Adult Medicine PRN Fall Newsletter

Edited by Ryan Owens, PharmD, BCPS and Lauren McCluggage, PharmD, BCPS

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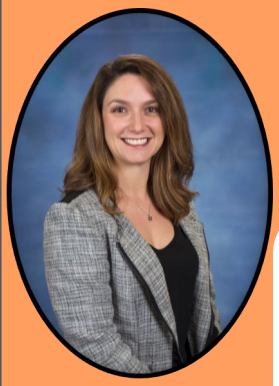


INSIDE THIS ISSUE:

Message from the Chair

Leigh Anne Hylton Gravatt, PharmD, BCPS

"We keep moving forward, opening new doors, and doing new things, because we're curious and curiosity keeps leading us down new paths." -Walt Disney

The ACCP Adult Medicine PRN continues to open new doors leading to practice advancement and professional connections. I can hardly believe that Fall is upon us and the ACCP Global Conference is almost here! There is so much excitement with the Conference this year and it is a great opportunity for our members to connect, strategize and forge new paths for our PRN.

As I reflect on my past year as Chair of our PRN, I am amazed at the accomplishments and progress that we have made. Our PRN has continued to open doors of opportunities for our members. This year our External Affairs decided to branch out and start a Student Case Presentation Series where students were able to present interesting cases for discussion to our PRN members. I was personally involved in this venture as two of my students presented in June. My students were grateful for the opportunity, but more than that they became interested in the ACCP Adult Medicine PRN and our activities. This provided a great introduction into the types of opportunities that the Adult Medicine PRN could provide for them as both students and practioners and I hope that we continue to look for ways to engage students with both ACCP and our PRN early on in their careers. Our monthly Journal Club meetings have continued to provide a forum for us to connect and discuss the most recent literature that affects our daily practice. Our presence on social media has continued to expand by ensuring our members are aware of the new guidelines and literature that help shape our clinical decisions. This year at our annual meeting we will be holding our second social outing, which will be held directly after our PRN Business meeting on Sunday, October 21st. Last year this event was very successful and a great way to connect with other members of our PRN in a relaxed environment. I want to thank the Ryan D'Angelo and Jennifer Austin Szwak as well as the members of the External Affairs committee to their hard work engaging and educating our PRN members.

Advancing practice through scholarship within our PRN has been another area of focus during the last year. This year for the first time, our PRN opened doors of opportunity through seed grant funding for one of our own members, Jennie Jarrett for her project titled, "Combating Implicit Bias in the Healthcare Team: A Pharmacist's Role." This group has also started work on a number of collaborative research plans that we are looking forward to seeing their results in the future. I applaud both Rachel Flurie and Rima Mohammed for their work on creating additional areas of research for our PRN. Are you looking for ways to improve your scholarship while working with individuals in similar practice settings? This is a great committee to join if you would like to be involved in the front lines of developing research ideas as well as developing other areas of scholarship.

Opening doors of education are equally important. Our programming committee under the lead of our Chair-Elect, Andrew Miesner has planned a fantastic educational seminar for the Global Conference. In collaboration with the HIV PRN, they will be presenting, "HIV Continuity, Part I: HIV Updates for the Inpatient Pratitioner" on Sunday afternoon at 2:15pm. I think this is going to be a great presentation and I applaud Andrew and his committee for their dedication in bringing this to fruition. I would also like to thank Ryan Owens and the Internal Affairs committee for their work in putting together our biannual newsletter and other publication materials.

So you may be thinking, how can I move forward in my career and experience the success of the Adult Medicine PRN? Joining a committee is the best way to experience the excitement and change coming ahead. Our PRN is only successful because of the members who give their time and service to this organization. This year alone we had over 90 members who to volunteered their time to this PRN. I would like to thank the Nominations, Programming, Training and Travel Awards, Internal and External Affairs, Walk-Rounds and the Research Committee leaders and their members. If you are interested in becoming more involved in the PRN I urge you join one of our committees. We are looking for curious minds just like yours!

As I close, I want to thank all of the members of this PRN for allowing me to lead you in this last year. This has been an amazing experience serving on the executive board for the last three years. I also want to thank my fellow Adult Medicine PRN officers for their leadership and dedication to this PRN. I know without a doubt that our PRN is being left with an excellent leadership team and is on a path to continued success.

Best wishes and hope to see you all soon in Seattle!

Annual Meeting Save the Dates:

October 20th-23rd

Sheraton Seattle

SUNDAY 2:15-3:45 PM

- Adult Medicine and HIV PRN Focus Session: HIV Continuity, Part I:

HIV Updates for the Inpatient Practitioner

SUNDAY 4:00-5:30 PM

- HIV and Ambulatory Care PRN Focus Session: HIV Continuity, Part II: Primary Care Management of Individuals Living with HIV

SUNDAY 6:30-8:30 PM

- AMED PRN Business Meeting and Networking Forum

SUNDAY 8:30-11:00 PM

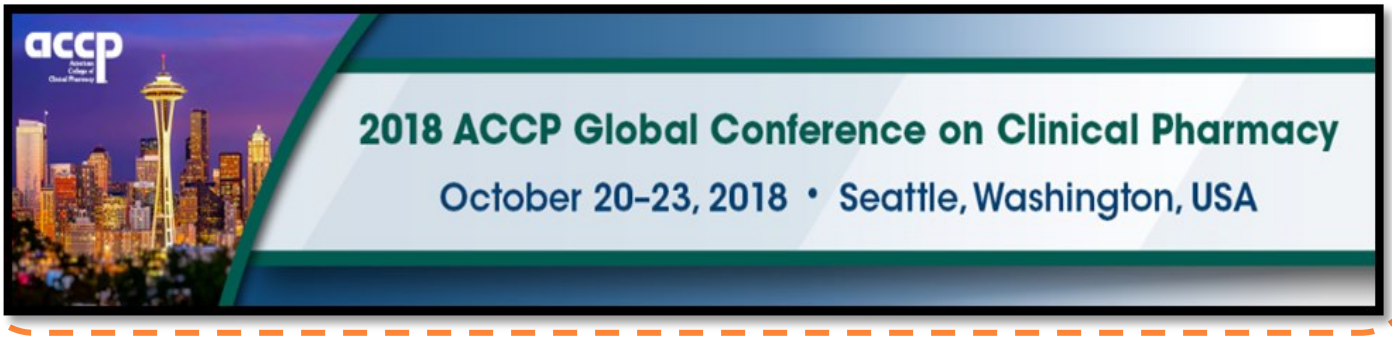
- AMED PRN Social and Happy Hour at Gordon Biersch Brewery
- **Please RSVP at**: https://www.surveymonkey.com/r/Z7JWH3S

