ACCP Adult Medicine PRN Newsletter

VOLUME 10, ISSUE 1 SPRING 2015

INSIDE THIS ISSUE:

Message from the Chair

Jacky Olin, Pharm.D., BCPS, FASHP, FCCP

"Nothing is impossible.
The word itself says
'I'm possible'!"
– Audrey Hepburn

These are exciting times in clinical pharmacy practice, research, and education! We are involved in a variety of medication management practices optimizing care and wellness for our patients. Our members are helping advocate legislatively to determine the details of provider status for qualified clinical pharmacists. We exemplify the purpose of the American College of Clinical Pharmacy (ACCP) by helping clinical pharmacists best serve patients and society. We are in this current place because of the tireless efforts and passion of ACCP's founders to extend the frontiers of clinical pharmacy. Today, we all strive to provide the best patient care possible. Nothing is impossible if we work together to achieve our collective goals.

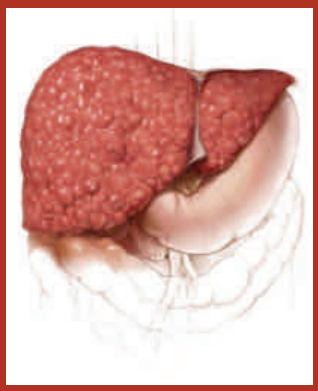
YOU can create possibilities for yourselves and others. Recognize the efforts of your colleagues and nominate them, or nominate yourself for an Adult Medicine PRN award. The Nominations and Travel & Training Committees, under the direction of **Rolee Das**, **Sarah Treadway & Jessica Wallace** will be issuing calls for award nominations. The award criteria are posted on the PRN website, and some awards include funding to attend the Global Conference on Clinical Pharmacy. Additionally, there will be a call for individuals to run for the Adult Medicine PRN offices of Chair-Elect and Secretary/Treasurer. You can serve the Adult Medicine PRN, and in the process, contribute to our success and achieve your own career goals. Please reach out to any of your Adult Medicine PRN officers and committee chairs if you have questions and want to become more involved.

Upcoming activities in progress for the Adult Medicine PRN include our PRN focus session at the ACCP Global Conference on Clinical Pharmacy in San Francisco (Oct 17 -21.) The Adult Medicine PRN Programming Committee, headed by Chair-Elect **Sarah Anderson**, is developing a session related to transitions of care in the heart failure population in collaboration with the Ambulatory Care PRN. We can all learn about best practices for medication reconciliation and patient education. You won't want to miss this session! Our newest committee, the PBRN Research Committee, led by **Antoine Jenkins**, has been developing a proposal to submit to the ACCP Research Institute.

In summary, I wish to thank the Adult Medicine PRN officers, committee chairs, and members who have provided their time and enthusiasm towards making our goals possible. Remember that nothing is impossible for you, either! All the officers will continue to encourage your involvement in shaping the Adult Medicine PRN to help us best serve our patients and society.

Hepatorenal Syndrome: Clinical Management and Review of Therapeutics

By: Yasar Tasnif, Pharm.D., BCPS and Daniela Bazan, Pharm.D.



The cirrhotic liver

"Unless liver transplantation can be performed, the condition (hepatorenal syndrome) is usually fatal."

Hepatorenal syndrome (HRS) is a complication of advanced cirrhosis that is characterized by a rapid deterioration in renal function. HRS is diagnosed by exclusion of other known causes of kidney disease. Unless liver transplantation can be performed, the condition is usually fatal. The main goal of pharmacologic therapy is to reverse HRS sufficiently so that appropriate candidates for liver transplantation can survive until suitable donor organs can be procured.[1,2] In cirrhotic patients with ascites, the most common causes of acute renal failure are: pre-renal (approximately 37%), acute tubular necrosis (approximately 42%), and post-renal failure (0.3%). HRS has an incidence of around 20% in patients with advanced cirrhosis. The cumulative probability of HRS in patients with cirrhosis and ascites is 18% after 1 year, and rises to 39% at 5 years.[3]

As cirrhosis progresses, a state of splanchnic arterial vasodilation and decreased vascular resistance occurs. This in turn leads to a decrease in effective arterial blood volume, thereby stimulating systemic vasoconstrictors. HRS is characterized by intense renal vasoconstriction, leading to low renal perfusion, decreased glomerular filtration rate, and ultimately pre-renal acute kidney injury (AKI) as a result of the aforementioned causes (see Figure 1).[1,2,4] The revised criteria for the diagnosis of HRS as defined by the International Ascites Club (IAC) are listed in Table 1.[5,6]

Two variants of HRS exist, type 1 and type 2. Type 1 is characterized by an acute and progressive kidney failure as defined by the doubling of the initial serum creatinine value to a concentration greater than 2.5 mg/dL in less than 2 weeks. Type 1 HRS is precipitated by factors such as spontaneous bacterial peritonitis (SBP) or large volume paracentesis, but can occur without a precipitating event. It may be associated with impaired cardiac and liver function as well as encephalopathy. The prognosis for patients exhibiting type 1 HRS is very poor.[6,7] In contrast, type 2 HRS is a progressive deterioration of kidney function with a serum creatinine from 1.5 to 2.5 mg/dL. It is often associated with refractory ascites and has a better survival rate compared to patients with type 1 HRS.[2,4-6]

Type 1 HRS is a life-threatening complication and, due to the rapid progression of this disease, emergent therapy becomes necessary.[8] Studies have shown the benefit of therapeutic modalities that may serve as a bridge to transplantation or a means to prolong survival.[8] The first step in therapy is to discontinue diuretics to prevent loss of volume which may further propagate AKI. Factors such as infection or blood loss should also be ruled out.[1] Splanchnic vasodilation and the resultant arterial under-filling has led to research evaluating vasoconstrictor therapy and volume expansion with albumin (see Figure 1). The hypothesis is that increasing the splanchnic arterial tone with vasoconstricting agents, while increasing the circulating plasma volume (with albumin), may effectively reverse HRS.[9] To date, clinical trials evaluating the role of vasoconstrictors along with albumin have shown success in treating type 1 HRS. Terlipressin, a vasopressin analog, has been studied extensively for type 1 HRS in clinical trials; however, it is unavailable in the United States. The American Association for the Study of Liver Disease (AASLD) guidelines advocate two main regimens for the treatment of type 1 HRS, midodrine, octreotide and albumin, or norepinephrine plus albumin.[1,11]

Angeli and colleagues evaluated patients with type 1 HRS (n = 13) treated with either midodrine (titrated up to a maximum of 12.5 mg orally 3 times per day to achieve an increase in mean blood pressure of 15 mm Hg), octreotide (target dose of 200 mcg subcutaneously 3 times per day), plus 50-100 mL of 20% human albumin solution daily for 20 days (n = 5), or intravenous dopamine (2-4 mcg/kg/min) and the same daily amount of albumin (n = 8). After 20 days of treatment with midodrine, octreotide, and albumin, there was an improvement in renal plasma flow, glomerular filtration rate, and urinary sodium excretion ($p < 0.001$), compared to dopamine and albumin for all variables with no side effects that led to discontinuation of therapy. Three patients were discharged from the hospital and one underwent liver transplant surgery. In contrast, seven out of eight patients who were treated with dopamine experienced a progressive deterioration in renal function and died during the first 12 days. The authors concluded that the administration of midodrine and octreotide was an effective and safe treatment for type 1 HRS.[10]

Esrailian and colleagues assessed the survival of patients receiving a combination of octreotide, midodrine, and albumin. This was a retrospective chart review of type 1 HRS patients (n = 60) who received octreotide, midodrine, and albumin compared to patients who received albumin alone (n = 21). The combination therapy was adjusted to increase the mean arterial pressure by at least 15 mm Hg from baseline. Octreotide was initiated at 100 mcg subcutaneously 3 times per day (titrated to 200 mcg subcutaneous 3 times per day, as needed) and midodrine was initiated at 5, 7.5, or 10 mg 3 times a day orally (titrated to 12.5 or 15 mg, if necessary). All patients received 1.5 liters of intravenous of saline combined with an average of 120 grams of human albumin after diuretic withdrawal. By day 30, 40% of treated patients had a sustained reduction in serum creatinine, compared to 10% of the patients who received albumin alone ($p = 0.01$). In that same time period, 43% of patients in the combination treatment group had died, compared with 71% of patients who received albumin alone ($p = 0.03$).[12]

