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Practical Management of Variceal Bleeding and Hepatorenal Syndrome

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And now, here's your host, Dr. Mary Katherine Cheely.

Dr. Cheeley:
This is CME on ReachMD. I'm Dr. Mary Katherine Cheeley and I'd like to welcome Dr. Andrew Keaveney to the program. He's a Consultant Hepatologist in the Departments of Medicine and Transplantation at the Mayo Clinic in Jacksonville, Florida. Today, we'll be taking a look at a patient case highlighting challenges and the best practices in decompensated cirrhosis, leading to multi organ failure. Dr. Keaveney, welcome to the program.

Dr. Keaveney
Thank you very much, Mary Katherine.

Dr. Cheeley:
Throughout this program, we'll also hear from Dr. Don Rockey and Dr. Michael Curry, both of whom spoke at a symposium on this subject at the American College of Gastroenterology Conference. It was held in Vancouver, Canada in October 2023. Dr. Rockey is a Professor of Medicine in the College of Medicine at the Medical University of South Carolina. And Dr. Curry is a Professor of Medicine at Harvard Medical School, and the Section Chief of Hepatology. He is also the Director of Liver Transplantation at the Beth Israel Deaconess Medical Center in Boston.

So, let's get started, Dr. Keaveney. Can you give us an overview of the progression of cirrhosis and how decompensation manifests?

Dr. Keaveney:
Thank you, Mary Katherine. As damage to the liver accumulates due to alcohol use, the presence of fatty liver, or viral hepatitis, one of the most significant pathologies is impaired blood flow through increased hepatic resistance. This results in portal hypertension where the hepatic venous pressure gradients increase. Initially the liver can continue to function but in the presence of this increased portal pressure along with a development of a hyperdynamic circulation esophageal varices can develop which we'll hear about in our patients.

As cirrhosis reaches a more advanced stage, you have this increased hepatic resistance in addition, outside of liver, the extrahepatic manifestation of the portal hypertension is the development of portosystemic collaterals and – and these will ultimately lead to the development again of esophageal viruses. But in addition, ascites, hepatic encephalopathy, and hepatorenal syndrome could all develop as complications of portal hypertension, and we call that decompensated cirrhosis.

And a very serious complication of decompensated cirrhosis is the development of hepatorenal syndrome, which is a type of acute

kidney injury where the renal vasculature undergoes intense vasoconstriction as a compensatory mechanism. Acute kidney injury is very important in decompensated cirrhosis, as it confers the highest additional mortality risk in our patients with cirrhosis.

There have been several guideline changes for maintaining kidney function and very important developments in the treatment of hepatorenal syndrome. And as we go forward, we will discuss these in this podcast because they're very important in terms of treating patients and preparing them for liver transplantation. And we'll hear about them more in our case today.

Dr. Cheeley:
With that background in mind, let's hear from Dr. Rockey about a patient case he recently encountered in clinical practice.

Dr. Rockey:
So, this is a patient that we saw a couple of years ago. A 39-year-old woman with known hepatitis C presented with hematemesis, blood pressure 90/40, heartrate 120, jaundice, spider angioma, probable ascites. Prothrombin time 19 seconds, that was an INR of about 1.7. Bilirubin 6, platelets low, hematocrit 29. NG lavage fresh blood. So, this is what we see in practice all the time.

Dr. Cheeley:
Given these initial details of Dr. Rockey's patient case, Dr. Keaveney, how might you approach treating this patient?

Dr. Keaveney:
So, I think the first challenge is to determine source of bleeding. And that's one of the things that Dr. Rockey emphasized in his talk. So, even though a patient has cirrhosis, other causes of bleeding can occur. So, it's very important to do – perform an endoscopy in a timely manner. And the current practice guidelines recommend performing endoscopy within 12 hours of presentation with GI bleeding because we simply cannot know what type of bleeding the person has until we perform the upper endoscopy. So, we have to perform the endoscopy, establish the cause of bleeding, and then ha - having a certain diagnosis appropriate therapy can be applied. In the presence of bleeding esophageal varices, the first-line therapy is endoscopic band ligation, as Dr. Rockey has mentioned.

Dr. Rockey:
So, it's, you know, it's 8 o'clock at night and you're scoping this patient and they've got bleeding varices. The fact is that there are little new data. There've been extensive studies in this area but there's not much new. And the data are that octreotide is equal to terlipressin, is equal to banding, and is equal to sclerotherapy. The reason that we use banding is that it's got the least number of side effects, and we generally, after the patient has – after you've stopped the bleeding, then we add pharmacologic therapy for secondary prophylaxis.

