

Management options in decompensated cirrhosis

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Abstract: Chronic injury to the liver from a variety of different sources can result in irreversible scarring of the liver, known as cirrhosis. Cirrhosis is a major cause of morbidity and mortality in the USA, and according to the Centers for Disease Control and Prevention was responsible for 31,903 deaths in 2010 alone. It is thus of the utmost importance to appropriately manage these patients in the inpatient and outpatient setting to improve morbidity and mortality. In this review, we address four major areas of cirrhosis management: outpatient management of portal hypertension with decompensation, hepatic encephalopathy, hepatorenal syndrome, and bleeding/coagulation issues. Outpatient management covers recommendations for health care maintenance and screening. Hepatic encephalopathy encompasses a brief review of pathophysiology, treatment in the acute setting, and long-term prevention. Hepatorenal syndrome is discussed in regards to pathophysiology and treatment in the hospital setting. Finally, a discussion of the assessment of coagulation profiles in cirrhosis and recommendations for bleeding and thrombosis complications is included. These topics are not all encompassing with regard to this complicated population, but rather an overview of a few medical problems that are commonly encountered in their care.

Keywords: portal hypertension, hepatic encephalopathy, hepatorenal, coagulation

Introduction

Chronic injury to the liver from a variety of different sources can result in irreversible scarring of the liver, known as cirrhosis. Cirrhosis is a major cause of morbidity and mortality in the USA, and according to the Centers for Disease Control and Prevention was responsible for 31,903 deaths in 2010 alone.¹ It is thus of the utmost importance to manage these patients appropriately in the inpatient and outpatient setting to improve morbidity and mortality.

In managing cirrhosis as an inpatient or outpatient, an important first step is determining the etiology of the disease. This determination may help prevent further progression of the disease or play an important part in management if the patient undergoes transplantation. In the USA, the most common causes of cirrhosis are alcoholic liver disease and chronic viral hepatitis, although there are other causes, include drug-related, autoimmune hepatitis, nonalcoholic steatohepatitis, cardiac or vascular causes (right-sided heart failure, Budd-Chiari syndrome, portal vein thrombosis), metabolic causes (hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency), or biliary causes (primary biliary cirrhosis, primary sclerosing cholangitis, cystic fibrosis, sarcoidosis).² Often a thoughtful history with careful attention to degree of alcohol consumption, sexual history, intravenous or intranasal drug use, body piercing/tattoos,

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transfusion history, personal history of autoimmune disease, and family history of autoimmune or liver disease can help point towards an etiology.

Manifestations of decompensation in cirrhosis include gastrointestinal bleeding, hepatic encephalopathy (HE), and ascites. In this review, we address four major areas of cirrhosis management: outpatient management of portal hypertension with decompensation, HE, hepatorenal syndrome, and bleeding/coagulation issues. These topics are not all encompassing with regards to this complicated population, but rather an overview of a few medical problems that are commonly encountered in their care.

Portal hypertension and decompensation

It is important to determine if a patient has progressed to portal hypertension because the management can change significantly with this determination. While cirrhosis often progresses undetected until a patient develops signs of decompensation, there are physical examination findings that suggest development of portal hypertension. Portal hypertension is defined as the elevation of hepatic venous pressure gradient above 5 mmHg, and in cirrhosis is a result of both increased intrahepatic resistance to blood flow and increased splanchnic blood flow due to vasodilation in the splanchnic vascular bed. The list of physical examination findings that suggest the development of portal hypertension is long, but includes ascites, asterixis, caput medusa, clubbing, constitutional symptoms (anorexia, fatigue, weakness, weight loss), Cruveilhier-Baumgarten murmur, fetor hepaticus, gynecomastia, hepatomegaly, jaundice, palmar erythema, scleral icterus, spider telangiectasias, splenomegaly, and testicular atrophy.

Gastrointestinal bleeding in cirrhosis is often a complication of gastroesophageal varices. Gastroesophageal varices form when the development of portal hypertension necessitates an alternative route for blood to return from the portal system to the systemic circulation.³ These collateral vessels are at high risk for rupture, and thus represent a major cause of morbidity and mortality in cirrhotics. Variceal bleeding is present in 25%–40%⁴ of cirrhotic patients and each bleeding episode has a 10%–30% mortality rate.⁵

HE is another manifestation of decompensated cirrhosis. It is defined as neuropsychiatric abnormalities, including disorders of personality, altered levels of consciousness, and impairment of intellectual function in addition to neuromuscular dysfunction as a result of liver insufficiency.⁶ HE was responsible for about 110,000 hospitalizations yearly between

2005 and 2009 in the USA.⁷ A more in-depth discussion regarding this entity follows later in this article.