The AASLD guidelines recommend that albumin infusion plus the administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type 1 HRS. Furthermore, studies mention that octreotide and midodrine in combination is required to be effective.[13,14] The guidelines mention that an additional benefit of this combination treatment is the ability to administer these agents outside of an intensive care unit.[11]

(Continued from page 2)

An unblinded pilot study aimed at assessing the efficacy and safety of norepinephrine versus terlipressin was conducted in patients with type 1 (n = 9) and type 2 (n = 13) HRS. Patients were randomized to norepinephrine (0.1-0.7 mcg/kg/min) and albumin (n = 10) or terlipressin (1-2 mg every 4 hours) and albumin (n = 12). Treatment was administered until HRS resolved or for a maximum of two weeks. The mean dose of norepinephrine was 0.3 ± 0.1 mcg/kg/min. During the study, albumin was given to maintain central venous pressure between 10-15 cm H20. The amount of albumin given ranged from 35-75 grams per day (p = NS between the two groups). Reversal of HRS was observed in 7 of the 10 patients treated with norepinephrine and in 10 of the 12 patients treated with terlipressin (p = NS). In patients showing reversal of HRS, serum creatinine decreased from 2.3 ± 0.2 mg/dL to 1.2 ± 0.1 mg/dL in the norepinephrine group ($p < 0.05$) and from 2.5 ± 0.3 mg/dL to 1.2 ± 0.1 mg/dL in the terlipressin group ($p < 0.05$). No patients developed signs of myocardial ischemia. This study suggests that norepinephrine may be a safe and effective alternative to terlipressin.[15]

Sharma and colleagues conducted an open label, randomized, pilot trial, comparing the efficacy of terlipressin and norepinephrine in patients with type 1 HRS. Patients were randomized to receive norepinephrine 0.5-3.0 mg per hour and albumin (n = 20) or terlipressin 0.5-2 mg, every 6 hours and albumin (n = 20), until reversal of HRS or completion of 15 days of therapy. Both groups received daily intravenous albumin 20–40 grams per day until the end of the study period. The study showed a significant decrease in serum creatinine from baseline ($p < 0.05$) and a progressive increase in creatinine clearance ($p < 0.05$) in both groups. Ten patients responding to therapy in the norepinephrine group and 8 responders in the terlipressin group survived until day 15 (p = NS). Reversible cardiac ischemia was seen in one patient in each group. The authors concluded that norepinephrine may be a safe and effective alternative to terlipressin in improving renal function.[16]

The AASLD guidelines recommend that albumin infusion plus administration of norepinephrine should be considered in the treatment of type 1 HRS but requires this to be conducted in an intensive care unit.[11]

Type 2 HRS is characterized as a moderate renal impairment with a steady progression that develops over months as opposed to weeks in type 1 HRS. There are no specific treatments for type 2 HRS; however, refractory ascites is the main challenge of type 2 HRS, with both therapeutic paracentesis and transjugular intrahepatic portosystemic shunt (TIPS) considered effective treatments.[2,17,18] A meta-analysis comparing the effects of TIPS and large-volume paracentesis in cirrhotic patients with refractory ascites demonstrated that ascites recurred in 42% of patients allocated to TIPS and in 89% receiving paracentesis ($p < 0.0001$).[19] The analysis also showed that TIPS improves transplant-free survival compared with large volume paracentesis, but the probability of post-treatment hepatic encephalopathy was increased, with a significantly higher number of episodes per patient in the TIPS group. A review by Israelson and colleagues recommends TIPS be considered in all patients with type 2 HRS and refractory ascites. Patients with cirrhosis and refractory ascites who do not qualify for TIPS should be offered therapeutic paracentesis.[18]

Given the poor prognosis once HRS develops, prevention is a priority. The most common precipitating factor for HRS is spontaneous bacterial peritonitis (SBP).[20] It is defined as an infection in the ascitic fluid with greater than 250 neutrophils/mm^3.[18] There are two possible mechanisms by which SBP can trigger HRS: (1) a release of pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor, and endotoxins leading to increased production of nitric oxide and other vasodilator substances or (2) sepsis-induced cardiomyopathy leading to decreased cardiac output.[21] Patients who present with SBP should be treated with intravenous albumin since this has been shown to reduce the incidence of renal impairment and death. Sort and colleagues performed a clinical trial in cirrhotic patients with SBP who were randomized to albumin plus cefotaxime or cefotaxime alone (n = 126).[22] Albumin was dosed at 1.5 grams/kg of body weight during the first six hours after enrollment, followed by 1 gram/kg on day 3. The study found that patients who received albumin plus cefotaxime had a lower incidence of developing renal impairment compared to the cefotaxime alone group (10% versus 33% respectively; $p < 0.01$). Mortality during hospitalization was also significantly lower among patients treated with cefotaxime and albumin than among those treated with cefotaxime alone (10% vs. 29% respectively; p = 0.01).

Pentoxifylline is a nonspecific phosphodiesterase inhibitor with anti-inflammatory properties, which has been proposed to prevent the development of HRS.[23] Tyagi and colleagues performed a randomized controlled trial involving patients with cirrhosis, ascites, a creatinine clearance between 41 and 80 mL/min, and a serum creatinine of less than 1.5 mg/dL in the absence of renal disease (n = 70). Patients were randomized to receive pentoxifylline 400 mg 3 times a day (n = 35) or placebo 3 times a day (n = 35). Kidney function tests were evaluated at baseline, one, three, and 6 months, and the primary endpoint was the development of HRS. Of the 12 patients that developed HRS in the study, 10 were in the placebo group and 2 were in the pentoxifylline group (32% versus 6%; p = 0.02). Pentoxifylline was well tolerated by all of the patients involved in the study.[23]

HRS is a complication of cirrhosis that is nearly always fatal unless liver transplantation can occur. Studies of pharmacologic treatment of HRS using vasoconstricting agents such as midodrine plus octreotide, or norepinephrine, along with plasma volume expansion using albumin have shown promise at delaying the progression of HRS. Ongoing randomized trials should provide further therapeutic options for type 1 and type 2 HRS. Pharmacists involved in the management of patients with cirrhosis are poised to optimize the care of patients with HRS through implementation of therapies that may improve their patients' outcomes.

(Continued from page 3)

