Renal dysfunction in liver disease

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Abstract

Acute kidney injury is a frequently encountered complication in patients with decompensated liver disease. As in the general population, pre-renal, renal and post-renal causes should be excluded, although particular consideration must be given to sepsis and bleeding. Hepatorenal syndrome (HRS) is a type of acute kidney injury found in patients with advanced liver disease, the diagnosis of which should be made only after excluding other causes. Acute and chronic renal dysfunction in cirrhosis is common, and both confer a negative impact on morbidity and mortality. As such, it is essential for all clinicians involved in the care of these patients to be able to identify them in both inpatient and outpatient settings, so that appropriate management strategies can be implemented. This article reviews the aetiology and management of renal dysfunction in patients with chronic liver disease. HRS has a high morbidity and mortality, and its pathogenesis, diagnosis and specific management are highlighted here.

Keywords Acute kidney injury; ascites; cirrhosis; hepatorenal syndrome; MRCP

Key points

- AKI is common in patients with chronic liver disease and timely management is essential
- HRS-AKI is a diagnosis of exclusion and other causes of AKI must be considered before making the diagnosis
- CKD is common in patients with chronic liver disease and signifies a poor prognosis
- Measuring renal function using creatinine alone in cirrhosis is unreliable therefore trend over time and clinical factors such as urine output must be given consideration

Introduction

Renal dysfunction is estimated to occur in nearly half of patients with cirrhosis admitted to hospital.[1] Acute deterioration in renal function (acute kidney injury (AKI)) is a poor prognostic marker and an independent predictor of inpatient mortality.[2] Serum creatinine is a component of scoring systems used to predict mortality in patients with cirrhosis, such as the Model for End-Stage Liver Disease (MELD) score, United Kingdom Model for End-Stage Liver Disease (UKELD) score and Chronic Liver Failure Consortium Acute on Chronic Liver Failure (CLIF-C ACLF) and Acute Decompensation (CLIF-C AD) scores.

The burden of chronic kidney disease (CKD) in the cirrhotic population is also increasing, in part due to more sensitive definitions of CKD but also because of the improved survival of these patients due to advances in clinical care. This article focuses primarily on the causes and management of AKI encountered in patients with cirrhosis, but also describes the coexistence of CKD with chronic liver disease.

Mechanisms contributing to impaired renal function in cirrhosis

The transition from compensated to decompensated cirrhosis is associated with multiorgan dysfunction, with the kidney being the most commonly affected organ. This results predominantly from haemodynamic alterations related to hepatic decompensation, which is characterized by elevated circulating levels of proinflammatory and vasodilatory mediators, including endotoxins from intestinal bacteria. Splanchnic vasodilatation and endothelial activation predominate, reducing the effective circulatory volume and renal perfusion. The kidney's juxtaglomerular apparatus senses this hypovolaemic state, resulting in activation of the renin–angiotensin–aldosterone system, sympathetic nervous system and arginine vasopressin. In cirrhosis, liver stiffness increases the hydrostatic pressure in the portal vasculature, and reduced protein synthetic function in the failing liver contributes to the fluid accumulation in the peritoneal cavity (ascites), which compounds the reduced effective renal perfusion.

These systems lead to compensatory peripheral vasoconstriction, but as disease progresses and in the context of cardiac dysfunction in cirrhosis (so-called cirrhotic cardiomyopathy), renal hypoperfusion is further compromised and sodium and water retention worsens. These mechanisms increase the susceptibility of the kidneys to further renal insult and can even lead to a form of kidney disease specifically found in patients with advanced liver disease – hepatorenal syndrome (HRS), described below.

Clinical and laboratory assessment

Diagnosing AKI in cirrhosis can be problematic as a reduced hepatic production of creatinine, reduced skeletal muscle mass

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and increased rate of tubular excretion of creatinine result in deceptively low serum creatinine levels and therefore misleading results from creatinine-based equations such as estimated glomerular filtration rate (eGFR) (See Yoo et al. 2019 in Further reading). In the presence of hyperbilirubinaemia, colorimetric assays of serum creatinine are unreliable so enzymatic assays of manually diluted serum samples may be needed. In a number of hospitals, this can require contacting the biochemistry laboratory to ensure the sample is processed correctly. Therefore, creatinine results should be interpreted with care, taking into account the trend of creatinine over time and other clinical parameters such as urine output (Table 1). Recent guidance has adopted the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI, based on either serum creatinine or urine output.