The third defining manifestation of decompensated cirrhosis is the presence of ascites. Ascites is the most common manifestation of decompensated cirrhosis and has been noted to affect 60% of all previously compensated cirrhotic patients within 10 years.⁸ The development of ascites is associated with poor survival, and studies have shown a 50% mortality rate within 3 years.⁹ Often ascites can be detected through a careful physical examination with special attention to the presence of flank dullness; in fact, studies have found the probability of ascites being present without flank dullness appreciated on examination to be less than 10%.¹⁰

Health care maintenance and screening

As a reflection of the high mortality associated with decompensated cirrhosis, much of the outpatient management of these patients is focused on prevention of these complications.

One of the most important elements of health care maintenance for cirrhotics is screening for varices. According to the American Association for the Study of Liver Diseases (AASLD), all newly diagnosed cirrhotics should undergo screening esophagogastroduodenoscopy for the diagnosis of esophageal and gastric varices. If esophagogastroduodenoscopy reveals no varices, then it should be repeated in 2–3 years. Small varices (<5 mm) necessitate repeat screening every 1–2 years, and decompensated cirrhotics should have a yearly esophagogastroduodenoscopy.^{11,12}

In an attempt to prevent complications and the morbidity associated with ascites, it is important for patients to adhere to a low sodium diet to prevent volume overload. Education on a low sodium diet with a goal of <2 g per day is typically recommended.¹³ It may seem that fluid restriction would be important for preventing accumulation of ascites, but the restriction of sodium plays a larger role as fluid typically follows sodium. It is not usually necessary to limit fluid intake unless serum sodium is less than 120–125 mmol/L. Oral diuretics are also useful in the management of ascites, with the typical starting regimen being 100 mg of spironolactone and 40 mg of furosemide daily.¹¹ These doses can be titrated maintaining a 100 mg to 40 mg ratio up to a maximum of 400 mg of spironolactone and 160 mg of furosemide daily. Ascites that persists despite a low salt diet and maximum diuretic therapy is defined as refractory ascites and necessitates a referral for transplant or treatment with repeated large-volume paracentesis, placement of a peritoneovenous shunt, or placement of a transjugular intrahepatic portosystemic shunt (TIPS).²

In addition to a low sodium diet, it is also important that cirrhotic patients consume a diet with adequate protein. It has been thought that a low protein diet will reduce the amount of ammonia production in the gut and thus treat HE. However, it has been shown that the occurrence of HE is not significantly different between protein-restricted diets and normal protein diets.¹⁴ Cirrhotic patients require 0.8–1.3 g protein/kg/day to maintain their nitrogen balance compared with healthy patients who require 0.6 g protein/kg/day.¹⁵ When protein requirements are not met, skeletal muscle breakdown can contribute to production of ammonia and HE.

As the number of patients living with chronic liver disease in the USA has increased, so has the incidence of hepatocellular carcinoma (HCC). Early detection of HCC improves the likelihood of survival, as those with limited stage disease are eligible for liver transplant or resection with intent to cure. Imaging and seromarkers such as alpha-fetoprotein have been used in screening for HCC in the past, but there is controversy surrounding the continued use of alpha-fetoprotein as a screening marker because recent studies have shown that it lacks adequate sensitivity and specificity. Therefore, in its 2011 practice guidelines, the AASLD recommends screening with ultrasound examination every 6 months.¹⁶

Regardless of the etiology of cirrhosis, it is important to immunize against both hepatitis A and B because they have been associated with high rates of morbidity and mortality in patients with cirrhosis.¹⁷ Thus, it is important to know vaccination status and vaccinate early in the course of the disease. Additionally, the Centers for Disease Control and Prevention recommends that patients with cirrhosis should receive the pneumococcal polysaccharide vaccine and yearly influenza vaccine in addition to standard tetanus/diphtheria/pertussis, varicella, human papillomavirus, zoster, and measles/mumps/rubella.¹⁸