Visit the ACCP website to plan your full meeting schedule:

https://www.accp.com/meetings/gc18/schedule.aspx

Don't forget to have some fun in Seattle too!

https://www.visitseattle.org/things-to-do/sightseeing/top-25-attractions/



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UPCOMING PRN JOURNAL CLUBS:

OCTOBER 17TH

NOVEMBER 14TH

DECEMBER 12TH

JANUARY 16TH

FEBRUARY 20TH

MARCH 20TH

2018 Adult Medicine PRN Award Winners

Practitioner Registration Award:

Jennifer Stark

Clinical Pharmacy Specialist

Veteran's Healthcare System of the Ozarks

Resident Travel Award:

Marina Maes

PGY-2 Ambulatory Care/Family Medicine

University of Colorado Hospital

Student Travel Award:

Caroline Dillion

Class of 2019

Duquesne University School of Pharmacy

Don't forget to sign up for a PRN committee for the 2018-2019 year!

Updates on Contrast-Induced Nephropathy Prevention

By: Melissa J. Ruble, PharmD, BCPS and Jaclyn D. Cole, PharmD, BCPS

"Identification of risk factors and early intervention strategies are essential in the prevention of contrast-induced nephropathy"

Contrast-induced nephropathy (CIN) is defined as the onset of acute kidney injury within 24 to 72 hours after receiving intra-arterial or intravenous iodinated radiographic contrast media.[1,2] The transient decline in renal function is observed by an increase of at least 0.5 mg/dL or 25% from baseline serum creatinine (SCr), or a decrease in creatinine clearance (CrCl) of at least 30 to 60 mL/min. Peak impact on renal failure is typically observed within 3 to 5 days after the administration of the contrast media, and patient renal function should return to baseline within 10 to 14 days. However, in some patients the reaction is more severe, resulting in oliguria, or a renal output of < 400 mL in 24 hours, and the need for hemodialysis with high risk of mortality.

CIN has been shown to increase the length of hospital stay, renal morbidity, cardiovascular morbidity, and all-cause mortality.[3] Incidence varies depending on the type of procedure associated with the radiographic contrast media, the properties of the contrast media, and patient specific risk factors. The type of procedure the contrast media is used for can also influence risk, with percutaneous coronary interventions and coronary angiography having the highest associated risks. It has been reported that ionic High-Osmolar Contrast Media (HOCM, osmolality of 1500-1800 mOsm/kg) has a higher incidence of CIN than nonionic Low-Osmolar Contrast Media (LOCM, osmolality of 600-850 mOsm/kg) or nonionic Iso-Osmolar Contrast Media (IOCM, osmolality 290 mOsm/kg). Examples of each type of dye commonly used in clinical practice can be found below in Table 1.[4]

Table 1. Commonly used contrast dyes in clinical practice

Contrast Agent Name	Osmolality Type
Ionic	
Ioxaglate (Hexabrix)	Low-osmolar (LOCM)
Diatrizoate (Hypaque 50)	High-osmolar (HOCM)
Metrizoate Isopaque (Conray 370)	High-osmolar (HOCM)
Non-Ionic	
Iohexol (Omnipaque 350)	Low-osmolar (LOCM)
Iopamidol (Isovue-370)	Low-osmolar (LOCM)
Iodixanol (Visipaque 320)	Iso-osmolar (IOCM)

In general, CIN only occurs in about 5% of patients with previously normal renal function, but this risk decreases to 1-2% in patients with a baseline estimated glomerular filtration rate (eGFR) >45 mL/min per 1.73 m^2.[2] However, this rate can significantly increase in high-risk patient populations. Patients with chronic kidney disease and diabetes have a CIN risk of up to 33%, and those with advanced age or congestive heart failure (CHF) have a risk of up to 20-30%.[3,5] About 10% of patient with pre-existing failure who have CIN require dialysis due to permanent severe renal failure. Patient with diabetes mellitus alone have an incidence of CIN

ranging from 5.7 to 29.4% and doubled the risk of CIN compared to non-diabetic patients regardless of baseline renal function. Other patient factors that increase CIN risk include age greater than 70 years, salt depletion and dehydration, congestive heart failure, renal transplant, sepsis, and concurrent use of other nephrotoxic drugs such as aminoglycosides, amphotericin, and cisplatin.

The pathophysiology behind CIN is multifactorial.[2] In a biphasic hemodynamic renal response there is a short and rapid renal dilation that causes an increase in renal blood flow. Then, prolonged renal constriction is associated with increased intravascular resistance that decreases renal blood flow. As a result, there is a decrease in GFR and renal ischemia occurs, particularly in the renal medulla, which can result in severe medullary hypoxia. It is also hypothesized that contrast media may induce osmotic diuresis which increases fluid delivery, tubular resorption, and ultimately energy and oxygen needs that also contribute to medullary hypoxia. Reactive oxygen species (ROS) formed in medullary hypoxia may create direct vascular and tubular endothelial injury and dysfunction that can further worsen the hypoxia. ROS also decrease nitrous oxide (NO) by reacting together; creating powerful oxidant peroxynitrate that may cause further endothelial damage. Finally, CIN may allow the sodium/potassium exchanger (NCX) to reversibly push out sodium for an influx of calcium instead of pumping the calcium outside of the cell, causing an intracellular overload. Overall, this increase in oxidative stress, ROS, and intracellular calcium overload all contribute to damaged cell membranes and lead to cell apoptosis and necrosis.

