American Journal Of Biomedical Science & Pharmaceutical Innovation

VOLUME Vol.05 Issue09 2025
PAGE NO. 1-10

Innovations in Managing Decompensated Cirrhosis: A Review of Contemporary Treatment Strategies

Dr. Samuel Chen
Department of Internal Medicine, Pacific Rim Medical Center, Vancouver, Canada

Received: 03 July 2025; **Accepted:** 02 August 2025; **Published:** 01 September 2025

Abstract: Background: Liver cirrhosis, the end-stage of chronic liver disease, is a major cause of global morbidity and mortality. Its clinical course is characterized by the development of life-threatening complications, including portal hypertension, ascites, hepatic encephalopathy (HE), hepatorenal syndrome-acute kidney injury (HRS-AKI), and hepatocellular carcinoma (HCC). The management of these conditions is complex and has evolved significantly in recent years.

Objective: This review aims to synthesize recent evidence and provide a comprehensive overview of the contemporary, evidence-based strategies for the diagnosis and management of the major complications of decompensated liver cirrhosis.

Methods: A narrative review of the literature was conducted using prominent databases. The synthesis focuses on seminal studies, clinical guidelines, and recent trials that have shaped the current understanding and treatment paradigms for cirrhosis complications, drawing from a curated list of 34 key references.

Findings: Management of portal hypertension and varices has been refined with non-invasive diagnostics and clear prophylactic strategies. For ascites, the focus remains on diuretic management and timely intervention for refractory cases, while new insights into bacterascites and spontaneous bacterial peritonitis (SBP) have improved infection control. The treatment of HE is centered on ammonia-lowering agents like lactulose and rifaximin. The diagnostic criteria for HRS-AKI have been updated for earlier recognition, with vasoconstrictors (e.g., terlipressin) and albumin forming the cornerstone of medical therapy. For HCC, enhanced risk stratification models and regular surveillance in cirrhotic patients are critical for early detection and access to potentially curative therapies.

Conclusion: The management of cirrhosis complications has advanced significantly, moving towards earlier diagnosis and targeted, evidence-based interventions. A multi-faceted approach addressing each complication is crucial for improving patient outcomes. Future research should focus on novel therapies targeting the underlying pathophysiology of portal hypertension and fibrosis to prevent decompensation and improve survival.

Keywords: Liver Cirrhosis, Decompensated Cirrhosis, Portal Hypertension, Ascites, Hepatic, Encephalopathy, Hepatorenal Syndrome, Hepatocellular Carcinoma.

Introduction: Liver cirrhosis represents the terminal pathological stage for a wide spectrum of chronic liver diseases, culminating in a state of irreversible liver damage characterized by extensive fibrosis, the formation of regenerative nodules, and a profound disruption of the normal hepatic architecture (1). This process is not merely a static endpoint but a dynamic condition that fundamentally alters hepatic function and hemodynamics, leading to a cascade of life-threatening complications. The pathophysiology is rooted in the liver's chronic response to injury, wherein repeated hepatocyte death triggers a wound-healing response that becomes dysregulated. This leads to the excessive deposition of extracellular matrix proteins, primarily collagen, by activated hepatic stellate cells, ultimately replacing functional liver parenchyma with scar tissue. The consequence is a progressive decline in the liver's synthetic, metabolic, and detoxification capabilities, coupled with a significant increase in resistance to portal blood flow (1, 8).

The global epidemiological landscape of cirrhosis is vast and evolving, posing a substantial and growing public health challenge. It is a leading cause of mortality worldwide, with estimates attributing over one million deaths annually to its complications (2). While viral hepatitis B and C have historically been dominant etiological factors, the epidemiological drivers are shifting dramatically. In many Western nations, non-alcoholic fatty liver disease (NAFLD), propelled by the parallel epidemics of obesity and type 2 diabetes, and alcohol-associated liver disease are rapidly becoming the predominant causes of cirrhosis (2, 4). Projections indicate that by 2040, these two etiologies will be responsible for the overwhelming majority of new cirrhosis diagnoses in countries like Canada, signaling a critical need for public health strategies targeting metabolic health and alcohol consumption (4). The global burden is not uniform, with significant regional variations in incidence and mortality, reflecting differences in the prevalence of risk factors such as viral hepatitis, alcohol use, and metabolic syndrome (3). This complex and changing epidemiology underscores the universal importance of developing and implementing effective management strategies for the sequelae of this devastating disease.