Finally, an important question facing the primary provider for a cirrhotic patient in the outpatient setting is the optimal timing to consider referral for transplant. Typically, once a patient has developed one of the manifestations of decompensated disease (ascites, gastrointestinal bleeding secondary to variceal hemorrhage, or HE), it is prudent to consider transplant. The widely accepted method to evaluate progression of liver disease is use of the Model of End Stage Liver Disease (MELD) score. This score consists of serum testing, which is a surrogate marker of the intrinsic function of the liver. The components of a MELD score are the patient's international normalized ratio (INR), creatinine, and total bilirubin. This value can range from a minimum value of 6 to a maximum value of 40. If a patient's liver disease

has progressed to a MELD score of 15 or above and there is evidence of decompensation, it is recommended to strongly consider transplant.

Hepatic encephalopathy

HE is a multifactorial neuropsychiatric disease that commonly affects patients with cirrhosis. It is estimated that in patients with cirrhosis, approximately 30%–40% will develop overt HE in the course of their disease.¹⁹ Patients who have had an episode of overt HE have a 40% chance of relapsing within one year, even if on prophylactic therapy. Hospitalized patients with overt HE have a 3.9-fold increased mortality risk.²⁰ Patients with TIPS represent the highest risk group, as the prevalence of overt HE is 10%–50% in this population.²¹ Minimal HE is a mild form of the disease, lacking apparent clinical symptoms.²² While minimal HE may not affect overall mortality, it may be an early sign of a high-risk patient who may progress to overt HE, and can play a vital role in quality of life. Studies are ongoing to determine the best method of diagnosing minimal HE, by specialized flicker frequency testing, psychometric testing, or self-reported quality of life questionnaires.^{23,24}

There are multiple proposed mechanisms for the pathophysiology of HE. The most widely accepted one involves hyperammonemia, which occurs due to an impaired breakdown of primarily glutamine due to impaired liver function. When there is decompensated liver function, there is an accumulation of this nitrogenous waste. It appears that hyperammonemia and systemic inflammation act synergistically to promote the development of HE. Ammonia is able to cross the blood–brain barrier, and results in neuroinflammation and oxidative stress to neurons.²⁵ In patients with HE, the excess ammonia metabolism can lead to swelling of astrocytes and mild cerebral edema, as these are the only cells in the brain that contain glutamine synthase.²⁶ HE has also been closely linked to alterations in neurotransmitter function of dopamine, serotonin, and noradrenaline. Further, most notably, the clinical effects may be linked to a net increase in inhibitory neurotransmission through gamma-aminobutyric acid.²⁷

Overt HE is a diagnosis of exclusion, and the differential diagnosis should include other conditions that can cause diffuse brain dysfunction and/or acute confusion, such as diabetes, alcohol, medications, metabolic disturbances, kidney disease, intracranial bleeding, stroke, delirium, dementia, and infection. With such a broad differential, the workup should be comprehensive, including laboratory, radiological, and clinical assessments.²⁸ When a patient presents with overt HE, they should be worked up for alternative causes

of cognitive derangement and/or secondary causes of HE; any identified source should be actively treated. Correcting the precipitating factor of HE has previously been shown by itself to correct HE in the majority of cases.²⁰

Asterixis and disorientation are reliable signs of grade II HE or the onset of overt HE. Blood ammonia level remains an elusive diagnostic criterion; the 2014 AASLD guidelines state that “high blood-ammonia levels alone do not add any diagnostic staging, or prognostic value in HE patients”.¹⁹ However, the diagnosis of overt HE may be questioned if a patient with HE presents with an ammonia level that is within normal limits.

Treatment of acute hepatic encephalopathy

Level of consciousness should be taken into consideration when admitting a patient with acute overt HE to hospital. For example, if the patient is unable to protect their airway, admission to an intensive care unit is necessary. Additionally, if the patient is unable to swallow, they should be monitored more closely for aspiration, and their oral therapies should be administered via a nasogastric tube.

Empiric treatment for acute overt HE includes nonabsorbable disaccharides and antibiotics.²⁹ Adjunct therapies and nutritional recommendations can also be taken into consideration, especially if the patient is not responding to the first-line agents. After stabilization of the acute episode, secondary prophylactic treatment should be initiated for the prevention of future episodes. Recurrent overt HE in the setting of liver failure is an indication for liver transplant.

