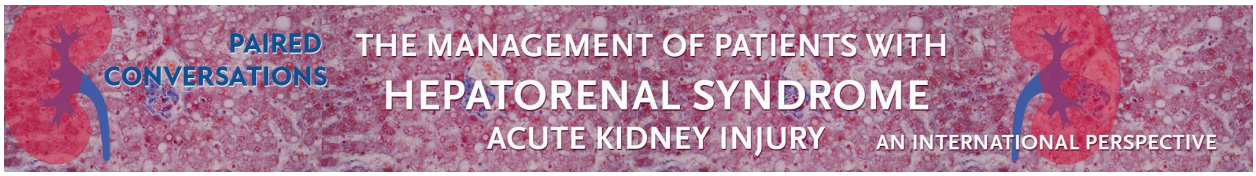

OVERVIEW

Hepatorenal syndrome (HRS) represents an acute complication of decompensated cirrhosis and is a subtype of acute kidney injury (AKI), with high associated mortality. This activity consists of 6 paired conversations with experts from Europe and the United States in the fields of hepatology, critical care, nephrology, and transplantation. During these paired conversations, the faculty explore revised diagnostic criteria, emerging treatment, and coordinating effective multidisciplinary care. In addition, the faculty panel collaboratively reviews a patient case about which they share international perspectives on the nonpharmacological and pharmacological treatment of patients with HRS-AKI.

CONTENT AREAS

- Evaluation and Diagnosis
- Burden of Disease
- Pathophysiology
- Prevention Strategies
- Pharmacologic Treatment
- Vasoconstrictors
- Nonpharmacologic Treatment
- Multidisciplinary Care

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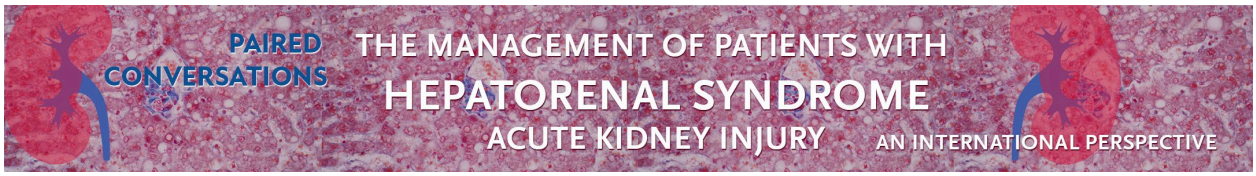

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Implement American Association for the Study of Liver Disease (AASLD) criteria in the diagnosis of patients with HRS-AKI
- Discuss the role of nonpharmacologic and pharmacologic therapies for the treatment of HRS-AKI according to current AASLD and Society of Critical Care Medicine (SCCM) guideline recommendations
- Compare the clinical pharmacology of currently available and emerging vasoconstrictors for HRS-AKI
- Describe the safety and efficacy of vasoconstrictor options for the treatment of patients with HRS-AKI, based on clinical trials and real-world, international experience
- Compare treatment approaches to HRS-AKI recommended in AASLD and SCCM guidelines
- Apply current guideline recommendations as a multidisciplinary care team in treating patients with HRS-AKI

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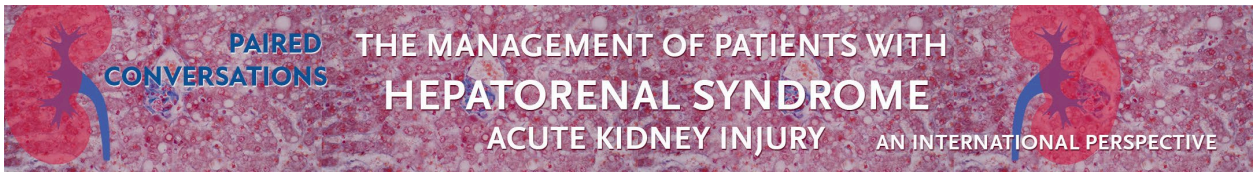

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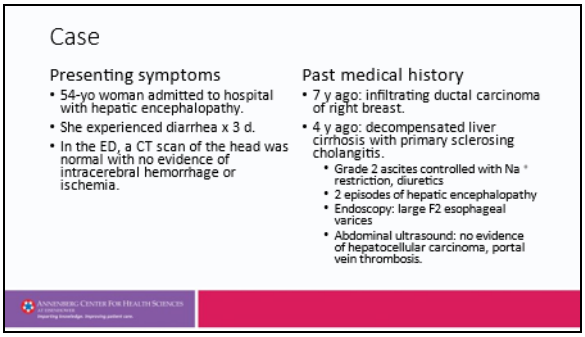
Editor's Note: This is a transcript of a presentation on May 27, 2022. It has been edited and condensed for clarity.

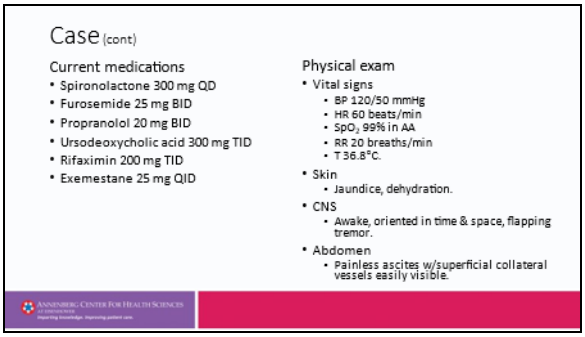
Module 1: Pathogenesis of Hepatorenal Syndrome (HRS)

Kevin Moore, PhD: Welcome everyone. I'm Kevin Moore from the University College London and the Royal Free Foundation Trust. Today, I'm joined with Paolo Angeli from University Hospital in Padova in Italy and we're going to be discussing the pathogenesis and clinical features of HRS-AKI, formerly known as hepatorenal syndrome. So, welcome Paolo.

Before we start, Paolo, I'd like us to talk a bit about the epidemiology and how hepatorenal syndrome develops, but I'd like to initially start off the discussion with a very simple case.

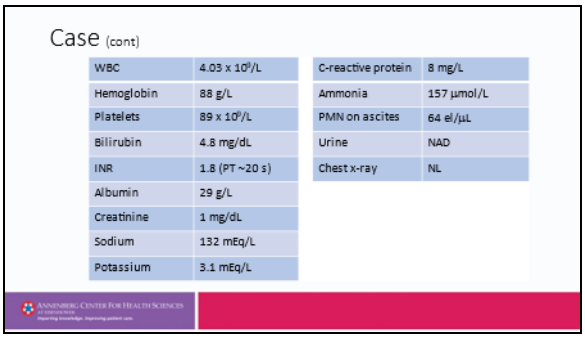


This is a case of a lady that was admitted earlier this year. She is 54 years old and she was admitted to hospital with hepatic encephalopathy. She had been unwell for 3 days with diarrhea and she was admitted with confusion. She had a past history of about 6, 7 years ago in 2015 of right breast cancer and was subsequently diagnosed with decompensated cirrhosis due to primary sclerosing cholangitis. She had ascites previously, hepatic encephalopathy and varices.



When she was admitted, she was taking diuretics. She was taking spironolactone 200 mg, a low dose of furosemide 25 mg, a beta blocker 20 mg twice daily, as well as ursodeoxycholic acid for primary sclerosing cholangitis. And she was on low-dose rifaxamin at 200 mg 3 times a day, as well as a drug for her breast cancer.

And when we examined her initially, her blood pressure was 120/50 which, given the diastolic was 50 mmHg, her mean arterial pressure was low at about 70 to 75 mmHg. She was bradycardic with a heart rate of 60. She was apyrexial, but she was clearly jaundiced. She had a flapping tremor and she had ascites.



Initial investigation showed that she was jaundiced, she had low platelet count,

prolonged INR and she had a high serum ammonia, about three times normal at 157. And we treated her initially with intravenous normal saline. We continued the rifaximin, added lactulose and then, a few days later, we noticed an increase in her serum bilirubin to 104 and her creatinine jumped to 182 µmol/L which is about twice normal at 2.1 mg/dL in non-SI terms.

In this patient, you have someone who has developed acute kidney injury, what features would make you think this lady had hepatorenal syndrome or HRS-AKI?

Paolo Angeli, MD: Thank you, Kevin. I think that the main factor in this patient is probably the development of a bacterial infection. You know, bacterial infection is, in 50 percent of the cases, the precipitating factor of organ failures in patients with cirrhosis and one of the most common organ failure is AKI that develops in 30 to 55% patients admitted to the hospital for a decompensating cirrhosis.

One other thing, I didn't see, in your presentation, any other potential precipitating event because dehydration was promptly corrected by saline infusion.

Kevin Moore, PhD: Yeah, yeah. You're right. I mean, she was admitted with normal renal function and, interestingly, her C-reactive protein was normal at 8 when she was admitted. But when we repeated it three days later, when she developed acute kidney injury, CRP had increased to 26 mg/L so that was consistent with a bacterial infection. And interestingly, her neutrophil count had also increased. So, it looks like there's some inflammatory process going on and you mentioned quite a staggering figure. You said 30 to 50% patients who develop bacterial infection with underlying cirrhosis develop acute kidney injuries.

Paolo Angeli, MD: So, then if we want to restrict the epidemiology to HRS-AKI, we should think of [the fact] that there are 4 different phenotypes of AKI in patients with cirrhosis, and HRS-AKI is not the most frequent. The most frequent is acute tubular necrosis AKI, followed by prerenal failure AKI, and HRS-AKI is only the third place in this classification. Only one-fifth of patients with AKI have HRS-AKI.

Kevin Moore, PhD: And how do you distinguish between the 2? Of course, with ATN, you're talking about acute tubular necrosis and hepatorenal syndrome, we really previously talked about it as being unexplained development of kidney failure in the absence of any identifiable cause, either pathologic or anatomic. How do you distinguish between HRS and the other causes? Prerenal you mentioned, you mentioned acute tubular necrosis, how do you distinguish between the 2, as a clinician?

Paolo Angeli, MD: As a clinician, I would start with the following: most of the cases of prerenal failure-AKI will be solved by plasma volume expansion.

Post-renal failure, the fourth phenotype of AKI in patients with cirrhosis is rare, so the real problem, the differential diagnosis is to differentiate between ATN-AKI and HRS-AKI. And what we apply is what you said before, our old definition of HRS. We defined HRS as a functional renal failure that means a renal failure without parenchymal damage. And how we rule out the parenchymal damage in the kidney, patient with HRS-AKI. First, because the patient does not have shock, as in this case. Second, because she was not treated with nephrotoxic drug, in this case. Third, because

she has no evidence of significant proteinuria and significant hematuria. The problem is that these old criteria are not sufficient to rule out the presence of parenchymal damage. What do you think on this?

Kevin Moore, PhD: Yes, it's a difficult one, isn't it, because patients with hepatorenal syndrome that have a functional renal failure in the whole way that we understand, as I understand it, electron microscopy studies have shown some degree of acute tubular necrosis, but it's quite clear that some of these patients progress from really being a functional renal failure that's quite easy to treat, to one that's very difficult to treat with established acute tubular necrosis. And it seems like there is a spectrum and at the far end of the spectrum is what we call classic acute tubular necrosis that doesn't respond to simple treatments that improve functional renal failure or renal function. There's obviously a spectrum and so people are now turning to biomarkers to try and distinguish between functional renal failure or HRS-AKI and acute tubular necrosis, and that can cause some problems because, say, if you had a urine sodium of 9 mmoles/L you have HRS, and if you have a urine sodium of 11 and you didn't, which, of course, doesn't really make sense. What do you do in your unit? Are you one of the, are you a fan of NGAL?

Paolo Angeli, MD: Yes, I fully agree on your comment. So, about the new biomarkers, if you use, for example, urinary NGAL or urinary IL-18, it is easy to show that normal values are present in patients with HRS-AKI according to the old diagnostic criteria, but not in patients with ATN-AKI. These 2 biomarkers can be used for facilitating the differential diagnosis in between the ATN-AKI and HRS-AKI. And let me say even to predict the response to terlipressin in patients with HRS-AKI according to your view that there is a continuum in the spectrum of the damage. The more severe parenchymal damage, the less probability to respond to the treatment.

Kevin Moore, PhD: Which is exactly what you would predict in the old days, you know, we're taught that patients with acute tubular necrosis wouldn't respond to terlipressin, whereas those with functional integrity of the renal endothelium and renal tubules and renal glomerular could respond.

Paolo Angeli, MD: Absolutely.

Kevin Moore, PhD: So, if you have, if you have a high NGAL and I can tell you, the NGAL in this particular patient was I think 145 or 148 mcg/mL, which is high. I can't remember the upper limits of normal, perhaps you can help me out there.

Paolo Angeli, MD: Normal.

Kevin Moore, PhD: What is the upper limits of normal, the NGAL?

Paolo Angeli, MD: I don't know the upper limit of normal. I can say if you have a value of urinary NGAL above 220 mcg/mL, it is very, very unlikely to respond to the treatment with terlipressin plus albumin.

Kevin Moore, PhD: Okay.

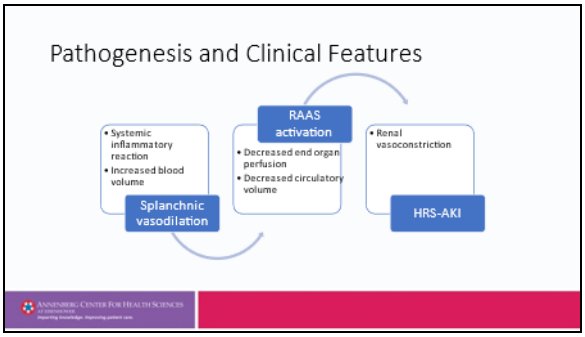
Paolo Angeli, MD: This is the threshold that we are using now in our unit to predict the response to terlipressin.