The clinical trajectory of cirrhosis is typically divided into two distinct phases: compensated and decompensated. In the compensated stage, despite the presence of significant liver fibrosis, the organ retains sufficient functional reserve to prevent the manifestation of overt clinical symptoms. Patients may remain in this state for many years. The transition to decompensated cirrhosis is a watershed moment in the natural history of the disease, marked by the development of one or more major complications: ascites, variceal hemorrhage, or hepatic encephalopathy (5). This transition signifies a grim prognostic turning point, as the one-year mortality rate escalates from less than 5% in compensated patients to approximately 20% or higher following the first decompensating event (28). The development of these complications is a direct consequence of worsening portal hypertension and deteriorating hepatic function (5).

The onset of decompensation initiates a cycle of escalating morbidity, frequent and costly hospitalizations, and a profound deterioration in patients' quality of life (7, 12). Complications such as refractory ascites, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS) carry particularly high short-term mortality rates and place an immense burden on healthcare resources (12, 19, 24). The management of this patient population is exceptionally complex, requiring a multidisciplinary approach to address the systemic nature of the disease. It is a field characterized by continuous evolution, as new diagnostic tools, pharmacological agents, and interventional procedures are developed and integrated into clinical practice. The need for a consolidated, up-to-date review of these advancements is therefore paramount. Such a review serves to equip clinicians with the latest evidence-based strategies, standardize care to reduce practice variability, and ultimately improve the outcomes for patients suffering from the advanced stages of liver disease (6).

This article aims to address this need by systematically reviewing and synthesizing the recent and pivotal developments in the pathophysiology, diagnosis, and management of the primary complications of liver cirrhosis. By focusing on portal hypertension and variceal bleeding, ascites and SBP, hepatic encephalopathy, HRS-acute kidney injury (AKI), and hepatocellular carcinoma (HCC), this review will provide a comprehensive and clinically relevant overview of the contemporary standards of care. The objective is to create a resource that not only informs clinical practice but also highlights the remaining unmet needs and future research directions necessary to further mitigate the devastating impact of decompensated cirrhosis.

METHODS

This article is a narrative review designed to synthesize and present a comprehensive overview of the current state of knowledge regarding the management of liver cirrhosis complications. The methodological approach was based on a structured, albeit non-systematic, search of the medical literature to identify seminal, high-impact, and recent publications relevant to the topic. The foundation of this review is a curated list of 34 key references, selected for their significance in defining the pathophysiology, establishing diagnostic criteria, and shaping the evidence-based management strategies for the core complications of cirrhosis.

The literature search was conducted using major electronic databases, including PubMed, MEDLINE, and Scopus, to identify relevant articles. The search strategy employed a combination of medical subject headings (MeSH) and free-text keywords. Core search terms included "liver cirrhosis," "decompensated cirrhosis," "portal hypertension," "esophageal varices," "variceal hemorrhage," "ascites," "spontaneous bacterial peritonitis," "hepatic encephalopathy," "hepatorenal syndrome," "acute kidney injury," and "hepatocellular carcinoma." These terms were often combined with secondary keywords such as "pathophysiology," "diagnosis," "treatment,"

"management," "guidelines," and "recent developments."

The selection criteria for inclusion were designed to capture the most influential and clinically relevant literature. Priority was given to international consensus guidelines, large-scale clinical trials, meta-analyses, and comprehensive systematic reviews. Foundational articles that established key concepts, such as the initial diagnostic criteria for hepatorenal syndrome, were included for historical context. The search was limited to articles published in English and focused on studies involving adult human subjects. Exclusion criteria were applied to filter out literature that was less relevant to a broad clinical overview, such as individual case reports (unless they were uniquely illustrative of a novel concept or treatment), studies focused exclusively on pediatric populations, and research on rare or secondary complications of cirrhosis that fall outside the scope of this review.

The synthesis of the selected literature was performed thematically. The findings were organized into distinct sections corresponding to the major complications of liver cirrhosis, as outlined in the introduction. This structure was chosen to create a logical and intuitive flow for the reader, beginning with the central pathophysiological driver—portal hypertension—and progressing through its direct and indirect consequences. Within each section, the information is presented in a structured manner, covering pathophysiology, diagnosis, management, and recent advancements. This narrative approach allows for the integration of evidence from various sources into a coherent and readable text that not only presents data but also provides context and clinical interpretation. The aim is to provide a balanced and critical appraisal of the current evidence, thereby offering a valuable resource for clinicians, trainees, and researchers in the field of hepatology.