Precautions and Prevention of CIN: Current Practices

Guidelines suggest that the single most important action that can be taken to decrease the risk of CIN is to provide fluid loading prior to the IV contrast media.[6,7] Benefits of this therapy include that it is low risk, has a limited side effect profile, and is cost-effective. It is hypothesized that the fluids dilute the intravascular contrast load, increase intravascular volume, promote vasodilation, and promote diuresis. The most commonly used fluids are crystalloids, either normal saline (0.9% sodium chloride solution) or sodium bicarbonate. It is thought that by decreasing acidification of both the urine and renal environment, sodium bicarbonate may reduce free radical injury. Initial studies had supported the benefit of sodium bicarbonate, but subsequent studies have not supported this sustained benefit. As a result, recommendations tend to favor normal saline use unless sodium bicarbonate use has already been established and practitioners would like it to continue. Standard inpatient management is normal saline solution at 1 mL/kg/hr for 12 hours prior to procedure and for 12 hours after. If the procedure is scheduled for the same day, either normal saline or sodium bicarbonate can be given at 3 mL/kg/hr for at least 1 hour prior to procedure and continued for 6 hours after. If sodium bicarbonate is used, the most common administration is 154 mEq/L given at a rate of 3 mL/kg/hr for 1 hour prior and a rate of 1 mL/kg/hr for 6 hours after contrast injection. Patients who are on hemodialysis do not need to be fluid loaded before the planned contrast injection.

Mucomyst® (N-acetylcysteine or NAC) is one of the most commonly utilized pharmacologic agents for prevention of CIN due to its antioxidant and vasodilatory effects.[6,7] The initially studied dose was 600 mg NAC given orally 2 days prior to planned contrast injection. More recent literature has evaluated alternative dosing of NAC that includes: 1200 mg by mouth twice daily for 48 hours; 1200 mg IV bolus followed by 1200 mg oral dosing twice daily for 48 hours after contrast media; intravenous administration ranging from 150 mg/kg mg given 30 minutes immediately before the planned contrast media followed by 50 mg/kg over 4 hours; and 1200 mg IV bolus prior to contrast media followed by 1200 mg IV twice daily for 48 hours. Although literature is controversial and generally does not show a direct benefit of NAC in reducing CIN incidence, there are no major associated adverse effects with its use. It should be noted that high-dose intravenous administration may carry an anaphylaxis risk. The general consensus is that this medication can be used for CIN prevention in combination with hydration, but it should not replace fluid loading as monotherapy.

Discontinuation of offending drugs can also help to decrease the risk of CIN development.[6,7] Although metformin itself is not a risk factor for CIN, it can cause rare, but serious complications such as lactic acidosis in patients who develop acute kidney injury (AKI). As a result, literature recommends discontinuation of metformin anytime between 48 hours prior to and the time of contrast

injection. However, the time before reinitiating treatment with metformin is clearly stated as at least 48 hours after the contrast media administration and patient renal function has been found to be normal. Other nephrotoxic agents that should be discontinued for 24 to 48 hours prior to and held for another 24 to 48 hours after the contrast injection include: aminoglycosides, amphotericin B, cyclosporine, loop diuretics, and vancomycin.

Additional Agents: Updates to Therapy

The development of CIN involves numerous pathophysiological processes as outlined above. Continued review of the roles that inflammation, oxidative stress, direct tubular injury, and osmotic loading have in causing CIN further emphasize the roles that additional agents may have in preventing this from occurring. Agents such as statins continue to be studied due to their ability to decrease local and systemic inflammation, modulate cell survival, and improve endothelial function.[8] C-reactive protein (CRP) is a marker of systemic inflammation and directly correlates with an increased risk of CIN. Studies have shown that early use of statins (3 days before and 2 days after contrast procedures) reduces CRP levels and the risk of CIN compared with placebo, NAC, and were beneficial when combined with NAC. Statins have also been found to reduce the activation of apoptosis in kidney cells leading to a decrease in cell necrosis and a decrease in contrast induced acute kidney injury. Statin selection and dosing have been controversial with recent meta-analyses favoring the use of high intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) to prevent CIN.[9,10]

Vitamin E (alpha-tocopherol) is another possible agent to recommend due to its potent antioxidant and anti-inflammatory properties.[11] Protective effects of vitamin E have been previously reported but its use in practice is still unclear. Cho et al. conducted a systematic review of the effectiveness of vitamin E in the prevention of CIN in high-risk patients undergoing contrast procedures. Only 4 randomized controlled trials evaluated the effectiveness but did find that vitamin E provided effective protection against CIN but limited significance for reducing serum creatinine (Scr) levels. Vitamin E was given mostly via the oral route with doses ranging from 350 mg starting 5 days prior and ending 2 days after the procedure to 600 mg given 12 hours prior and 400 mg at 2 hours after the procedure. With the low cost and lack of serious side effects, authors concluded that the data justifies the use of vitamin E in addition to intravenous hydration at this time. It is still unknown as to the recommended regimen for this indication.

Vitamin C (ascorbic acid) has also been used as a pre-procedural treatment option due to its antioxidant effects and ability to protect the kidneys from oxidative damage.[12] Literature supporting its use is limited and controversial. Vitamin C is used as an adjunctive agent and has not been proven to be superior when used in combination with sodium bicarbonate and NAC compared to those agents alone. [12,13] When studied against NAC, patients in the Vitamin C group had significantly higher post contrast serum creatinine levels but no difference in CIN. Vitamin C dosing in most studies was given orally as 3 g two hours before the procedure and 2 g after the procedure. Some studies provided patients with an additional 2 g the morning after the procedure (12 hours after the procedure). Intravenous dosing followed a 1:1 conversion when used. All patients also received pre-procedural hydration according to their protocols.

Prostaglandins including prostaglandin E1 (PGE1) have a variety of effects including the regulation of contraction and relaxation of smooth muscles.[14] PGE1, also known as alprostadil, has been studied in several randomized controlled trials for the prevention of CIN due to its strong vasodilation properties. Geng et al. conducted a systematic review of 7 trials evaluating the use of PGE1 compared with hydration, statin + hydration, or placebo. The use of PGE1 was superior in 5 of the 7 trials. Dosing ranged from a set dose of 10 mcg/d to an infusion of 20 ng/kg/min 1 hour before and 5 hours after for a total of 6 hours. Authors concluded that the use of periprocedural PGE1 use reduced the incidence of CIN but was not associated with lower post-procedural Scr levels at 48 hours.

Finally, in response to the risk for osmotic loading with contrast media use, agents such as tolvaptan have been studied due to their ability to increase free water excretion of the renal tubules without inducing electrolytes abnormalities.[16] A case study was published outlining the use of tolvaptan 15 mg per day for 3 days in a patient with hypervolemic hyponatremia that prevented the patient from having to undergo hemodialysis secondary to CIN. Authors concluded that larger studies are warranted to further study the role of tolvaptan in rescuing the oliguric phase of CIN.