Kevin Moore, PhD: And, presumably that corresponds to some extent with the elevation in serum creatinine because we know that the

higher the serum creatinine, the less likely patients are to respond to terlipressin.

Paolo Angeli, MD: Absolutely. When we perform the multivariate analysis to detect predictor of response to terlipressin plus albumin, there were only 2 negative predictors, a high urinary NGAL value and the high plasma creatinine value. These were the only 2 negative predictors of the response. But we go back on this, I think, later on during the discussion.

Kevin Moore, PhD: Okay, so let's just change the conversation. So, we agree this lady has hepatorenal syndrome or HRS-AKI. What are the factors do you think that have led to her developing renal failure?



We know that she has cirrhosis. She's had a background history of decompensated liver disease. She presumably has some degree of systemic vasodilation, and we know that she's developed a bacterial infection. What is it that you think that's tipped her over into developing HRS-AKI?

Paolo Angeli, MD: You know, changing completely our mind over the pathophysiology of decompensation and development of organ failure during the last 10 years. Nowadays, we think that there are 2 important drivers, systemic inflammation and oxidative stress. And we think that even the presence of parenchymal damage are probably related to inflammation and oxidative stress. Other factors may be microvascular dysfunction and a direct tubular damage related, for example, to cholestasis. You know? To biliary salts not to bilirubin.

Kevin Moore, PhD: Okay.

Paolo Angeli, MD: You develop a lot of bilirubin inflammation and oxidative stress. What do you think?

Kevin Moore, PhD: Well, as you know, we were I think the first to describe in the mid-1990s, that if you inject low-dose endotoxin into cirrhotic rats, they develop kidney failure and have a high mortality. And we've put that down to increased oxidative stress, increased constitutional upregulation of NF-kappaB. In 1992, some 30 years ago, we published the first paper measuring the plasma F2-isoprostanes as being increased in patients with hepatorenal syndrome. And, of course, these are the gold standard for the measurement of oxidative stress. So, we know that patients with HRS have a marked oxidative stress. We know that patients with, or at least animal models with cirrhosis, are exquisitely sensitive to endotoxins and I think you're right, I think it's a combination of the 2, the inflammation, and we also know that these factors, at least endotoxemia, affects cardiac function. And, of course, we've not covered or mentioned the fact that many of these patients, whether they have an increased cardiac output, also have an impaired cardiac responsiveness to either sepsis or vasodilatation or hypotension. So, they will increase their cardiac output, but if you or I were to run for a bus, we'd increase our cardiac output by twofold. A patient with cirrhosis

might only increase it by 30%, which isn't really enough. In the same way, when they become septic, they increase their cardiac output but it's not enough to maintain the blood pressure.

And this lady, when she was admitted, her blood pressure was really quite low for an adult, 72 mean actual pressure, 72, 73, so it didn't take a lot to tip her down, to push her into renal failure. What do you think about the role of the heart?

Paolo Angeli, MD: Yes, I fully agree with you. I think that, you know, systemic inflammation and oxidative stress are the real cause of deterioration of the cardiovascular function. There are no other mechanisms by which portal hypertension and liver failure may induce the cardiocirculatory dysfunction. So, I think that these 2 drivers, together with portal hypertension, are crucial in the pathophysiology of decompensation and development of organ failure, particularly AKI.

Kevin Moore, PhD: Yes. And 1 of the things that we also identified some time ago was that increased nitration of cardiac proteins in animal models with impaired cardiac function. So, how that plays into the inflammatory cascade is a different question.

Just as we draw this conversation towards a close, we know that HRS occurs in patients with ascites, and that 40% of patients with cirrhosis develop ascites, we know that these patients have a 50% mortality, at 3 years. If there is refractory ascites, it's 50% mortality at 6 to 9 months. If they develop a hydrothorax, it's again very high mortality. You have done a lot of studies in patients with ascites, and in 1 of your studies 50% of them present with hyponatremia. What % of these go on to develop HRS during that, say, 1- or 5-year period? Do you have any figures on that?

Paolo Angeli, MD: I don't have a figure on that, but, you know, the presence of hyponatremia is for sure a predictor of the development of HRS because it is, let me say, a biomarker of what we discussed before, a very deteriorated cardiovascular function. And so this is a condition that may favor the development of AKI and, particularly, of HRS-AKI.

And unfortunately, we have not an effective treatment for this clinical condition in western countries, you know.

Kevin Moore, PhD: Okay, so what you're saying, just to be clear so I'm understanding this, you're saying that when patients present with spontaneous hyponatremia or hyponatremia for whatever cause, they are the group most at risk of developing HRS-AKI.

Paolo Angeli, MD: They should be followed more closely, more closely.

Kevin Moore, PhD: I think what I have in my mind is something, 19%, up to 15% to 19%, say 15% to 20% of patients will develop HRS-AKI who present with ascites over a 1- to 2-year period, something like that. So, it's quite a high percentage. And if you look at the discharge diagnosis of cirrhotics, about 3% to 4% have HRS-AKI as a diagnosis.

Module 2: Recognition and diagnosis

Mitra Nadim, MD: Today I'm joined with Dr. Ram Subramanian from Emory University and we're going to be talking about recognition and diagnosis of HRS-AKI. As many of you know, the definition for hepatorenal syndrome over the last 5 to 10 years has undergone a lot of

changes. Prior to 2012, there was no definition for AKI in patients with liver disease and, in 2012, the Acute Disease Quality Initiative, the ADQI group, came up with the first definition of AKI. Prior to that, it was just the definition of hepatorenal syndrome. And over the past decade, the International Club of Ascites has further modified these definitions, slightly revised the definitions of AKI and, because of that, the definition of HRS has also undergone some changes compared to what was prior to 2012. And again, over the years again, various societies have tweaked it a bit. The Society of Critical Care Medicine, the AASLD, have all made some slight changes to these definitions, but they have all pretty much followed the definition that was created in 2012.

I'm a nephrologist. Ram, you're a hepatologist and an intensivist, so I wanted to ask you, when you see a patient with liver disease and AKI, how do you, first of all, define that acute kidney injury in your patient population compared to maybe other patients that you may see in the ICU?

Ram Subramanian, MD: When I see a patient with preexisting cirrhosis and AKI, as you know, we need to start with a broad differential diagnosis and wearing my intensive care hat for a moment, the differential diagnosis widens even more. So, apart from a focus on HRS-AKI, we think about all the usual suspects, whether it's prerenal azotemia, whether it's ATN, especially in the setting of a septic-cirrhotic patient. So, I think, as we all know, the differential diagnosis needs to be broad to begin with and then you need the diagnostic criteria that we'll talk about more and initial therapeutic interventions that will help us tease out what could be the major driving etiology for the AKI.

The other brief comment I would make is, as you know, sometimes in the patient with cirrhosis with AKI, there could be multiple etiologies of the AKI coexisting at the same time and that is something that makes the diagnosis and management even more complicated, if you will, as we manage these patients. So, for example, you can have HRS-AKI coexist with a septic AKI, especially as we think about the newer concept of acute and chronic liver failure.

Mitra Nadim, MD: That becomes a problem for us also, as a nephrologist, because many of these patients have coexisting, they have NASH cirrhosis, they have diabetes, they have proteinuria and, right now, the definition excludes all of these patients for HRS if they have underlying proteinuria or if they have hematuria from let's say IgA nephropathy from alcohol. So, that kind of becomes a challenge for us. As a nephrologist, we tend to try to see if there's any previous urinalysis because, if there is, that proteinuria, at least in my mind, if that has not gotten worse and the patient meets the other criteria for HRS or HRS physiology, then I go ahead and treat that with whatever available medications there are, whether it's Levophed (norepinephrine) in the US or terlipressin outside of the US.

Going back to the current International Club of Ascites (ICA) definition, this is also what the ADQI group had come up with, is just this 0.3 mg increase in serum creatinine to define AKI within a 48-hour period or this change in creatinine by 1.5 times or 50%. But, when you put your ICU cap on, outside of hepatology, there's also this urine output criteria that currently does not exist in the current ICA definition. I wear a lot of hats similar to you. I'd like to hear what you think first, because again if you put on your hepatology hat, does the

presence of a drop in urine output or anuria, which is the current Kidney Disease Improving Outcomes (KDIGO) criteria, that should be included? Is that something that you think about when you're defining in clinical care, even if the creatinine doesn't go up in the patient?

Ram Subramanian, MD: Wearing my ICU hat, we have programs that look at the urine output very closely, especially as you're trying to stage the degree of AKI. I think this may be 1 of the limitations of the current HRS-AKI guidelines [which] is to deemphasize, or to not mention urine output, or the decrease in urine output as a criteria to gauge the progression of AKI. I echo your concerns about the current guidelines as far as whether moving forward we need to incorporate urine output, as well, in addition to the increase in creatinine that is currently existing in the revised guidelines.

Mitra Nadim, MD: One of the arguments has always been, well, to monitor urine output in clinical care, you need a Foley catheter, which is true. However, there are cases where we don't need the catheter or the catheter is in there for other reasons, the patient's encephalopathic. Now, the amount of drop may not be similar to the KDIGO criteria, but again it's something to consider when we think of AKI, because that ultimately will determine the presence of kidney injury. Then you go through that route of is this then HRS-AKI or other causes of AKI in these patients? But the awareness of "the creatinine may not go up but the urine is starting to drop so that there's a problem." Practically, if you're going to do a CT scan, maybe think a twice or dosing antibiotics. I don't know how it is at Emory, but in Los Angeles, a lot of these patients just show up on our doorsteps from a transfer from another hospital and the baseline serum creatinine is very tough sometimes to find. What do you do? Do you just pick whatever you have available? Or if it's 2½ months prior, it didn't meet that 1-week criteria, do you still consider that in the back of your head as the potential baseline?

Ram Subramanian, MD: You bring up a valid point. This is something that we struggle with as well: what is the baseline? This becomes very challenging, especially if it's a new transfer from outside the hospital and we have no access to immediate records. That is a problem as far as not having a baseline and then trying to define what is the delta increase. And then 1 limitation that we deal with and then we are left with re-zeroing the baseline to some degree when they hit the door.

This has implications regarding immediate management, but also this has implications regarding consideration for combined liver-kidney transplant, as well, because you have no idea about what is the baseline GFR of these patients. You bring up very valid issue that we deal with all the time.

Mitra Nadim, MD: Once you say "this patient has AKI," at our institution the MELDs are very high, I don't think we even, in the last 20 years I've worked [there], maybe 2 times we've done a kidney biopsy to determine if we thought it was acute glomerulonephritis (GN). I wonder, I know in the US, it's very few centers [that] may do a kidney biopsy, especially again the MELD has to be very low, but also the coagulation parameters have to be acceptable for a kidney biopsy. What algorithm do you follow and does kidney biopsy play a role?

Ram Subramanian, MD: We've experienced some unfortunate side effects from our kidney biopsies over the years and so we have shied away from using kidney biopsy for the reasons

that you've spoken about, primarily the risk of bleeding. Even if we optimize the hematologic parameters from a platelet standpoint, from an INR standpoint, it's been unpredictable as far as avoiding the risks of a kidney biopsy. From a diagnostic standpoint, we are deemphasizing kidney biopsies and then we are stuck with more noninvasive diagnostic criteria.

Mitra Nadim, MD: What are those? Let's say someone comes in with the creatinine doubled, what algorithm do you follow? Do you mainly only work in the ICU? Or do you also do the floor?

Ram Subramanian, MD: I spend time on both.

Mitra Nadim, MD: Because those are 2 different scenarios when a patient discharges to the floor. What's your approach, someone comes in and the creatinine's double, and they have anasarca and the creatinine's 2. What's your algorithm that you use?

Ram Subramanian, MD: One of the things we do is we have a low threshold to trigger a consult from our wiser nephrology colleagues. We get them on board sooner than later, and a significant part is to look at the urine. Looking at the urine microscopy and you look at a urinalysis to get more insight into the etiology, whether it's prerenal azotemia or frank acute tubular necrosis (ATN). And then we put it in the context of the clinical scenario as well. If you have a patient coming in with a history of lactulose-induced diarrhea, for example, or they've had hypovolemic trigger that may increase your clinical concern for a prerenal azotemia state. From a diagnostic standpoint, we're looking at serum creatinine, we're looking at urinalysis, a nephrology consult, and then we use our albumin challenge as an initial diagnostic step, if you will, replete the tank. The current guidelines would suggest 2 days of albumin therapy, in a 1 to 1.5 g/kg dose on day 1 and day 2, with a goal to see if you can potentially reverse the prerenal azotemia components.

That is the initial algorithm that we have. And then we're watching the numbers closely. And so I think it's important, especially if the patient originally shows up on the floor, to watch that AKI closely to make sure you don't have indication for escalating therapy to the ICU setting. As you know, these patients are so tenuous to begin with that we need to have a low threshold to look for progression of AKI that will have metabolic acidosis complications, for example, that can have major implications.

Mitra Nadim, MD: I personally still use the fractional excretion of sodium (FENa), I look at the urine sodium. There are a lot of studies coming out, some in the liver world, but even in the non-liver world, of just patients with AKI, that the fraction excretion of sodium can still be low in patients with ATN. This was recently shown, the data, in, again, noncirrhotic patients, that a percentage of patients even with a low fraction excretion of sodium can have granular cast which we, as nephrologists, say that's ATN. So, I still use it. Again, it's debatable. If it's low, it's hepatorenal, it can be either. If it's very, very low, less than some say 0.1%. Our urine sodium at our institution can't go less than 20%, it won't give us a number. It'll just say less than 20%. Do you personally consider a low FENa or a low fractional excretion of urea (FEUrea) to help you say, "yes, it looks more like one vs the other [ATN vs HRS-AKI]"?

