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Preamble

Ascites is the most common of the three major complications of cirrhosis, the other complications being hepatic encephalopathy and variceal hemorrhage. Cirrhosis is the most common cause of ascites in the United States. Development of ascites may be the first evidence of the presence of cirrhosis. Obesity makes the physical examination less helpful in detecting ascites. Imaging may provide the first evidence of the presence of ascites. Patients with ascites are frequently admitted to hospitals. Effective care of these patients can reduce the frequency of these readmissions. This version of the American Association for the Study of Liver Diseases Practice Guideline is the fourth iteration of this guideline and represents a thorough update of the 2009 version.

Introduction

In this revision, the treatment options are now divided into first-line, second-line, third-line, and experimental options. There is a new section on drugs to be avoided or used with caution. Blood pressure in patients with cirrhosis and ascites is supported by elevated levels of vasoconstrictors; these vasoconstrictors are compensating for the vasodilatory effect of nitric oxide. Arterial pressure independently predicts survival in patients with cirrhosis; those with a mean arterial pressure (MAP) >82 mmHg have a 1-year survival of 70%, compared to 40% for those ≤82 mmHg. Drugs that inhibit the effects of these vasoconstrictors would be expected to lower blood pressure; they have been documented to do so. Lowering blood pressure might worsen survival.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided or used with caution in patients with cirrhosis and ascites. The European Association for the Study of the Liver practice guideline on ascites recommends that “...they should generally not be used in patients with ascites.” This revised guideline reinforces this admonition.

“Cirrhosis cures hypertension.” In the current era, many patients, especially those with obesity and a component of nonalcoholic steatohepatitis (NASH), have hypertension before they decompensate. Normalization of systemic blood pressure is perhaps the only perquisite of cirrhosis. In the situation where angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are used, blood pressure and renal function must be monitored carefully to avoid rapid development of renal failure. Monitoring of blood pressure at home provides useful information for the provider to factor into the decision when to taper or stop antihypertensives.

Propranolol has been shown to shorten survival in patients with refractory ascites in a prospective study. This could be the result of its negative effect on blood
pressure and the increase in the rate of paracentesis-induced circulatory dysfunction that is noted in patients who are taking propranolol in the setting of refractory ascites.\textsuperscript{9} Blood pressure and renal function should be monitored closely in patients who have refractory ascites. The risks versus benefits of beta blockers must be weighed carefully in each patient. Consideration should be given to discontinuing beta blockers or not initiating beta blockers in those patients with refractory ascites and those who develop worsening hypotension or worsening azotemia.

In the current version of this guideline, there are also new sections on umbilical hernias, hepatic hydrothorax, and cellulitis. Chest-tube insertion in hepatic hydrothorax is advised against, based on older and newer studies.\textsuperscript{16,11} Percutaneous endoscopic gastrostomy is advised against in patients with cirrhosis and ascites.\textsuperscript{12}

Advances in Management of Ascites

Many patients with cirrhosis and ascites in the current era have multiple insults to the liver, including alcohol. Cessation of alcohol intake can dramatically improve their degree of liver failure, despite the continued presence of hepatitis C and/or NASH. Refractory ascites can revert to diuretic sensitive and can even disappear such that diuretics can be tapered and even stopped over time. Baclofen has been shown, in a randomized trial that included only patients with alcoholic liver disease, to reduce alcohol craving and alcohol consumption; it can be given at a dose of 5 mg orally three times daily (TID) for 3 days and then 10 mg TID.\textsuperscript{13} The dose can be tailored upward, with the patient carrying “a pill in the pocket” and taking an extra pill as needed to reduce alcohol craving.\textsuperscript{14}

An outpatient appointment within 7 days of discharge from the hospital has been shown to correlate with lower readmissions rates of patients with heart failure.\textsuperscript{15} Rapid return to clinic may also reduce the readmission rates of patients with cirrhosis and ascites by frequent adjustment of doses of diuretics and prevention of dehydration versus tense ascites.