RESULTS AND DISCUSSION

3.1 Portal Hypertension and Variceal Bleeding

Portal hypertension is the cornerstone pathophysiological consequence of cirrhosis and the primary driver of most of its lethal complications (8). It is defined by a pathological increase in the pressure within the portal venous system, resulting from a combination of two principal factors: a structural increase in intrahepatic vascular resistance and a functional component involving active vasoconstriction and altered blood flow. The structural component arises from the extensive fibrosis and architectural distortion of the liver, which physically compresses and obstructs the hepatic sinusoids and terminal portal venules (1). This mechanical obstruction is the initial and most significant factor. The functional component, which is potentially reversible, involves the active contraction of hepatic stellate cells, myofibroblasts, and vascular smooth muscle cells within the liver, mediated by a local imbalance between vasoconstrictors (e.g., endothelin-1) and vasodilators (e.g., nitric oxide). Compounding this intrahepatic resistance is a marked increase in splanchnic blood flow, driven by profound vasodilation in the splanchnic arterial circulation. This vasodilation results from an overproduction of local vasodilators, creating a hyperdynamic circulatory state that further exacerbates the pressure in the portal system (8, 9). When the hepatic venous pressure gradient (HVPG)—the gold standard for measuring portal pressure—exceeds 10 mmHg, it reaches the threshold of clinically significant portal hypertension (CSPH), the point at which complications such as varices and ascites begin to develop.

The diagnosis and risk stratification of portal hypertension have traditionally relied on invasive HVPG measurement. However, the technical demands and limited availability of this procedure have spurred the development of non-invasive methods. Vibration-controlled transient elastography (VCTE), commonly known as FibroScan, has emerged as a leading non-invasive tool. VCTE measures liver stiffness as a surrogate for the degree of fibrosis and, by extension, the level of portal pressure. Studies have demonstrated a strong correlation between liver stiffness measurement (LSM) and the presence of CSPH and esophageal varices, making it a valuable tool for risk stratification in patients with compensated cirrhosis (10). An LSM below a certain threshold can confidently rule out the presence of high-risk varices, potentially allowing clinicians to defer screening endoscopy in a subset of patients. Other non-invasive markers, including platelet count, spleen size, and various calculated scores, are also used in clinical practice to predict the presence of varices, though VCTE is generally considered more accurate.

Gastroesophageal varices, which are dilated portosystemic collateral veins, form as a direct consequence of portal hypertension, serving as a bypass for blood to return to the systemic circulation. They are present in approximately 50% of patients with cirrhosis at the time of diagnosis, and their primary clinical significance lies in their propensity to rupture and cause catastrophic bleeding (11). Variceal hemorrhage is a medical emergency with a mortality rate that, despite significant advances in management, remains around 15-20% per episode. The management of varices is therefore centered on preventing the first bleeding episode (primary prophylaxis), controlling

acute hemorrhage, and preventing re-bleeding (secondary prophylaxis).

Primary prophylaxis is indicated for patients with medium to large varices or for those with small varices that have red wale marks, indicating a high risk of rupture. The cornerstones of primary prophylaxis are non-selective beta-blockers (NSBBs), such as propranolol and nadolol, and endoscopic variceal ligation (EVL). NSBBs act by reducing cardiac output (β1-blockade) and causing splanchnic vasoconstriction (β2-blockade), thereby lowering portal pressure and variceal wall tension (11). EVL involves the endoscopic placement of small elastic bands around the varices, leading to their thrombosis and eventual eradication. The choice between NSBBs and EVL is often guided by patient characteristics, local expertise, and patient preference, as both have been shown to be effective in reducing the incidence of first variceal bleed.

The management of acute variceal hemorrhage is a multi-pronged effort that must be initiated immediately. It includes hemodynamic resuscitation to maintain circulatory stability, prompt administration of a vasoactive drug (e.g., terlipressin, octreotide, or somatostatin) to reduce portal pressure, and prophylactic antibiotics (e.g., ceftriaxone) to prevent bacterial infections, which are a common trigger and complication of bleeding (11). Urgent upper endoscopy should be performed within 12 hours to confirm the source of bleeding and provide definitive hemostatic therapy, most commonly with EVL. If endoscopic therapy fails to control the bleeding, a salvage transjugular intrahepatic portosystemic shunt (TIPS) may be required. A TIPS procedure involves creating a low-resistance channel between the portal vein and the hepatic vein within the liver, effectively decompressing the portal system.