Ram Subramanian, MD: We do look at the urine sodium and FENa values, but for the reasons you pointed out, I don't hang my hat, if

you will, on that piece of data knowing the caveats of how to interpret the FENa. Your point is well-taken: if it's (FENa) really low, then that may point towards HRS-AKI rather than prerenal azotemia. I think that's a useful clinical pearl. But having said that, we both acknowledge the limitations of using the FENa to make a firm diagnosis. And then the other thing that is complicating is that you can have 2 coexisting etiologies in that patient. That makes it even more complicated as far as using a specific diagnostic test to rule in a single diagnosis.

Mitra Nadim, MD: There's a lot of studies with biomarkers. The problem with a lot of these studies is that none of them have been biopsy-proven, but again it seems like the direction is going towards "can the biomarkers be added to some of the knowledge we have with, you put the FENa together, you put the physical exam"? Can it help guide mainly who's going to respond to certain treatments that exist for patients with HRS or is this not going to be a patient who's going to respond? I know in Europe, it's (biomarkers) used a little bit more. In the US, we really don't have much access to these biomarkers, NGAL, as easily. I think the pediatric world has started to use the NGAL in their pediatric population outside of liver, but it hasn't really made its way to the adult world. But, maybe, maybe that'll be the future of trying to help kind of narrow this.

Going back to the differential diagnosis, based on the ICA criteria, there's this algorithm: give 20%, 25% albumin. I personally think we sometimes think of 25% albumin as the same as the 5%. Where 5% is really volume, appropriate for someone who may be in septic shock or had too much diuretics. I sometimes feel that when we give the 25%, because we're going by the guidelines, we may not see an improvement because we really haven't volume-resuscitated them. If it's someone who has no edema, no peripheral edema where they can pull some of this volume, 25% may not be sufficient. I feel like sometimes it really should be 5% if they're really volume down vs those iffy, "can't really tell, okay let's give the 25%" that it may be a better differentiation. It's just that the way the guidelines are written, people may just stick to the 25% and I think, in some patients, that's not enough volume to reverse their AKI from, again, too much diuretics. Or if they have a massive bleed and you're waiting to get blood, the first treatment would be either 5% albumin or other crystalloids, LR volume. Putting on your hepatology hat, which is the floor patients vs your ICU patients, in the different kind of way they come to you, what do you think about the types of volume that we give them in order to make the differential between prerenal HRS and ATN?

Ram Subramanian, MD: You bring up a very interesting issue. I don't know of any studies that compare 5% to 25% in the setting of HRS-AKI. But your point is very valid, depending on the history of the patient and the volume status of the patient, I think there is latitude as to what resuscitation fluid you can use, whether it's crystalloids, blood, especially if you've got a severe bleed, and then 5% albumin, as you suggest, vs 25%. What is the right resuscitation fluid in that specific clinical context?

In the ICU setting, we have better tools than the floor to gauge volume status or adequacy of volume resuscitation. You've got echocardiography, you've got central lines to look at, central venous saturations. If the patient is intubated for some reason, then you have systems like Vigileo that can give you further assessment or preload and adequate volume resuscitation. We have opportunities to

have a better assessment of volume status in the ICU setting. And, as a sidebar note, I think, as we think about HRS-AKI diagnosis and management, I think point-of-care ultrasounds (POCUS). POCUS, which has become a standard of care that we use in many ICUs, will I think enhance our ability to assess volume status real-time and to . . .

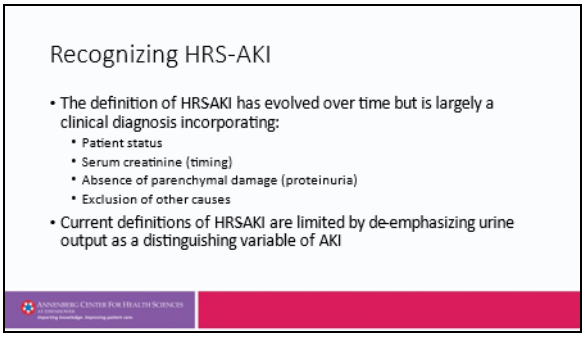
Mitra Nadim, MD: Is it easy to do with the patient if they have ascites?

Ram Subramanian, MD: I think the echocardiogram, when you're looking at intracardiac volumes, that should not be affected by what's happening below the diaphragm. But your point is well-taken. One of the things you look at is infrarenal cava (IVC) compressibility or, so that's right below the sternal notch. That can be affected by the presence of ascites. You've got to position the patient a certain way to sort of optimize the IVC imaging, but with those caveats I still feel that POCUS will have a potentially important application, especially in more of a critical care setting. In the ideal state, we have POCUS training on the floor that would be great for diagnosis and management, even if we're looking for complications following resuscitation. Pulmonary edema, you can do lung ultrasound to look for the evolution of the risk of pulmonary edema.

Mitra Nadim, MD: Somehow these patients can hide their fluid without, you know, it takes a lot, maybe they're used to this ascites and maybe not taking deep breaths, but all of a sudden they just, with 1 little insult, then they tip over and pulmonary edema and, you know, so it would be nice to be sort of saying, okay, there's some increase here. I like chest x-rays if the, oxygenation, if the saturations (sats) are dropping because it would be nice to be able to quickly just look with a POCUS, if they are starting to demonstrate B lines and starting to have evidence of congestion to maybe put a halt on whatever resuscitation is ongoing.

Once you've diagnosed "this is AKI," you've volume resuscitated them, and you've taken away the prerenal, then, what do you do after that?

Ram Subramanian, MD: If you've not seen evidence of ATN, you've given adequate volume challenge with albumin and you've seen no response to therapy or reversal in the creatinine rise, then, getting into stage II AKI, as defined by building of the creatinine, then it is time to consider vasoconstrictor therapy and that goes more to the sort of therapeutic aspect of this. But I think that our current algorithm is adequate volume challenge for 48 hours, get further input regarding the urinalysis and to rule out renal ischemia and rule out ATN. And I'll just mention, as a sidebar note, the other thing that, especially in the ICU setting, is to make sure you're not dealing with intraabdominal hypertension from tense ascites that could compromise renal dysfunction.



So, once you have ruled out all the other potential etiologies, then you start zooming in more on a presumptive diagnosis of HRS-AKI. It's almost a diagnostic exclusion, if you will.

And then that sets the stage for moving on to vasoconstrictive therapy.

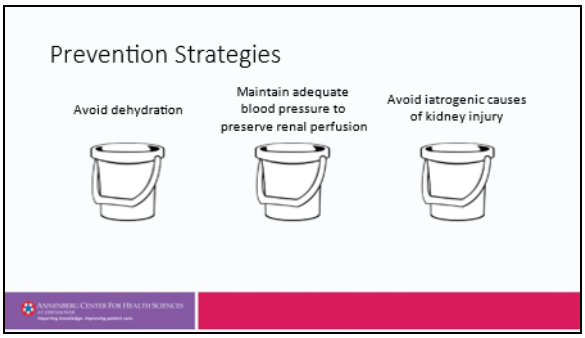
Module 3: Prevention strategies

Mitra Nadim, MD: I am Mitra Nadim and I'm joined today with Amanda Chaney and we're going to be discussing prevention strategies of HRS-AKI.

Patients with liver disease are at high risk for developing acute kidney injury and we're going to be talking about, before they develop this acute kidney injury, the most important thing is what should we do is to not only identify those who are going to be at risk for AKI, but more so identify which of these patients will develop hepatorenal syndrome and are there things that we can do as providers to prevent that from happening.

Amanda, I'm going to kind of start off by asking you, again as a provider for these patients, when they come to the hospital and, for reasons with no AKI, whether it's encephalopathy or paracentesis, what are some of the things that we should be thinking about to ensure that whatever we are doing during their hospitalization does not tip them over to develop acute kidney injury and potentially hepatorenal syndrome?

Amanda Chaney, DNP: Yeah, that's a really good question. For me, I like to lump it into 3 different buckets.



So, 1 bucket would be hydration status. So, anything that's going to make them dehydrated, I want to avoid those things. So, when I think of hydration, I'm thinking about diuretics. I'm thinking about large volume paracentesis, taking off too much volume too soon. So, that's 1 bucket. The second bucket would be blood pressure. I want them to have good renal perfusion to the kidneys. So, things that could decrease their blood pressure are going to be beta blockers. Do they really need to be on a beta blocker? Sepsis, any sort of infection. So, that definitely is going to drop their blood pressure if they're actively infected. So, thinking about hydration and blood pressure are 2 buckets and then the third is medications. Are there medications or anything given to the patient that could hurt the kidneys? And so, thinking about NSAIDs that can be toxic and injuring to the kidneys in patients with cirrhosis and also thinking about IV contrast. If we're sending them for imaging studies or if we're sending them for MRI, CT with contrast, number 1, is it a good idea to do that? And number 2, is the risk of hurting their kidneys outweighing any benefit that we would get with that imaging study? So, I kind of think of that in those 3 buckets as I approach a patient in the hospital.

Mitra Nadim, MD: And I think it's important what you just mentioned about the risks and benefits because we used to, the idea used to

be, well, if they have acute kidney injury or they're at risk, try to avoid all IV contrast. But a lot of times, they really need that in order to either get them ready for listing for liver transplantation or you're trying to diagnose some perforated bowel or something that you really need that contrast. I think it's very important what you mention is really this risk/benefit: that if the risk of not doing the study kind of outweighs it [proposed benefit], then we should go ahead and just kind of support them. And your comment about the nephrotoxic is very correct. Unfortunately, everything in this day and age, especially everything that a liver patient is on, is considered nephrotoxic. You have the proton pump inhibitors (PPIs) that are now considered nephrotoxic. You have vancomycin a lot of these patients are on and do you—because 1 of the problems I think is we forget, based on their nutritional status, that their creatinine of 1.0 mg/dL may be serious injury—is there a way that you communicate? Because the pharmacists, a lot of times they just look at the computer glomerular filtration rate (GFR) and it looks great. Is there a way that you, as a team, kind of communicate to say, hey, even though this creatinine is 0.9 mg/dL, this patient's GFR is really low and kind of watch some of these medications, whether it's vancomycin or we rarely use gentamicin anymore, but once in a while because they have resistant organisms, but is there a way that you kind of alert them to prevent things from happening which you know may happen if you get these medications?

Amanda Chaney, DNP: That's a really good point. Especially in the hospital setting, we do have a multidisciplinary team and so every day, sitting at rounds, going through those very specific details and making sure that we are covering all of those bases at the time, and then paying attention to what the patient's trends have been. So, if they, for months and months, have been a normal creatinine of 0.6 mg/dL and now they're 1.0 mg/dK, yes, that's still within the normal range, but it is high for them. And so, really taking into those considerations of the patient-specific and then watching those trends to see if there are adjustments that should be made. And should we have that goal for them be back down to 0.6 mg/dL or is 1.0 mg/dL okay? And having that conversation with the multidisciplinary team is really, really important.

Mitra Nadim, MD: It is, because these little things get missed and because these patients are very sarcopenic, they don't have any muscle mass to even generate, to even have a creatinine. And you mentioned also about this kind of large volume paracentesis or infections. Are there things that you do, again, if they have spontaneous bacterial peritonitis (SBP) or you predict they're going to have large volume and the question is what the definition of large volume is, what kind of prevention methods do you use? What are you giving? If you give them volume, what kind of volume? And at what dose you kind of do that? Again, this is with the goal of mitigating vs the treatment of HRS. But someone has SBP or large volume, what do you do to kind of hopefully prevent them from tipping over?

Amanda Chaney, DNP: One key piece of that is prevention of SBP. So, the patient with cirrhosis and ascites, we know that that's really what we're looking for when we're talking about HRS is that they do have cirrhosis and they have ascites. And so, when they are, when we are doing those paracenteses and we are evaluating that fluid, if the fluid has a low protein content, that is a risk factor for developing SBP. So, if we identify that early and we have that information really on their first ever tap, then we can go

ahead and put them on a preventative antibiotic to hopefully prevent SBP in the future. And so that would be one of the first things I would recommend is to really identify, if they are at a higher risk for developing SBP, and if they are, put them on a prevention antibiotic so that we have sort of nipped that in the bud, if you will.

The second piece is the large volume [paracentesis], as you mentioned. So, some people may think that that's 15 L and some people may have a lower threshold and say, no, that's more like 5 L. So, our practice guidelines do reflect more of an 8-L volume loss as being consistent with that definition of a large volume paracentesis. With that being said, if the patient normally gets 15 L off at a time which is, honestly, a huge amount of fluid to lose, then we want to prevent, again, the volume loss, the dehydration, the low blood pressure that can come from such a huge volume shift and we would want to err more toward that lower 8 L vs 15 L. And so, what I've done frequently in the past is if I've noticed a patient's creatinine starting to creep up, or even if I know that they are getting to that sort of volume that they're taking off at a time, I would discuss that with the ultrasound team. At the prior hospital I worked at, there was an ultrasound suite and so they would do those procedures in and out every day, every day. It could be a patient with cirrhosis, it could be not a patient with cirrhosis. So, they didn't really have that specialty practice sort of geared in their minds. They were just taking the volume off. And so, having that communication with them in the morning to say, hey, you've been getting 15 L off this person, but we really should aim more for 8 L. Don't take off more than 8 L today when you do that and just having that open, transparent conversation so that we're all on the same page to understand that the volume loss is critical to preventing harm to the kidneys for that particular patient.