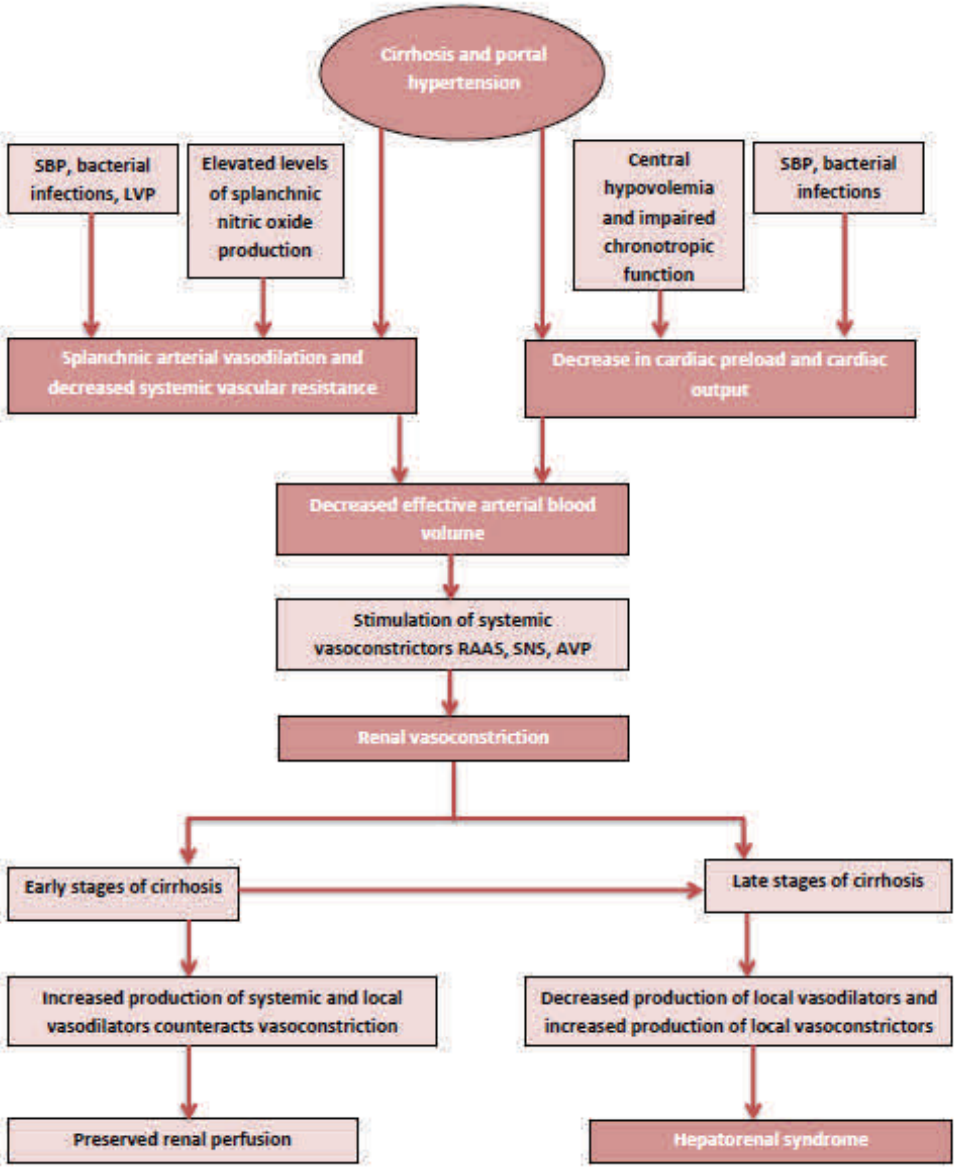


Figure 1 – Pathogenesis of hepatorenal syndrome and its precipitating factors. AVP, arginine vasopressin; LVP, large-volume paracentesis; RAAS, renin-angiotensin-aldosterone system; SBP, spontaneous bacterial peritonitis; SNS, sympathetic nervous system. Adapted from Cardenas A, Gines P. Therapy insight: management of hepatorenal syndrome. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:338-48.[4]

Table 1 – Diagnostic criteria for hepatorenal syndrome in cirrhosis

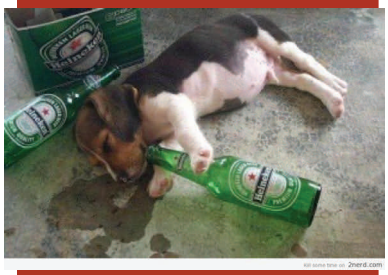
Cirrhotic patients with ascites Serum creatinine >1.5 mg/dL The absence of shock No current or recent treatment with nephrotoxic drugs	No improvement of serum creatinine (↓ to concentration ≤1.5 mg/dL) after at least 2 days with Diuretic withdrawal and Volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/d)	The absence of parenchymal kidney disease as indicated by Proteinuria >500 mg/d Microhematuria (>50 red blood cells per high-power field) and/or Abnormal renal ultrasonography

Adapted from Salerno F, et al. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis. A consensus workshop of the international ascites club. Gut 2007;56:1310-18.[6]

The Role of Pentoxifylline in Alcoholic Hepatitis

By: Tadd Hellwig, Pharm.D., BCPS

Alcoholic hepatitis (AH) is an acute inflammatory process in the liver occurring after chronic alcohol ingestion. AH is associated with significant morbidity and mortality with short-term mortality as high as 40%-50%.[1] Patients with AH report a history of an average daily consumption of over 80 g of ethanol over 5 years.[2] Development of AH is multifactorial and the damage may be secondary to ethanol metabolism, inflammation, and innate immunity. Metabolic pathways lead to the production of reactive oxygen species which are inducers of lipid peroxidation leading to hepatocyte death. Additionally, cytokines, including tumor necrosis factor-alpha (TNF-α), are released and induce systemic inflammatory responses and necrosis of hepatocytes. AH is likely the result of both immunologic and nonimmunologic factors.[3] Common laboratory manifestations include elevations in aspartate aminotransferase (AST) to a concentration 2-6 times the upper limit of normal while elevations in alanine aminotransferase (ALT) over 200 IU/L are uncommon in AH. An observed AST:ALT ratio higher than 2 may suggest AH with ratios higher than 3 being highly suggestive of AH.[4]



Alcoholism

***No puppies were harmed in the making of this picture (as far as we know)...**

"Alcoholic Hepatitis is associated with significant morbidity and mortality with short-term mortality as high as 40%-50%."

The primary treatment for AH is abstinence from ethanol. The most studied pharmacologic treatment for AH is the use of corticosteroids, with the majority of trials assessing prednisolone. Prednisolone has been used to suppress the immune system and inhibit the production of TNF-α while pentoxifylline primarily inhibits TNF-α production. Prednisolone is primarily used instead of prednisone because it does not require conversion to the active form by the liver, a process that is theoretically diminished in AH. The 2010 American Association for the Study of Liver Disease (AASLD) guidelines recommend that patients with a Maddrey score <32 (mild-moderate AH), likely will not benefit from pharmacologic intervention while patients with a Maddrey score ≥32 (severe AH) should be evaluated for a 4-week course of prednisolone (Class I, Level A) or pentoxifylline (Class 1, Level B).[4] The Maddrey score, or Maddrey discriminant function (DF), is the most commonly used model to predict success of pharmacologic treatment in AH. This score is calculated as: 4.6 x (patient's PT (sec) – control PT) + total bilirubin (mg/dL).[5] The role of pentoxifylline in AH is uncertain secondary to differing clinical trial results.

De and colleagues compared the efficacy of pentoxifylline and prednisolone in patients with severe AH in a randomized double-blind controlled trial.[6] Patients were included in this trial if they had a history of chronic alcohol intake of >50 g/d and clinical and biochemical features of severe AH (Maddrey score ≥32, AST:ALT ratio >2:1). Patients with other potential etiologies of liver disease were excluded. A total of 34 patients received pentoxifylline 400 mg there times a day and 34 patients received 40 mg daily of prednisolone therapy. Therapy was continued for 4 weeks and subjects receiving prednisolone were then tapered by 5 mg/wk over 7 weeks while patients in the pentoxifylline group were able to continue therapy for an additional 8 weeks. All baseline characteristics were similar between treatment groups and patients had an average Maddrey score of approximately 54. At the end of four weeks of therapy, 12/34 (35.3%) of patients receiving prednisolone versus 5/34 (14.7%) of patients receiving pentoxifylline expired (p= 0.04). The development of hepatorenal syndrome (HRS) occurred in 6/34 (17.6%) of patients receiving prednisolone and 0/34 (0.0%) of patients receiving pentoxifylline. Pentoxifylline was well tolerated but was associated with more frequent nausea and vomiting, while patients receiving prednisolone had higher rates of gastrointestinal bleeding and sepsis. This study demonstrated a significant reduction in 4 week mortality and development of HRS in patients receiving pentoxifylline versus prednisolone. This study was limited by the small number of participants, short duration, and single center design.

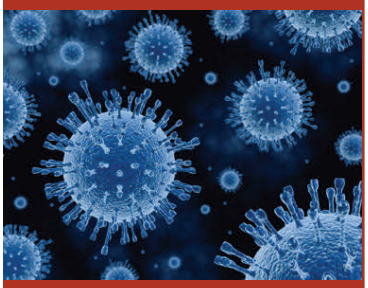
Parker and colleagues conducted a systematic review of pentoxifylline for the treatment of severe AH to clarify the varying results seen in different trials on reduction in mortality and reduction in the development of HRS.[7] This review assessed ten trials including a total of 884 subjects. Treatment with pentoxifylline was given for a total of 28 days in 9 of the 10 trials. All of the trials defined severe AH as a Maddrey score ≥32. There was significant heterogeneity between trials with regard to methodology. Pooling of trial data showed a reduced incidence of fatal HRS with pentoxifylline compared to placebo (RR: 0.47, 0.26-0.86, p= 0.01), but demonstrated no overall survival advantage of pentoxifylline over placebo at 1 month (RR: 0.58, 0.31-1.07, p= 0.06). Additionally, no significant difference was seen with pentoxifylline compared to corticosteroids in reduction of HRS or mortality, however only 3 trials evaluated this parameter. A limitation to this systematic review is the significant heterogeneity between trials.