Future Studies

Since oxidative stress and ROS are significant causes of CIN, the nicotinic amide adenine dinucleotide 3-phosphate (NADPH) oxidases (Noxs) are gaining attention.[15] Current studies have shown that Nox4 is a key source of ROS and a novel potential option for the prevention of CIN. By inhibiting Nox4 transcription and inhibiting the receptor, there was a decrease in intracellular oxidative stress and ROS-mediated apoptosis in renal proximal tubular cells. Currently researchers are studying the use of GKT127831 for the use in this patient population. Further studies are needed to assess efficacy and safety in humans for this indication.

Conclusion

Identification of risk factors and early intervention strategies are essential for the prevention of CIN. There are several pathophysiological implications of contrast media with a focus on minimizing exposure and direct destruction of the renal medullary cells. Although several preventative strategies have been studied, hydration remains the preferred therapy for CIN prevention. Additional agents have been studied due to their anti-inflammatory, vasodilatory, anti-oxidative properties. The agents mentioned previously have limited side effect profiles, minimal cost, with positive outcomes. Unfortunately, most of the studies are retrospective in nature and/or include a small number of patients. More robust prospective studies are needed in order to replace current preventative strategies.

Acknowledgements: Article peer-reviewed and edited by: Sarah Petite, PharmD, BCPS and Emily Christenberry, PharmD, BCPS

Oral Antibiotics for Treatment of Gram-Negative Rod Bloodstream Infections

By: Casey S. Washington, PharmD, BCPS

"A barrier to the use of PO antibiotics is the availability of PO formulations that adequately treat gram negative rods in the era of multi-drug resistance"

In addition to the expected severity of illness with gram negative rod (GNR) bloodstream infections (BSI), treatment can be complicated due to increased presence of multidrug resistance (MDR), defined as when the bacterial isolate is resistant to at least 1 agent in ≥ 3 antimicrobial categories.[1] Data published in 2017 reported the inpatient cost of a GN BSI was $43,929 (SD 92,344) with MDR BSI costs 63% higher (p=0.0001) than non-MDR BSI.[2] Practices to minimize cost include treatment for a shorter duration and to convert intravenous (IV) antibiotics to oral (PO) when possible. Treatment for GNR BSI traditionally includes β-lactams (BL), aminoglycosides, and fluoroquinolones (FQ), which are the most studied PO antibiotic for GNR BSI.

Traditional duration of therapy for BSI ranges from 7-14 days of therapy.[3] A meta-analysis found no differences in clinical cure (45/52 versus 47/49, risk ratio 0.88, 95% confidence interval [CI] 0.77-1.01) or survival (15/17 versus 26/29, risk ratio 0.97, 95% CI 0.76-1.23) comparing durations of 5-7 and 7-21 days.[4] Administration of PO antibiotics can decrease the need for long-term catheters, risk of catheter-related infections, duration of admission/need for home health care, risk of thrombosis, healthcare workforce cost, and often, medication cost.[5] A retrospective analysis of 128 Veteran Affairs hospitals during 2006-2010 found that PO FQ could replace IV FQ in 45.9% of days after 2 days of IV FQ use in a non-ICU setting.[6]

A barrier to the use of PO antibiotics is availability of PO formulations that adequately treat GNR in the era of MDR. Data from 172 hospitals between2009-2013 identified 46,521 unique isolates of gram-negative (GN) bacteria from BSI cultures and 22% displayed resistance to at least 1 fluoroquinolone (FQ). More specifically, 27.3% of *E. coli*, 9.7% of *Klebsiella* spp., 6.9% of *Enterobacter* spp., 18.5% of *P. aeruginosa*, and 49.5% of *A. baumannii* isolates were FQ resistant.[7] Antibiotic stewardship programs recommend utilizing only highly bioavailable PO antibiotics for BSI. The bioavailability of FQ varies by specific medication however is considered acceptable for PO use for BSI (Table 1).[8] BL do not consistently reach serum concentrations needed to successfully treat a BSI when administered PO.[9,10] A statement published by the British Society for Antimicrobial Chemotherapy does not recommend oral therapy for BSI caused by GN bacteria due to MDR.[11] The severity of illness and increased morbidity and mortality with BSI coupled with the paucity of available data evaluating PO antibiotics may lead clinicians to avoid the practice.

Table 1: Categorization of Antibiotic Bioavailability[8]

Bioavailability	Antibiotics
H ≥ 95%	Levofloxacin
M = 75-94%	Ciprofloxacin Trimethoprim/sulfamethoxazole
L <75%	Amoxicillin/clavulanic acid Amoxicillin Cephalexin Cefuroxime Cefdinir Cefaclor Cefpodoxime

Literature on PO treatment of BSI

Six publications were found with outcomes reported for PO antibiotics used to treat GNR BSI, summarized in Table 2.[8,12-16]

Retrospective Cohorts:

Mercurio and colleagues compared BL and FQ PO options after initial IV antibiotics for an Enterobacteriaceae BSI in a retrospective cohort.[12] There was no difference in the primary results of clinical success between the 2 classes of medications and subgroup analysis showed comparable success with early (≤3 days) and late (>3 days) transition to PO therapy. Complicated diabetes (OR=0.35, 95% CI, 0.15-0.83) and urinary abnormality (OR=0.39, 95% CI, 0.16-0.94) were identified as a negative predictors of clinical success. Rieger and colleagues compared patients that received IV only to patients that were transitioned to PO with Enterobacteriaceae UTI and BSI.[13] There was no difference in the primary outcome of treatment failure of either group and statistically significantly differences in length of stay (for IV/PO 4.6 [3.1–7.8] days vs IV-only 7.1 [4.0–17.5] days, p<0.001) and hospital days on antibiotics (IV/PO, median 5 [IQR 3–7] days vs IV-only antibiotics 6 [4–10] days, p<0.001;) were lower in the IV/PO group. Another retrospective cohort by Kutob and colleagues evaluated treatment failure in GN BSI comparing antibiotics with high (H), moderate (M), and low (L) bioavailability (Table 2) in hospitalized patients that were discharged with PO antibiotics.[8] UTI served as the source of infection in the majority (70.2%) of patients and 67.1% had an *E. coli* BSI. All isolates were susceptible to the prescribed antibiotics and patients received 4-5 days of IV antibiotics before completing therapy with ~9 days of PO antibiotics. Treatment failure was 2% in the H bioavailability group, 12% in M, and 14% for L (p=0.02). An increased risk of failure compared to the H bioavailability group was found with both the M and L groups of antibiotics.