And then you also mentioned [volume] replacement. So, ascites does and should be replaced with some volume and so the volume replacement typically is with albumin and we typically go . . . there's different albumin concentrations. So, there's the 12.5% and then there's the 25%. In my clinical practice, we're geared more for that 25%, that more concentrated albumin when the patient needs more protein, if you will, but doesn't need a huge amount of volume. And so, really that 25%, you can get 50 g and that could be 200 cc vs if you give 12.5% and you give 50 g, that's closer to a liter of fluid. And so, really paying attention to the different concentrations is important and then knowing why you're giving it is important.

Mitra Nadim, MD: You bring up a great point about what constitutes a large volume paracentesis and depending on the threshold, if we stay strictly to the guidelines of the EASL, the European guidelines, and the AASLD, it's 5 L. Anything more than that is considered high volume and then the amount of albumin, they have some specific guidelines, but at the end of the day, it comes to what does the patient look [like]? Do they need more than what it is? But it's typically, again as you mentioned, over 5 L, if you're starting to have 1 L per every 5 L above that, is you start giving them about 5 to 10 g of albumin per liter. The problem is that we kind of forget all of these, and a lot of times, if they're even 2 L, people throw in the albumin but they may need that albumin because they may not tolerate even that 2 L. And there's really never been any great randomized study, multicenter, to show should we be starting the albumin at a lower volume? Is it 5, is it 8, is it 10 where we should be? I think Dr. Angeli and

his group had shown that just people who come weekly for paras [paracentesis], giving them albumin long-term like every time has some benefit, but again very small study and a single study. There are things that, yes, it probably does mitigate hoping that they won't tip over. I think we all are just struggling what is that amount and I think it's going to be, as you said, what the patient looks like, can they even tolerate more than that. Sometimes when I see them take 10 L, I'm shaking [nervous].

And then for the SBP, as you mentioned, I agree with the antibiotics and things. I think what we tend to confuse, a lot of us, is that any infection—and I'm just curious—do you give albumin for any infection to mitigate this AKI or is it very specific to just SBP?

Amanda Chaney, DNP: I do think it is patient-specific. So, if a patient's coming in with ascites, with cirrhosis and they have a pneumonia, then yes, we would, we would treat the infection, treat the pneumonia. But then thinking about if they had an intraabdominal abscess that likely needs to be cultured, needs to be source of infection taken out, a drain put in, and then broad spectrum antibiotics until we find susceptibilities and narrow it down, those are the kind of patients that are going to get septic and have a tendency to get septic really, really quick. And so, thinking about when you put a patient on a prophylactic antibiotic vs being really aggressive at the time of them coming into the emergency room with maybe a low-grade fever, maybe some signs from sepsis, like do we go ahead and put them on prophylactic antibiotics when it's really a soft call, whether or not they have infection or not, but they're coming in, say, with encephalopathy too. And so, an infection might be brewing a little bit underneath and have precipitated a little bit of encephalopathy.

I tend, in my practice, to be a little bit more aggressive than not just because I've seen how bad it can get in the hospital setting with these patients. When they're so decompensated already, just 1 small little trigger can really throw them over the edge.

Mitra Nadim, MD: And do you have a cut-off? Because there's the cost of albumin, but there's also now more and more coming out that it can cause more pulmonary edema. Is there a cut-off value, once it's over 3.5 g/dL, I try to say, "you know what, maybe it's enough." I know it's in none of the guidelines, but do you have any set limit to say "no more albumin."

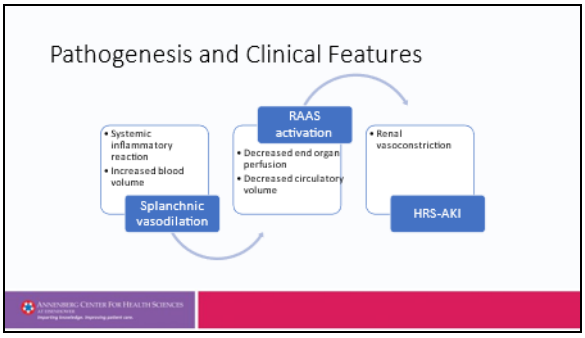
Amanda Chaney, DNP: Absolutely. So, when we get, most of the time for these patients, they're pretty critically ill and we're getting daily labs at least and so when I see that albumin come up from 1.4 g/dL when they came in, to now they're at 3.4 g/dL, 3.5 g/dL, I do go ahead and think about other routes for volume than albumin at that point. Because that is common in the literature where we're finding that more and more that there is this, there's some sort of magic number, we don't know what it is, but there's something in there that these patients cross this threshold between being euvolemic to being in volume overload. And so we do want to be very careful and look at that on a case-by-case basis and really that physical exam every day, maybe multiple times a day, is hugely important to make sure we're not crossing that threshold.

Module 4: Pharmacological treatments

Mitra Nadim, MD: Before we dive into the treatment, the pharmacologic treatment or the goals of treatment, I want to ask you, Ram, first

to give an overview of what your thoughts are on the pathophysiology of hepatorenal syndrome and that will help us kind of understand the treatment options and how they actually work in these patients.

Ram Subramanian, MD: One of the central drivers in decompensating cirrhosis and acute or chronic liver failure is the classic pathologic splanchnic vasodilation. And that has implications, both at the mesenteric level such as exacerbation of portal hypertension and ascites, variceal bleeding, but the other important concept is that because of the pathologic splanchnic vasodilation, even though you have an adequate or supranormal cardiac output, you have a shunting of your cardiac output into your splanchnic bed which then deflates the effective arterial blood volume, the central arterial blood volume, and that is what the kidneys see.



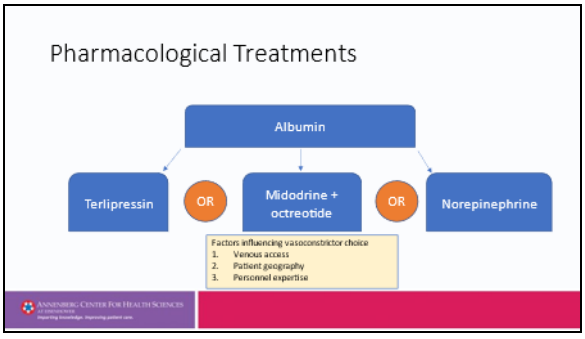
And that is, I think, a useful construct to think about the pathophysiology of HRS where you almost have a prerenal state and it is not because of traditional volume depletion, as we see in general prerenal azotemia, but it's a selective shunting of inadequate cardiac output into your splanchnic bed that then causes a decreased effective arterial blood volume and decrease in renal perfusion. So that physiology and that pathophysiology really sets the stage for and provides the mechanistic rationale for why a splanchnic vasoconstrictor could be useful in the treatment of hepatorenal syndrome.

Mitra Nadim, MD: Which is interesting because it's very counterintuitive to what you think with the kidney part because, as you mentioned, the kidney's seeing it as a low flow state so you have the activation of these renin angiotensin system with vasoconstriction and the thought of giving a vasoconstrictor can sometimes feel like is that counterintuitive, but based on what you said, it's actually trying to vasoconstrict the rest of the arterial, arteries, in order for the kidney to actually perfuse better in these cases.

If you want to broadly talk about some of the various vasoconstrictors that we use because there's certain vasoconstrictors that we use in the US, different from other countries, but also there's a difference, again, if you put your hepatology hat on when you see the patient on the general ward vs now you're an intensivist and the patient comes there, and how do these treatments vary, not only on location in the hospital, but their location as far as which country they actually present in with these problems.

Ram Subramanian, MD: We will start with the floor setting, the non-ICU setting, and again I think the presence of or the availability of terlipressin in the rest of the world, apart from North America, is a certainly useful construct to think about because, as a lot of us know, terlipressin is a potent, splanchnic vasoconstrictor. And proof of concept, going back to our pathophysiology, is terlipressin works very well for variceal bleeding because it squeezes in the splanchnic circulation and decreases inflow, but interestingly it is also standard of care in the rest of the world for the treatment of HRS-AKI.

And it sort of goes back to the pathophysiology we're talking about where it shuts off the splanchnic shunt, thereby rediverting blood flow to the central circulation and increases mean arterial pressure, interestingly, and then that translates and predictably translates to an improvement in renal perfusion and a reversal of HRS-AKI.



So, talking about specific therapies, terlipressin is a good example of a drug that'll work very well in a non-critically ill patient who is developing HRS-AKI on the floor, but also can be extended in the right setting to the ICU. Other potential therapies, in North America, our current standard of care is midodrine and octreotide which the data show good evidence to suggest that it is inferior to terlipressin and norepinephrine that we'll talk about with regard to reversal of HRS-AKI. And just of sort to go over the mechanistic rationale for that, even in the absence of great efficacy, is that midodrine is an alpha agonist which will improve your central mean arterial pressure, thereby trying to offset the splanchnic vasodilation of the splanchnic shunt. Octreotide is a surrogate, if you will, for terlipressin with regard to splanchnic vasoconstriction and we use it for variceal bleeding as well, but that is an example of an attempt to cut off the splanchnic shunt and redivert blood flow into the central circulation.

So that would be, in a nutshell, the mechanistic rationale for midodrine and octreotide. The third agent that now takes us into the ICU is norepinephrine and there the current evidence would suggest that norepinephrine is comparable in efficacy to terlipressin in the reversal of HRS-AKI. And the mechanistic rationale for norepinephrine, as you know, is again we use it all the time in a non-cirrhotic, critically ill patient for septic shock, to increase mean arterial pressure by venous vasoconstriction and even to improve sort of systemic vascular resistance. So, there is another example similar to midodrine where you're trying to increase your mean arterial pressure, thereby improve your effective arterial blood volume, and then try to improve renal perfusion.

Mitra Nadim, MD: One thing I see when, again as you mentioned, we have midodrine-octreotide that we start on the general ward in the US and I'm sure that's true of Emory. Many centers, it's very difficult to move a patient from the general ward to the ICU only for norepinephrine for HRS only. So, we start with this cocktail of midodrine and octreotide on the floor, but I think what people forget to look at is what's the goal for that and what mean arterial pressure, so if the patient, do you have a certain cut-off of the level mean arterial pressure they have to reach? And if they don't, forget it, it's not working? Or is it a change? So, if they're 55 mmg Hg, they have to be a certain number or do you have a cut-off they have to reach a MAP of? This is to say they have reached the targeted MAP for this medication is working or not working?

Ram Subramanian, MD: I'll share with you our practice here. For midodrine and octreotide, we are looking for response from a renal

standpoint, creatinine, urine output, on the floor we're talking about. We don't have clear guidelines regarding, similar to what we have for norepinephrine as far as an increase in mean arterial pressure. So, this from a practical standpoint, you start midodrine at 10 mg TID, do you increase that dose to a target a MAP increase of 10 mm Hg? We currently don't do that and I'd love to hear your thoughts on how you're doing it at your institution. But we're basically starting in a 10 mg TID, we can escalate to 15 TID of midodrine and we have octreotide. And we have, especially in the anasarcic patient, we are moving away from subcutaneous octreotide which is in 1 of the guidelines to move more to an IV infusion, similar to what we do for variceal bleeding and what you can do on the floor.

Mitra Nadim, MD: That's very interesting. So, instead of the TID of 200 microgram TID, it's a continuous infusion.

Ram Subramanian, MD: Similar to what we do for variceal bleeding. So, typically for variceal bleeding, you do a 50-microgram bolus then you do 50 micrograms per hour. If we have the typical cirrhotic, decompensated patient on the floor with massive anasarca and we have concern about subcutaneous absorption, we sometimes switch to an IV infusion in order to maximize the chance of achieving the splanchnic vasoconstriction that we're looking for with octreotide. So, that's sort of our strategy on the floor.

In the ICU, there is the opportunity to start norepinephrine and the open line is well-taken. Logistically, how do you justify in this day and age with limited ICU beds to make HRS-AKI indication for ICU transfer for norepinephrine? That is always a challenge. I feel fortunate at our center, we have the bandwidth to make that choice, especially if the patient is getting a bit shocky as well. So, if we have an added indication to get the patient to the ICU, let's say the MAP was at 65 mm Hg and now it's drifting down to 60 mm Hg, 55 mm Hg and you're concerned about a building septic process, that is an added sort of justification to get the patient to the ICU. And once you get them in the ICU, then you have the opportunity to place a central line which you'll need for norepinephrine and then you can start targeting that mean arterial pressure, not just for septic shock, over shock guidelines to a MAP of 65 mm Hg, but then you can say let's titrate the norepinephrine up so that we can take it to 75 mm Hg. And, as you know, there's data in the norepinephrine literature suggesting that if you increase your mean arterial pressure by 10 mm Hg in the setting, as you are trying to treat HRS-AKI, that is when you can start seeing a therapeutic benefit.

So, we use that strategy at times, not just shooting for a septic shock MAP target of 65 mm Hg but taking it to 75 mm Hg and with some success. I think our experience would mirror what is described in the literature with regard to norepinephrine efficacy for HRS-AKI.

Mitra Nadim, MD: So, what we do here, well, what I kind of do here is a lot of these algorithms for AKI-HRS, I feel, are sometimes a bit too slow. The treatment is 7.5 mg TID of midodrine. If it doesn't work, 10 mg TID the next day. If it doesn't work, 15 mg TID. If the creatinine's just going up too fast, I tell them to hit them with the maximum dose of octreotide, we don't do the IV, and the maximum dose of midodrine because, in 24 hours, if the MAP doesn't go up or you don't see a slowing, you kind of know they basically are going to fail this. They're not going to get better. Instead of waiting, again, 3 days to up-titrate the

midodrine. By that time, usually in 24, 48 hours if they've failed it, they always have pretty much an indication to go to the ICU because they most likely have a low MAP, renal failure, they're warranting CRT, a little bit of shock. Then, when they get there, again, sometimes we do give the Levophed to see if they improve, great, but very quickly, again within 24, 48 hours, but as you mentioned, are indications for the ICU. It's very difficult for us to move to say a patient that looks good, even though they're not really good, to send to the ICU just for Levophed. But there's always a little bit of shock, renal failure, probably is going to end up on CRT and if in the first 24 hours overnight, the ICU team wants to start norepinephrine, then so be it. If they end up urinating, great. If not, we've had a few cases you mentioned where the MAP, when it suddenly goes up but it has to go really up, and again that's where I think we fail is, what's that target? We say 15 points, but if we don't achieve it, then all of these medications are of no help to treatment of these patients.