To help address the conflicting results of AH trials, Thursz and colleagues conducted a large trial to assess the effects of prednisolone and pentoxifylline on mortality.[8] This trial was a randomized, double-blind trial of patients with a clinical diagnosis of AH (did not have to be biopsy proven), age 18 years or older, bilirubin >4.7 mg/dL, and DF of 32 or higher. Patients were excluded if they had jaundice for 3 months, other liver diseases, AST > 500 or ALT > 300. The primary outcome was mortality at 3 months with secondary outcomes of mortality at 90 days and one year. A total of 1103 patients were randomized to receive placebo, prednisolone 40 mg daily, pentoxifylline 400 mg TID, or combination therapy for 28 days. Mortality at day 28 occurred in 17% in the placebo group, 14% with prednisolone, 19% with pentoxifylline, and 13% in the combination group. The OR for 28 day mortality in patients who received prednisolone as compared to patients who did not receive prednisolone was 0.72 (95% CI, 0.52 to 1.01; P=0.06) and the OR among patients who received pentoxifylline as compared to patients that didn't receive pentoxifylline was 1.07 (95% CI, 0.77 to 1.49; P=0.69). A secondary analysis consisting of a multivariate logistic-regression model adjusted for prognostic variables (age, encephalopathy, WBC, prothrombin ratio, bilirubin, creatinine, urea) found an OR for 28 day mortality amongst patients who received prednisolone as compared to those not receiving prednisolone of 0.61 (95% CI, 0.41 to 0.91; P=0.02). Neither prednisolone nor pentoxifylline was found to influence mortality at 90 days or 1 year. Prednisolone was associated with a higher risk of infection but no difference in mortality due to infection was identified between groups. This was by far the largest study to date and demonstrated that pentoxifylline did not improve survival in patients with AH while prednisolone was associated with a reduction in 28-day mortality that did not reach significance.

Overall, there is much conflicting data regarding the use of pentoxifylline for AH. Small clinical trials have shown a mortality benefit of pentoxifylline versus placebo or prednisolone. However, a systematic review of pentoxifylline studies failed to demonstrate an overall mortality benefit however it did demonstrate a significant reduction in fatal HRS compared to placebo while the largest trial to date has demonstrated that pentoxifylline did not improve survival in patients with AH.

Worth the Wait? Management of Hepatitis C without Interferon

By: Jennifer Andres, Pharm.D., BCPS and Lindsey W. Crist, Pharm.D., BCPS



Hepatitis C Virus

"These drug combinations no longer require the use of peg-interferon, increasing the tolerability of drug therapy, and are approved for a shortened treatment duration compared to past regimens."

At the end of 2014, two new drug combinations for the treatment of Hepatitis C genotype 1 infection were approved in the United States. Additionally, results of the COSMOS trial were published addressing the use of the combination of simeprevir and sofosbuvir with or without ribavirin.[1] These drug combinations no longer require the use of peg-interferon, increasing the tolerability of drug therapy, and are approved for a shortened treatment duration compared to past regimens. Sustained virologic response (SVR) is now evaluated 12 weeks following completion of therapy in clinical trials, rather than at 48 weeks as previously done. The American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) have published collaborative guidelines for the diagnosis of and treatment for hepatitis C.[2] Guidelines are updated frequently as new literature and trials are published and more drugs gain FDA approval. Drug information on the two new agents outlined below can be seen on page 7.

Ledipasvir/sofosbuvir (LED/SOF) (Harvoni®) was approved for the treatment of genotype 1 infections on October 10, 2014. Treatment duration is dependent on treatment experience and presence of cirrhosis. All treatment-naïve patients and treatment-experienced patients without cirrhosis can be treated for 12 weeks. The duration should be extended to 24 weeks for treatment-experienced patients with cirrhosis.

The ION-1 study was a randomized, open-label phase III study that evaluated LED/SOF with or without ribavirin in treatment-naïve patients with genotype 1 infection for 12 and 24-week treatment durations.[5] Less than 20% of the patient population had cirrhosis. The primary endpoint was SVR12 (sustained virologic response at week 12). The SVR12 rates in all four treatment arms were above 97% and were superior to the selected historical rate. There were no significant differences between the two treatment durations or with the inclusion of ribavirin in the regimen. Ribavirin-containing treatment arms resulted in higher incidences of adverse effects, but did not improve SVR12 rates. Virologic failure was rare and only occurred in 0.3% of the patients.

An 8-week treatment duration was compared to a 12-week duration in the ION-3 trial.[6] The patient population consisted of treatment naïve, non-cirrhotic patients with genotype 1 infection. Patients were randomly assigned to one of three treatment groups: LED/SOF for 8 weeks, LED/SOF+ ribavirin for 8 weeks, or LED/SOF for 12 weeks. The primary endpoint of SVR12 was >90% in all three treatment arms. Similar to the previous trial, the addition of ribavirin to LED/SOF therapy did not provide an additional efficacy benefit (LED/SOF+ ribavirin for 8 weeks treatment arm), but resulted in higher pill burden and decreased tolerability. The response rates in 8-week regimen with LED/SOF were noninferior to the other two treatment arms. Virologic relapse was more common in patients treated with the 8-week regimen (rates of 5% with the LED/SOF regimen and 4% in the LED/SOF +ribavirin regimen compared to 1% in the LED/SOF 12-week arm). Due to the small number of patients with relapse, the investigators could not identify factors associated with relapse. The authors concluded that all three regimens led to high rates of SVR12 and the shorter duration may be an option in treatment naïve patients without cirrhosis.

Currently, the 8-week duration is only recommended for use in patients with pre-treatment HCV levels <6 million IU/mL.[3] This recommendation is the result of a post-hoc analysis of data from the ION-3 trial showing higher rates of relapse in the 8-week regimen of LED/SOF with patients who had pre-treatment HCV levels >6 million IU/mL. LED/SOF has additionally been evaluated in patients with HIV co-infection (ERADICATE), in patients with decompensated cirrhosis awaiting liver transplant (SOLAR-1), and post-liver transplant (SOLAR-1).[16-18] Studies have evaluated shorter treatment durations and combining LED/SOF with other direct acting antiviral agents (NIAID SYNERGY).[7]

The cost for a 12-week treatment course with LED/SOF is $94,500. A patient assistance program is available through Gilead Sciences. The benefits of choosing LED/SOF include a simple dosage and administration regimen, a favorable side-effect profile, and the possibility of shorter treatment durations. Unfortunately, it is currently the most expensive interferon-free oral option.

Ombitasvir/paritaprevir/ritonavir with dasabuvir (OBV/PTV/r + DSV) (Viekira Pak™) was approved for the treatment of genotype 1 infections on December 19, 2014. Treatment duration and use of concomitant ribavirin with the OBV/PTV/r + DSV regimen is dependent on genotype subtype and presence of cirrhosis. Patients with genotype 1b infection without evidence of cirrhosis do not require the addition of ribavirin. All other patients will need weight-based concomitant ribavirin therapy. For patients with genotype 1a, the recommended treatment duration is 12 weeks and extends to 24 weeks in patients with cirrhosis. In genotype 1b infections, treatment duration is 12 weeks regardless of the presence or absence of cirrhosis.

Treatment-naïve genotype 1a patients without cirrhosis were the primary patient population included in the PEARL IV trial which ran concomitantly with the PEARL III trial evaluating patients with gentotype 1b.[12] PEARL IV compared the OBV/PTV/r + DSV regimen in two groups with and without weight-based ribavirin. The primary endpoint was SVR12. Historical successful treatment data (72% of patients with SVR) with a regimen of telaprevir, peg-interferon, and ribavirin was used for the noninferiority endpoint. Both treatment regimens met noninferiority and superiority endpoints when compared to the historical data. Of the 205 patients that did not receive ribavirin, 16 patients had virologic failure. Additionally, more patients in the ribavirin group (97%) attained SVR, than patients not receiving ribavirin (90%), indicating the need for concomitant ribavirin therapy in this group of patients.

