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Hospital Medicine

Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

Vol. 11, Issue 12, February 2017
AHCMedia.com

ABSTRACT & COMMENTARY

Fecal Transplant vs. Oral Vancomycin Taper for Recurrent *Clostridium difficile* Infection

By Richard R. Watkins, MD, MS, FACP, FIDSA

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General Medical Center, Akron, OH

Dr. Watkins reports that he has received grant/research support from Allergan.

SYNOPSIS: In a small randomized, controlled trial that compared fecal microbiota transplant (FMT) administered by enema to a six-week oral vancomycin taper, FMT was not more effective for patients with recurrent *Clostridium difficile* infection.

SOURCE: Hota SS, Sales V, Thomlinson G, et al. Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent Clostridium difficile infection: An open-label, randomized controlled trial. *Clin Infect Dis*. First published online Nov. 9, 2016. Fecal Transplant vs. Oral Vancomycin Taper for Recurrent *Clostridium difficile* Infection

The management of recurrent *Clostridium difficile* infection (CDI) is challenging. The most common therapy for the past several years has been a prolonged course of oral vancomycin, frequently prescribed as a taper. Recently, fecal microbiota transplant (FMT) has become more widely available and utilized, especially in recalcitrant cases. Hota and colleagues sought to determine which of these two treatments was more effective for cases of recurrent CDI. The study was a randomized, controlled trial from Canada that compared a 14-day course of oral vancomycin followed by an FMT vs. a six-week vancomycin taper. The inclusion criteria were patients 18 years of age and older with at least two episodes of CDI who had received at least one 10-day or more course of oral vancomycin. There were numerous exclusion criteria, including pregnancy, neutropenia, immunocompromised status, intensive care admission, severe colitis not responding to oral vancomycin, allergy or intolerance to oral vancomycin, chronic gastrointestinal diseases that cause chronic diarrhea, bleeding disorder, expected chemotherapy in the next 120 days, or inability to tolerate FMT.

Financial Disclosure: *Hospital Medicine Alert's Physician Editor, Kenneth P. Steinberg, MD, Peer Reviewer Kevin M. Tompkins, MD, Editor Jill Drachenberg, and Ebook Design Specialist Dana Spector have no relevant relationship related to the material presented in this issue.*

Hospital Medicine
[ALERT]

Hospital Medicine Alert,
ISSN 1931-9037, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry NE, Suite 2850
Atlanta, GA 30326.
AHCMedia.com

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to
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P.O. Box 550669,
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The primary outcome was recurrence of symptomatic, laboratory-confirmed CDI within 120 days of the intervention.

Of 140 patients assessed for eligibility, 12 patients in the vancomycin taper arm and 16 in the FMT arm were included in the interim analysis. Most of the patients were women (8/12 and 11/16, respectively) with a history of four to five CDI episodes (range 2-9) before starting the trial. Nine out of 16 (56.2%) patients who received FMT and five out of 12 (41.7%) in the vancomycin taper arm suffered a recurrence of CDI. This happened a median of nine days after FMT and 35 days after starting vancomycin tapering (seven days after finishing the taper). Four of the five patients who failed a vancomycin taper crossed over to FMT, and all four had another recurrence of CDI after the procedure. One of the FMT patients suffered a bowel perforation 35 days after the procedure, which was attributed to long-standing diverticulitis and not the FMT. Furthermore, there were no significant differences in fecal microbiota composition and diversity between the FMT donors and no significant differences between those associated with successful vs. unsuccessful FMT. After 30 patients were randomized, the trial was stopped due to futility.