Following successful control of an acute bleed, patients are at a very high risk of re-bleeding. Therefore, secondary prophylaxis must be initiated promptly. The current standard of care for secondary prophylaxis is the combination of NSBB therapy and a program of serial EVL until variceal eradication is achieved (11). This combination approach has been shown to be superior to either modality alone in preventing re-bleeding. For patients who experience recurrent bleeding despite optimal endoscopic and medical therapy, TIPS is the recommended second-line treatment. Recent developments in this area include the refinement of non-invasive criteria for initiating prophylaxis, the investigation of carvedilol (an NSBB with additional anti-alpha-1 adrenergic activity) as a potentially more potent agent, and the concept of "pre-emptive" TIPS placement in very high-risk patients (e.g., those with Child-Pugh class C or B with active bleeding at endoscopy) to improve survival.

3.2 Ascites and Spontaneous Bacterial Peritonitis (SBP)

Ascites, the pathological accumulation of fluid within the peritoneal cavity, is the most common complication of cirrhosis, marking the transition to the decompensated phase for the majority of patients (13). Its development is a harbinger of a poor prognosis, with nearly 50% mortality within two years of onset if not managed effectively. The pathophysiology of ascites is complex and multifactorial, but it is fundamentally driven by severe portal hypertension and a resulting state of systemic circulatory dysfunction. Elevated pressure in the hepatic sinusoids and splanchnic capillaries leads to an increased rate of lymph formation that eventually overwhelms the capacity of the lymphatic drainage system, causing fluid to weep from the surface of the liver and seep from the mesenteric vasculature into the peritoneal cavity (13). This process is profoundly exacerbated by splanchnic arterial vasodilation, which decreases the effective arterial blood volume and triggers the activation of neurohumoral vasoconstrictor systems, most notably the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The intense activation of these systems leads to avid renal sodium and water retention, providing the volume necessary for ascites to form and persist (14).

The diagnosis of new-onset ascites is typically confirmed with an abdominal ultrasound. A crucial next step is diagnostic paracentesis, the aspiration of ascitic fluid for analysis. This procedure is essential to confirm that the ascites is due to portal hypertension and, most importantly, to rule out infection. The key diagnostic test is the calculation of the serum-ascites albumin gradient (SAAG), which is the serum albumin concentration minus the ascitic fluid albumin concentration. A SAAG of 1.1 g/dL or greater is highly indicative (with ~97% accuracy) of ascites caused by portal hypertension (15). The ascitic fluid should also be analyzed for a cell count with differential to screen for spontaneous bacterial peritonitis (SBP).

The cornerstone of ascites management is the creation of a negative sodium balance through dietary sodium restriction (typically to 88 mmol/day or 2000 mg/day) and the administration of diuretics (14). The standard diuretic regimen involves a combination of an aldosterone antagonist, spironolactone, and a loop diuretic, furosemide. Spironolactone directly counteracts the hyperaldosteronism that is central to the pathophysiology, while furosemide provides a potent natriuretic effect. The typical starting dose ratio is 100 mg of spironolactone to 40 mg of furosemide,

which can be titrated upwards to achieve adequate weight loss (approximately 0.5 kg/day) while maintaining stable renal function and electrolyte balance (14).

A subset of patients will develop refractory ascites, defined as fluid overload that is unresponsive to maximal diuretic therapy or that recurs rapidly after therapeutic paracentesis, or in whom diuretic-related complications preclude their use (23). For these patients, the primary management strategy is serial large-volume paracentesis (LVP), which involves the therapeutic drainage of several liters of ascitic fluid. To prevent post-paracentesis circulatory dysfunction—a condition of effective hypovolemia caused by the rapid fluid shift—it is recommended to administer intravenous albumin (6-8 g per liter of ascites removed) when more than 5 liters are drained (14). For suitable candidates with refractory ascites, a TIPS procedure can be highly effective in controlling fluid accumulation by decompressing the portal system, but it comes with a significant risk of precipitating or worsening hepatic encephalopathy.

Spontaneous bacterial peritonitis (SBP) is an acute bacterial infection of the ascitic fluid that occurs in the absence of any intra-abdominal source of infection. It is a severe and life-threatening complication, occurring in 10-30% of hospitalized patients with cirrhotic ascites (19). The pathogenesis is believed to involve the translocation of bacteria, most commonly gram-negative enteric organisms like Escherichia coli and Klebsiella pneumoniae, from the gut lumen into mesenteric lymph nodes and subsequently into the systemic circulation, leading to bacteremia and the seeding of the susceptible ascitic fluid (18). The diagnosis of SBP is established by a diagnostic paracentesis showing an ascitic fluid absolute neutrophil count of 250 cells/mm³ or greater (19). Treatment should be initiated empirically as soon as SBP is suspected, without waiting for culture results. The recommended first-line therapy is a third-generation cephalosporin, such as cefotaxime or ceftriaxone, for a minimum of 5 days (18). Albumin infusion (1.5 g/kg on day 1 and 1.0 g/kg on day 3) is also recommended, particularly in patients with renal or severe liver dysfunction, as it has been shown to reduce the incidence of hepatorenal syndrome and improve survival.