Nonabsorbable disaccharides are among the most accepted and widely used treatments for acute episodic overt HE, even though clinical trials have shown variable efficacy. The most widely referenced study on these agents is a 2004 meta-analysis, which reported that nonabsorbable disaccharides were superior to placebo but did not improve survival.³⁰ Nonabsorbable disaccharides, such as lactulose (β -galactosidofructose), acidify the colon, thus encouraging the conversion of ammonia to ammonium as well as changing the colonic microbiota to urease-producing bacterial species. Therapeutic lactulose dosing is achieved by titrating up by 25 mL every 1–2 hours until the patient has two or more soft stools each day. Side effects of lactulose therapy can include excessive flatulence, aspiration, dehydration, hypernatremia, and perianal irritation. In patients with overt HE and concomitant hyponatremia, the response rate to lactulose decreases. Of note, a 2014 trial compared polyethylene glycol (PEG) 3350-electrolyte solution with lactulose and found that PEG led to more rapid resolution of HE in the

acute setting. The conclusions suggested that PEG may be superior to standard lactulose therapy in patients with type C overt HE, but further long-term studies are needed.^{31,32}

Antibiotics are another mainstay of treatment for acute overt HE and are usually used in conjunction with nonabsorbable disaccharides.²⁹ The antibiotic therapies can reduce the enteric bacterial flora that may play a vital role in the production of neurotoxins leading to encephalopathy. Over recent years, rifaximin has become the most widely used antibiotic in the empiric and prophylactic treatment of overt HE due to its limited side effect profile. Rifaximin is typically not used as monotherapy due to a lack of robust trials and evidence; there is currently more evidence for its use in combination therapies.³³ Even though neomycin, vancomycin, and metronidazole have been shown to be as effective as lactulose, their side effect profile limits their use, particularly in the long term.

Malnutrition is a concern in patients with HE, as 75% of patients suffer from moderate to severe protein-calorie malnutrition.¹⁹ There is consensus that restricting protein intake via a low protein diet beyond the first few days of treatment is not recommended due to concern about increasing a patient's risk for muscle breakdown, and the subsequent increased risk for developing HE.³⁴

As mentioned earlier, patients with TIPS are the group at highest risk for HE, in particular intractable and recurrent HE. Patients with intractable recurrent HE in the absence of a TIPS should also be evaluated for spontaneous portosystemic shunt. In both cases, embolization of the shunt may provide the fastest and most effective relief from overt HE. A study has shown that shunt diameter reduction is effective in reducing the shunt flow and thereby rapidly improving the patient's clinical condition.³⁵

Maintenance of remission and prevention

Similar to the mainstays of medical treatment for acute overt HE, the primary agents used in secondary prophylaxis of HE are lactulose and rifaximin. A 2012 study of 78 cirrhotics who recovered from HE showed that rifaximin and lactulose were equally effective for the maintenance of remission from overt HE; however, rifaximin was superior for reducing the risk of HE-related hospitalization.³⁶ In practice, it is common to continue prophylactic therapy indefinitely after the first episode of overt HE. Primary prevention, which includes using lactulose in patients who have never had HE, is less commonly practiced. Counseling and education on the appropriate use of lactulose is a very important part of successful outpatient maintenance.

Hepatorenal syndrome

The development of hepatorenal syndrome (HRS) is a serious complication of decompensated cirrhosis and is associated with a high degree of mortality.³⁷ The probability of developing HRS is 18% at one year and 39% at 5 years.³⁸ Recent studies have determined that acute kidney injury develops in 19% of patients hospitalized with cirrhosis and ascites, and that HRS is responsible for 23% of these cases.³⁹ The one-month mortality for cirrhosis patients who develop renal failure is 58% and the 12-month mortality is 63%. For patients with HRS, the overall mortality is 80% for type 1 HRS and 56% for type 2 HRS.⁴⁰