The utility of monitoring urine sodium/potassium ratios is reiterated based on new data.\textsuperscript{16} Vaptans are discussed in this revision. Earlier studies of vaptans had focused on heart failure and included a relatively small number of patients with cirrhosis. These drugs are very expensive and may cause thirst. The largest randomized trial that specifically included only patients with cirrhosis demonstrated no clinical benefit in long-term management of ascites and provided a signal that mortality could be increased in patients taking drugs in this class.\textsuperscript{17}

Oral midodrine at a dose of 7.5 mg TID has been shown, in a randomized trial in patients with refractory or recurrent ascites, to increase urine volume, urine sodium excretion, MAP, and survival.\textsuperscript{18} Nurses and care givers may be reluctant to give diuretics to profoundly hypotensive patients. Midodrine can be added to diuretics to increase blood pressure and convert refractory ascites back to diuretic sensitive.

Albumin (ALB) infusion after large-volume paracentesis has been controversial. A meta-analysis of 17 trials involving 1,225 patients has been published, demonstrating a reduction in mortality with an odds ratio of death of 0.64 (95% confidence interval [CI]: 0.41-0.98) in the ALB group.\textsuperscript{19} ALB infusion (6-8 g per liter of fluid removed) is recommended when more than 5 L of ascitic fluid are removed.

Information on the use of transjugular intrahepatic stent-shunt to treat ascites has also been updated.

Bacterial Infections

Widespread use of quinolones to prevent spontaneous bacterial peritonitis (SBP) in high-risk subgroups of patients, as well as frequent hospitalizations and exposure to broad-spectrum antibiotics, have led to a change in flora of infections in patients with cirrhosis; there are more Gram-positives and extended-spectrum \emph{B-lactamase-producing Enterobacteriaceae} in recent years.\textsuperscript{20-22} Risk factors for multiresistant infections include nosocomial origin of infection, long-term norfloxacin prophylaxis, recent infection with multiresistant bacteria, and recent use of \emph{B-lactam} antibiotics.\textsuperscript{20}

Infections with these resistant organisms are associated with a higher mortality\textsuperscript{20} and can affect and complicate post-transplant care. We may encounter bacteria for which we have no effective treatment.\textsuperscript{22} To minimize bacterial resistance, it is prudent to limit prophylactic antibiotics to patients with well-defined criteria for SBP prophylaxis, limit duration of antibiotic treatment of infections, and narrow the spectrum of coverage, once susceptibility testing results are available.

Hepatorenal Syndrome

A new biomarker may assist with the diagnosis of hepatorenal syndrome (HRS) and may make it less of a diagnosis of exclusion.\textsuperscript{23} Urinary neutrophil gelatinase-associated lipocalin is 20 ng/mL in healthy controls, 20 ng/mL in prerenal azotemia, 50 ng/mL in chronic kidney disease, 105 ng/mL in HRS, and 325 ng/mL in
acute kidney injury. This test has been shown to be superior to three other urine biomarkers, but is not presently available in the United States. A meta-analysis of vasoconstrictor treatment (including terlipressin, octreotide/midodrine, and norepinephrine) of type I and II HRS reports that vasoconstrictor drugs with or without ALB reduced mortality, compared with no intervention or ALB alone (relative risk [RR]: 0.82; 95% CI: 0.70-0.96). Terlipressin plus ALB reduced mortality, compared to albumin alone (RR, 0.81; 95% CI: 0.68-0.97) with a reduction in mortality in type I, but not type II, HRS.

Enthusiasm is high for these new treatments. There are ongoing randomized, controlled trials that should help place these options in the treatment algorithm. Terlipressin is not yet available in the United States. Until further data are available, ALB, octreotide, and midodrine should be considered in the treatment of type I HRS. ALB and norepinephrine or vasopressin can be considered in the intensive care unit.

Information on the use of transjugular intrahepatic stent-shunt to treat HRS has also been updated.

References