ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Acute Renal Dysfunction in Liver Cirrhosis

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G&H How common is acute renal dysfunction in liver cirrhosis, and what are the main causes?

FW The prevalence of acute renal dysfunction has been assessed at 19% to 20% in all inpatients with cirrhosis. There are no data on the prevalence of acute renal dysfunction in outpatients. By and large, acute renal dysfunction is an inpatient condition. The main cause is prerenal renal failure; specifically, the cause is a reduction in perfusion of the kidneys that may be related to too much removal of volume from the circulation or a relative or apparent reduction of circulatory volume. This can occur, for example, in patients who have been overdiuresed, or it may be related to an expanded capacitance of the circulation, as in the case of exaggerated systemic arterial vasodilatation following a bacterial infection.

G&H Given the high mortality rate of patients with cirrhosis and renal complications, what screening measures are taken?

FW Currently, the only screening tool for renal dysfunction in cirrhosis is a measure of serum creatinine, although a serum creatinine level does not become abnormal until there is significant renal dysfunction, and therefore it is not a good marker of renal injury. This is because creatinine is derived from creatine, which comes from muscles, and cirrhotic patients who are susceptible to renal injury are usually wasted and therefore have low creatine levels. This can lead to a low creatinine production, and therefore the serum creatinine does not accurately reflect the extent of renal dysfunction in cirrhosis. However, the test is readily available, and physicians are familiar with it. Therefore, in the absence of better markers of renal dysfunction, hepatologists would like to continue using the serum creatinine level to diagnose renal dysfunction in cirrhosis.

Traditionally, the serum creatinine has to reach a level of 1.5 mg/dL to meet a diagnosis of hepatorenal syndrome, the best-known form of renal dysfunction in cirrhosis, which has a grave prognosis if untreated. However, data are emerging to suggest that smaller increases in serum creatinine also may have clinical significance.

There are various groups, such as the Acute Kidney Injury Network (AKIN), that apply criteria to stage changes in serum creatinine. For example, according to AKIN criteria, stage 1 renal injury is defined as an increase in serum creatinine levels of 0.3 mg/dL in less than 48 hours or a 50% increase in the serum creatinine level from baseline, stage 2 is a doubling from baseline, and stage 3 is a tripling, a final serum creatinine level of 4 mg/dL, or the need for dialysis. In addition, the AKIN criteria take into account the reduction in urine output in their definition of the various stages of renal dysfunction.

All clinicians caring for patients with decompensated cirrhosis recognize that when cirrhotic patients reach the stage of predisposition to acute renal dysfunction, their urine output is usually significantly reduced compared with patients without cirrhosis. A normal person will produce a urine volume of somewhere between 1 to 2 liters per day, whereas cirrhotic patients with liver decompensation and ascites probably will only produce 300 to 500 mL per day due to severe salt and water retention. Therefore, hepatologists are beginning to think that it is more useful to monitor for changes in serum creatinine levels rather than absolute serum creatinine levels or urine output to indicate renal dysfunction.

About 3 years ago, the International Ascites Club, which is a loosely formed association mainly consisting of hepatologists and scientists who are interested in promoting science and research related to ascites, worked with a group of nephrologists and intensivists from the Acute Dialysis Quality Initiatives. Together, they proposed to define acute renal dysfunction in cirrhosis as a rise in serum creatinine levels of more than 0.3 mg/dL in less than 48 hours. This definition is equivalent to stage 1 of acute kidney injury in the AKIN criteria but without the urine output criteria. Data are now emerging to suggest that these small increases in serum creatinine levels in cirrhotic patients have prognostic implications, with a worse survival, compared with cirrhotic patients in whom no increase in serum creatinine levels is seen. This is especially true in patients with cirrhosis in whom bacterial infections develop. Therefore, the focus is now being centered on evaluating how much of a serum creatinine level increase defines a significant clinical event. The smallest increase currently being used is more than 0.3 mg/dL in less than 48 hours.

G&H Are biomarkers being used in the diagnosis and prognosis of renal disease in cirrhotic patients?

FW Renal biomarkers are not yet broadly available. Some of them have begun to be validated, but, by and large, they are not in common clinical use. Biomarkers under study include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin 18, and kidney injury molecule (KIM)-1. NGAL is showing some promise as a clinically useful marker of renal dysfunction. There are also a few papers published on cystatin C, as well as data emerging on KIM-1. However, none of the biomarkers have reached a point in which they can be used in clinical practice. Other techniques used to screen renal dysfunction include the Modification of Diet in Renal Disease (MDRD) formulae. These formulae use various variables to calculate the glomerular filtration rate. The MDRD formulae are open to inaccuracies, though, because they also depend on serum creatinine measurements, which are themselves inaccurate.

G&H Are certain patients with liver cirrhosis more at risk than others for renal injury?

FW The higher the Model for End-Stage Liver Disease (MELD) score, that is, the more severe the liver dysfunction, the more likely that the cirrhotic patient is at risk for acute kidney injury, especially if the patient has a bacterial infection. Evaluation of the MELD score is done routinely when patients are evaluated during their routine follow-up visits. In patients who are admitted with a bacterial infection, serum creatinine levels are measured every day so that corrective measures can be applied as soon as acute renal dysfunction is diagnosed.

G&H What steps are taken to intercept progression of renal injury in patients with cirrhosis?