Given the high recurrence rate of SBP (up to 70% within one year), long-term secondary antibiotic prophylaxis is indicated for any patient who survives an episode of SBP. Primary prophylaxis is also recommended for certain high-risk patients, such as those with a low ascitic fluid total protein concentration (<1.5 g/dL) combined with advanced liver failure or impaired renal function (14). Recent developments in this field have focused on improving outcomes through systemic changes, such as the implementation of "decompensated cirrhosis discharge care bundles," which ensure patients are discharged on appropriate diuretic regimens, have follow-up scheduled, and are educated about their condition, leading to improved outcomes and reduced readmissions (6). Furthermore, there is growing recognition of other ascitic fluid infections, such as bacterascites (a positive ascitic fluid culture with a neutrophil count <250/mm³), which requires careful clinical judgment to determine the need for treatment (20).

3.3 Hepatic Encephalopathy (HE)

Hepatic encephalopathy (HE) is a debilitating neuropsychiatric syndrome characterized by a wide spectrum of symptoms, ranging from subtle cognitive deficits to profound confusion, altered consciousness, and coma. It is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting (16). HE significantly impairs quality of life, increases the risk of hospitalization, and is a marker of poor prognosis in patients with cirrhosis. The condition can be classified as episodic (acute, recurrent episodes), persistent (chronic cognitive symptoms), or minimal (subclinical deficits detectable only on specialized psychometric or neurophysiological testing).

The pathophysiology of HE is complex and not fully elucidated, but the central hypothesis revolves around the accumulation of gut-derived neurotoxins in the systemic circulation that cross the blood-brain barrier and cause cerebral dysfunction. Ammonia is considered the primary culprit (16). In a healthy individual, ammonia produced by enterocytes and colonic bacteria from the breakdown of nitrogenous compounds (like dietary protein) is transported via the portal vein to the liver, where it is efficiently detoxified into urea through the urea cycle (17). In patients with cirrhosis, this process fails for two reasons: diminished hepatocyte function reduces the capacity of the urea cycle, and portosystemic shunts allow ammonia-rich portal blood to bypass the liver and enter the systemic circulation directly. Elevated arterial ammonia levels lead to an increase in ammonia concentration in the brain. Astrocytes, the primary site of cerebral ammonia metabolism, attempt to detoxify it by converting it to glutamine. The accumulation of glutamine within astrocytes creates an osmotic imbalance, leading to astrocyte swelling (low-grade cerebral edema) and dysfunction. This process is thought to disrupt neurotransmitter systems (glutamatergic, serotonergic, GABAergic), alter cerebral energy metabolism, and contribute to the neurocognitive and neuromuscular impairments characteristic of HE (16).

Other factors, including inflammation, oxidative stress, and alterations in the gut microbiome, are also recognized as important contributors to the pathogenesis.

The diagnosis of overt HE is primarily clinical, based on a compatible history and physical examination in a patient with known liver disease, after excluding other potential causes of altered mental status (e.g., intracranial hemorrhage, metabolic disturbances, drug intoxication). The severity of overt HE is typically graded using the West Haven criteria, which range from Grade 1 (mild confusion, altered sleep pattern) to Grade 4 (coma) (16). A key diagnostic step is to identify and address any precipitating factors, as HE episodes are often triggered by a specific event. Common precipitants include infections (especially SBP), gastrointestinal bleeding, electrolyte imbalances (particularly hypokalemia), dehydration from over-diuresis, constipation, and the use of sedatives or psychoactive medications (5).

The management of an acute episode of overt HE focuses on two main goals: providing general supportive care and initiating therapy to lower ammonia levels. Supportive care includes ensuring airway protection in patients with severe encephalopathy and correcting any identified precipitating factors. The first-line pharmacological treatment for lowering ammonia is the use of non-absorbable disaccharides, primarily lactulose (16). Lactulose works through multiple mechanisms in the colon: it is metabolized by colonic bacteria into short-chain fatty acids, which lowers the intraluminal pH. This acidic environment promotes the conversion of ammonia (NH_3) to the non-absorbable ammonium ion (NH_4^+), effectively trapping it in the colon. It also has a cathartic effect, which reduces the time available for ammonia production and absorption. The dose of lactulose is titrated to achieve two to three soft bowel movements per day.