■ COMMENTARY

Most studies of FMT for recurrent CDI have demonstrated a cure rate of about 90%. The present investigation by Hota and colleagues, which found a 44% cure rate for FMT, is notable therefore for being an outlier. There are a couple of possible explanations as to why this occurred. One is that the overall number of patients in the study was small and a larger study may have shown similar outcomes to previous ones. Another is that the methods used by Hota and colleagues were different from those employed by prior investigators. These included the delivery of FMT by enema instead of colonoscopy or nasojejunal tube, randomization of patients as soon as they experienced a recurrence of CDI and not during a symptom-free interval, only performing one FMT as opposed to multiple ones as was done in other studies, the 120-day follow-up, and no attempt to match donors and recipients (e.g., family members). Finally, pretreating patients with oral vancomycin for 14 days might have negatively affected the intestinal microbiota since oral vancomycin can be present in feces four to five days after discontinuation of therapy.

Oral vancomycin tablets have been expensive, and the cost of a six-week taper previously has cost several thousand dollars. The recent availablilty of a generic form has resulted in reduced cost. A study that compared the cost-effectiveness of different treatments found that FMT by colonoscopy was the most cost-effective initial strategy for management of recurrent CDI.[1] However, the researchers did not use vancomycin as a taper and their conclusion should be re-examined in light of the findings by Hota and colleagues.

Unfortunately, FMT may not be as effective as previous studies have shown, leading clinicians to overestimate its benefits compared to prolonged courses of vancomycin. However, one also must be aware of the economic impact that oral vancomycin can have on patients and their families, as mentioned above. Perhaps the take-away message from this study can be summarized by the old dictum "an ounce of prevention is worth a pound of cure." That is, it is far better to prevent CDI than to try to cure it with the therapies currently available. ■

REFERENCE

1. Konijeti GG, Sauk J, Shrime MG, et al. Cost-effectiveness of competing strategies for management of recurrent *Clostridium difficile* infection: A decision analysis. *Clin Infect Dis* 2014;58:1507-1514.

Bezlotoxumab Injection (Zinplava)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a selective, fully human monoclonal antibody directed at *Clostridium difficile* toxin B. Binding of toxin B neutralizes its toxic effect. Bezlotoxumab is marketed as Zinplava.

INDICATIONS

Bezlotoxumab is indicated to reduce recurrence of *C. difficile* infection (CDI) in patients ≥ 18 years of age who are receiving antibacterial treatment of CDI and are at high risk for CDI recurrence.[1]

DOSAGE

The recommended dose is a single dose of 10 mg/kg administered intravenously over 60 minutes during antibacterial treatment.[1] Bezlotoxumab is available as a single-dose vial containing 1 g of bezlotoxumab or 25 mg/mL.

POTENTIAL ADVANTAGES

Bezlotoxumab neutralizes the effect of toxin B and reduces the rate of recurrence of CDI.

POTENTIAL DISADVANTAGES

In subjects with underlying congestive heart failure, the frequency of heart failure was 12.7% in those randomized to bezlotoxumab compared to 4.8% in the placebo group.[1] More deaths were associated with this population (19.5% vs. 12.5%). Bezlotoxumab was associated with infusion-specific adverse reactions in 10% of subjects compared to 8% for placebo. Other adverse events vs. placebo include nausea (7% vs. 5%), pyrexia (5% vs. 3%), and headache (4% vs. 3%).

COMMENTS

The efficacy and safety of bezlotoxumab was assessed in two similar randomized, double-blind, placebo-controlled studies in subjects receiving standard of care (SoC) antibacterial treatment (metronidazole, vancomycin, or fidaxomicin) for a confirmed diagnosis of CDI.[1] Subjects were randomized to a single-dose of bezlotoxumab or placebo. In study one, 403 patients were randomized to bezlotoxumab and 404 to placebo. Study two randomized 407 and 399, respectively. The median time for the single-dose bezlotoxumab infusion was three days after the start of SoC (range -1 to 14). The efficacy endpoint was clinical cure, and those who achieved cure were assessed for recurrence through 12 weeks after infusion. Clinical cure was defined as no diarrhea for two consecutive days following the completion of ≤ 14 days of treatment. Recurrence was defined as development of a new episode of diarrhea and positive stool test of toxigenic *C. difficile*. Sustained clinical response was defined as clinical cure and no recurrence through 12 weeks after infusion. Sustained clinical response was 60.1% for bezlotoxumab vs. 55.2% for placebo in study one, and 66.8% vs. 52.1%, respectively, for study two. Statistical significance was achieved in study two only. Recurrence was significantly lower with bezlotoxumab (17.4% vs. 27.6% and 15.7% vs. 25.7%, respectively).