(Continued from page 6)

The OBV/PTV/r + DSV regimen has been studied in a broad range of infected patients including patients with compensated cirrhosis (TURQUOISE II).[19] This regimen has also been studied in patients with HIV co-infection (TURQUOISE I) and in patients post-liver transplant (CORAL-I).[20,21]

Unfortunately, OBV/PTV/r + DSV requires twice daily dosing and necessitates a higher pill burden than other regimens, especially when combined with ribavirin. In order to minimize confusion about dosing, OBV/PTV/r + DSV is packaged in a daily box with instructions for use. Drug-drug interactions are more likely to occur due to the presence of ritonavir than other treatment regimens. HIV co-infected patients must be on a fully suppressive HIV regimen to minimize the risk of HIV resistance.

The cost for a 12-week treatment course with OBV/PTV/r + DSV is $83,319. Patient assistance is available through the manufacturer, AbbVie. Addition of ribavirin therapy will add cost to the regimen.

First-line options for treatment-naïve patients with genotype 1 currently include the following drug regimens: LED/SOF; OBV/PTV/r + DSV with or without ribavirin; or sofosbuvir with simeprevir with or without ribavirin. Although these options are effective and generally well-tolerated, the high costs and potential for adverse effects and drug-drug interactions will need to be considered when making treatment decisions. AASLD/IDSA guidelines should be reviewed for most current and accurate treatment regimens.

Drug Information: Harvoni® and Viekira Pak™ [3,4]

	Ledipasvir/sofosbuvir (Harvoni®)	**Ombitasvir/ paritaprevir/ritonavir/dasabuvir (Viekira Pak™)**
Class	Ledipasvir: NS5A inhibitor Sofosbuvir: nucleotide analog NS5B polymerase inhibitor	Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Dasabuvir: NS5B polymerase inhibitor Ritonavir: Booster for paritaprevir (via CYP 3A4 inhibition)
Absorption	Ledipasvir/Sofosbuvir: well absorbed	Dasabuvir: ~70%
Metabolism	Ledipasvir: Slow oxidative metabolism Sofosbuvir: Hepatic conversion to active metabolite	Ombitasvir: amide hydrolysis and oxidative metabolism Paritaprevir: CYP3A4, CYP3A5 Ritonavir: CYP3A, CYP2D6 Dasabuvir: CYP2C8, CYP3A
Half-life	Ledipasvir: 47 hours Sofosbuvir: 0.5 hours (metabolite 27 hours)	Ombitasvir: 21 to 25 hours Paritaprevir: 5.5 hours Ritonavir: 4 hours Dasabuvir 5.5 to 6 hours
Excretion	Feces and urine	Feces and urine
Drug-Drug Interactions	P-glycoprotein substrates Use of acid suppression agents can lead to decreased ledipasvir concentrations Concomitant use of amiodarone may increase risk of bradycardia	Ritonavir: 3A4 inhibitor Concomitant use of ethinyl estradiol-containing medications can result in significant elevations in hepatic aminotransferase levels
Adverse Events	Fatigue and headache	Fatigue, nausea, pruritus, skin reactions, insomnia, and asthenia
Dosing	One combination tablet (ledipasvir 90 mg/sofosbuvir 400 mg) once daily with or without food	Two combination tablets (ombitasvir 12.5 mg/paritaprevir 75 mg/ ritonavir 50 mg) once daily with one tablet of dasabuvir 250 mg twice daily with food
Adjustments	None for mild to moderate renal impairment. Sofosbuvir exposure increased in severe renal impairment and end-stage renal disease, however, no data for dose adjustments None for Class A, B, or C hepatic impairment.	None for renal impairment. Not studied in dialysis. Not recommended with Class B hepatic impairment. Contraindicated with Class C impairment
Treatment-Naïve **Treatment-Experienced**	ION-1[5]; ION-3[6]; NIAID SYNERGY[7]; LONESTAR[8]; ELECTRON[9] ION-2[10]; SIRIUS[11]; LONESTAR[8]; ELECTRON[9]	PEARL III[12]; PEARL IV[12]; SAPPHIRE I[13] SAPPHIRE II[14]; PEARL II[15]
Other Information	Refer to package insert regarding concomitant use and maximum dosages of acid-suppressing agents Amiodarone should not be used with sofosbuvir-containing regimens due to risk of symptomatic bradycardia	In HIV positive patients, must use with fully active HIV regimen Ethinyl estradiol products should be discontinued prior to use Increased chance of significant drug interactions due to ritonavir

Nephrotoxicity with Concomitant Vancomycin and Piperacillin/tazobactam

By: Kristina M. Thurber, Pharm.D., BCPS

Acute Kidney Injury

"In 2014, four retrospective, single center studies were published which implicated concomitant vancomycin/PT use with nephrotoxicity."

At many institutions, combination antimicrobial therapy with vancomycin and piperacillin/tazobactam (PT) provides a reliable, cost-effective regimen to treat a broad array of pathogens. Utilization of these antimicrobials has trended up as a result of increased bacterial resistance, most notably with methicillin-resistant *Staphylococcus aureus* and multi-drug-resistant *Pseudomonas aeruginosa*. Additionally, several guidelines now recommend combination therapy with vancomycin and PT as empiric agents for multiple infection types, further escalating utilization.[1-6] In parallel with rising use of this antimicrobial combination, some clinicians have anecdotally reported higher rates of acute kidney injury (AKI), leading them to determine if there is direct causality. This review will recap the potential mechanism(s) involved in AKI related to vancomycin and PT, discuss recent literature, and provide recommendations for clinical practice.

The mechanisms by which vancomycin and PT may induce AKI are distinctly different yet could be additive. Vancomycin, a large molecule that is filtered through the glomerulus, can accumulate in the proximal tubule and potentially lead to direct cellular necrosis.[7] Previous studies demonstrated an association between nephrotoxicity and vancomycin dose (≥ 4 grams/day)[8] and trough (≥ 20 mcg/dL).[9] Alternatively, penicillins such as PT may induce nephrotoxicity by acute interstitial nephritis (AIN), whereby penicillin molecules cause an inflammatory reaction in the interstitial space of the nephron leading to tubule damage.[10] A study by Jensen and colleagues[11] reported significant differences in glomerular filtration rates from baseline in patients that received PT compared to meropenem. It is plausible to implicate vancomycin or PT as a single culprit for AKI; however, conclusive evidence is lacking to determine if combination vancomycin/PT may cause additive nephrotoxicity.

Prior to 2014, few studies reported clinical and safety outcomes with combination vancomycin/PT regimens. In 2014, four retrospective, single center studies were published which implicated concomitant vancomycin/PT use with nephrotoxicity.[12-15] The first, a descriptive study by Meaney and colleagues, described incidence, time-course, outcomes, and risk factors for vancomycin-associated nephrotoxicity (VAN).[12] VAN was defined as a serum creatinine increase by 0.5 mg/dL or 50% above baseline ≥ 48 hours after vancomycin initiation. Adult internal medicine patients that received vancomycin for ≥ 72 hours were included; while those excluded had admission diagnosis of AKI or chronic kidney disease (CKD) or initial serum creatinine ≥ 1.4 mg/dL or 1.5 mg/dL for women and men, respectively. The study consisted of 2 cohorts: patients with VAN (N = 17) and without VAN (N = 108). Notable differences in baseline characteristics included significantly higher rates of sepsis in the VAN cohort (12% vs. 0%, p=0.02) and significantly higher PT use in the VAN cohort (77% vs. 42%, p=0.01). Multivariable logistic regression analysis demonstrated four significant VAN risk factors: concurrent PT receipt, an acute hypotensive event, Charlson Comorbidity Index (per one unit increment), and baseline creatinine clearance (per 10 mL/min increment).[12] A limitation of this study's statistical analysis is that the number of variables included in the logistic regression model surpassed the general rule of thumb that only one variable should be used per ten events.[16]