Table 2: Trials with oral antibiotic data for use to treat GNR Enterobacteriaceae BSI

Study	Design	Patients	Comparators	Duration of Therapy	Primary Outcome
Mercuro et al (2018)[12]	Retrospective cohort	224	IV antibiotics transitioned to PO BL (amoxicillin/ clavulanic acid, cephalexin, amoxicillin and cefdinir) or FQ (levofloxacin, ciprofloxacin, moxifloxacin)	3-15 days	Clinical success of BL was non-inferior to FQ
Rieger et al (2017)[13]	Retrospective cohort	241	IV-only antibiotics versus IV/ PO antibiotics (ciprofloxacin, trimethoprim-sulfamethoxazole, various BL)	3-10 days	No statistically significant difference found in treatment failure
Kutob et al (2016)[8]	Retrospective cohort	362	H,M,L bioavailability (Table 2)	5 days IV 9 days PO	Treatment failures increased with decreased bioavailability.
Bouza et al (1989)[14]	Retrospective	68	Ciprofloxacin IV, PO, or IV/PO	6-48 days	Ciprofloxacin was effective for BSI
Mombelli et al (1999)[15]	Prospective, randomized	141 (53 with BSI)	Ciprofloxacin 500 mg PO twice daily vs 200 mg IV twice daily as empirical therapy of UTI	Not specified	No significant difference in treatment failures or clinical response.
Park et al (2014)[16]	Prospective, randomized	59	Ciprofloxacin 500 mg PO twice daily starting on day 6 compared to PO initiation on day 10 or later	14 days	Eradication of bacteria in early PO switch was non-inferior to conventional therapy

Prospective, Randomized Trials:

Bouza and colleagues reported data from an assumed retrospective review of 68 BSI treated with IV (30), PO (13), or IV followed by PO (25) ciprofloxacin.[14] The causative microorganisms were GNRs in the majority of patients. Overall clinical efficacy of ciprofloxacin was 94% (64/68). The authors concluded that ciprofloxacin regardless of administration was effective for BSI. Mombelli and colleagues compared empiric ciprofloxacin PO to IV in hospitalized patients with pyelonephritis or severe UTI. Results for a subset of these patients with BSI found no difference in the duration of fever in patients with BSI between the 2 treatment groups (oral ciprofloxacin, 2.2 days [95% CI, 1.7-2.6 days], vs IV 2.6 days [95% CI, 2.0-3.2 days]) (*P*=.18).[15] Patients with acute cholangitis and BSI treated with biliary compression and empiric IV third generation cephalosporin therapy were transitioned to PO ciprofloxacin on day 6 or day 10+ and compared by Park and colleagues.[16] There was no difference in eradication of bacteria in early PO therapy (93.1%) or conventional IV therapy (93.3%) proving noninferiority of early PO ciprofloxacin (95% CI - 0.13-0.14, P=0.97). Time to resolution of fever, length of hospital stay, acute cholangitis and 30-day mortality rates were also not statistically different.

Limitations:

Not all BSI caused by GNR have data to support PO treatment. All the trials discussed in this article focused on treatment of Enterobacteriaceae infections. Data is absent for PO agents used to treat BSI caused by Pseudomonas.[17] A vital consideration is the emerging resistance of bacteria that is constantly changing, before deciding to utilize a PO medication, which is essentially limited to FQ, verifying with local antibiograms and culture results is imperative.

When to switch to PO:

Most trial methods have 3-6 days of IV antibiotics before conversion to PO. Due to the severity of illness with BSI and presence of MDR with GN bacteria, specific criteria (listed in Table 3) need to be met before transitioning from IV to PO antibiotics.[5,17-19] Transition to PO therapy should be avoided in patients with an increased risk of low serum concentrations (rapid drug elimination, increased volume of distribution) or that do not meet all criteria in Table 3.[18]

Table 3: Criteria for PO antibiotic use in GNR BSI

Clinical Course	Bacteria	Patient	Antibiotic
Uncomplicated (No diagnosis of: severe sepsis, fasciitis necroticans, CNS or endovascular infection)	Speciated with susceptibilities	Clinically stable (stable blood pressure, afebrile)	Penetrates tissue at source of infection
Source of infection identified	Low MIC*	Response to IV therapy	PO formulation available
	Low risk of acquired resistance	No allergies to antibiotic	Well tolerated
		Able to swallow	No drug interactions
		No impairment of absorption (malabsorption syndrome, short bowel syndrome, severe gastroparesis, ileus, continuous nasogastric suction, vomiting,)	In stock/Immediate access at discharge
		Understands importance of adherence	
		Available for follow up	

*MIC = minimum inhibitory concentration pathogen identified

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No Flu for You! Influenza Treatment and Prevention

By: Adam Jones, PharmD/MBA Candidate 2019; Tressa McMorris, PharmD, BCPS; Ben Pullinger, PharmD, BCPS

"Anyone with an egg allergy of any degree or history thereof may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). "

Background

Influenza is an acute viral respiratory illness that occurs in seasonal epidemics and less frequently as pandemics. Epidemic (seasonal) influenza is caused by Type A and B viruses that undergo antigenic drift, or small point mutations in surface glycoproteins that mitigate antibody activity in a previously exposed individual. Influenza A viruses are capable of the more dramatic antigenic shift, resulting in the formation of a novel virus strain and the potential for a pandemic.