CLINICAL IMPLICATIONS

C. difficile is the leading cause of antibiotic-associated diarrhea. Two endotoxins (A and B) are secreted by the disease-causing strains.[2] The original Phase III studies included bezlotoxumab, actoxumab (antibody to toxin A), or the combination. Treatment with actoxumab or the combination provided no benefit; therefore, only bezlotoxumab was marketed.[3] Toxin B is thought to be primarily responsible for disease symptoms.[2] The drug appears to have marginal effect in producing sustained clinical effect but appears to reduce recurrence. The effect may be greater in those with high risk of CDI recurrence. These include ≥ 65 years of age, history of CDI in the past six months, immunocompromised state, severe CDI at presentation, or *C. difficile* ribotype 027. In patients with a history of congestive heart failure, risk vs. benefit must be assessed before treatment.[1] The cost for bezlotoxumab was not available at the time of this review. It is expected to be available in the first quarter of 2017. ■

REFERENCES

1. Zinplava Prescribing Information. Merck & Co., Inc. October 2016.
2. Carter GP, Chakravorty A, Pham Nguyen TA, et al. Defining the roles of TcdA and TcdB in localized gastrointestinal disease, systemic organ damage, and the host response during clostridium difficile infections. *MBio* 2015 Jun 2;6:e00551. doi: 10.1128/mBio.00551-15.
3. Merck. Pivotal Phase 3 Studies of Bezlotoxumab, Merck's Investigational Antitoxin to Prevent *clostridium difficile* Infection Recurrence, Met Primary Endpoint. Available at: *http://bit.ly/1F9lrXv*. Accessed Nov. 21, 2016.

Early Initiation of Continuous Renal Replacement Therapy May Reduce Mortality in Patients Who Require Dialysis

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Initiation of continuous renal replacement therapy for patients with Kidney Disease: Improving Global Outcomes stage 2 renal failure reduced 90-day all-cause mortality.

SOURCE: Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs. delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. *JAMA* 2016;315:2190-2199.

The decision to start continuous renal replacement therapy (CRRT) in critically ill patients requires careful analysis of risks and benefits. The timing of initiating CRRT remains unclear. The ELAIN trial sought to inform this decision in a single center, randomized trial of early vs. late initiation of CRRT. Inclusion criteria were: Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 acute kidney injury (AKI) (i.e., two-fold increase in serum creatinine or urine output < 0.5 mL/kg/hr for > 12 hours), neutrophil gelatinase-associated lipocalin (NGAL) > 150 ng/mL, 18-90 years of age, and one additional condition such as severe sepsis, vasopressor requirement, refractory fluid overload, PaO_2/FiO_2 < 300, or increase in Sequential Organ Failure Assessment (SOFA) score > 2. Patients who presented with chronic kidney disease, dialysis, previous AKI, pregnancy, or kidney transplantation were excluded.

Patients were randomized to early vs. late initiation of CRRT. Early CRRT started within eight hours of diagnosis of KDIGO stage 2 AKI. Delayed CRRT started within 12 hours of patients progressing to KDIGO stage 3 AKI (urine output < 0.3 mL/kg/hr for 24 hours and/or three-fold increase in serum creatinine or serum creatinine > 4 mg/dL with an acute increase of at least 0.5 mg/dL within 48 hours), or if any of the criteria for renal replacement therapy (RRT) were met: blood urea level > 100 mg/dL, potassium > 6 mEq/L and/or with ECG changes, magnesium > 8mEq/L, urine output < 200 mL per 12 hours, or organ edema resistant to diuretics. Once started, all patients received identical prescriptions for CRRT that continued until urine output exceeded 400 mL/24 hours without diuretic treatment or 2,100 mL/24 hours with diuretics.