Next, Burgess and Drew designed a study to assess the nephrotoxic impact of vancomycin/PT combination therapy compared to vancomycin monotherapy.[13] Included patients received vancomycin/PT or vancomycin alone for ≥ 48 hours. Exclusion criteria were an admission diagnosis of AKI or CKD or underlying renal dysfunction (i.e. creatinine clearance < 30 mL/min). Nephrotoxicity was defined as ≥ 1.5-fold increase in baseline serum creatinine within the first 7 days of antibiotic initiation. The patient cohorts were similar in size (vancomycin/PT, N = 92 and vancomycin monotherapy, N = 99). A notable difference in baseline characteristics was a greater incidence of severe sepsis and septic shock in the combination cohort (11% vs. 3% respectfully, p-value not reported), which may have put this group at greater risk for nephrotoxicity. For the primary outcome, nephrotoxicity was higher in the vancomycin/PT group compared to the vancomycin monotherapy group (16.3% vs. 8.1% respectively, p=0.04).[13]

Unlike the previously mentioned studies, the last two studies compared incidence of AKI with combined PT/vancomycin versus combined cefepime/vancomycin. To be included in the study by Gomes and colleagues, patients had to receive concomitant antibiotics for ≥ 48 hours.[14] Exclusion criteria were underlying renal dysfunction (i.e. creatinine clearance < 60 mL/min) or an inappropriately drawn vancomycin trough. The primary outcome was to compare incidence of AKI with either antibiotic regimen. AKI was defined as (1) an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, (2) ≥ 1.5-fold increase in baseline serum creatinine, or (3) urine volume < 0.5 mL/kg/hour for 6 hours. Any one of these had to occur during therapy or within 72 hours of discontinuation. Most patient characteristics were similar. An unmatched analysis and matched-pair analysis were completed, highlighting one of the strengths of this study. A total of 224 patients were included in the unmatched analysis (N = 112 in each group) and 110 patients were included in the matched analysis (N = 55 in each group). For the primary outcome, the incidence of AKI was 36.4% in the PT/vancomycin cohort vs. 10.9% in the cefepime/vancomycin cohort in the matched analysis (p=0.003). The outcomes in the unmatched analysis were similar.[14]

The patient cohort included in the study by Moenster and colleagues was narrower than the patient populations in the previous studies.[15] Patients had to have osteomyelitis as their antibiotic indication with underlying diabetes. Exclusion criteria were underlying renal dysfunction (i.e. creatinine clearance ≤ 40 mL/min) and receipt of concomitant antibiotics known to be nephrotoxic (e.g. aminoglycosides). The primary outcome for this study was incidence of

(Continued from page 8)

nephrotoxicity defined as a serum creatinine increase by 0.5 mg/dL or 50% above baseline. A total of 139 patients were included (PT/vancomycin, N = 109 vs. cefepime/vancomycin, N = 30). A notable difference in the patient characteristics was higher receipt of intravenous contrast dye in the PT/vancomycin group (14% vs. 3%, p=0.036). For the primary outcome, incidence of nephrotoxicity in the PT/vancomycin cohort was higher than the cefepime/vancomycin cohort, but did not reach statistical significance (29.3% vs. 13.3%, p=0.09). This was likely due to small sample size in the cefepime/vancomycin cohort.[15]

All 4 studies have notable limitations. Since they were retrospective, the association of nephrotoxicity with combination vancomycin/PT is worthy of further prospective investigation. In a retrospective study, it is difficult to conclude whether nephrotoxicity was due to the antibiotics or to the underlying clinical scenario. Additionally, known vancomycin-associated nephrotoxicity risk factors were not controlled for (i.e. total daily dose and trough). Also, all four studies excluded patients with underlying renal dysfunction who may be even more at risk for acute kidney injury. Definitions of nephrotoxicity were different, making direct comparisons of the rates reported difficult, and standardizing this definition would be ideal for future studies. Lastly, none of the studies could describe the type of acute kidney injury observed.

Despite the limitations of the available data, all four studies report an association between combined vancomycin/PT use and nephrotoxicity. A prospective, multicenter trial is needed to further characterize this phenomenon. Until then, we should be aware of the current data and its limitations. If there is concern, early discontinuation of vancomycin/PT should be encouraged and de-escalation of antibiotics emphasized when clinically appropriate. Hopefully, future evidence will further help guide clinical practice.

References for all articles

HRS

1. Garcia-Tsao G, Lim J. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program [published correction appears in Am J Gastroenterol 2009;104:1894]. Am J Gastroenterol 2009;104:1802-29.
2. Tasnif YO, Hebert MF. Complication of end-stage liver disease, In: Aldredge BK et al., ed. Applied Therapeutics. 9th ed, Philadephia, PA: Lippincott Williams &Wilkins; 2009. 720-48.
3. Fabrizi F, et al. Hepatorenal syndrome and novel advances in its management. Kidney Blood Press Res 2013;37:588-601.
4. Cardenas A, Gines P. Therapy insight: management of hepatorenal syndrome. Nat Clin Pract Gastroenterol Hepatol 2006;3:338-48.
5. Arroyo V, et al. New treatments of hepatorenal syndrome. Semin Liver Dis 2006;26:254-64.
6. Salerno F, et al. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis. A consensus workshop of the international ascites club. Gut. 2007;56:1310-18.
7. Alessandria C, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005;41:1282-9.
8. Cai Cx, et al. A treat-to-target concept to guide the medical management of hepatorenal syndrome. Dig Dis Sci 2014. DOI 10.1007/s10620-014-3483-x.
9. Gluud LL, et al. Systematic review of randomized trial on vasoconstrictor drugs for hepatorenal syndrome. Hepatology 2010;51:576-84.
10. Angeli P, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. Hepatology 1999;29:1690-7.
11. Runyon BA. Management of adult patients with ascites due to cirrhosis: update 2012. Hepatology 2013;57:1651-3.
12. Esrailian E, et al. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. Dig Dis Sci 2007;52:742-8.
13. Kiser TH, et al. Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol Dial Transplant 2005;20:1813-20.
14. Pomier-Layrargues G, et al. Octreotide in hepatorenal syndrome: a randomized, double-blind, crossover design. Hepatology 2003;38:238-43.
15. Alessandria C, et al. Norepinephrine vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. J Hepatol 2007;47:499-505.
16. Sharma P, et al. An open label, pilot, randomized controlled trial of norepinephrine versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol 2008;103:1689-97.
17. Angeli P, Merkel C. Pathogenesis and management of hepatorenal syndrome in patients with cirrhosis. J Hepatol 2008;48,S93-103.
18. Israelson ME, et al. Acute kidney injury and hepatorenal syndrome in cirrhosis. J Gastroenterol Hepatol 2015;30:236-43.
19. Salerno F, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology. 2007;133:825-34.
20. Leithead JA, et al. Advances in the management of patients with cirrhosis and portal hypertension-related renal dysfunction. Aliment Pharmacol Ther 2014;39:699-711.
21. Low G, et al. Hepatorenal syndrome: aetiology, diagnosis, and treatment. Gastroenterol Res Pract 15; 2015:207012.
22. Sort P, et al. Effect of Intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341:403-9.
23. Tyagi P, et al. Prevention of hepatorenal syndrome in patients with cirrhosis and ascites: a pilot randomized control trial between pentoxyfylline and placebo. Euro J Gastroenterol Hepatol 2011:23:210-7.

Pentoxifylline

1. Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. J Clin Gastroenterol 2011;45:714-9.
2. Mendenall CL. Alcoholic hepatitis. Clin Gastroenterol 1981;10:417-41.
3. Chayanupatkul M, Liangpunsakul S. Alcoholic hepatitis: A comprehensive review of pathogenesis and treatment. World J Gastroenterol 2014;28:6279-86.
4. O'Shea RS, et al. Alcoholic liver disease. Hepatology 2010;51:307-28.
5. Maddrey WC, et al. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193-99.
6. De BK, et al. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: A randomized controlled trial. World J Gastroenterol 2009;15:1613-9.
7. Parker R, et al. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013;37:845-54.
8. Thursz MR, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619-28.

Hepatitis C

1. Lawitz E, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014; 384: 1756-65.
2. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org. Accessed 15 January 2015.
3. Harvoni [package insert]. Foster City; Gilead Sciences; October 2014.
4. Viekera Pak [package insert]. Titusville, NJ: AbbVie; Februrary 2015.
5. Afdhal N, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. New Engl J Med 2014;370:1889-98.
6. Kowdley KV, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. New Engl J Med 2014;370:1879-88.
7. Kohli A, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. Lancet. 2015 Jan [Epub ahead of print]
8. Lawitz E, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014;383:515-23.
9. Gane EJ, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology. 2014;146:736-43.