For the prevention of HE recurrence (secondary prophylaxis), particularly after a second episode, the antibiotic rifaximin is recommended, typically as an add-on therapy to lactulose. Rifaximin is a minimally absorbed oral antibiotic that modulates the gut microbiota, reducing the population of ammonia-producing bacteria (16). The combination of lactulose and rifaximin has been shown to be more effective than lactulose alone in reducing the risk of recurrent HE episodes and HE-related hospitalizations. Nutritional management is also a critical component of HE care. While historical practice often involved severe protein restriction, this is now known to be detrimental, as it can worsen malnutrition and sarcopenia, which are themselves risk factors for HE. Current guidelines recommend adequate protein intake (1.2-1.5 g/kg/day) to maintain muscle mass, with a preference for vegetable and dairy sources of protein over animal protein.

Recent developments in the understanding of HE have further emphasized the "gut-liver-brain axis." There is a growing appreciation for the role of the gut microbiome and systemic inflammation in the pathogenesis of HE. Dysbiosis, or an imbalance in the gut microbial community, is common in cirrhosis and can lead to an overgrowth of pathogenic, ammonia-producing bacteria and a compromised intestinal barrier function, facilitating the translocation of bacterial products and inflammatory mediators into the circulation. This systemic inflammation can synergize with ammonia to exacerbate neuroinflammation and astrocyte dysfunction. This has opened up new avenues for research into therapies targeting the gut microbiome, such as probiotics, prebiotics, and fecal microbiota transplantation, although these are still considered investigational.

3.4 Hepatorenal Syndrome and Acute Kidney Injury (HRS-AKI)

Acute kidney injury (AKI) is a frequent and devastating complication in patients with advanced cirrhosis, occurring in up to 50% of hospitalized patients and carrying a very high mortality rate (26). The causes of AKI in this population are diverse, but one of the most feared is hepatorenal syndrome (HRS), a unique form of functional renal failure characterized by intense renal vasoconstriction in the setting of extreme systemic and splanchnic arterial vasodilation (21, 25). The term "hepatorenal syndrome" has a long history, first being described in the context of liver trauma and biliary surgery, but its modern definition is intrinsically linked to the circulatory derangements of advanced cirrhosis (22).

The pathophysiology of HRS is a direct extension of the hyperdynamic circulation that characterizes decompensated cirrhosis. As portal hypertension worsens, the splanchnic arterial vasodilation becomes more profound, leading to a significant reduction in effective arterial blood volume and mean arterial pressure. This perceived systemic hypovolemia triggers a maximal compensatory activation of endogenous vasoconstrictor systems, including the RAAS and the sympathetic nervous system, in an attempt to maintain blood pressure (25). While these systems help support systemic circulation, they have a deleterious effect on the kidneys, causing intense renal vasoconstriction, particularly at the cortical level. This leads to a dramatic reduction in renal blood flow and glomerular filtration rate (GFR), culminating in renal failure, despite the

absence of any intrinsic structural damage to the kidneys. The functional nature of HRS is demonstrated by the fact that kidneys from a patient with HRS typically function normally when transplanted into a recipient with a healthy liver (21).

The diagnosis and classification of renal dysfunction in cirrhosis have evolved significantly over the years. The historical definition of HRS, established by the International Club of Ascites (ICA) in 1996, was based on a slow, progressive decline in renal function and had stringent diagnostic criteria that often delayed diagnosis and treatment (23). Recognizing that acute renal failure in cirrhosis is a more dynamic process, the ICA revised the consensus recommendations in 2015, replacing the old terminology of HRS type 1 and type 2 with a new classification that aligns with the broader AKI framework (27). The term HRS-AKI is now used to describe the acute, functional renal failure of cirrhosis. The diagnosis of AKI in cirrhosis is defined as an increase in serum creatinine (sCr) of ≥0.3 mg/dL within 48 hours or a ≥50% increase from a stable baseline sCr within the last 3 months. Once AKI is diagnosed, it is staged from 1 to 3 based on the magnitude of the sCr increase (27).