Dr. Cheeley:
And with that in mind, let's come back to Dr. Rockey one last time and hear some key take-home messages that he shared at the 2023 ACG Conference regarding approaches to patients with acute variceal bleeding.

Dr Rockey:
So, practical clinical approach here for acute bleeding. Everybody in the United States gets octreotide. In Europe, most people would get terlipressin. Everybody gets antibiotics. I think if you have a low MELD or Child-Pugh score you should be banded, and then probably get secondary prophylaxis with a beta blocker. I think if you have a moderate to high MELD score, or you are listed for transplant – and we can talk about this with the experts here, the transplant guys – I think TIPS is probably the way to go. You want that patient to stop bleeding, you don't want them to get a lot of blood transfused, and the sooner you can cut off the bleeding the better off you are.

Dr. Cheeley:
Dr. Keaveney, do you have anything to add?

Dr. Keaveney:
I think as Dr. Rockey mentioned, I would like to briefly talk about the role of preemptive TIPS. In the most recent AASLD practice guidance documents the guidance document really has emphasized that we should consider preemptive TIPS; that means TIPS performed within 72 hours of upper GI bleed due to portal hypertension in specific categories of patients. Those are patients who have Child-Pugh score , Child-Pugh score class B, with active variceal bleeding or those who have Child-Pugh scores class C with a score between 11 to 13 who've had bleeding from esophageal varices.

Now, there are some important caveats in those situations. All the studies that looked at the role of preemptive TIPS excluded older patients, patients with cancer, patients with very high MELD scores, and patients with advanced chronic kidney disease. So, I think TIPS has clearly a role, but it should be used in the appropriate setting.

I would also like to mention that we've re - recognized too the importance of stopping proton pump inhibitors when possible, because they are associated with – with increased risk of infections in our cirrhotic patients. So, patients should not be routinely prescribed

proton pump inhibitors on discharge. Now, if patients do not proceed to TIPS, really it's quite important to consider starting a nonselective beta blocker at the time of discontinuing vasoactive therapy in an effort to reduce the risk of further bleeding.

Dr. Cheeley:
For those just tuning in, this is CME on ReachMD. I'm Dr. Cheeley, and today we're hearing from doctors Andrew Keaveney, Don Rockey, and Michael Curry about patient cases in decompensated cirrhosis.

Now we're going to hear from Dr. Curry, who's sharing some additional developments on the case that Dr. Rockey first introduced to us. Let's tune in.

Dr. Curry:
I'm going to continue with Don's case. This is the young lady who had hepatitis C cirrhosis who had a variceal bleed, and as you can see, she's undergone endoscopic variceal band ligation. She also had mild ascites and underwent a paracentesis with an absolute neutrophil count of 342, and therefore was continued on the antibiotics and the albumin as per standard of care for patients with spontaneous bacterial peritonitis.

Unfortunately, despite this our patient's creatinine has risen from 1.1 to 1.7 over 48 hours.

Dr. Cheeley:
So, Dr. Keaveney, could you explain a little bit about what is happening in this patient? And how to identify what's happening?

Dr. Keaveney:
So, as we all know, an elevated serum creatinine is indicative of kidney injury, and it's our primary marker for acute kidney injury, or AKI. So, this patient's creatine has increased 0.6 mg/dL in a 48-hour span, which meets the, guideline criteria for AKI, acute kidney injury.

The key question here is what the etiology of the AKI is. We need to determine that as many different et – etiologies that can be seen in patients with cirrhosis. There are different management strategies for patients who have postrenal obstruction compared to patients who have kidney injury from acute tubular necrosis, or patients who have prerenal impairment because of volume depletion. So, different etiologies have very different management strategies. And it's going to be very important to distinguish between the etiology of kidney disease so appropriate therapy can be instituted.

Dr. Cheeley:
That's a great explanation. Let's see what Dr. Curry had to share about this at the 2023 ACG Conference.

Dr. Curry:
So, really when we're trying to assess the causes of acute kidney injury in patients with cirrhosis, we have to take a very broad approach and go back to first principles and try and figure out what the correct answer is here. So, we would use renal ultrasound to rule out obstruction, and to make sure that the patient doesn't have any evidence of chronic kidney disease. And this patient did not have any obstructive uropathy, had normal size kidneys, had a small liver with moderate ascites. The urinalysis did not reveal any cells or casts. There was no evidence of any muddy brown cast to suggest ATN. There was no evidence of proteinuria or red cells to suggest glomerulopathy or a chronic kidney disease. And then the urinary sodium, while not a part of the diagnostic criteria for hepatorenal syndrome anymore, at least is supportive of the fact that this patient is intravascularly dry and potentially not perfusing the kidneys.