HRS is functional renal failure that develops as a result of multiple pathophysiological derangements that occur in the cirrhotic patient. The portal hypertension that develops in cirrhosis leads to splanchnic arterial vasodilation, mediated in part by the release of endogenous vasodilators such as nitric oxide, carbon monoxide, and glucagon.⁴¹ This pooling of blood in the splanchnic arterial bed results in a decreased effective circulating volume and off-loading of the carotid sinus and aortic arch baroreceptors. Subsequently, the sympathetic nervous system and the renin–angiotensin–aldosterone system are activated, increasing cardiac output as well as sodium and fluid retention in an attempt to compensate for the decreased systemic vascular resistance.⁴² Despite increased levels of norepinephrine, renin, and angiotensin, a perpetuating cycle of decreased effective circulatory volume and progressive peripheral vasodilation leads to renal vasoconstriction and the development of renal failure.^{43,44}

The definition of HRS was most recently updated in 2007.⁴⁵ The criteria put forth by the International Ascites Club include cirrhosis with ascites, a serum creatinine of >1.5 mg/dL, no improvement of serum creatinine with at least 2 days of diuretic withdrawal and volume resuscitation with albumin, absence of shock, no recent history of exposure to nephrotoxic drugs, and absence of evidence for intrarenal disease such as proteinuria >500 mg/day or microhematuria.⁴⁵ Type 1 HRS is characterized by rapidly progressing renal failure, indicated by a rise in serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks. Type 2 HRS is defined by gradually developing renal failure reflected by an increase of serum creatinine values to between 1.5 mg/dL and 2.5 mg/dL. This type is more likely to occur spontaneously and is often associated with refractory ascites.⁴⁶

The initial work-up includes discontinuing diuretics, reviewing medications, and assessing for signs of infection (spontaneous bacterial peritonitis) or gastrointestinal bleeding.⁴⁴

Volume expansion with albumin 1 g/kg up to 100 g should be initiated, and a lack of response after 2 days can be used to distinguish HRS from pre-renal acute kidney injury.⁴⁵ Other important diagnostic tests include the fractional excretion of sodium once diuretics are stopped and microscopic urine analysis. A fractional excretion of sodium >1% and/or the presence of granular casts are more suggestive of acute tubular necrosis as a cause of renal failure.⁴⁴

Treatment of hepatorenal syndrome

The only definitive treatment for both types of HRS is liver transplantation. Due to the high degree of mortality associated with HRS, many patients require other forms of management, either to act as a bridge until they can undergo transplant or to achieve improved survival outcomes. Volume expansion is accomplished with albumin 1 g/kg of body weight up to a maximum dose of 100 g on the first day, with a subsequent dose of 20–40 g per day.⁴⁵ Studies of pharmacological management of HRS have reported the effects of α -adrenergic agonists (midodrine and norepinephrine), vasopressin analogs (terlipressin and ornipressin), and a somatostatin analog (octreotide) on improving renal function and survival. For those patients being treated in the USA and Canada where terlipressin is not available, midodrine and octreotide are reasonably well-studied alternatives. Midodrine, an α -agonist, acts as a systemic arterial vasoconstrictor, and octreotide, a somatostatin analog, antagonizes vasodilation in the splanchnic circulation in order to improve the effective circulatory volume. Midodrine was administered orally at doses of 7.5 mg to 12.5 mg three times daily. The dosing of octreotide was 100 μ g to 200 μ g three times daily subcutaneously. The specific amount given was titrated to produce an increase in mean arterial pressure of at least 15 mmHg. A retrospective review comparing patients treated with midodrine and octreotide with those who only received volume resuscitation demonstrated a decrease in mortality for both type 1 and type 2 HRS patients.⁴⁷

A difficult decision that becomes inevitable in those who do not recover is the use of renal replacement therapy (RRT). If a patient is ineligible for transplant, the use of RRT is controversial. For patients who are on RRT at the time of transplant, recovery of renal function post-transplant is positively associated with a shorter duration of pre-transplant RRT, an absence of pre-transplant diabetes, and younger age.⁴⁸ Patients who have been on pre-transplant RRT for longer than 8 weeks due to renal failure in the setting of decompensated cirrhosis should be considered for combined liver and kidney transplantation, as this group is more likely

to have persistently impaired renal function.⁴⁹ While medical therapy and interventions can improve renal function, the only definitive treatment is liver transplantation to correct the underlying disease. The prognosis for those patients who develop HRS is poor, so avoidance of this complication is paramount.