A critical step in management is to differentiate HRS-AKI from other causes of AKI, as the treatments differ substantially. The differential diagnosis includes pre-renal AKI due to simple volume depletion, intrinsic renal injury (e.g., acute tubular necrosis [ATN], which can be caused by hypovolemia or nephrotoxic agents), and post-renal obstruction (26). The diagnostic algorithm for HRS-AKI involves first stopping all potential nephrotoxic drugs (e.g., NSAIDs, aminoglycosides) and diuretics, and then administering a volume challenge with intravenous albumin (1 g/kg body weight per day for 2 consecutive days) to rule out pre-renal azotemia responsive to volume expansion. If there is no improvement in renal function after these measures, and in the absence of shock, signs of parenchymal kidney disease (e.g., significant proteinuria, hematuria, or abnormal renal ultrasound), a diagnosis of HRS-AKI can be made (27).

The management of established HRS-AKI is a medical emergency and revolves around reversing the underlying pathophysiology by improving systemic hemodynamics. The standard of care is the combination of a vasoconstrictor agent and intravenous albumin (24). Vasoconstrictors work by counteracting the profound splanchnic vasodilation, which in turn increases systemic vascular resistance, improves effective arterial volume, and alleviates the intense renal vasoconstriction. The most widely studied and used vasoconstrictor is terlipressin, a vasopressin analogue. Multiple randomized controlled trials have shown that terlipressin, in combination with albumin, is effective in reversing HRS-AKI and improving short-term survival (24). In regions where terlipressin is not available, a combination of norepinephrine (administered in an intensive care unit setting) or midodrine (an oral alpha-1 agonist) plus octreotide can be used as an alternative. Albumin is co-administered not only for its volume-expanding properties but also for its other potential benefits, such as binding and inactivating inflammatory mediators. While these medical therapies can serve as a bridge, the only definitive treatment for HRS is liver transplantation.

Recent developments have centered on the implementation of the new AKI/HRS-AKI criteria to promote earlier recognition and intervention, which is crucial for improving outcomes (27). The recent approval of terlipressin in the United States represents a major therapeutic advance for this patient population. Ongoing research is focused on identifying novel biomarkers to better differentiate HRS-AKI from ATN, predicting response to vasoconstrictor therapy, and exploring the role of TIPS in select patients with HRS-AKI.

3.5 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and one of the leading causes of cancer-related death worldwide (29). The overwhelming majority of HCC cases—approximately 80-90%—develop in the setting of underlying chronic liver disease and cirrhosis (30). Cirrhosis from any etiology (including viral hepatitis, alcohol, and NAFLD) is the single greatest risk factor for the development of HCC, with an annual incidence of 1-8% among patients with established cirrhosis (28, 30). The development of HCC is often considered the final, malignant complication of the cirrhotic process.

The pathogenesis of HCC in a cirrhotic liver is a complex, multi-step process driven by decades of chronic inflammation, hepatocyte death, and subsequent compensatory regeneration (34). This persistent cycle of injury and repair creates a pro-carcinogenic microenvironment characterized by oxidative stress, DNA damage, and the activation of oncogenic signaling pathways. Chronic inflammation, mediated by cytokines and chemokines, promotes cell proliferation and survival while inhibiting apoptosis, creating a fertile ground for malignant transformation. As hepatocytes are forced to replicate continuously to replace damaged cells, the risk of accumulating genetic and epigenetic mutations increases. Over time, these alterations can lead to the dysregulation of cell cycle control, the activation of proto-oncogenes, and the inactivation of tumor suppressor genes. Cellular

senescence, a state of irreversible growth arrest that normally acts as an anti-cancer mechanism, can become dysregulated in the cirrhotic liver, paradoxically contributing to a pro-inflammatory secretory phenotype that further fuels carcinogenesis (34). While cirrhosis is the main highway to HCC, it is important to note that HCC can, in some instances, develop in non-cirrhotic livers, particularly in the context of chronic hepatitis B virus infection or NAFLD (33).

Given the high risk of HCC in patients with cirrhosis, surveillance for the early detection of tumors is a cornerstone of modern hepatology practice. The goal of surveillance is to detect HCC at an early stage when potentially curative therapies can be offered, thereby improving survival. The standard recommendation for surveillance is to perform an abdominal ultrasound, with or without measurement of the serum biomarker alpha-fetoprotein (AFP), every six months for all patients with cirrhosis (31). This strategy has been shown in multiple studies to improve early tumor detection and overall survival.