FW The main products used to halt the progression of renal injury are volume expanders, which increase the intravascular volume. This ensures that the expanded circulatory capacitance is properly filled to dampen the various compensatory vasoconstrictors that can cause renal vasoconstriction and, hence, renal failure. The best volume expander is albumin. Albumin also has the ability to bind various cytokines, many of which are vasodilators and, therefore, can reduce the extent of vasodilation in these patients, making it easier to fill the circulation.

Of the various precipitants of renal injury, which are events that could either disturb the intravascular volume or cause further vasodilation of the systemic circulation, the most common precipitating event is bacterial infection. It causes increased vasodilation, and so it is now customary to give albumin infusions to patients at risk for kidney injury when they have a bacterial infection. Administering albumin is the standard of care for patients who present with spontaneous bacterial peritonitis. Evidence is emerging that albumin is also useful in patients with other types of bacterial infections.

When acute kidney injury is a result of overdiuresis, diuretics are stopped and albumin is administered to expand the circulation. Albumin also is routinely administered to patients receiving large-volume paracentesis. During large-volume paracentesis, the presence of portal hypertension will favor the transfer of volume from the circulation to the peritoneal cavity, resulting in ascites. With volume leaving the circulation into the peritoneal cavity, a relative deficit in the circulation results, defined as postparacentesis circulatory dysfunction. This will lead to a reduction in the intravascular volume, with compensatory increases in various vasoconstrictor levels. The kidneys are particularly susceptible to the vasoconstrictive effects of these vasoconstrictors, and so, acute renal dysfunction will occur in an estimated 20% of patients receiving large-volume paracentesis if volume expansion is not given.

G&H What defines hepatorenal syndrome in relation to acute renal dysfunction in cirrhosis?

FW Hepatorenal syndrome is a type of prerenal renal failure. Pathophysiologically, it is the result of a relative deficiency in the intravascular volume, leading to activa-

tion of various systemic vasoconstrictors. The kidneys respond by undergoing renal vasoconstriction, which will trigger them to conserve salt and water. This physiologic response is the body's attempt to replenish the intravascular volume. Hepatorenal syndrome differs from prerenal renal failure, in which, although there is a reduction in the intravascular volume, serum creatinine levels return to normal when volume is replaced. In hepatorenal syndrome, the renal function does not return to normal despite fluid replacement.

Hepatorenal syndrome may be acute or chronic. Diagnosis of acute, or type 1, hepatorenal syndrome is defined as a doubling of the serum creatinine level in less than 48 hours to a final reading of 2.5 mg/dL or greater. Other causes of renal failure must be ruled out; therefore, the patient cannot have been exposed to nephrotoxic drugs or radiographic dye or have nephritis. In addition, prerenal renal failure has to be ruled out; therefore, diuretics have to have been withdrawn for 48 hours and the patient given volume replacement in the form of 1 g of albumin per kg of body weight for 48 hours. Shock has to be ruled out as well. Structural renal disease also has to be ruled out by excluding the presence of urinary casts, hematuria, or proteinuria.

Chronic, or type 2, hepatorenal syndrome develops over weeks to months. It is a complication of refractory ascites in decompensated cirrhosis. Usually, the patient is less sick compared with patients with type 1 hepatorenal syndrome. A serum creatinine level of 1.5 mg/dL is diagnostic for chronic hepatorenal syndrome after other causes are ruled out, and, again, it is observed that serum creatinine level does not improve with volume expansion.

G&H How is hepatorenal syndrome best managed?

FW In Europe and elsewhere, but not yet in North America, the vasopressin analogue terlipressin is used to manage hepatorenal syndrome. Terlipressin constricts blood vessels in the abdomen, forcing more blood from the abdominal vessels draining the gut into the general circulation. This, in turn, will deliver more blood to the kidneys. The use of terlipressin for the treatment of hepatorenal syndrome is still under evaluation in North America.

The most common regimen used in the United States is a combination of midodrine, octreotide (Sandostatin, Novartis), and albumin. Midodrine is a sympathomimetic agent that increases systolic blood pressure and, therefore, increases the renal perfusion pressure. Octreotide blocks the various vasodilators in the abdominal or splanchnic circulation. The drugs are used in conjunction with albumin. This combination regimen is effective in approximately 40% of patients, and it works very slowly. Terlipressin also is effective in approximately 40% of patients but is associated with a faster response. Intravenous norepinephrine, given under monitoring in the intensive care setting, also has been used in the United States to achieve results similar to those seen with terlipressin.

G&H What advice can you give to office-based hepatologists regarding vigilance about renal dysfunction in patients with cirrhosis?

FW The most important point is to watch for bacterial infection, overdiuresis, and changes in serum creatinine levels. Whenever an outpatient presents to the office, he or she should receive renal function monitoring in addition to liver function monitoring. In fact, all liver transplant units should monitor patients' blood work at least once a month to assess for changes in serum creatinine levels. Increases must be identified even if the creatinine level remains in the normal range. For example, if the patient's serum creatinine level increases from 0.5 to 1.0 mg/dL, the clinician should inquire as to whether the patient is on diuretics, and, if so, should stop the diuretics. If necessary, the clinician should volume-expand the patient with a colloid such as albumin to determine whether the serum creatinine will return to baseline value. The physician should also search for other causes of the renal dysfunction, such as the presence of occult infection or receipt of a recent large-volume paracentesis without volume expansion.

Dr Wong has no conflicts of interest to disclose.

Suggested Reading

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