The primary endpoint was 90-day mortality with secondary outcomes, including 28- and 60-day mortality, SOFA scores, recovery of renal function, need for hemodialysis after day 28, duration of CRRT, hospital length of stay (LOS), and biologic markers of inflammation. Overall, 231 patients were included in the intention-to-treat analysis, although 11 patients in the delayed group did not receive dialysis. Many patients were recruited after surgical procedures, including coronary artery bypass grafting (CABG), valve replacements, trauma, bowel resection, and liver transplantation. Most were mechanically ventilated and required vasopressors. Early initiation of CRRT was associated with decreased 90-day mortality (39.3% vs. 54.7%; odds ratio, 0.66; $P = 0.03$). In contrast, 28-day and 60-day mortality were not statistically different between the early and late groups, although there was a trend toward benefit for the early group. There were reductions in hospital LOS and duration of mechanical ventilation for those who were randomized to early initiation of CRRT.

■ COMMENTARY

The ELAIN trial was published just before the AKIKI study group published a similar study[1] with contrasting results, and any analysis should consider both studies. The AKIKI study was a multicenter, randomized trial of 630 patients that examined when to start CRRT. In that trial, early initiation occurred within six hours of the diagnosis of stage 3 AKI while delayed initiation occurred if oliguria/anuria lasted for > 72 hours or severe electrolyte abnormalities occurred. In the AKIKI trial, no benefit was seen in 28- or 60-day mortality, although patients in the early initiation arm did exhibit higher rates of catheter-related infections.

Three factors may explain the differences between the ELAIN and AKIKI results. First, the patient populations in each study were different. As noted, much of the recruitment for the ELAIN trial involved post-surgical patients, while the AKIKI trial involved primarily medical

patients. Although many co-morbidities were similar, surgical and medical ICU patients often follow different hospital courses. Many of the AKIKI patients in the delayed initiation group never received dialysis, and it is likely many of the patients in the early initiation group would not have required CRRT. In contrast, the inclusion of NGAL criteria in the ELAIN trial was intended to improve discernment for those who would ultimately require CRRT. Second, the ELAIN trial started CRRT sooner than AKIKI. The "delayed" group in ELAIN started at a similar time to the "early" group in AKIKI. A subgroup analysis of the ELAIN trial comparing patients in the delayed arm that started CRRT due to stage 3 disease (similar to AKIKI "early" group) and patients that required CRRT for electrolyte disturbances (similar to the AKIKI "delayed" group) found no difference in duration of CRRT, ICU, or hospital stay. Thus, earlier initiation of CRRT may have an effect on outcomes. Third, while ELAIN reported a 90-day mortality benefit for early initiation of CRRT, both studies failed to show 28- and 60-day mortality benefits. It is unclear why there was only a 90-day mortality benefit as neither trial seemed to show less dependence on long-term dialysis, although the ELAIN trial indicated less dependence when excluding patients who died during the trial.

Comparing the ELAIN and AKIKI trials informs the decision when to start CRRT in the ICU. In patients who will require CRRT, early initiation may have benefits. However, identifying these patients is challenging as commonly used endpoints such as KDIGO stage are not reliable predictors. Clinical judgment and patient-specific factors remain important in the risk-benefit analysis of patients presenting with AKI in the ICU. ■

REFERENCE

1. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375:122-133.

Zika Virus Infection and Guillain-Barré Syndrome: The Evidence Grows

By Joseph E. Safdieh, MD

Vice Chair and Associate Professor, Weill Cornell Medical College

Dr. Safdieh reports no financial relationships relevant to this field of study.