Ram Subramanian, MD: Can I ask you a question as far as, and this goes to that empiric albumin challenge for 48 hours without vasoconstrictor therapy. Let's say you have a patient who's coming in with AKI and the creatinine's just rising right in front of your eyes and you have a sense that this is probably HRS-AKI. Do you wait for that 48 hours of albumin before you trigger vasoconstrictor therapy or, in certain cases, do you preemptively strike, let's say in the 24-hour time point of albumin with vasoconstrictor therapy?

Mitra Nadim, MD: If they have anasarca, in my judgment, they're not prerenal. They may be intravascular volume down, but they have so much total body water overloaded that it most likely is going to be an HRS kind of feeling to it. ATN, from my experience, doesn't go up as quick as HRS does. Hepatorenal is just, as you said, in front of your eyes, it's just going. So, if they have anasarca, I personally, if I'm on service, I say just forget that albumin, it's not going to work. This patient most likely has HRS and is going to go downhill. If they have no edema or they're iffy, I do the 25% if they're iffy with trace edema. If no edema, I actually go by the very, very old guidelines of hepatorenal where it was 1.5 L in the first 24 hours of diagnosis. I actually like that, if they have no edema, I throw in like 500 mL Q8 of albumin to them because it's a volume resuscitation vs 24, 48 hours. But if they have anasarca, I automatically assume it's HRS. It's that middle group that it's hard to tell and then I do the 25% for 24, 48 hours. But if the next day it's going up very quickly, most likely it's not going to slow down.

Ram Subramanian, MD: That's an interesting strategy. Just one of the concerns I have with the current guidelines is this waiting period of 48 hours.

Mitra Nadim, MD: Exactly.

Ram Subramanian, MD: Are we losing valuable time? And, as we know, early treatment results in a higher rate of reversal of HRS-AKI.

Mitra Nadim, MD: So, I think they have to be phenotyped. Again, I think the HRS-AKI, the AKI patient with no edema vs we can't tell, maybe POCUS will help us, but we can't really tell, there's some trace vs anasarca. I think anasarca and I think those are the patients who, if they're not treated quickly and that would be terlipressin-albumin but with diuretics. Otherwise, you're going to go into heart failure. And I do believe, as you said, we lose ground on waiting for 48 hours, because by the time you

get lab results, you're more than 48 hours. It ends up being 72 hours.

So, I think they should be phenotyped. I don't know what would be the way, but I kind of go by a volume status of very, very dry, very, very wet and then that middle ground is the harder one.

Ram Subramanian, MD: Yeah, I'm going to use that strategy now.

Again, a lot of our hepatologists still go by the guidelines of 24 hours and I think that's why we run into problems with albumin alone in an anasarca patient for 48 hours. And then they end up in the ICU and I think that becomes very late to give a vasoconstrictor in this. So, I think we really need to categorize these patients. They're don't behave the same, they just don't.

Module 5: Vasoconstrictors

Paolo Angeli, MD: In this module, we will review the pharmacological treatment of HRS-AKI and, as you know, it is a matter of fact that, in most of the countries in the world, the most common therapeutic option for HRS-AKI is the use of terlipressin plus albumin.

Terlipressin is not available on the market in the US, so our US colleagues should use other options, for example, norepinephrine plus albumin, midodrine plus octreotide and albumin in the management of these severe complications.

Terlipressin was introduced in the management of HRS-AKI because it is the most powerful vasoconstrictor capable to counteract the splanchnic arterial vasodilation, the most powerful vasoconstrictor capable to reduce portal pressure. So, to develop a positive action in the pathophysiological cascade of HRS.

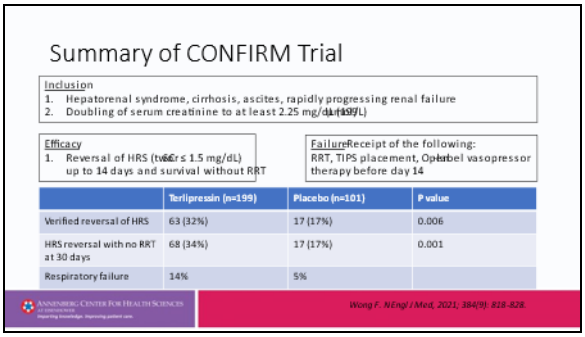
Welcome, Rahul, and I want to ask you, first of all, what are your thoughts on vasoconstrictor and particularly on the use of terlipressin according, for example, to the 3 US trials that were performed on this specific topic?

Rahul Nanchal, MD: As you well know, terlipressin is not available in the United States and therefore we do not have, in the US at least and elsewhere in Canada, there is not an option to use terlipressin for the treatment of HRS. However, my thoughts sort of echo your sentiments that terlipressin is probably the best agent that we have to use in the reversal of hepatorenal syndrome. I think 2 dozen trials or 2 dozen randomized, controlled trials, the largest 1 of them being the CONFIRM study, which randomized approximately 200 patients to terlipressin, 100 patients to placebo. And the results speak for themselves that the reversal of hepatorenal syndrome and the reversal without dialysis was—and sustained reversal over 30 days—was much better with terlipressin.

Now, you know the data as to whether to use terlipressin or as compared to norepinephrine and albumin are a little less clear. I think the last Cochrane analysis did suggest that there were not very big differences between terlipressin and norepinephrine, however the strength of evidence was very weak. In the US, we are sort of bound to using norepinephrine, because of the nonavailability of terlipressin, or midodrine and octreotide, again because of the nonavailability of terlipressin. However, I'm curious to [know on] your part what you think, in countries or in regions where terlipressin is not available, what your thoughts are on what sort of vasoconstrictor should be used.

Paolo Angeli, MD: Well, it is a difficult task because if you look to what we have in terms of randomized, controlled clinical trials, on potential alternative to terlipressin, we have 2 small randomized, controlled clinical trials, both coming from India, comparing norepinephrine plus albumin vs terlipressin plus albumin. And in both these trials, norepinephrine was shown to be as effective as terlipressin in terms of recovery of renal function and 1-month survival.

But, when HRS-AKI develops in the setting of acute and chronic liver failure, it has been shown in another controlled clinical trial coming from India that terlipressin is much more effective than norepinephrine. I don't know why, but probably terlipressin is not only capable to counteract the splanchnic arterial vasodilation, it is capable to develop an anti-inflammatory action. For example, in the arterial vascular wall, it has been shown that it is capable to counteract the activity of nitric oxide synthesis at that level. And this may be important, and this probably makes the difference in the treatment of HRS-AKI in this setting at least.



May I ask you, going back to the US trials and particularly the last one, the CONFIRM trial, do you think that the final results could have been completely different, I mean much more positive, if the protocol had used the new criteria for the definition of HRS-AKI? Because, you know, the CONFIRM trial was based on the old criteria, so they expected the serum creatinine to go beyond 2.5 mg/dL before making the diagnosis. And, at the end, the mean serum creatinine at randomization was very high, equal or higher than 3.5 mg/dL. And you know that the higher level of serum creatinine at which you start the treatment, the lower rate of response you will get from the treatment. What do you think?

Rahul Nanchal, MD: So, Paolo, you know, that's an excellent point and you also bring up an interesting sort of perspective on the use of serum creatinine regardless of what drug you use or what vasoconstrictor you choose for defining of acute kidney injury syndromes and we all know the sort of drawbacks of this. And I completely agree with you that if the newer criteria had been used it is very possible that we would have had a much, much more positive result in terms of reversal of hepatorenal syndrome. I am not so sure that we would have still seen a mortality benefit or not, but I'm pretty certain that we would probably have seen a reversal of, you know, much more robust reversal of hepatorenal syndrome.

Now, again, that still leaves us in a conundrum. I hear what you said about the clinical trials for norepinephrine. I think there have been, I think, 6 or 7 more trials out of a variety of places, very, very small, but that is the limitation of most of these trials that have compared terlipressin and albumin vs norepinephrine and albumin: they're very, very small sample size and, therefore, even in the meta-analyses, you do not get a directional effect in any of these trials. And that is, I think, 1 argument I've heard as well, there is no difference between norepinephrine and terlipressin. I wonder what would happen if you did a well-powered, large,

randomized, controlled trial comparing terlipressin and norepinephrine. Again, curious about your thoughts and curious as to what you think.

Paolo Angeli, MD: Well, great point about, we need these trials. We need these trials, Rahul, but based on the new criteria for the definition of HRS-AKI.

I want to complete the answer to your question. I didn't speak about midodrine and octreotide. I was the first to introduce this therapeutical option, but when we had the opportunity to compare it with terlipressin plus albumin in a small, but randomized, controlled clinical trial, we proved that it was quite less effective because midodrine, even given with octreotide, is not capable to increase enough the mean arterial pressure. And you know, there is a relationship between the level of serum creatinine at which you start the treatment and the increasing mean arterial pressure you need to get the response from the treatment. And, let me say that midodrine plus octreotide is not capable, again, to increase enough mean arterial pressure.

Rahul Nanchal, MD: So again, that's a good point, Paolo, and just so that the viewers sort of know, the latest meta-analysis and systematic review that is coming out of the Canadian Critical Care Trials group, sorry not the Canadian Critical Care Trials, but the Guide group which shows the inferiority of midodrine and octreotide as compared to terlipressin in a much more robust fashion. Even in that meta-analysis now, we are shown that terlipressin is much better than midodrine and octreotide. However, so has norepinephrine, norepinephrine has demonstrated to be better as well and for exactly the same reasons you are talking about.

In the United States and in countries and regions where terlipressin is not available, I think the limitation becomes the need for a central venous line and a continuous infusion of norepinephrine which, in most countries, requires admission to an intensive care unit vs. midodrine and octreotide where you can administer on the floor. And so, even if you start out with norepinephrine, the conundrum again becomes how long you keep these people on norepinephrine? When do you transition them to some oral therapy? What are the risks vs. benefits and what are the risks of central line and infusions of these vasopressor agents? And, what are the costs associated with keeping someone [in the ICU]? I think all of these questions are good questions and I think therefore a lot of people sort of use midodrine and octreotide for these reasons, even though I think in clinical trials and meta-analyses, it is likely that norepinephrine and terlipressin are superior to these, to this modality of treatment.

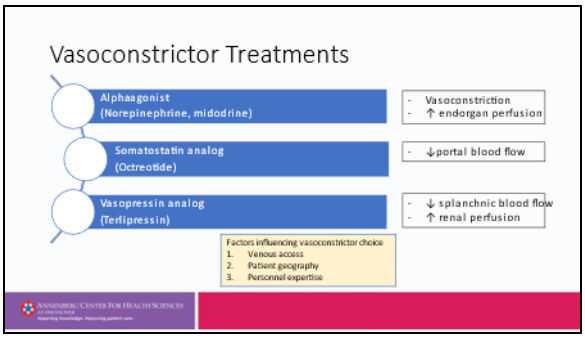
Paolo Angeli, MD: Yeah, absolutely. I fully agree with your comment. So, what do you think about the way of administration of terlipressin? Because I saw that in the CONFIRM trial, the rate of severe adverse effect was high enough, particularly they describe respiratory failure related to the use of terlipressin plus albumin. I don't think it was respiratory failure, but a volume overload that is a quite common adverse effect of this treatment.

Rahul Nanchal, MD: So first, I am in total agreement that a lot of respiratory failure in hepatorenal, especially with hepatorenal syndrome, comes because of hypervolemia. I think people don't pay close attention to volume status. You know, albumin is continued and there is not enough guidance on when to

stop albumin therapy and when to limit it and things of that nature. And so, I think that is an incredibly important point and people should be very, very cognizant of carefully evaluating volume status in people with cirrhosis, acute on chronic liver failure, end-stage liver disease, whatever you may call it.

As to the route of administration of terlipressin, I was pleasantly surprised by a couple of colleagues in Australia when they had said that they actually do terlipressin infusions at home. They send people home and there's a nurse that comes out there and does these things at home and so we don't have terlipressin, so I actually don't have a lot of experience using the drug. I have read the literature on these bolus infusions vs continuous infusions and there does seem like there might be an advantage to doing continuous infusions of terlipressin.

Paolo Angeli, MD: I think that if we look to the real-world evidence in most of the countries, terlipressin is now used by intravenous continuous infusion.



And the reason is quite simple: when you use terlipressin by continuous intravenous infusion, you assure a continuous lowering effect on portal pressure. This is not the case when you use terlipressin by intravenous bolus because the time between 1 bolus and the next one ranges from 4 to 6 hours and the effect of terlipressin on portal pressure does not last for more than 3 hours. So, when you use terlipressin by continuous intravenous infusion, you can use a lower dose than intravenous bolus. You can reduce almost by half the rate of adverse effects. You can treat a larger number of patients. You can continue and finish the treatment in a larger number of patients. And we are speaking about the treatment that is life-saving, not only in responders, but in all treated patients, that can change the outcome of liver transplantation, can reduce the rate of development of CKD at 1 year after liver transplantation. So, I think it is important to use terlipressin by continuous intravenous infusion.