Coagulation profiles

Liver disease patients have a tenuous coagulation profile. There are prohemostatic and antihemostatic factors that are affected by cirrhosis.⁵⁰ Due to the complexity of this balance, it is often difficult to predict if these patients are predisposed to bleed or clot. In a survey at a tertiary care liver transplant center, the inpatient hepatology service showed an average of six bleeding events and one clotting event per week.⁵¹ While these complications are well recognized, developing a good management plan in these situations is often complex and multifactorial. In order to guide therapy, it is important to understand the underlying pathophysiological issues with coagulation in liver disease patients.

Multiple factors due to end-stage liver disease predispose cirrhosis patients to bleeding. The primary hemostasis provided by platelets is often reduced.⁵² Thrombocytopenia due to portal hypertension and splenic sequestration often results in an increased bleeding risk. The decreased carboxylation of vitamin K results in lower levels of coagulation factors. Even in the setting of adequate coagulation factors, decreased production of fibrinogen can prevent the formation of a fibrin clot. The lower levels of glycoprotein adhesion factors on the endothelium in cirrhosis can also affect proper hemostasis.⁵³ Finally, in cirrhosis, the constant state of inflammation can cause increased clot breakdown, called hyperfibrinolysis.⁵⁴

As mentioned earlier, bleeding is not the only complication affecting these patients, and a legitimate concern for hypercoagulability and thrombosis formation is also present in this population. A study demonstrated that 0.5% of cirrhosis patients admitted to hospital developed peripheral venous thromboembolisms.⁵⁵ Splanchnic clots (ie, portal vein thrombosis) are even more common and may cause rapid progression of liver disease and decompensation. Decreased levels of proteins C and S may predispose these patients to form a clot. Another key protein, which is decreased in production, is ADAMTS13. This protein is responsible for the cleaving of von Willebrand factor multimers, but with a relative deficiency this process can go unchecked. This can lead to higher levels of von Willebrand factor in cirrhosis and aggregation of platelets, which can potentiate thrombus formation.⁵⁶

Assessment of coagulation

Traditional measures of bleeding risk with platelet counts and prothrombin time (INR) are an incomplete assessment of the coagulation profile in liver disease patients. Whole blood functional analysis of clot formation would be more useful in the accurate determination of bleeding and clotting risk. These tests, which include thromboelastography or rotational thromboelastometry, may provide this insight.^{57,58} However, accurate results are difficult to achieve due to high variability depending on user familiarity, and the output is often complicated and hard to understand. Newer technology is needed and remains a large void in this field.

The more common complication in cirrhosis patients is bleeding. Many procoagulant factors can be used to correct bleeding, but currently there is no sequential algorithm that is the standard of care. Procoagulant factors work on different steps in the bleeding/clotting cascade.⁵⁹ Fresh frozen plasma should be used judiciously, as it may worsen portal hypertension by increasing blood volume, but may not have as profound an effect on bleeding risk.⁶⁰ Platelet counts may be vital in ensuring that the patient has adequate thrombin generation. Platelet values above 50,000 seem to result in almost normal clot formation.⁵² It is also important to recognize low fibrinogen levels, which may benefit from cryoprecipitate transfusions.

Recommendations for coagulation

Through our extensive studies, we have worked out possible working recommendations to manage bleeding and thrombosis in cirrhosis patients.⁵⁹ In the case of bleeding, it is essential to obtain an accurate bleeding or clotting history, including a family history. Second, after controlling for infection and renal disease, it is important to optimize platelet counts for a goal above 50,000/dL. Further, it is important to replete fibrinogen to a target above 120 mg/dL to ensure fibrin clot formation. On the other hand, in the setting of thrombosis, it is important to rule out a hypercoagulable state. Consultation with a hematologist can ensure that a full serological panel of testing can rule out common causes that may predispose to clot formation. If anticoagulation is considered, hematology working in concert can guide therapy of low molecular weight heparin or newer anticoagulants. As our understanding of bleeding and thrombosis in this population develops, treatment algorithms may change and more comprehensive testing may become available. Until that time, disruption of the hemostatic balance in end-stage liver disease patients will continue to be a challenging dilemma.

Conclusion

The management of cirrhosis patients with decompensation, HE, HRS, and coagulation issues is very complicated. There are many other problems that affect this population. The complicated pathophysiology of these patients can lead to derangements that require the utmost attention. With some of the recommendations made above, we hope to provide a framework to treat a few of these issues.

Disclosure

The authors report no conflicts of interest in this work.

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