(**References continued…**)

10. Afdhal N, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014; 370: 1483-93.
11. Bourliere M, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy .65th AASLD 2014. Abstract LB-6.
12. Ferenci P, et al. ABT-450/r-Ombitasvir and Dasabuvir with or without Ribavirin for HCV. New Engl J Med. 2014; 370:1983-92.
13. Feld JJ, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24; 370(17):1594-603.
14. Zeuzem S, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014; 370: 1604–14.
15. Andreone P1, et al. ABT- 450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014; 147: 359–65 e1.
16. Osinusi A, et al. Use of sofosbuvir/ledipasvir fixed dose combination for treatment of HCV genotype-1 infection in patients coinfected with HIV. AASLD: Abstract 84.
17. Flamm SL, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective, multicenter study. 65th AASLD. 2014: Abstract 239.
18. Reddy KR, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with post transplant recurrence:preliminary results of a prospective, multicenter study. 65th AASLD 2014: Abstract 8.
19. Poordad F, et al. ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med. 2014;370: 1973-82.
20. Wyles D, et al. 3D (Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir) + RBV in GT1. 65th AASLD. 2014: Abstract 1939.
21. Kwo PY, et al. An interferon-free antiviral regimen for HCV after liver transplantation. New Engl J Med. 2014;371: 2375-82.

Nephrotoxicity

1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388-416.
2. Freifeld AG, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56-93.
3. Solomkin JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133-164.
4. Lipsky BA, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132-73.
5. Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.
6. Stevens DL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-52.
7. Nishino Y, et al. Inhibition of vancomycin-induced nephrotoxicity by targeting superoxide dismutase to renal proximal tubule cells in the rat. Redox Rep. 2002;7(5):317-319.
8. Lodise TP, et al. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 2008;52(4):1330-6.
9. Lodise TP, et al. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis. 2009;49(4):507-514.
10. Baldwin DS, et al. Renal failure and interstitial nephritis due to penicillin and methicillin. N Engl J Med. 1968;279(23):1245-1252.
11. Jensen JU, et al. Kidney failure related to broad-spectrum antibiotics in critically ill patients: secondary end point results from a 1200 patient randomised trial. BMJ Open. 2012:e000635.
12. Meaney CJ, et al. Vancomycin-associated nephrotoxicity in adult medicine patients: incidence, outcomes, and risk factors. Pharmacotherapy. 2014;34(7):653-661.
13. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. Pharmacotherapy. 2014;34(7):670-676.
14. Gomes DM, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. Pharmacotherapy. 2014;34(7):662-9.
15. Moenster RP, et al. Acute renal failure associated with vancomycin and beta-lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. Clin Microbiol Infect. 2014;20(6):O384-389.
16. Peduzzi P, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-1379.

PRN Member Accomplishments

Daniel Abazia
Abazia DT. The Mail: Stopping drug deaths [letter]. The New Yorker. 2014 Sep 29.

Hind Almodaimegh
Added Qualifications in Cardiology from BPS

Mohammad H. Alshaer
Mohammad H. Al-Shaer, Tarek Ibrahim. Safety and efficacy of fondaparinux in renal impairment. Journal of pharmacy technology. January 14, 2015 [Epub]

Lama Nazer, Taghreed Alnajjar, Mohammad Al-Shaer, et al. Evaluating the effectiveness and safety of hydrocortisone therapy in cancer patients with septic shock. Journal of Oncology Pharmacy Practice. 2014 Apr 29 [Epub].

Mohammad Al-Shaer, Lama H. Nazer, Mazen Kherallah. Rifampicin as Adjunct to Colistin Therapy in the Treatment of Multidrug-Resistant Acinetobacter baumannii. Ann Pharmacother. 2014 Jun;48(6):766-71.

Sarah L. Anderson
Anderson SL. Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf 2014;5(6):242-54.

Fosmire Rundgren EW, Anderson SL, Marrs JC. Evaluation of aspirin use in patients with diabetes receiving care in community health. Ann Pharmacother 2015;49(2):170-7.

Fosmire Rundgren EW, Anderson SL, Marrs JC. Response to comment "evaluation of aspirin use for primary prevention in diabetic patients." Ann Pharmacother 2015;49 (2):262-3.

Anastasia Armbruster
Armbruster A, Buehler K, Min S, Riley M, Daly M. D. Evaluation of Dabigatran for Appropriateness of Use and Bleeding Events in a Community Hospital Setting. Am Health Drug Benefits.2014;7(7) 1-8.

Luigi Brunetti
Brunetti L, Poustchi S, Cunningham D, Toscani M, Nguyen J, Lim J, Ding Y, Nahass RG. Clinical and economic impact of empirical extended-infusion piperacillin-tazobactam in a community medical center. Ann Pharmacother 2015 Apr 8. pii: 1060028015579427. [Epub ahead of print].

Brunetti L, DeSantis EH. Patient tolerance and acceptance of colesevelam hydrochloride: focus on type 2 diabetes mellitus. P T 2015;40(1):62-7.

Awad NI, Brunetti L, Juurlink DN. Enhanced elimination of dabigatran through extracorporeal methods. J Med Toxicol 2015;11(1):85-95.

Brunetti L, Hermes DeSantis ER. (2015). Secondary Resources. In: Gabay M. (ed), The Clinical Practice of Drug Information (Chapter 4). Burlington, MA: Jones & Bartlett.

Kyle Davis
Miyares MA, Davis KA. Evaluation of aspirin use for primary prevention in diabetic patients. Ann Pharmacother. 2015 Jan;49(1):150-1.

Miyares MA, Davis KA. Community-based interventions to improve outcomes for cardiovascular disease [letter]. Prev Chronic Dis. 2014 Oct 9;11:E172.

Dietrich E, Davis K. A Statin a Day to Keep the Doctor Away? Comparing Aspirin and Statins for Primary Prevention of Cardiovascular Disease. Ann Pharmacother. 2014 Sept 23;48(9):1238-1241.

Davis KA, Miyares MA. Lomitapide: A novel agent for the treatment of homozygous familial hypercholesterolemia. Am J Health Syst Pharm. 2014 Jun 15;71(12):1001-8.

Robert L. Deamer
Low KJ, Pelter MA, Deamer RL, Burchette RJ. Identification and Evaluation of Risk Factors in Patients With Continuously Uncontrolled Hypertension. J Clin Hypertens (Greenwich). 2015: 1–9.

Paul Dobesh
Dobesh PP, Fanikos J. New oral anticoagulants for the treatment of venous thromboembolism: understanding the differences and similarities. Drugs 2014;74:2015-2032.

Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetic, pharmacodynamics, clinical efficacy, and safety. Pharmacotherapy 2014;34:1077-1090.

PRN Member Accomplishments

Brian Hemstreet

Hemstreet B. Improving your public speaking skills. Experts in Training: News for Resident, Fellow, and Graduate Student Members of the American College of Clinical Pharmacy. Published online December 2014 (http://www.accp.com/resfel/newsletter.aspx)

Krinsky D, Ferreri SP, Hemstreet BA, Hume AL, Newton GD, Rollins CJ, Tietze KJ. Handbook of Nonprescription Drugs, 18th Edition. American Pharmacists Association, Washington DC 2015.

Hemstreet B. Vitamin B12 Deficiency and Use of Acid Suppressive Drugs: The Association Revisited Pharmacy Today, July 2014;20(7):20.

Hemstreet B. Navigating the P4 Year. American College of Clinical Pharmacy Emerge from the Crowd: How to Become a Standout Residency Candidate program. Spring Meeting. Austin, Texas, October 2014.

Hemstreet B. Updates in Therapeutics: Gastrointestinal and Hepatic Disorders American College of Clinical Pharmacy 2014 Summit on Clinical Pharmacy. Manila, Philippines, September 2014.

Jennie Jarrett

Received the New Faculty Scholar Award from the Society of Teachers of Family Medicine (STFM)

Antoine Jenkins, Janene Marshall

Jenkins AT, Marshall JL. Chapter 7: Cardiovascular Exam. In: Hardy YM ed. Patient Assessment in Pharmacy: A Culturally Competent Approach. Burlington MA, Jones & Bartlett Learning; 2016. 129-153.