Dr. Cheeley:
Dr. Curry also addressed the overall management algorithm for patients with AKI and cirrhosis.

Dr. Curry:
Now, the algorithm here is proposed to try and standardize the management of patients with cirrhosis and AKI. So, patients who come in with an initial AKI stage 1a, these patients can be monitored. You remove the risk factors such as nephrotoxic agents, vasodilators, nonsteroidal anti-inflammatories, beta blockers, and consider volume expansion. Work these patients up for infection and treat it. If there is resolution, these patients can just be followed closely. If there's persistence of acute kidney injury, you have to go down further investigation on a case-by-case basis. But if there is progression or if a patient presents with an initial AKI stage 1b, 2, or 3, again, apply the standard approach of withdrawal of diuretics, volume expand these patients for a period of 1 or 2 days. If there is response, these patients can be followed. And response is arbitrarily defined as a reduction in their serum creatinine by 20%. If there is no response, you have to then figure out whether the patient meets the criteria for HRS and if they do, consider vasoconstrictor therapy and albumin.

Dr. Cheeley:
Dr. Keaveney, could you briefly talk us through vasoconstrictor therapy for HRS?

Dr. Keaveney:

Thank you, Mary Katherine. So, the first step in HRS management, as Dr. Curry mentioned, is to assess the volume status of these patients and expand their plasma volume using albumin if indicated. These patients have ascites and peripheral edema, and very commonly, they can have intravascular impaired intravascular volume, so we need to increase their effective arterial blood volume.

Once we've done that, we can determine further strategies. Many patients with prerenal AKI will respond simply to volume expansion alone and they will not need vasoconstrictor therapy. However, if after volume expansion, and risk factor management such as treating active infection, if you've done all those measures and serum creatinine has not improved, then the next step is to initiate vasoconstrictor therapy.

So, the goal with vasoconstrictor therapy is to reduce the systemic vasodilation that we've discussed earlier that is driving the decreased effective arterial blood volume and the renal impairment. And by using vasoconstrictor therapy, we can address that spike in the arterial vasodilation.

So traditionally, midodrine]and octreotide have been the only options within the United States outside of ICU to treat hepatorenal syndrome. However, really there's very little efficacy to support their use as Dr. Curry presented, there are – when the studies have been performed, really no better than placebo. On the other hand, terlipressin, a splanchnic vasoconstrictor, has been approved recently by the Federal Drug Administration, and has been shown to reverse hepatorenal syndrome. It can be used in the hospital floor, and it is recommended now as, by most guidance to treat HRS-AKI in an effort to improve renal function. In patients who are in the intensive care unit, norepinephrine through a central line is also another option.

Dr. Cheeley:
Terlipressin has a number of safety concerns associated with it. Let's hear Dr. Curry discuss risk mitigation.

Dr. Curry:
So, the idea of mitigating treatment is not necessarily new to us in hepatology, we've done so for years. The Child-Pugh score was used to determine whether patients would have a good outcome or a poor outcome after surgical shunt surgery. And similarly, MELD score was introduced to try and predict the outcomes after TIPS. And as you can see here, we have a red light/green light strategy here. If we apply this to the treatment of HRS-AKI, those individuals with a serum creatinine of less than 5, those individuals of grade 1 or 2 ACLF, are suitable candidates for treatment with terlipressin. Individuals with an oxygen saturation of greater than 90 are also suitable candidates, and those with a MELD score of less than 35. In all individuals however, who develop HRS-AKI, liver transplantation should also be considered in addition to trying to reverse renal failure.

In the individuals with a serum creatinine of greater than 5, we should not consider treatment with terlipressin because these individuals are unlikely to respond. Those with ACLF grade 3 and those with an oxygen saturation of less than 90% should not be treated with terlipressin because we're more likely to cause harm, particularly the development of respiratory failure that might then preclude them from becoming transplant candidates. A MELD score greater than 35 should also be excluded from terlipressin because we're more likely to harm them, rather than benefit them in terms of potential transplant candidacy.

Dr. Cheeley:
Dr. Keaveney, in your clinical practice, is there anything that you would add?

Dr. Keaveney:
I think Dr. Curry's red light green light is a great analogy. I think it's essential to consider that approach. Patient selection here is key. And I would just really like to emphasize here the importance of early identification and early therapy. Because we know that patients will do better if we identify patients who have HRS-AKI early, initiate therapy at that time rather than waiting until they become sicker with a higher serum creatinine.