And I'm very happy to see that also in the AASLD practical guidance, this option is highlighted. And I hope that you will have soon terlipressin on the market to develop the same experience that we developed during the last years.

Rahul Nanchal, MD: I think the evidence is there. It is clear that we do need terlipressin and, again, it is easier to administer, it does not require admission to the intensive care unit, it is easier to administer on the floor because, in some countries, people take it at home. And so, it's just a fantastic treatment option, I think, and both the AASLD guidelines and the SCCM guidelines actually allude to the use of vasoconstrictors. The SCCM guidelines, I think, we were sort of intentionally a little vague and just said, you have to consider a vasoconstrictor because, again, all of the meta-analyses did not, for 2 reasons: 1, terlipressin is not available in North America and, 2, that the meta-analyses did not really show very much difference between the use of norepinephrine or vasopressin, or terlipressin.

Paolo Angeli, MD: Another point that we can develop briefly is the contraindication to the use of terlipressin and other most powerful vasoconstrictors. And also to highlight how to monitor patients during the treatment, you know. Because it is a matter of fact that there are some serious cardiovascular effects and so it is important in my view to select carefully the patient before starting the treatment, avoiding the treatment in patients with ischemic heart disease, severe peripheral ischemic arterial disease, for example. What do you think?

Rahul Nanchal, MD: I think you're right, Paolo, the main side effects are related to ischemic events, ischemic events of the digits, ischemic heart disease or ischemic cardiac events and so that is the main, I think sort of the main thing to watch out for and to carefully select patients who don't have terrible ischemic heart disease or terrible peripheral vascular disease. In terms of norepinephrine, really it's probably worthwhile watching people with arrhythmias from the vasoconstrictor infusion or the norepinephrine infusion. I think that's another area that you have to watch more carefully. But I think that is the main group of patients that need careful monitoring.

Paolo Angeli, MD: Of course, these patients should be closely followed during the treatment and I want to highlight that, in most of them, the development of abdominal pain of the area, in most of the cases is only a transient event. So, my advice is to monitor closely and not to stop immediately the treatment. What you can do is to reduce initially the dose and to wait and see how this adverse effect may develop or may disappear, you know.

Module 6: Late-stage treatments

Kevin Moore, PhD: So, Rahul, many of us will have experienced the patient with hepatorenal syndrome who has been given vasoconstrictor therapy, intravenous fluids, intravenous albumin, but who, despite everything, has an inexorable decline in renal function. What are the things that go through your mind in terms of alternative treatments or other therapies that we could apply to see whether we could approve that renal function?

Rahul Nanchal, MD: I think all of us are faced with these, anyone who takes care of patients with liver disease and hepatorenal syndrome. It's not frequently, I should say, that we are faced with such a circumstance where vasoconstrictor therapy and expansion of intravascular volumes fail and there's still a decline in overall renal function and the patient status. I think the thoughts that go through my mind at that time are, obviously, renal replacement therapy, especially if you're using it as a bridge to liver transplantation and the other thing that crosses your mind, especially in people who have refractory ascites or have chronic kidney disease, to see if you can get their renal function to get better.

Kevin Moore, PhD: Let's take a patient who has end-stage liver disease. They're not listed for liver transplant, for whatever reason. And let's say they're 65 years old, not too old for liver transplant, they've been drinking right up until recently, but HRS. And they fail to respond. Would you, and if you've been treating them now for 2 weeks or so and renal function just got worse and worse, would you offer them renal support?

Rahul Nanchal, MD: You know, the perspective in North America and especially in the US is a little different. So, I think the short answer to your question is, depending on family wishes,

yes on a limited trial. Even if you were to offer a time-limited trial, saying, "hey you know, let's talk in a week or 2 weeks or whatnot, and if all of this fails, then we are sort of looking at removing life-sustaining therapies."

Kevin Moore, PhD: Okay, and if they were on a transplant list, presumably you'd recalculate their MELD score, see whether or not one's available, but, in the meantime, you'd offer them renal support. Is that roughly how . . .

Rahul Nanchal, MD: Yeah, I think that is likely how it works. I'm very curious, maybe I should ask you what your perspective in England is to the same patient: someone who comes in and is not listed, is on the older end of the spectrum, is not listed for liver transplant and has failed sort of the existing therapies.

Kevin Moore, PhD: The way I work it is if they have a reversible element to their deterioration in their liver function, then I would consider treatment because most patients who develop HRS-AKI normally have a deterioration in their liver function. Occasionally, you have patients who have end-stage cirrhosis who just gradually creep on and on and on and then their liver fails. It's end-stage liver failure and there's nothing you can do. Dialysis just prolongs death; it's not worth it. On the other hand, you've got some patients who may develop, say, alcoholic hepatitis on the background of the cirrhosis and then I would support them because the alcoholic hepatitis will reverse in maybe 20%, 30% of patients and, in that situation, if you keep them alive long enough, the kidneys will recover.

And I remember years ago, probably 20, 30 years ago, I remember dialyzing I think we had, this was before terlipressin, we had about 20 patients with alcoholic hepatitis who I dialyzed and our survival rate was about 3 out of 20. Wasn't many, but it was still 15% which, if you're 50 years old or 60 years old, is worth it against 100% mortality. So, I think renal support is worth it, providing there's a reversible element to their liver dysfunction and that includes sepsis, alcoholic hepatitis or some acute event that's caused them to tip over, that you can reverse. Does that make sense?

Rahul Nanchal, MD: It makes sense.

Kevin Moore, PhD: When do you use TIPS?

Rahul Nanchal, MD: Usually with refractory ascites. So, I think you have some who has refractory ascites and I think the physiological, if you think about, honestly if you look at the evidence for TIPS in hepatorenal syndrome, I don't know, 8, 9 sort of properly done or semi-properly done randomized, controlled trials of 130 overall patients in all, across all of the trials and so not the greatest of evidence, but if you look at what it does physiologically, I think it makes sense in refractory ascites. Probably consider it in someone who has chronic kidney disease.

Kevin Moore, PhD: I mean, it makes sense for refractory ascites which is what used to called HRS type II or chronic kidney disease HRS, because that has quite a slow course and, of

course, TIPS doesn't work overnight. It takes a while to become most effective. So, the idea of using TIPS for rapidly progressive HRS doesn't really work, in my experience. But for slow HRS, if you want a better word chronic kidney disease-HRS or whatever nomenclature you use, we know the patients we're talking about, refractory ascites patients, there it can have a big benefit, providing the heart can withstand it and providing they don't have background of low grade hepatoencephalopathy.

The other situation that we're sometimes faced with is the patient who presents with, I had 1 just last week, young woman, recently discharged, alcoholic liver disease, re-presents to my clinic [with] tense ascites and gross peripheral edema. Had started drinking again. And it didn't even occur to me that she was going to have HRS-AKI, but she did. She had a blood creatinine of about 3.3 mg/dL in your terms. And when you have a patient who has tense ascites, do you treat them? Do you drain the ascites? I mean, it's quite a controversial, obviously attack the ascites looking for spontaneous fracture or peritonitis and let's say for the sake of argument it came back with a high neutrophil count. Would you drain off the fluid because there are hemodynamic advantages to doing so? Or do you just give them antibiotics and hope for the best? What is your approach?

Rahul Nanchal, MD: It's an interesting question and I think there are likely different approaches to it, depending on where you are. Now, as you had mentioned, there are some hemodynamic benefits in terms of both hemodynamics in the arterial and venous side and intraabdominal hypertension, if they really have tense ascites. And obviously, as I think everyone knows, you drain the ascites, you cause a reduction in afterload because of vasodilation, especially in the splanchnic bed and so they're both sort of counteracting forces. And so, I think careful drainage of ascites, especially monitoring intraabdominal pressure as you do it, probably can be beneficial because it can lead to both renal perfusion benefits, both on the venous and the arterial side.

Kevin Moore, PhD: Yeah, so we actually published a study in 1990, so that's a long time ago now, in which we took 26 patients, maybe it was 22, maybe 25 patients, and we put in a Swan-Ganz catheter and we drained off around about 10.5 L of fluid. And we drained them as fast as we could. So, if we could drain them in 2 hours, we'd drain off 10.5 L in 2 hours. And what we observed is, as you'd expect, the intraabdominal pressure just falls exponentially. And because the pressure inside the sphere is proportional to $1/r^4$ (radius). Once you start, when you have a tense sphere, once you remove even 1 L of fluid out of 10 L, the pressure drops dramatically.

So, for that reason alone, actually the speed of paracentesis, once you drain off the first liter, you might as well just drain the whole off really because all the hemodynamics sequelae are proportional to the pressure changes. And you can even show that when you did an echocardiogram that the ascites compressed the right atrium. So, as you drain the fluid off, not only did intraabdominal pressure fall, the right atrial pressure fell acutely as well. And that was followed by an increase in cardiac output at about 3 hours. It was only later, at about 6 hours and beyond, that the cardiopulmonary wedge pressure fell as intravascular volume fell. So, in other words, what you have is a window when you drain off the fluid, you have an abrupt reduction in intraabdominal pressure and renal venous pressure. And that causes renal vasodilatation

but you also get splanchnic vasodilatation. So, providing you can give a vasoconstrictor to reduce the decrease in blood pressure and therefore the decrease in renal perfusion pressure, theoretically you can have a renal benefit with large volume paracentesis, with a vasopressor together with large volume paracentesis. And that's sort of the kind of theory or at least theoretically what we believe, or I believe anyway, can happen.

Rahul Nanchal, MD: That's interesting that you say that because I guess the right atrial pressure fall is probably the improved thoracoabdominal compliance that you're getting once you drain the ascites and reduction in external pressure because it just follows probably becoming more compliant once you drain the ascites and make the abdominal, or abdomen, more compliant.

So, very interesting physiology.

Kevin Moore, PhD: Yeah, it's very interesting. And in terms of your overall approach, do you involve people from different teams in discussing the care of these patients? I mean, I've worked in teams where the hepatologist dictates the treatment; other teams where the nephrologist dictates the treatment; others where intensive care dictates the treatment. How does it work where you work? Is it multi minds medicine or is it 1 person in charge and they decide?

Rahul Nanchal, MD: Yeah, I think there is nothing without a team these days. Everything is a team sport. One person can't know everything, can't do everything. So, we have a very robust team model. I think that is not, you know . . . Obviously, the patient's admitted under 1 person and that person is responsible for their overall care. But the treatment and the plan is . . . we make a plan collaboratively and it's a team of hepatologists and nephrologists and intensivists that do it.

Kevin Moore, PhD: And just 1 last question. Going back to where we were talking, right at the beginning, about a patient who is on the liver transplant waiting list. They develop HRS, they're on renal support. I think it's fair to say in the UK, there's been a bit of a reluctance to transplant these patients, even though the data clearly show it's a really great treatment for HRS. In the States, I get the impression that you transplant quite a lot of these patients, don't you, because it tips their MELD criteria high and they prioritize over and above everyone else anyway. Is that how it works?

Rahul Nanchal, MD: It does and, you know, we do. Obviously there are liver-kidney transplants, combined liver-kidney transplants as well and so, yes, you essentially are right. That's how it works.

Kevin Moore, PhD: How do you decide whether you do liver and kidney or just a kidney, just a liver alone?

Rahul Nanchal, MD: I think the OPTN, Organ Procurement Transplant Network, here has criteria and so some of them, without going into a lot of detail, some of the criteria are if you have AKI for more than 6 weeks.

Kevin Moore, PhD: Okay, so acute, if it's acute, just liver. If it's chronic, then there is some discussion?

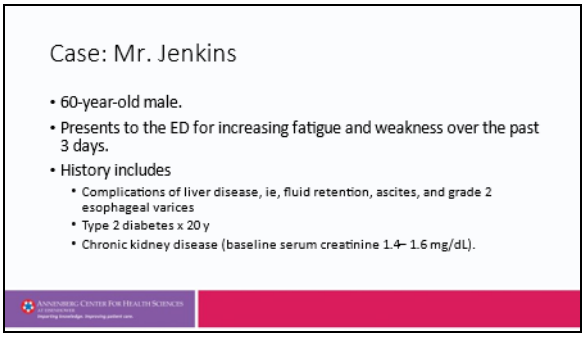
Rahul Nanchal, MD: Or if you have, you know, AKI for more than 6 weeks, then you're eligible for a liver-kidney transplant as well.

Kevin Moore, PhD: Is there anything else that we ought to perhaps cover in terms of the late

nonpharmacologic treatment options that we have available? Especially 1 thing I would say if you want to think about it is always check the drug chart. I always remember coming in 1 day and finding a patient gone in to renal failure and I couldn't figure out what the hell it was and some well-meaning doctor, because the nurse said, "oh so-and-so's got back pain," had started my patient on a nonsteroidal anti-inflammatory drug and they've written it on the PRN chart and it was being given and it wasn't on the main chart. And it just didn't flag up. And so be careful of what others prescribe in your name! They may be well-meaning, but it may not do the patients the best. So, again, always look back at the chart and make sure nobody's tried to poison your patient behind your back.

Module 7: Faculty panel

Kevin Moore, PhD: Okay, welcome everyone. Now, we're going to turn to module 7 where we discuss a real-life patient. We've heard throughout the modules that there are a number of different treatment options that are available, ranging from vasoconstrictor therapy, important antimicrobials, fluid replacement as well as alternative treatments when those treatments fail. Let's just take it and discuss a real patient.