Complications from influenza can be broadly divided into pulmonary and extra-pulmonary sequelae.[1] Influenza can cause a diffuse bilateral viral pneumonia as well as exacerbate underlying chronic lung disease. Additionally, a secondary bacterial pneumonia (frequently *Streptococcus pneumoniae, Streptococcus pyogenes,* or *Staphylococcus aureus*) can emerge 1-2 weeks after the resolution of viral illness. Extra-pulmonary complications include myositis and rhabdomyolysis; myocarditis and pericarditis; and multiple neurological manifestations, including encephalitis, aseptic meningitis, Guillain-Barre syndrome, and Reyes syndrome. In severe illness, other organ dysfunction can be observed, such as renal failure and acute myocardial infarction. Box 1 lists patient groups at greatest risk of influenza complications.[2]

Box 1: Patients at highest risk for influenza-related complications[2]

- Children <2 years
- Adults ≥65 years
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression, including that caused by medications or by HIV infection
- Women who are pregnant or immediately postpartum (within 2 weeks after delivery)
- Persons <19 years who are receiving long-term aspirin therapy
- American Indians/Alaska Natives
- Persons who are morbidly obese (i.e., body-mass index ≥40)
- Residents of nursing homes and other chronic-care facilities

Review of 2017-2018 Flu Season[3]

In 2017, the CDC introduced a new classification of flu season severity, which has been retrospectively applied to seasons beginning with 2003-2004.[4] The new system uses 4 categories (low, moderate, high, very high), and draws upon 3 primary severity metrics: percentage of outpatient visits for influenza-like illness, rate of influenza-associated hospitalizations, and percentage of deaths resulting from pneumonia or influenza. The 2017-2018 flu season was the first season to be characterized in the new system as high severity for all age groups. Nationally, peak activity occurred during 5 weeks between January 13 and February 10. Of the influenza test results reported to the CDC, 71% were influenza A. Among influenza A specimens that were subtyped, influenza A(H3N2) was predominant (85%), with the balance being influenza A(H1N1)pdm09. Only 1% of H1N1 viruses were resistant to oseltamivir and peramivir, and no resistance to neuraminidase inhibitors was noted among H3N2 or influenza B isolates. As noted in past H3N2-dominant seasons, rates of hospitalization were high. As of June 1, 2018, the CDC estimates that the cumulative incidence of laboratory-confirmed influenza hospitalizations was 107 per 100,000 population, which is the highest all-ages hospitalization rate recorded in the current surveillance system. The CDC collects influenza-specific mortality for children, but groups pneumonia- and influenza-associated (P&I) mortality for adults. P&I mortality exceeded the epidemic threshold for 16 consecutive weeks, outpacing the average of 11 weeks over the past 5 seasons. These 2 metrics, along with outpatient visits, exceeded those from the 2016-2017 flu season, which was moderate severity for all age groups.

Treatment of Influenza

Benefits of Antivirals

Neuraminidase inhibitors are the only sufficiently active antivirals for influenza A and B, and 3 are now FDA-approved for use (Table 1).

The CDC recommends early antiviral use (without delay for laboratory confirmation) in any patient with suspected or confirmed influenza who:

is hospitalized;

has severe, complicated, or progressive illness;

or is at higher risk for influenza complications (Box 1).

These recommendations remain unchanged from the last full publication of the Advisory Committee on Immunization Practices (ACIP) recommendations in 2011,[2] although meta-analyses have been published in the interim that help delineate those who are most likely to benefit from treatment. No randomized controlled trials have evaluated the use of antivirals in hospitalized patients, but in a meta-analysis of observational studies, oseltamivir was found to possibly reduce mortality in hospitalized patients versus no treatment (odds ratio [OR] 0.23 [95% CI 0.13- 0.43]).[5] A large patient-level meta-analysis of patients hospitalized with pandemic H1N1 (H1N1pdm09) also found a reduction in mortality with neuraminidase inhibitors (OR 0.81 [95% CI 0.70-0.93]).[6] Both of these studies indicate far greater benefit if treatment is initiated within 48 hours of illness onset, with the latter trial showing a complete loss of mortality benefit versus no treatment for late (> 48 hours) treatment initiation.[6] However, a retrospective study found that in elderly adults hospitalized for influenza, initiation of antivirals within 4 days of illness onset reduced hospital length of stay and need for extended care at discharge.[7] In a smaller dataset of critically ill patients with H1N1pdm09, survival benefit was observed in patients receiving neuraminidase inhibitors within 5 days of illness onset.[8] In the critically ill population, there has also been interest in using a higher dose of oseltamivir (150 mg twice daily). However, pharmacokinetic data suggests that enteral absorption of oseltamivir in critically ill patients is sufficient,[9] and a small prospective study in hospitalized adults did not show a difference in duration of symptoms or hospitalization for double versus standard dose.[10]

Meta-analyses have also focused on rates of hospitalization and secondary lower-respiratory tract infections (LRTIs) as patient-important outcomes that are meaningful for justifying use in the high-risk ambulatory population. A patient level meta-analysis of all Roche-sponsored oseltamivir randomized controlled trials (RCTs) found fewer LRTIs requiring antibiotics (risk ratio [RR] 0.56, 95% CI 0.42-0.75) and less all-cause hospital admission (RR 0.37, 95% CI 0.17-0.81).[11] A more recent patient-level meta-analysis of observational data from a consortium of research centers evaluated patients with H1N1pdm09 and found a reduction in hospitalization with neuraminidase use (adjusted OR 0.24, 95% confidence interval, 0.20-0.30).[12]

Antiviral treatment can be considered for healthy ambulatory individuals (no risk factors from Box 1) with confirmed or suspected influenza, providing it can be started within 48 hours of illness onset. In this population, early use of oseltamivir and zanamivir has been widely shown to reduce the duration of symptoms by 0.5-1 days, but is unlikely to reduce complication and hospitalization rates, which are low in the general population.[13] During times of drug shortage, providers and health systems should be prudent in their use of antivirals and reserve these agents for higher-risk individuals.

Choice of Agent

Oseltamivir is generally preferred on account of availability and experience. Zanamivir is approved for treatment of uncomplicated influenza, but should be avoided in patients with underlying lung disease due to the risk of bronchospasm. The inhalation powder contains lactose and should also be avoided in patients allergic to milk proteins. It should not be used in conjunction with mechanical ventilation or nebulizers due to the potential to clog tubing. Additionally, it should be avoided in hospitalized or complicated patients due to a lack of data in these patients. Peramivir may be considered in patients with lack of enteral access or suspected malabsorption. Resistance to antivirals is rare, but is most frequently found in H1N1 strains and in severely immunosuppressed patients. The most common neuraminidase mutation (H274Y) confers resistance to both oseltamivir and peramivir, but zanamivir will remain active. Oseltamivir is preferred over zanamivir in pregnancy, and was the predominant antiviral used in a study that demonstrated reduced mortality and ICU admission with antiviral use in pregnant women with H1N1.[14]

Novel Strategies

In a small open-label RCT, the addition of 2 days of naproxen and clarithromycin to a standard 5-day oseltamivir course reduced 30 day mortality and hospital length of stay in patients hospitalized with H3N2 and radiographic pneumonia.[15] Of note, all patients received 5 days of amoxicillin-clavulanate, and the median patient age was 80 years. The possible benefit of this combination is thought to be due to the immunomodulatory and antiviral effects of both clarithromycin and naproxen. More data are needed before this approach can be broadly endorsed.