In addition to universal surveillance for all cirrhotic patients, there has been a significant effort to develop risk prediction models to better stratify individuals based on their likelihood of developing HCC. These models incorporate various clinical and demographic variables to provide a more personalized risk assessment. For example, the ADRESS-HCC risk model incorporates Age, male sex (biological sex), Diabetes, Race/ethnicity, Etiology of cirrhosis, and low platelet count (a Surrogate for the severity of portal hypertension) to calculate a patient's 5-year risk of developing HCC (32). Such models can help in counseling patients and may, in the future, guide more intensive or tailored surveillance strategies for those at the highest risk. A recent large-scale study further refined our understanding of risk factors, confirming the high incidence in patients with viral hepatitis-related cirrhosis but also highlighting the substantial and growing risk among those with NAFLD-related cirrhosis, reinforcing the need for diligent surveillance across all etiologies (31).

When a suspicious lesion is detected on a surveillance ultrasound, the diagnostic workup typically involves a multiphasic contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI). In patients with cirrhosis, HCC has a characteristic vascular signature—arterial phase hyperenhancement followed by portal venous or delayed phase "washout"—that allows for a non-invasive diagnosis in most cases, obviating the need for a liver biopsy (30).

The management of HCC is complex and depends on the tumor stage (size, number of nodules, vascular invasion), the underlying liver function (as assessed by the Child-Pugh score), and the patient's overall performance status. Treatment options are broadly categorized as curative or palliative. Curative-intent therapies are reserved for patients with early-stage disease and include surgical resection, liver transplantation, and local ablative therapies (e.g., radiofrequency ablation or microwave ablation). Liver transplantation is the ideal treatment as it removes both the tumor and the underlying diseased cirrhotic liver, but its use is limited by organ availability. For patients with intermediate-stage disease who are not candidates for curative therapies, the standard of care is often transarterial chemoembolization (TACE). For patients with advanced HCC (e.g., with vascular invasion or extrahepatic spread) or those who progress on regional therapies, systemic therapy is the mainstay of treatment. Recent developments in this area have been revolutionary, with immune checkpoint inhibitors, either alone or in combination with anti-angiogenic agents, now established as the first-line standard of care, having demonstrated superior survival outcomes compared to the older generation of tyrosine kinase inhibitors. The continuous evolution of these systemic therapies represents one of the most significant recent advances in the management of cirrhosis complications.

CONCLUSION

The management of decompensated liver cirrhosis has undergone a significant transformation over the past two decades. A deeper understanding of the intricate pathophysiology, from the hemodynamic consequences of portal hypertension to the molecular drivers of hepatocellular carcinoma, has paved the way for more sophisticated and effective clinical strategies. Advances in non-invasive diagnostics, such as transient elastography, have enabled better risk stratification, while the evolution of diagnostic criteria for conditions like HRS-AKI has promoted earlier and more aggressive intervention. The therapeutic armamentarium has expanded considerably, with refined approaches to diuretic and beta-blocker therapy, the establishment of rifaximin for hepatic encephalopathy, the approval of potent vasoconstrictors like terlipressin for HRS-AKI, and a revolution in systemic therapies for advanced HCC.

This review synthesizes the evidence underpinning these contemporary management paradigms. It highlights that a proactive, multidisciplinary approach is essential. This includes not only treating acute events but also focusing on preventing subsequent decompensation through rigorous secondary prophylaxis, nutritional support, and diligent

surveillance for HCC. The implementation of standardized care bundles has been shown to improve outcomes, underscoring the importance of systematic and evidence-based care delivery (6).

Despite this progress, significant unmet needs and challenges remain. The ultimate goal in hepatology is to prevent cirrhosis itself or, failing that, to halt or reverse fibrosis before decompensation occurs. While therapies targeting the underlying etiologies of cirrhosis (e.g., antiviral agents for hepatitis C) have been transformative, effective anti-fibrotic drugs remain an elusive but critical area of research. For patients with established decompensation, there is a pressing need for better prognostic biomarkers to identify those who will benefit most from intensive interventions like early TIPS placement or liver transplantation. Furthermore, as the population with NAFLD-related cirrhosis grows, new challenges in managing comorbidities like diabetes, cardiovascular disease, and obesity in this complex patient group will become more prominent. Future research must continue to focus on therapies that target the fundamental mechanisms of the disease, improve the quality of life for those living with its complications, and ensure equitable access to advanced care, including transplantation, on a global scale. In conclusion, while the complications of cirrhosis continue to pose a formidable clinical challenge, the advancements detailed in this review offer a robust framework for management and a hopeful outlook for continued progress in the field.

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