Mr. Jenkins is a 60-year-old male. He presents to the emergency room with increasing fatigue and weakness over the previous 3 days. He's known to have a background history of chronic liver disease with previous fluid retention, ascites and he's known to have grade 2 esophageal varices. Ram, can I just take you through, back to just that initial presentation. You've got somebody who presents with a background of known chronic liver disease with previous ascites and grade 2 varices. I should tell you he's also known to have type 2 diabetes and chronic kidney disease. And he presents with this increasing fatigue and weakness. And I know we're talking about hepatorenal syndrome, but we, as clinicians, we need to keep our horizons broad because we have to think about other things that aren't necessarily within our specialty. What would go through your mind when the patient presents in that way?

Ram Subramanian, MD: So, as I hear the scenario, sort of a few, sort of top of the list options. One, I would be concerned about a potential infectious trigger when we're dealing with an immunocompromised host. We have cirrhosis and the chronic kidney disease, so is there an infectious process brewing that's causing these nonspecific symptoms? So, that would be something I would think about. Then, again, thinking more broadly, is there a metabolic disturbance? He's got a history of chronic kidney disease, does he have worsening kidney dysfunction that is causing, for example, uremic symptoms? The other thing on the differential would be worsening hepatic derangement. Is he developing worsening hepatic dysfunction that could be presenting as the early signs of maybe hepatic encephalopathy? And then the other thought would be just, again, going down the biochemical pathway, he has a history of varices, we haven't heard anything about melena or obvious signs of bleeding. Are these

not specific symptoms, a first sign of a symptomatic anemia? So, those would be some initial thoughts as far as to explain these general, sort of constitutional symptoms.

Kevin Moore, PhD: Yeah, and I think that kind of covers everything really: sepsis, worsening anemia, perhaps a former background of bleeding, as well as hepatic decompensation or further decompensation of his renal disease.

Paolo Angeli, MD: May I have some comments?

Kevin Moore, PhD: Yeah, of course. Of course, Paolo.

Paolo Angeli, MD: Well, the first thought in front of a patient like this I have is that probably we know nothing about alcohol consumption, but we think about a NASH cirrhosis with evidence of decompensation and in order to explain the last appearing symptoms, I will ask if she was taking beta blocker, at which dosage for example, and then I will start immediately a work-up for bacterial infection because every patient with decompensated cirrhosis admitted to the hospital, even with no specific symptom of bacterial infection, should be investigated for bacterial infection.

Kevin Moore, PhD: Well, I can tell you this patient has never had a heavy alcohol history. They've been abstinent, pretty well abstinent. They're not teetotaler, but they only have a drink once or twice a year on special occasions. Known to have background type 2 diabetes for about 20 years and they have previously been investigated and have excluded chronic viral hepatitis, chronic liver disease, all the other diseases have been excluded. So, the presumption, I agree with you is NASH cirrhosis and then they present with this fatigue.

Paolo Angeli, MD: Yeah, sorry, another thing I would like to know if he has some value on serum creatinine during the last week, during the last 3 months.

Kevin Moore, PhD: Well, we haven't got there yet. We're coming on to that bit shortly. So, we know that the patient has type 2 diabetes and chronic kidney disease and their baseline creatinine, as you just so asked, is around about 1.4 to 1.6 mg/dL. And the serum creatinine, on presentation today to the emergency department, was 3.5 mg/dL. Mitra, what would your reaction be to that? You've got this 60-year-old man, NASH cirrhosis, fatigue and weakness and clear deterioration in their renal function. So, the creatinine's gone up, just to remind you, from about 1.5 mg/dL to about 3.5 mg/dL. So, a really 2½-fold increase. What does that tell you and how does that help you classify, there's all these different RIFLE classifications.

Mitra Nadim, MD: Well, the RIFLE criteria are 20, but as a nephrologist, the creatinine number really means absolutely nothing. It really comes down to what does the patient look like. Even at a creatinine of 1.4 mg/dL, if you have a patient who is sarcopenic, they could have NASH cirrhosis but over time, for whatever reason now, they just are sarcopenic, a creatinine of 1.4 mg/dL, the GFR for that may be already like 20 or 22 mL/min if they're very sarcopenic. So, a 3.5 mg/dL, and again depending on how it is, the patient could be very uremic, in fact, with 3.5 mg/dL vs someone who doesn't have sarcopenia, has a sudden increase in creatinine, usually we don't see that sudden uremic. That's more of a chronic kind of state. Again, diabetic, most likely if you put NASH and diabetes together, it's very . . . and chronic kidney disease, again they have microvascular disease, so if there's a concern of

GI bleed or whatever, again what is the BUN of this patient to cause this fatigue? But again, I think we fixate so much on the creatinine vs what is the GFR of a 60-year-old, this patient whose creatinine is 1.4 mg/dL? And if that's low, they could just be chronically getting sicker and sicker and now they're uremic.

Kevin Moore, PhD: Okay, I can tell you he weighs 90 kg, you're going to ask me what this is in llb, aren't you? But let's say he weighs 220 llb for the sake of argument. So, well-built, not massive, but well-built. I think that's right, 220 sounds quite a lot, maybe 180 llb. So, how does that compute in terms of, how does that alter what you think?

Mitra Nadim, MD: So, that would be a little bit, I wouldn't be thinking the 1.4 mg/dL is a GFR of less than 20 mL/min. And then going back to what Paolo said, when did that change happen? So, if the 1.4 mg/dL was from let's say 3 months ago and a week after that lab that was drawn [that was] 1.4 mg/dL, it hit the 2.5, 3 mg/dL and has been slowly, so for 3 months now they're at this GFR, that could explain their weakness. If it's a little bit more rapid, usually again the weakness shouldn't be from this sudden increase in creatinine and, as Paolo mentioned, I would look for other things. Were they on beta blockers? Were they bleeding? Were they septic? Sepsis is usually the first kind of cause and then you add the kind of . . . but it becomes difficult when they have CKD, diabetic, if they have proteinuria, let's say they had baseline as 1 g of proteinuria baseline, they don't fit the algorithm for hepatorenal, but these patients still can develop hepatorenal. They just have diabetic nephropathy, now they got tipped over, liver got worse, sepsis, everything, but I think that's where the definitions kind of, [where] people need to start including these as if nothing has changed as far as proteinuria, then maybe this patient can still have hepatorenal syndrome, regardless of the fact that they have proteinuria in the urine. Renal ultrasound, sorry, just to add, because everyone always orders a renal ultrasound, I can say, as a nephrologist, there's 2 values I kind of see in it. In a diabetic, you can have normal or enlarged kidneys with a GFR of 10. It's only helpful if both kidneys are really small, then you say, you know what, maybe this patient has really chronic disease or if they have 1 kidney, so in your head you know. Other than that, a normal ultrasound, normal size kidney or . . . doesn't mean that they don't have significant kidney disease.

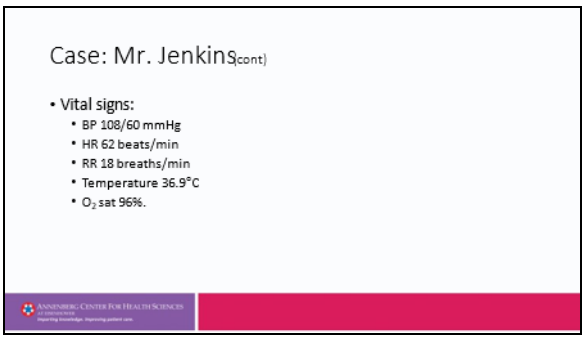
Kevin Moore, PhD: No, I realize that. Can I ask maybe a stupid question, but as a non-nephrologist, when you have patients with chronic kidney disease and say a creatinine stable at 1.4, do they often develop significant anemia? And if they have chronic kidney disease that extends to like a creatinine of 3.5 mg/dL, I'm assuming the anemia would worsen. Is that roughly true?

Mitra Nadim, MD: Usually we'd look at the GFR again. So, usually, over 30 mL/min, you don't see sudden anemia in patients. Less than 30, you may start seeing it trickle. It's closer to less than 25 or 20 mL/min when we start thinking of Procrit and things like that.

Kevin Moore, PhD: Alright, anyway. So, we've got this patient now that, just to get in my mind, they're NASH cirrhosis, they could have chronic kidney disease because of the diabetes, they could have chronic kidney disease because of refractory ascites. We've mentioned the fact that they may have microvascular disease that could have affected the myocardium which may affect their response to different treatments. And then they presented with this weakness

and fatigue. They could have bleeding, they could have worsening anemia, they could have worsening renal function, worsening liver function. So, Amanda, the observations on arrival in the A&E department: Blood pressure's 108/60, heart rate is 62, respiratory rate 18. They are apyrexial, so, temperature's 36.9° C. And they have an oxygen saturation of 96%. What does that tell you?

Amanda Chaney, DNP: Yeah, so knowing that their baseline creatinine is in the range of 1.4 to 1.6 mg/dL and then seen today, it went up to 3.5 mg/dL, that is concerning to me that something significant is going on, whether that's infection, whether that's dehydration, something is obviously not right. And so, definitely taking a deeper dive into figuring out what could be affecting him would be great. So, 1 of the first things that I would initially do is do a diagnostic para to see if he does have any SBP to see if there is any infection going on in the belly.



The blood pressure is 108/60 and that, honestly, is pretty darned common for our patients with cirrhosis. So, honestly, that's a pretty good blood pressure so that doesn't concern me much at the moment. Temperature is normal, he's afebrile. Respiration rate is 18, so not breathing too fast and sats are good. And the heart rate is 62, so . . .

Kevin Moore, PhD: Yeah, I suppose the high respiratory rate of 18, it's not they're acidemic.

Amanda Chaney, DNP: Right, right, yeah, I mean clinically, according to those numbers, he looks pretty darned good except for that creatinine. So, that creatinine is pretty concerning.

Kevin Moore, PhD: I mean, the only other thing I would say in terms of blood pressure 108/60, because if you work out the mean arterial pressure, it works out about 76, doesn't it? Which is, although it's normal, it's like on the low end of normal which means that there's not much scope for dropping any further. And the heart rate of 62 which kind of goes back to 1 thing that Paolo asked earlier, is he on beta blockers? Because if someone's sick and I say those numbers don't make it sound like he's sick, although the creatinine being high, just that he is sick, you think that he might be a bit more tachycardic or heart rate a bit higher? So, a blood pressure, a heart rate of 62 might suggest that he's on beta blockers. Going back to you, Paolo, if this patient had presented to you and I know we haven't done a tap or anything else like that, but you've got a heart rate, let's say they were on beta blockers and let's say subsequently we know that renal function's worse, would you stop the beta blockers?

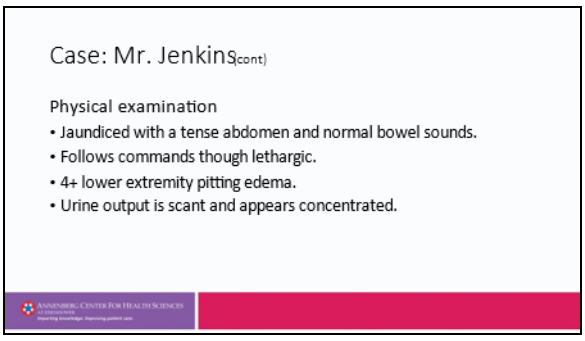
Paolo Angeli, MD: Immediately.

Kevin Moore, PhD: Fine, okay. That's very clear. Clear answer.

Paolo Angeli, MD: We didn't speak about their therapy at home before admission, but if this patient was taking a beta blocker and diuretics, of course, I would stop immediately both them.

Kevin Moore, PhD: Yeah, so in answer to your question, he was on beta blockers.

He was taking propanolol 20 mg twice daily. He was also taking spironolactone 200 mg for previous ascites. He wasn't on any furosemide, had been previously but that had been stopped recently. And he had been on long-term omeprazole to prevent any gastric reflux. Other than that, he was on metformin for his diabetes and there had been consideration to starting him on something like semaglutide to see if they could promote weight loss, but he hadn't actually started that recently. So, that's where we're at the moment and I think there was also consideration of other SGLT-2 inhibitors.



But let's go on to the next finding. So, the next findings are, on examination, he is clearly jaundiced. He has tense abdomen which could mean anything really. He's got normal bowel sounds and he's able to follow commands, although he's lethargic. And he's got gross pitting edema and, although he's not catheterized, when he does pass urine, it's a tiny amount and is quite dark. So, Rahul, what would you take from that? You've got this man, he's jaundiced. You've got this extra history with the drug history. We know that his renal function has deteriorated, but know that he's dysuriating himself. What would you do next?

Rahul Nanchal, MD: Well, maybe I'll take that in 2 parts: what should be done and what actually happens. So, what should be done is a better physical exam. What actually happens is someone's going to take a point-of-care ultrasound and ultrasound the man from top to bottom. So, obviously, the physical findings are concerning for hyperbilirubinemia, there's jaundice, physical findings are concerning for tense ascites. The physical findings may be concerning for hypervolemia, intravascular volume overload as well and so, especially given deterioration of renal function and chronic kidney disease at baseline, and so, I think a more thorough physical examination should be performed including exam for intravascular volume status, although I can tell you I'm not sure anyone does that.

Kevin Moore, PhD: Well, there is a saying, of course, if in doubt, examine the patient. I don't think many doctors follow that advice. So, when you examine the patient, it's quite an important point actually because you have a distended abdomen. Sometimes, even though you assume they can have gross ascites, but actually when you tap it, it's just resonant all over and they sometimes develop what may even be an infection in a small pocket of ascites and they've got some sort of pseudo-obstruction. I don't know if you've seen that before, but sometimes it can be quite a catch, so just bear

that in mind. But let's assume that he has tense ascites. How would you, would you tap the ascites in the A&E department or do you do them always under ultrasound scan guidance? Do you do blind ascitic taps or do you do ultrasound scan-guided ascitic taps?