SYNOPSIS: A recent Zika outbreak in Colombia was associated with a significant increase in Guillain-Barré syndrome (GBS) rates, with laboratory evidence of definite or probable Zika infection in more than half of the GBS cases.

SOURCE: Parra B, Lizarazo J, Jimenez-Arango JA, et al. Guillain-Barre syndrome associated with Zika virus infection in Colombia. *N Engl J Med* 2016;375:1513-1523.

Zika virus is a mosquito-born flavivirus that has recently emerged in Central and South America as well as the Caribbean and southern parts of the United States. Although humans typically are infected with Zika via a mosquito bite, Zika virus can be transmitted from an infected human to an uninfected human via sexual contact. Much attention has been paid to the Zika virus-associated microcephaly in children born to some mothers infected during pregnancy. During an earlier Zika virus outbreak in French Polynesia, there was an indication of an association with Guillain-Barré syndrome (GBS). As Zika has moved through the Americas, surveillance for GBS cases has been set up in a number of countries to document the case rate and to determine association with recent Zika virus infection. This paper presents data from the GBS surveillance program in Colombia.

Colombia reported its first case of Zika virus infection in October 2015, and by January 2016, cases were reported in most regions of the country. At the same time, hospitals were noting an uptick in the number of patients diagnosed with GBS. Surveillance of GBS cases was set up to track the number of GBS cases, the clinical features, and the laboratory testing to assess for recent or current Zika virus infection. GBS cases were diagnosed based on Brighton criteria. For Brighton criteria, level 1 requires both abnormal nerve conduction (NCS) studies and cerebrospinal fluid (CSF) cytoalbuminologic dissociation, level 2 requires either NCS or CSF abnormalities, and level 3 is based on clinical features alone without support from testing. Zika virus infection was categorized as definite (confirmed by Zika RNA-PCR in serum, urine, or CSF), probable (positive CSF and/or serum ELISA for flavivirus with negative Dengue serologies), or suspected (supportive clinical syndrome without supportive testing). Supportive clinical symptoms of Zika are quite nonspecific and include rash, fever, conjunctivitis, arthralgia, myalgia, and periarticular edema.

Parra et al reported on the results of GBS surveillance in Colombia from January through March 2016. Of note, 270 cases of GBS were reported throughout the country over these three months, as compared to an estimated baseline in Colombia of 250 cases per year. Sixty-eight GBS patients presented to the specialized centers that were involved for the purposes of this study. Of the 68 cases, 82% fulfilled Brighton criteria level 1 or 2 for the diagnosis of GBS. The majority of the patients had a typical ascending limb weakness pattern, with 50% developing bifacial paresis. A small number of cases of Miller Fisher variant also occurred. Median age of the patients was 47 years, with 56% male predominance. Eighty-two percent of those who underwent lumbar puncture demonstrated elevated CSF protein, with median CSF white blood cell count of 0 per CC. Seventy-eight percent of those who underwent electrophysiologic testing demonstrated features consistent with acute inflammatory demyelinating polyradiculopathy. Most patients were treated with intravenous immunoglobulin. Thirty-one percent of the patients required mechanical ventilation, and three patients died.

Of the 68 GBS patients included in this analysis, 97% had a recent illness suspicious for Zika virus infection in the previous four weeks. These symptoms lasted a median of four days and occurred a median of seven days before GBS symptom onset. Forty-two of the 68 patients with GBS underwent diagnostic testing for Zika virus. On laboratory testing, 17 (25%) of the patients had definite Zika infection, 18 (26%) of the patients had probable Zika infection, and the rest were considered suspected cases. Of note, 16 of the 17 patients with definite Zika virus demonstrated positive PCR in the urine, but only three in the CSF and one in the serum. Of the patients with definite and probable Zika infection, two developed GBS symptoms at the same time as the Zika symptoms, 20 (48%) patients developed GBS symptoms immediately after Zika infection with no post-Zika recovery period, and the remainder of the patients developed GBS with a more typical post-infectious course.