There is significant interest in the influenza viral polymerase as a novel therapeutic target. In a recently published phase III double-blind RCT, single-dose oral baloxavir (a polymerase acidic protein inhibitor) decreased duration of symptoms similarly to oseltamivir, and reduced viral load more rapidly than oseltamivir in previously healthy patients with predominantly A3H2 influenza.[16] Nearly 10% of patients displayed emergence of mutant influenza strains with resistance to baloxavir after treatment. The novel mechanism of action and ease of a single-dose antiviral is promising, but more research is needed to explore the benefit in patient-important outcomes and the clinical significance of emergent resistance.

Table 1. Summary of FDA-approved neuraminidase inhibitors

Antiviral	Adult Doses	Notes
Oseltamivir (Tamiflu®)	PPX: 75 mg PO once daily x 7 d[a] TX: 75 mg PO twice daily x 5 d[b]	Common AEs: nausea, vomiting, headache Requires renal dose adjustment
Zanamivir (Relenza®)	PPX: 10 mg (two 5-mg inhalations) once daily x 7 d[a] TX: 10 mg (two 5-mg inhalations) twice daily x 5 d[b]	Do not use in hospitalized patients Do not use in nebulizers or mechanical ventilators Avoid in patients with asthma or COPD Common AEs: headache, sore throat and pharyngitis, cough
Peramivir (Rapivab®)	TX: 600 mg IV x 1 dose[c]	Common AEs: diarrhea Requires renal dose adjustment

a) Longer durations are appropriate in institutional outbreak settings. The manufacturer for oseltamivir recommends 10 days, but the CDC recommends 7 days.

b) Duration of therapy in severe and complicated illness is not well established. Extended durations may be considered in immunosuppressed patients and patients who remain critically ill, as viral replication can be prolonged in these patients. RT-PCR testing of lower respiratory tract specimens can guide extended therapy.

c) Although FDA approved for a single dose, it has been used off-label as 600 mg once daily for up to 5 days[20]

PPX = prophylaxis; TX = treatment; RT-PCR = real-time reverse-transcriptase polymerase chain reaction; AE = adverse effects

Combination antiviral therapy[17] and intravenous immunoglobulin[18] have also been evaluated in RCTs, but have not shown clinical benefit over standard of care. A meta-analysis of observational trials found an increase in mortality with adjunctive corticosteroids for influenza treatment, but the authors recommended interpreting this with caution due to the low quality of included studies and possible confounders.[19]

Prevention of Influenza Infection

2018-2019 Vaccine Recommendations[21]

The influenza vaccine is recommended as an annual routine vaccination for all persons aged ≥6 months without contraindications according to the CDC and should be received by the end of October. This season there are four updates of which pharmacists should be aware. To summarize those updates, the ACIP has (1) reintroduced the intranasal live attenuated quadrivalent vaccine (LAIV4); (2) updated the virus strains contained in the vaccines; (3) recommended that those with any form of egg allergy may receive any influenza vaccine when indicated; and (4) explained labeling changes, which include lowering the age for receipt of some vaccines. While there are multiple options for immunization, no one type is preferred over another unless based on contraindications.

One major update is the option for the use of LAIV4 (Flumist® Quadrivalent) for individuals with no contraindications. This has not been an option for the previous two influenza seasons. In February 2018 the ACIP determined that, based on the data from three different sources, it would be a reasonable option as it has improved replicative fitness over the previous LAIV vaccines. The evaluations used to determine the effectiveness included an individual patient-level analysis, a systematic review and meta-analysis, as well as manufacturer's data. There is only one option for the LAIV4 and it is approved for those aged 2-49 years old. Some pearls to note is that it is a single use spray device, which contains 0.2 mL, where 0.1 mL is sprayed in one nostril and the remaining 0.1 mL in the other. This is done in an upright position. If the person sneezes there is no need to repeat the dose. There are several contraindications, which include pregnancy, any antiviral medication in the last 48 hours, if the patient is immunocompromised or has close contacts and caregivers of severely immunosuppressed persons who require a protected environment, and children aged 2 to 4 years who have had asthma or wheezing in the last 12 months.

Another update on this year's flu shot is the types of viruses it contains. The FDA, through recommendations of the World Health Organization and the Vaccines and Related Biological Products Advisory Committee, determined the trivalent influenza vaccine will consist of an A/Michigan/45/2015 (H1N1)pdm09–like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017–like virus (Victoria lineage). The quadrivalent influenza vaccine will include the above three viruses as well as an additional influenza B strain (B/Phuket/3073/2013-like virus, Yamagata lineage).

A third update is guidance that anyone with an egg allergy of any degree or history thereof may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). No anaphylactic reactions occurred in three studies of egg-allergic children that the ACIP evaluated in 2016. Currently licensed influenza vaccines have been approved for those with egg allergies. However, influenza vaccination is contraindicated for those who have experienced a severe allergic reaction to previous influenza vaccines.

Finally, information on recent licensures and labeling changes have lowered the age on two of Quadrivalent (IIV) vaccines to expand the age to include more individuals. The Afluria Quadrivalent (IIV4) is now appropriate for individuals ≥5 years, instead of ≥18 years. The Fluarix Quadrivalent (IIV4), is now licensed for anyone ≥6 months, lowered from ≥3 years. Children aged 6 through 35 months may receive the Fluarix Quadrivalent at the same 0.5 mL per dose (containing 15 μg of hemagglutinin [HA] per vaccine virus) as is used for older children and adults, thus creating a third option for that age group. Pictured below in Table 2 is a list of the influenza vaccines for the 2018-2019 season.