Rahul Nanchal, MD: Yeah, I think sticking needles in blindly has sort of fallen by the wayside, so everything's under ultrasound these days. Even we use, you know, whether we like it or not, we sort of, for safety reasons, use ultrasound to tap the ascites.

Kevin Moore, PhD: Yeah, no, it's interesting. I mean the reason I think you saw me pulling my face is because I felt maybe I'm just getting really old-fashioned, but the question asked is about having a point-of-care ultrasound scan machine available and knowing how to use it. Because you're absolutely right, using an ultrasound scan guidance is much safer. If you have to send the patient to the radiology department for them to do an ultrasound scan-guided aspiration, that can take a long time and it's much better to get a diagnosis and start patients on intravenous antibiotics, if it's indicated, than to delay until you've got the appropriate investigation. So, I assume, probably in the US, am I right in thinking ultrasound scan-guided aspiration, everyone uses an ultrasound scan probe, everyone is trained in that. Is that correct in any ED?

Mitra Nadim, MD: Yes.

Rahul Nanchal, MD: I think . . .

Kevin Moore, PhD: They are in Italy as well. I think the UK, we're the ones that are lagging behind the rest of the world. So, I admit that we're not that good. We just, we are increasingly using it, but . . .

Mitra Nadim, MD: I just want to comment because I forgot to mention you have a 60-year-old, he's male, 20 years of diabetes, was on metformin so the metformin could've caused his worsening, but we really need to make sure that the patient's not obstructed, especially since you said very minimal urine output, whether it's from bladder issues, from the diabetes, neurogenic bladder or BPH from a prostate, and we can do, we sometimes tell the nurses to do a bladder scan. The problem is that with ascites, it becomes difficult. So, sometimes, we do have to check a post-void residual just to make sure that the patient, male, is not obstructed to cause this sudden increase in creatinine.

Kevin Moore, PhD: I think that's a really good point. I was going to make the point earlier when you talked about ultrasound, of course it can show up by actual hydronephrosis. But, of course, 1 of the commonest causes in a 60-year-old male is benign prostatic hypertrophy. So, having, okay, so let's say you've got this patient, you do an ultrasound scan ascitic tap and it comes back with a neutrophil count of 550 neutrophils/mm^3, scanty red cells. What else do you want to know from the ascitic fluid? Rahul, I'll ask you since we're talking about ascitic fluid, Rahul, what else would you ask for?

Rahul Nanchal, MD: Well, I mean, obviously you would want to ask for a gram stain and culture and the albumin level to see and to calculate a serum: ascitic albumin gradient. So, those are some of the basic investigations that you would like to ask for. Again, I'll wait for the next question but those are some basic things.

Kevin Moore, PhD: So, let's say, so ascitic albumin is, for sake of argument, is 15. His blood albumin is 32. So, he's got a gradient now

of 17. So, that is greater than 11, so that means he has likely portal hypertension causing his ascites. Is that correct? Yeah?

Rahul Nanchal, MD: That is correct.

Kevin Moore, PhD: And in terms of gram stain, I thought gram stain, although we often do do a gram stain, they're often not that positive, are they, when you have bacterial peritonitis? I mean, the majority are negative. Is that correct?

Rahul Nanchal, MD: Yeah, that's correct, as well.

Paolo Angeli, MD: May I?

Kevin Moore, PhD: Yeah, of course you can, Paolo.

Paolo Angeli, MD: So, I think that if I have the neutrophil count that you mentioned, I have enough to start immediately empirical antibiotic treatment because this means that this patient developed a bacterial infection-induced AKI over an AKD or a CKD. So, the first treatment is to start immediately empirical antibiotic treatment. And let me say about this staining that the main problem today is to know if this infection is sustained by multidrug resistant bacteria or not. So, we should investigate predictors of multidrug resistant bacteria. This patient was treated with antibiotics during the last 3 months. This patient received an invasive procedure during the last month. This patient was admitted to a 1-day hospital or an outpatient clinic during the last 6 months. This is, in my view, the main problem.

Kevin Moore, PhD: Okay, so what you're saying is you go back over the history with the family to find out if he's had any procedures or previous admissions or previous antibiotics in the previous 3 to 6 months because that would be an important predictor factor for the development of a multidrug resistance in patients with bacterial peritonitis. You treat them with a broad-spectrum antibiotic. Would you give them any other fluids as well? Obviously, you'd give some intravenous fluids. What fluids could you give?

Paolo Angeli, MD: Albumin, of course. This is the only setting of bacterial infection in which albumin has been proved to prevent AKI and to improve mortality. You can say, well, this patient has already developed AKI. But give albumin, I also made a stat to see if the AKI is related or not to a reduction in plasma volume, you know, if the AKI will respond or not to plasma volume infusion.

Kevin Moore, PhD: But after the ATTIRE study that was published in the *New England Journal of Medicine* last year, the use of albumin is more controversial, how much albumin we give, whether a small amount is beneficial, whether large amounts are harmful. Do you have any thoughts on that at all?

Paolo Angeli, MD: But not in SBP, you know. In infection other than SBP.

Kevin Moore, PhD: Well, I think the ATTIRE study was in a whole range of patients.

Paolo Angeli, MD: No, no, but in ATTIRE, the administration of albumin was given at a completely different dose to a more heterogeneous population, only for 1 or 2 weeks, just to maintain a normal value of albumin in the plasma, not to make an acute plasma volume challenge.

Kevin Moore, PhD: Alright, let's not change our ATTIRE at the moment. Let's go back to the . . .

Rahul Nanchal, MD: I will bring up 1 point he made. You know, I would probably give albumin, but at the same time, I would do a very careful intravascular volume examination however difficult that it is to do. I mean, that's 1 of the most difficult things to do, I think, in medicine. But I will make a good faith effort at least to establish . . .

Mitra Nadim, MD: But I want to, I just want to add, as a nephrologist because I know I disagree with a lot of the hepatologists, this patient, on physical exam, has 3+ or anasarca. And from a nephrology standpoint, the patient's not in shock. The volume intravascular may be low, but no matter what you give, this patient has severe liver disease, it's just going to third space and, in fact, one would argue you have to find a way to bring the extravascular intravascular and that'll help, not to just keep giving more fluid. And sometimes, you may have to just make him a little bit drier to kind of float that fluid the other direction. So, I'd be very cautious in flooding the patient because the creatinine's up and if you want to give some 25% albumin, I would give it even with diuretics.

Kevin Moore, PhD: I would . . .

Paolo Angeli, MD: When we speak about giving albumin, we speak always to give 20% albumin solution, not 5% or 4%.

Mitra Nadim, MD: No, 25%. Ours is 25, we don't have 20. Ours is 25.

Paolo Angeli, MD: Okay, 20 or 25, they're the same.

Mitra Nadim, MD: Yeah, that's what I said. I would give 25%, but I would start giving diuretics, to be cautious, because this patient has anasarca.

Kevin Moore, PhD: The issue, I mean the issue around here is how much albumin and can you cause more harm by giving too much albumin. Rahul, you've made the point that you'd monitor the intravascular volume very carefully. How would you do that? Do you use one of these Dopplers, these intraesophageal Dopplers or how would you do that? Or Ram, maybe an even more appropriate person to answer that question. But careful fluid management is critical in this case, I think, isn't it?

Paolo Angeli, MD: Absolutely. These are patients that should be closely . . .

Kevin Moore, PhD: Paolo, can I just ask Ram to comment on this, on the fluid balance.

Ram Subramanian, MD: Yeah, so as Rahul had mentioned, I think point-of-care ultrasound is, especially in the ICU setting, becoming more and more used to help guide our therapy. So, if that is an option, that would definitely give you . . . so, for example, you can look at the cardiac chambers, you can look at IVC compressibility. If you have the option for a more invasive monitoring with an arterial line, you can actually, and especially if the patient heads towards intubation, which is separate scenario, you can even get a better idea on the preload that the heart is receiving. So, there are diagnostics available to get a better assessment of the intravascular volume status despite the anasarca. So, this may be something for the future where, even in a non-ICU setting, on the floor or even the emergency room, you develop that skill set where you use POCUS to really get a better idea of intravascular volume status in

real time and then use it to gauge the response to therapy.

Kevin Moore, PhD: Okay. So, let's just take it that we've got real-time ECHO, we've given a small dose of albumin, we've decided, we've perhaps given some diuretics to try and maintain some urine output, we've got the situation where we think the patient's volume replete, we started him on antibiotics, the blood pressure's still got a mean arterial pressure of 76, maybe even sometimes 72. What else would you do at this stage? I know what we would do in Europe, but what would you do in the US?

Paolo Angeli, MD: So, what you want to do in this patient is, after an ICG, a cardiac ECHO . . .

Kevin Moore, PhD: You mean, so electrocardiogram, you'd do an echocardiogram? Okay.

Paolo Angeli, MD: Cardiac ultrasonography and getting a baseline value of troponin because we are speaking about a patient with diabetes, arterial hypertension, so diurese to have an ischemic cardiac disorder. I will start terlipressin plus albumin at a very low dose of terlipressin, 2 mg every 24 hours, by continuous intravenous infusion and close monitoring of ICG and troponin level.

Kevin Moore, PhD: Okay. And I would agree with you, that's exactly what I would do. Rahul, Mitra, Ram or Amanda, what would you do in the US?

Rahul Nanchal, MD: So, Kevin, maybe I can just, can I bring us back to the intravascular volume question because I think that's incredibly important. And, while this is a discussion on HRS, a lot of modalities that we have to investigate volume status, for example, and Ram's absolutely right about the ECHO and the point-of-care ultrasonography, most of it indicates hypervolemia where there is not a very good indicator of hypovolemia. So, for example, IVC size and noncollapsibility indicates hypervolemia. All of our IVCs are supposed to be small and collapsible. If they are not, I would be very worried. And so you have to put a lot of pieces of data together to sort of figure out intravascular volume status. But in someone like this, I think again we would start some sort of vasoconstrictor and I would love to hear from Ram and Mitra as well, but we would start some sort of vasoconstrictor therapy and this is, if he had not, personally if only a diagnostic tap was done, I would probably be very interested in intraabdominal pressure. I would be very interested in perhaps what the venous waveforms look like.

Kevin Moore, PhD: Okay, I can tell you, if you measure the intraabdominal pressure, well we did, it was 23 mm of mercury.

Rahul Nanchal, MD: Okay. If there was no artifact and it was truly 23 mm of mercury, before draining the ascites, I would actually target a higher mean arterial pressure that gives me a mean arterial pressure target with the norepinephrine and I would probably perform a therapeutic paracentesis and drain off and measure intraabdominal pressure at the same time.

Kevin Moore, PhD: Okay. Mitra or Ram or Amanda, what would you do?

Ram Subramanian, MD: So, just to add on to those comments and just sort of further diagnostics, somebody already mentioned it, but I would just make sure you have blood cultures and sort of look for sort of a systemic

effect of the SBP. Is there something that is now causing or putting the patient at risk for a systemic cytokine surge that can further contribute to the acute kidney injury? For example, for a septic AKI in addition to the HRS-AKI.

Rahul Nanchal, MD: So, I would broaden the infectious work-up as well.

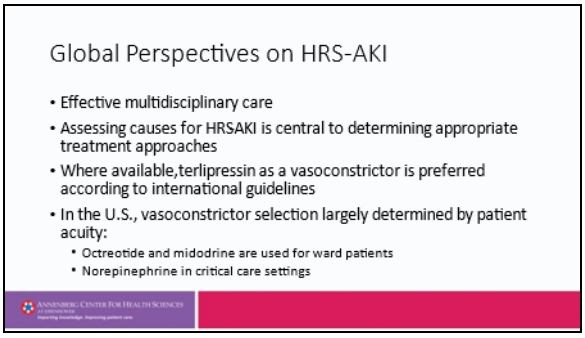
Kevin Moore, PhD: Okay. Mitra?

Mitra Nadim, MD: So, depending, if this was a patient who was on the general ward, again I would not flood them with fluid which people tend to end up doing. I would just . . . we only have midodrine-octreotide. If we believe this patient has hepatorenal and we excluded the fact that he was on metformin, that he doesn't have some, I would tap that ascites because that intraabdominal pressure and sometimes just relieving that pressure can actually kind of cause people to start picking up urine and getting better. So, here in the US, we would probably, if they're in the general ward, they would end up on octreotide and midodrine. With that creatinine and anasarca, I can guarantee they would end up pretty soon on dialysis, some form of dialysis, unless they quickly reverse because the next one probably would be either higher or the patient would be tipped over into heart failure somehow. He's 60, diabetic, creatinine 3.5 and anasarca. If they are in the ICU, again, we don't have terlipressin. Whether or not you give norepinephrine just for that, again that's debatable. You have that, but again this patient, with that creatinine, that volume status, if they don't reverse in the next 24 hours, they're headed towards dialysis.

Kevin Moore, PhD: Okay. Amanda, do you want to have the last say in this case?

Amanda Chaney, DNP: I think what everybody has said is spot on. One thing that we didn't really dive into too much, but the patient's pretty darned sick so it's maybe assumed, but stopping their diuretics, stopping the beta blocker, not taking off too much volume at one time, stopping the lactulose if they are having a lot of bowel movements and having fluid losses there. So, anything that we can do to optimize their blood pressure and to reduce their dehydration risk, that's what we should do.

Kevin Moore, PhD:



Well, I think, on that note, I think we should call the discussion to close because, Amanda, you've reminded us of the key points which is always look at the drug chart, stop anything that's nephrotoxic, make everything that works well for the patient and so I, like you, I stop everything unless it's absolutely essential and just focus on what are the essential drugs to keep the patient alive for the next 24 hours, to minimize any chance of any drug interactions.