Dr. Cheeley:
And if we revisit our patient, now Dr. Keaveney will tell us about the next step in management from the 2023 ACG Conference.

Dr. Keaveny:
So, I want to just go back to our case. So, the patient remains on the floor and continues on terlipressin, 5 mg every 6 hours. Blood pressure improves, urinary output increases 250 mL in 24 hours, creatinine reduces to 1.4 mg on day 4 after initiating terlipressin, baseline prior to treatment is 1.1 mg/dL. MELD score remains 28, and the patient is listed for liver transplantation. [01:10:17]

Dr. Cheeley:
With all those additional details in mind, Dr. Keaveney, how would you approach treating this patient now?

Dr. Keaveney:
So, Mary Katherine, the key issues here are whether we say the patient has responded or is a partial responder to therapy, and then

whether treatment should be continued or stopped. The package insert for terlipressin, and the recommendations state that we should stop terlipressin if the creatine isn't changed, or continues to increase by day 4, or if the patient has achieved a complete response. Now, complete response is defined as reaching serum creatinine within 0.3 mg/dL at baseline, or two consecutive measurements of serum creatinine less than 1.5.

So, for this patient, the baseline was 1.1 and a went up to 1.7. And with terlipressin treatment, we reached 1.4. So, we definitely saw a response to treatment. And we can actually document a complete response if it – if the serum creatinine remains less than 1.5 after the 24 hours.

So, we have options. You can stop the treatment, recognizing that in patients, there is a risk that ter – that the HRS-AKI can relapse, but we know that we can retreat patients with terlipressin again. Or, in some circumstances, treatment could be continued to maintain a lowest possible serum creatine. Because we know, especially in patients who are listed for transplant, there are data from the Italian group that those patients who responded to, terlipressin continued on terlipressin, those patients had improvement in renal function after transplantation. So, there are options there. And I think it has to be taken on a case-by-case basis.

Dr. Cheeley:
Dr. Keaveney, could you talk briefly about the options if the patient doesn't respond well to vasoconstrictors?

Dr. Keaveney:
So, if the patient hasn't responded to albumin terlipressin, and the serum creatinine continues to rise, then the next option in that situation is really to stop the terlipressin. And if the patient is being considered for transplantation, then transfer the patient to ICU for norepinephrine. Short-term renal replacement therapy, dialysis, is an option in patients who are listed for transplantation or being considered for transplantation, or potentially have a form of liver disease that is reversible and that we want to support their AKI plus we hope that their liver function will reverse. So, in those patients, we want to optimize treatment of their AKI with the hope to get into transplantation or that the liver recover. Ideally, we'd like to improve the renal function even if a patient's listed for transplantation. Uh, because we know that if they continue to be required dialysis for longer than 6 weeks, then we'll have to consider them for simultaneous liver and kidney transplantation.

Dr. Cheeley:
Well, we have certainly covered a lot today, Dr. Keaveney. So, before we close, what are some key points from our discussion that our audience should take home with them?

Dr. Keaveney:
Well as a transplant hepatologist, I really want to emphasize the importance that our jobs are to optimize care of patients. Because for a patient who is heading into transplantation it's always much better that they have good renal function. We know that those patients post transplantation, they have shorter length to stay, less complications, and indeed potentially a lower chance of mortality in the 6 to 9 months post transplantation, because renal failure causes significant morbidity in the post-transplant setting. So, addressing renal failure pre transplantation will give patients a better chance to do, doing well and a better kidney function post transplantation.

Standing back, we presented a case of a patient who had cirrhosis, developed decompensated disease, and then showed a very serious manifestation of decompensated cirrhosis, HRS-AKI. It's very important in patients who develop acute kidney injury in the presence of hepatic decompensation, you have to consider a differential diagnosis. Treat prerenal conditions, look for obstructive disease, carefully use IV albumin to resus the individuals and to – to correct any intravascular volume depletion. Once you've done that, and there's ongoing AKI, HRS really is – is the top of mind for the differential. And we are now fortunate to have terlipressin as the FDA approved treatment of choice for AKI-HRS, which can be used in select individuals. When used appropriately, we – we can see a reversal of AKI-HRS. In patients who don't respond, then additional interventions such as norepinephrine should be considered while waiting for liver transplantation as the optimal therapy for patients who manifest decompensated cirrhosis.

Dr. Cheeley:
This has been a wonderful discussion on management strategies for patients who have decompensated cirrhosis. And I want to thank Dr. Andrew Keaveney for being here today. Dr. Keaveney, it was such a pleasure speaking with you.

Dr. Keaveney:
Thank you very much, Mary Katherine.

Announcer Close:
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