■ COMMENTARY

This is an important study because it offers more evidence of a possible connection between Zika virus and the development of GBS. Although it cannot be stated with certainty that Zika can trigger GBS, the evidence in this study, in addition to the previously described GBS outbreak after Zika infection in French Polynesia, lends further support to the association. It is worth noting that more than half of the GBS cases in this cohort had definite or probable Zika exposure. It is interesting that in some of the GBS cases, the symptoms developed either concurrently or immediately following the Zika symptoms, suggesting a possible para-infectious pathogenesis. This is distinct from the usual post-infectious temporal onset of GBS in patients with other known triggers such as Campylobacter jejuni. It is not known if the Zika virus is directly pathogenic to peripheral nervous system structures.

The symptoms, signs, and diagnostic testing findings in Zika-associated GBS are similar to the GBS typically seen in traditional clinical settings. The paper does not provide follow-up on outcomes, but it would be important to know whether these patients responded to therapy. Zika virus cases transmitted via mosquito vector already have been reported in Florida and Texas. Sexually transmitted cases of Zika have been reported in multiple states. U.S. neurologists should be familiar with the possible association between Zika and GBS and should ask about recent travel history (of the patient and any sexual partners) when encountering a patient with GBS. ■

Sacubitril/Valsartan Associated with Reduced Risk of Hyperkalemia

By Van Selby, MD

Assistant Professor of Medicine, University of California, San Francisco, Cardiology Division, Advanced Heart Failure Section

Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: In a secondary analysis of the PARADIGM-HF trial, the risk of severe hyperkalemia in heart failure patients taking a mineralocorticoid receptor antagonist was lower among patients treated with sacubitril/valsartan compared to those receiving enalapril.

SOURCE: Desai AS, Vardeny O, Claggett B, et al. Reduced risk of hyperkalemia during treatment of heart failure with minteralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: A secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol* 2016. [Epub ahead of print].

Current guidelines recommend mineralocorticoid receptor antagonists (MRAs) for patients with symptomatic heart failure with reduced ejection fraction (HFrEF). MRAs are associated with hyperkalemia, and the risk increases when administered with angiotensin-converting enzyme (ACE) inhibi-

tors. Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) that is approved as an alternative to ACE inhibitors for HFrEF. Whether the risk of MRA-associated hyperkalemia is lower in patients receiving sacubitril/valsartan than ACE inhibitors is unknown.

To evaluate differences in risk of hyperkalemia, Desai et al analyzed data from PARADIGM-HF, which randomized 8,399 patients suffering from chronic HFrEF to sacubritil/valsartan vs. enalapril. The trial ended early due to a marked reduction in the composite outcome of cardiovascular death or hospitalization for heart failure in the sacubitril/valsartan arm. Use of MRAs was encouraged, though left to investigators' discretion. For this secondary analysis, the authors compared the rates of hyperkalemia (defined as any serum potassium > 5.5 mEq/L) and severe hyperkalemia (> 6.0 mEq/L) in patients receiving MRAs.

Among 4,671 taking an MRA at baseline, the overall rate of hyperkalemia was similar between patients treated with sacubitril/valsartan and enalapril. However, the rate of severe hyperkalemia was significantly higher in the enalapril group (3.1 vs. 2.2 per 100 patient-years; hazard ratio [HR], 1.37; $P = 0.02$), and the difference persisted after adjusting for baseline differences between the two treatment groups. Similarly, when including all patients who started MRAs during the study period, those receiving enalapril demonstrated significantly higher rates of hyperkalemia (HR, 1.43; $P = 0.003$).

Changes in serum creatinine were similar between the two groups, and changes in potassium levels did not correlate with serum creatinine over time. Patients who did not receive an MRA during the study period demonstrated lower rates of hyperkalemia, and among these patients there were no significant differences in hyperkalemia or severe hyperkalemia between those randomized to enalapril vs. sacubitril/valsartan. The authors concluded that among HFrEF patients treated with an MRA, severe hyperkalemia is more common during treatment with enalapril than with sacubitril/valsartan, suggesting neprilysin inhibition may attenuate the risk of MRA-associated hyperkalemia.