Jeff Kyle

Erwin BL, Kyle JA, Allen LN. Time to guideline-based empiric antibiotic therapy in the treatment of pneumonia in a community hospital: a retrospective review. [published online ahead of print January 19 2015]. J Pharm Prac. 2015. http://jpp.sagepub.com/content/early/2015/01/19/0897190014566303.abstract (doi: 10.1177/0897190014566303). Accessed January 19, 2015.

Mercadel CJ, Skelley JW, Kyle JA, Elmore LK. Dolutegravir: An integrase strand transfer inhibitor (INSTI) for the treatment of human immunodeficiency virus 1 (HIV-1) in adults. J Pharm Technol. 2014:30: 216-226.

Lewis T, Kirby E, Kyle JA. Infection in kidney transplantation. US Pharm. 2014;39(8):HS10-HS16.

Rima A. Mohammad

Smith MA, Chan J, Mohammad RA. Ledipasvir-Sofosbuvir: Interferon-/Ribavirin-Free Regimen for Chronic Hepatitis C Virus Infection. Ann Pharmacother. 2014 Dec 16. pii: 1060028014563952. [Epub ahead of print] Review.

Mohammad RA, Bulloch MN, Chan J, Deming P, Love B, Smith L, Dong BJ. Provision of Clinical Pharmacist Services for Individuals With Chronic Hepatitis C Viral Infection: Joint Opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks of the American College of Clinical Pharmacy. Pharmacotherapy. 2014 Dec;34(12):1341-54. doi: 10.1002/phar.1512. Epub 2014 Oct 31.

Smith MA, Mohammad RA. Vedolizumab: an α4β7 integrin inhibitor for inflammatory bowel diseases. Ann Pharmacother. 2014 Dec;48(12):1629-35. doi: 10.1177/1060028014549799. Epub 2014 Sep 3.

Smith MA, Mohammad RA, Benedict N. Use of virtual patients in an advanced therapeutics pharmacy course to promote active, patient-centered learning. Am J Pharm Educ. 2014 Aug 15;78(6):125. doi: 10.5688/ajpe786125.

Monique Mounce

Completing a PGY2 Pharmacotherapy program at Philadelphia College of Pharmacy and has accepted a position as Assistant Professor in the Clinical & Administrative Sciences Department at Notre Dame of Maryland University School of Pharmacy

Erin Neal

Salanitro A, Neal E, Bell S, Powers J, Kripalani S. Care transitions: a leverage point for safe and effective medication use in older adults. Gerontology. 2015;61(1):32-40.

McDonald M, Salanitro A, Neal E, Sponsler K. Teaching the Best Possible Medication History. MedEdPORTAL Publications; 2014. Available from: https://www.mededportal.org/publication/9850 http://dx.doi.org/10.15766/mep_2374-8265.9850

PRN Member Accomplishments

Jacky Olin
Promotion to Full Professor at Wingate University
Awarded Fellowship in ACCP

Olin JL, St. Pierre M. Aromatase inhibitors in breast cancer prevention. Annals of Pharmacotherapy 2014; 48: 1605-10.

Bulloch MN, Olin JL. Instruments for evaluating medication use and prescribing in older adults. Journal of the American Pharmacists Association 2014; 54: 530-537.

Keith Pappa
Granier C, Cuffe R, Martin-Carpenter L, Smith K, Brennan C, Pappa K, Wynne B, Almond S, Givens N and Aboud M. Consistency of Dolutegravir Treatment Difference in HIV+ Treatment Naives at Week 96. 22nd Conference on Retroviruses and Opportunistic Infections; February 23-26; Seattle, WA.

Raffi F, Rachlis A, Brinson C, Arasteh K, Gorgolas M, Brennan C, Pappa K, Almond S, et al. Dolutegravir Efficacy at 48 Weeks in key subgroups of Treatment-naive HIV-infected Individuals in Three Randomized Trials. AIDS.. DOI:10.1097/QAD 0000000000000519, 2014.

Pappa K, Baumgarten A, Felizarta F, Florence E, Portilla J, Walmsley S, Granier G, Wong D, and Wynne B; Once-Daily Dolutegravir + Abacavir/Lamivudine vs. Tenofovir/Emtricitabine/Efavirenz in Treatment-Naïve HIV Subjects: 144-Week Results-SINGLE (ING114467). Oral Presentation at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 5-9, 2014; Washington, D.C.

Beth Resman-Targoff
Salvatore D J, Resman-Targoff B H. Treatment Options for Urinary Tract Infections Caused by Extended-Spectrum B-Lactamase-Producing Escherichia coli and Klebsiella pneumonia. Journal of Academic Hospital Medicine 2015; 7 (1).

Invited speaker: "Optimizing clinical outcomes in rheumatoid arthritis therapy", American Pharmacists Association Annual Meeting, San Diego, CA, March 30, 2015

Manny Saltiel
Lead Author of Aminoglycoside Pharmacokinetics chapter in: Casebook in Clinical Pharmacokinetics and Drug Dosing Paperback - January 7, 2015 By Henry Cohen (ed.) ISBN-13: 978-0071628358 ISBN-10: 0071628355 Edition: 1st http://www.amazon.com/Casebook-Clinical-Pharmacokinetics-Drug-Dosing/dp/0071628355/ref=sr_1_1?ie=UTF8&qid=1422316372&sr=8-1&keywords=henry+cohen

April Smith
Integrated Health Pharmacology Course. Moderator & Course Developer. Invited faculty at Obesity Week (combined annual meeting of The Obesity Society and the American Society for Metabolic & Bariatric Surgery). Boston, MA. November 3rd, 2014.

Drug Absorption Challenges Post-Bariatric Surgery. Invited faculty/speaker at Obesity Week (combined annual meeting of The Obesity Society and the American Society for Metabolic & Bariatric Surgery). Boston, MA. November 3rd, 2014.

Medication Issues in the Post-Bariatric Surgery Patient. Invited speaker at the 6th annual Bariatric Symposium presented by Alegent Health Weight Management. Omaha, NE. September 12th, 2014.

Diana M. Sobieraj
Diana M. Sobieraj (co-investigator) has been awarded a 5 year contract from the Agency for Healthcare Research and Quality as a core researcher at the University of Connecticut Evidence-based Practice Center for comparative effectiveness research, beginning in January 2015.

Sobieraj DM, Coleman CI, Pasupuleti V, Deshpande A, Kaw R, Hernandez AV. Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: a network meta-analysis. Thromb Res 2015 [e-pub ahead of print] doi: 10.1016/j.thromres.2015.02.032

Elizabeth A. Stone
Credentialed as an Allied Health Professional in December, will be performing CDTM in a Hepatitis C clinic

Geoffrey Wall, Michelle Bottenberg, Erik Maki, Andrew Miesner
Wall GC, Bryant GA, Bottenberg MM, Maki ED, and Miesner AR. Irritable bowel syndrome: A concise review of current treatment concepts. World J Gastroenterol.2014;20 (27):8796-806.

Kurt Wargo, Jonathan Edwards
Wargo KA, Edwards JD. Aminoglycoside-Induced Nephrotoxicity. J Pharm Prac. 2014;27:573-77. DOI: 10.1177/0897190014546836
Kurt Wargo accepted a position as Regional Dean of the Hendersonville Campus of Wingate University School of Pharmacy

Andy Woods
Promotion to Associate Professor at Wingate University

Adult Medicine PRN Officers

Chair: Jacky Olin

Chair-Elect: Sarah Anderson

Secretary-Treasurer: Kurt Wargo

Prepared by the Adult Medicine PRN Newsletter Committee

Chair: Kurt Wargo

Jennifer Andres
Jane Bowen
Luigi Brunetti
Hope Campbell
Lindsey Crist
Maria Guido
Christine Hanks
Tadd Helwig
Erin Hennessey
Corrie Lowe-Malphrus
Kristina Marchese
Janene Marshall
Andrew Miesner
Beth Moore
Veronica Nieto
Sonalie Patel
Sweta Patel
Maegan Patterson
Sarah Petite
Ben Pullinger
Beth Resman-Targoff
Taryn Satterwhite
Yasar Tasnif
Suzanne Wortman