genes for breast cancer, and BRAF mutations in melanoma.[3,5] Genetic testing in patients to identify such notorious gene mutations has helped with early detection of cancer and has acted as an early predictor of how the patient will respond to certain treatments. Through revealing such information, genetic testing has helped eliminate unnecessary ineffective drug treatment and oriented cancer treatment to be patient specific.

One example of the importance of genetic testing is the BCR-ABL mutation in chronic myeloid leukemia (CML). Discovery of this infamous gene mutation has led to the development of a kinase inhibitor, imatinib, which specifically targets this gene mutation. Imatinib has shown great success in treating CML, but not all CML patients were responding to this medication.[3] With complementary DNA (cDNA) microarray expression profiling, a subset of CML patients with point mutation in the BCR-ABL kinase domain was identified. While patients with genotype rs460089-GC had a significantly higher response rate to imatinib, genotype rs460089-GG was associated with a much lower response rate. The latter point mutation was responsible for the resistance to imatinib, and as a result, mutation analysis became a mandatory patient workup before choosing a treatment plan for the patient.

By doing so, the physicians are aware of what kind of response they should expect from the treatment. The patient can also avoid undergoing unnecessary drug treatment that will not improve their disease.

Genetic testing has been used substantially in breast cancer as well. Over the years, thorough studies of breast cancer have helped develop a very concise treatment plan, broken down into each gene mutation and extent of cancer metastasis.[4] However, still there were certain populations in which no single treatment plan was identified to be most effective. In a study, breast cancer patients with hormone receptor positive, HER-2 negative, axillary node negative cancer with intermediate assay scores were identified and randomly assigned to chemo-endocrine or endocrine therapy alone.[4] Results of the study showed no benefit of getting chemotherapy with endocrine therapy. This subset of patients can be adequately treated with just endocrine therapy and can avoid receiving chemotherapy. Identifying these patients with genetic testing before treatment is initiated can save the patients from the difficult course of chemotherapy.

Genome sequencing not only helps select a therapy course for the patient, but can also help shape cancer treatment at multiple time points during the patient's journey. Even before a diagnosis is made, a full genome sequencing can be used to predict any individual's risk of having cancer in the future.[5,6] Hence, the treatment course starts even before the diagnosis is made. Identified patients with high penetrance inherited genomes have been given intensive screening programs and prophylactic surgery, which has significantly improved outcomes in patients with Li-Fraumeni syndrome or inherited BRCA1 or BRCA2 genes.[5]

Research is now ongoing to identify additional genetic variants with predictive values for cancer and determine the cancer risks associated with each in order to better patient outcomes.[6,7] In addition, methods to better identify, treat, and prevent cancer are currently undergoing testing.[7] Such methods would lead to better the prognosis of cancer patients and hopefully better treatment outcomes. Genetic testing has already had a profound effect on cancer treatments in the formulation of patient specific therapy and its predictive value. It will likely have a large effect on medical care moving forward.

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Welcome New Pharmacists

Irene Yang, Pharm. D.

Dr. Irene Yang is a graduate from Ernest Mario School of Pharmacy, Rutgers University. Prior to starting at University Hospital, Irene completed a PGY1 Pharmacy Residency at NYU Langone Health in Manhattan, NY and a PGY2 Pharmacy Residency in Emergency Medicine at Hackensack University Medical Center in Hackensack, NJ. Irene enjoys working collaboratively with everyone on the healthcare team to improve patient care. In her free time, she enjoys outdoor activities including hiking, biking and snowboarding as well as trying new restaurants. She is excited to be part of the team here at UH.

Tiffany Jomoc, Pharm.D.

Dr. Tiffany Jomoc, PharmD, is originally from San Diego, CA. She completed her Bachelor of Science in Pharmaceutical Sciences at the University of California, Irvine and her Doctor of Pharmacy from Midwestern University College of Pharmacy in Glendale, AZ. Tiffany completed her PGY1 Pharmacy Residency at Peconic Bay Medical Center - Northwell Health in Riverhead, NY and her PGY2 Emergency Medicine Residency at Touro College of Pharmacy/SBH Health System in Bronx, NY. Her other interests include competitive Polynesian dance, culinary arts, and traveling. Tiffany is excited to work with pharmacy and the emergency department collaboratively.

Gianna Girone, Pharm. D.

Dr. Gianna Girone graduated from Thomas Jefferson University College of Pharmacy in Philadelphia prior to making her way up to New England for residency. She completed a PGY1 Pharmacy Practice and PGY2 in Solid Organ Transplant Pharmacy residency from Yale New Haven Hospital in New Haven, Connecticut. She is super excited to be continuing to care for abdominal organ transplant patients, especially liver transplant, now that she is at University Hospital. Outside of work she enjoys photography, reading, and adventuring!

Katie McCrink, Pharm. D.

Dr. Katie McCrink completed her PGY2 in infectious diseases at Jackson Health System/ University of Miami in Miami, FL and completed her PGY1 residency training at Massachusetts General Hospital in Boston, MA. Prior to residency, Katie obtained a Bachelor of Science degree from Florida State University followed by a Doctorate of Pharmacy from Nova Southeastern University College of Pharmacy. Katie has special interests in transplant ID and multidrug-resistant gram-negative infections. Outside of infectious diseases, Katie enjoys discovering new restaurants, running outdoors, and baking. She also cannot wait to travel outside of the country once COVID-19 settles down.