Antiviral Prophylaxis[2]

The FDA approved agents for chemoprophylaxis are oseltamivir and zanamivir (Table 1). These medications are approximately 70 to 90% effective in preventing influenza, but are not substitutes for the influenza vaccination and are considered adjuncts to either the IIV or RIV4 flu vaccine. Widespread utilization of antiviral prophylaxis is generally discouraged due to concerns of resistance and medication availability. Postexposure prophylaxis can be considered for those at high risk for influenza complications (Box 1) who have had close exposure to a person with suspected or confirmed influenza and have not received influenza vaccination, who have not been vaccinated against currently circulating influenza virus strains, or who have received the vaccine <2 weeks prior to exposure.

Postexposure prophylaxis does mitigate the risk for symptoms of influenza, however, the person may still acquire the virus. Prophylaxis, if indicated, should be started within 48 hours of exposure and be continued for no more than 10 days after exposure. Preexposure prophylaxis may be considered for patients who are at very high risk for influenza complications, such as those who are severely immunocompromised. The antiviral medication should be taken during the time when there is an expected high risk of exposure. The duration of pre-exposure prophylaxis for oseltamivir of 42 days and zanamivir of 28 days has been well tolerated. Data is limited for continuing prophylaxis beyond 6 weeks. Chemoprophylaxis may be utilized as a strategy for outbreak control in the institutional setting, in addition to vaccination efforts. If utilized, antiviral medications should be administered as soon as possible and continued for a minimum of 2 weeks. The CDC provides more detailed information to assist long-term care providers prevent and manage institutional influenza outbreaks.

Table 2. Summary of influenza vaccines

Trade Name	Age Indication	Egg-grown or other
Quadrivalent (IIV4)		
Afluria® Quadrivalent[a,b]	≥5 years; 18-64 years (jet injector)	Egg
Fluarix® Quadrivalent	≥ 6 months	Egg
Flulaval® Quadrivalent[a]	≥ 6 months	Egg
Fluzone® Quadrivalent[a]	≥6 months	Egg
Flucelvax® Quadrivalent[a]	≥4 years	Cell culture[c]
Flublok® Quadrivalent (RIV4)	≥18 years	Recombinant
Trivalent (IIV3)		
Afluria®[a,b]	≥ 5 years; 18-64 years (jet injector)	Egg
Fluzone® High-Dose	≥ 65 years	Egg
Fluad® (Adjuvanted)	≥ 65 years	Egg
Quadrivalent LAIV		
FluMist® Quadrivalent	2-49 years	Egg

a) Available as multi-dose vial (MDV) which contains thimerisol. All other products are preservative-free. No FDA approved influenza vaccines contain latex.

b) Available as jet injector

c) Initial H1N1 strain provided to manufacturer is egg-derived

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PRN Member Accomplishments

Publications:

Erika Lambert:

Hawes EM, **Lambert E**, Reid A, Tong G, Gwynne M. Implementation and evaluation of a pharmacist-led electronic visit program for diabetes and anticoagulation care in a patient-centered medical home. Am J Health Syst Pharm. 2018;75 (12):901-910.

Jeremy Vandiver:

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Anna Kabakov:

Kabakov A, Kolanczyk D. The Effective Pharmacy Preceptor, MM Soric, SR Schneider, SS Wisneski. American Society of Health-System Pharmacists, Bethesda, MD (2017). ISBN: 9781585285549. Price: $39.00 (print) and $35.00 (eBook). Currents in Pharmacy Teaching and Learning. 2018 Jun;10(6):816-7.

Emily J. Christenberry:

Christenberry EJ, Padilla ME, Aguirre M, Loya AM, Aragon L. Reliability of point-of-care international normalized ratio testing in an academic family medicine clinic. Point Care. 2018;17:55-58.

Kelly Covert:

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Ryan G. D'Angelo:

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Sarah L. Anderson:

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Alex Ebied:

Ebied AM, Cooper-DeHoff RM. 2017 Is Banner Year for Drug Approvals by the Food and Drug Administration. Am J Med. 2018; [Epub ahead of print].

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PRN Member Accomplishments

Publications:

Ifeanyi Onor:

Ezebuenyi MC, Brakta F, **Onor IO**, Sarpong DF, Burks KB, Figueroa JE. Evaluation of Physician Prescribing Patterns for Antibiotics in the Treatment of Nonnecrotizing Skin and Soft Tissue Infections. P T. 2018;43(5):287-292.

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Caitlin Gibson:

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Gibson CM, Basto AN, Howard ML. Direct oral anticoagulants in cardioversion: a review of current evidence. Ann Pharmacother. 2018;52:277-284.

Promotions:

Jeremy Vandiver: Clinical Associate Professor- University of Wyoming School of Pharmacy

Awards:

Jordan L. Kelley: UK College of Pharmacy PGY1 Residency Scholarship for devotion to research and publishing

Jeremy Vandiver: Colorado Pharmacists Society Distinguished Young Pharmacist 2018

Jennifer Austin Szwak: Choosing Wisely Challenge Winner for “Nebs No More after 24” Initiative

Sarah L. Anderson: Denver Health Quality, Safety, and Service Team Award for improving safety and quality for anticoagulation patients, June 2018

Aaron Hartmann: St. Louis College of Pharmacy Clinical Pharmacy Excellence Award

PRN Member Accomplishments

Awards:

Alex Ebied: Pharmacy Recurring Opportunity Seed Program for Education and Research Award

Caitlin Gibson: M.E.T. Award for Outstanding Junior Faculty Achievement from the University of North Texas System College of Pharmacy

Grants:

Jennifer Austin Szwak: University of Chicago Medicine Innovation Grant for "ACT VALUE Program for Asthma and COPD"; Funding: $100,000

Other Notable Achievements:

Angela Miller: Poster presentation at the 2018 Pulmonary Hypertension Association International Pulmonary Hypertension Conference- Evaluation of a pharmacist discharge counseling process in pulmonary hypertension patients

Alex Ebied: Interview with CNN regarding the safety of breakthrough drugs: https://www.cnn.com/2018/07/17/health/fda-breakthrough-drugs-study/index.html

New ACCP Fellow

Jennifer E. Stark, PharmD, BCPS, FCCP

Veterans Health System of the Ozarks

2018 AMED PRN Seed Grant Recipient:

Jennie Jarrett, PharmD, BCPS, MMedEd

University of Illinois Chicago College of Pharmacy

"Combating Implicit Bias in the Healthcare Team: A Pharmacist's Role"

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