■ COMMENTARY

In large, randomized trials, both spironolactone and eplerenone have been shown to improve outcomes in HFrEF. Despite the overwhelming evidence and strong recommendations from practice guidelines, studies show that many eligible HFrEF patients are not treated with MRAs. This often is due to concern regarding hyperkalemia, especially in patients already treated with ACE inhibitors. This secondary analysis provides strong evidence that switching from an ACE inhibitor to sacubitril/valsartan reduces this risk of severe hyperkalemia by approximately one-third and hopefully will encourage clinicians to prescribe MRAs more frequently.

Among patients not receiving MRAs, there was little difference in the risk of hyperkalemia between those randomized to enalapril vs. sacubitril/valsartan. The authors suggested that by increasing levels of circulating natriuretic peptides, neprilysin inhibition specifically attenuates the risk of hyperkalemia when combining MRAs with other inhibitors of the renin-angiotensin-aldosterone system (RAAS). Given the importance of both MRAs and RAAS inhibition in the treatment of HFrEF, this is a clinically relevant advantage for sacubitril/valsartan.

This was a secondary analysis, with important limitations. Patients were not randomized according to MRA use, and there may have been residual differences between MRA-treated patients randomized to enalapril vs. sacubitril/valsartan. PARADIGM-HF included a run-in period during which patients who did not tolerate either sacubitril/valsartan or enalapril were excluded. Therefore, the true rate of hyperkalemia may have been underestimated in both groups.

Is the lower risk of hyperkalemia enough to warrant switching all HFrEF patients from ACE inhibitors to sacubitril/valsartan? Taken in the context of the overall markedly positive results of PARADIGM-HF, this substudy adds further weight to the argument for switching most patients with symptomatic HFrEF despite ACE inhibitors to sacubitril/valsartan. At the very least, patients who are not receiving MRAs due to perceived concern regarding the risk of hyperkalemia should be considered candidates for switching.

Another relevant question is whether to initiate an MRA before or after switching from an ACE inhibitor to sacubitril/valsartan. Current American guidelines do not specifically address this issue. However, European guidelines recommend initiating an MRA before switching. The results of this substudy suggest clinicians switch patients to sacubitril/valsartan before adding an MRA to minimize the risk of hyperkalemia. Regardless of the exact strategy used, the importance of monitoring serum potassium and creatinine after any initiation or dose adjustment cannot be overstated. With close monitoring, clinicians should now feel even more empowered to reach target doses for all major therapeutic classes for HFrEF. ■

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CME QUESTIONS

1. What was the primary outcome of the open-label randomized control trial of fecal microbiota transplant (FMT) versus a prolonged vancomycin taper in patients with recurrent CDI:

a. Improved survival at hospital discharge in patients receiving FMT

b. No significant benefit of FMT compared to prolonged vancomycin

c. An increase in the number vancomycin-resistant enterococcal infections in the vancomycin treated group.

d. An increased risk of diverticulitis in the FMT group.

2. Bezlotoxumab (Zinplava®) when given by injection along with appropriate antibacterial treatment for CDI appears to be associate with which of the following outcomes:

a. Improved mortality

b. Decreased risk of recurrence of *C. difficile* infection

c. Decreased hospital length of stay

d. An increased risk of an exacerbation of heart failure in patients with CHF

e. B and D only

3. In the report by Parra and colleagues, Zika-associated Guillain-Barre syndrome (GBS) may differ from usual GBS in the following way:

a. Greater incidence of descending versus ascending paralysis

b. Greater likelihood of CSF pleocytosis seen with lumbar puncture

c. More rapid temporal onset after Zika infection

d. Decreased frequency of findings on electrodiagnostic testing

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

[IN FUTURE ISSUES]

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