In patients with liver disease and AKI, a detailed history and examination should elucidate the likely precipitants of AKI: pre-renal, renal and post-renal causes. Causes specific to cirrhotic patients include sepsis (particularly spontaneous bacterial peritonitis), gastrointestinal bleeding, excessive diuretic use, therapeutic large-volume paracentesis without adequate volume replacement and use of nephrotoxic drugs including non-steroidal anti-inflammatory drugs (NSAIDs). β-Adrenoceptor blockers (carvedilol, propranolol) are often used as prophylaxis against variceal bleeding but should be withheld in AKI due to their haemodynamic effects.

Clinical assessment of fluid balance should be comprehensive. Clinical features such as dry mucous membranes and reduced skin turgor can be insensitive and should be supplemented with lying and standing blood pressures, bladder catheterization and measurement of hourly urine output, venous blood gases, laboratory biochemistry and invasive central venous monitoring. Early discussion with the critical care team is recommended for patients not responding to initial treatment after the first 6 hours, particularly those with a first presentation of decompensation and with good baseline performance status.[3] Urinary dipstick analysis and estimation of sodium concentration should be performed to exclude intrinsic renal disease and distinguish between pre-renal causes and acute tubular necrosis.

AKI is frequently detected when a patient presents with a decompensating liver event; therefore a thorough assessment of patients with decompensated chronic liver disease is recommended, following, for example, the British Association for the Study of the Liver (BASL) bundle (www.bsg.org.uk/resource/bsg-basl-decompensated-cirrhosis-care-bundle.html). This includes blood cultures, ascitic tap for fluid neutrophil count and ultrasonography scan with Doppler studies of the liver and renal vasculature. If the cause of underlying chronic liver disease is not already established, a full liver screen should be performed, along with a renal screen (Table 2).

The European Association for the Study of the Liver (EASL) has recently published guidance on the management of AKI in cirrhosis adapted from the most recent consensus from the International Club of Ascites. Figure 1 illustrates the recommended algorithm for the management of AKI in patients with cirrhosis, and also plays a role in the diagnostic process.

Causes of AKI in cirrhosis

Patient with cirrhosis are more likely to develop AKI than those without underlying liver disease (see Cárdenas 2001 in Further reading). However, the spectrum of causes of AKI in cirrhosis is similar to that in general medical patients and should be investigated as such. Pre-renal failure as a result of renal hypoperfusion is caused by hypovolaemia resulting from bleeding, diuresis or diarrhoea, sepsis or reduced cardiac output; it is the most common cause of AKI in cirrhotic patients, accounting for approximately one-third (27–50%) of cases.[2] Post-renal causes should be excluded by renal ultrasonography.

Intrinsic renal disease in cirrhotic patients is predominantly the result of acute tubular necrosis after prolonged pre-renal failure or sepsis. Drug causes should also be excluded, and nephrotoxic drugs and diuretics withheld. Glomerulopathies are important causes, and urinalysis can help with the diagnosis. Hepatitis B virus can be associated with membranous glomerulonephritis, and hepatitis C virus (HCV) infection can cause renal

KDIGO clinical guidelines for the diagnosis of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥26.5 micromol/litre increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥353.6 micromol/litre OR Initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Table 1

Investigations to identify causes of liver and renal disease

Liver screen	Renal screen
• Liver function tests (ALT, AST, ALP, GGT, bilirubin) • Clotting • Full blood count • Virology: HBsAg, HCV IgG, HIV I + II antibodies • Autoantibody screen: ANA, AMA, anti-SMA • Immunoglobulins • α-Fetoprotein • Iron studies including ferritin • α_1-Antitrypsin • Caeruloplasmin • Thyroid function tests	• Urea and electrolytes • Virology: HBsAg, HCV IgG, HIV I + II antibodies • Autoimmune screen: ANA, ANCA, complement C3 and C4 • Immunoglobulins • Myeloma screen • Rheumatoid factor • Cryoglobulins

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ANCA, antinuclear cytoplasmic antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; HBsAG, hepatitis B surface antigen; IgG, immunoglobulin G; SMA, smooth muscle antibody.

Table 2

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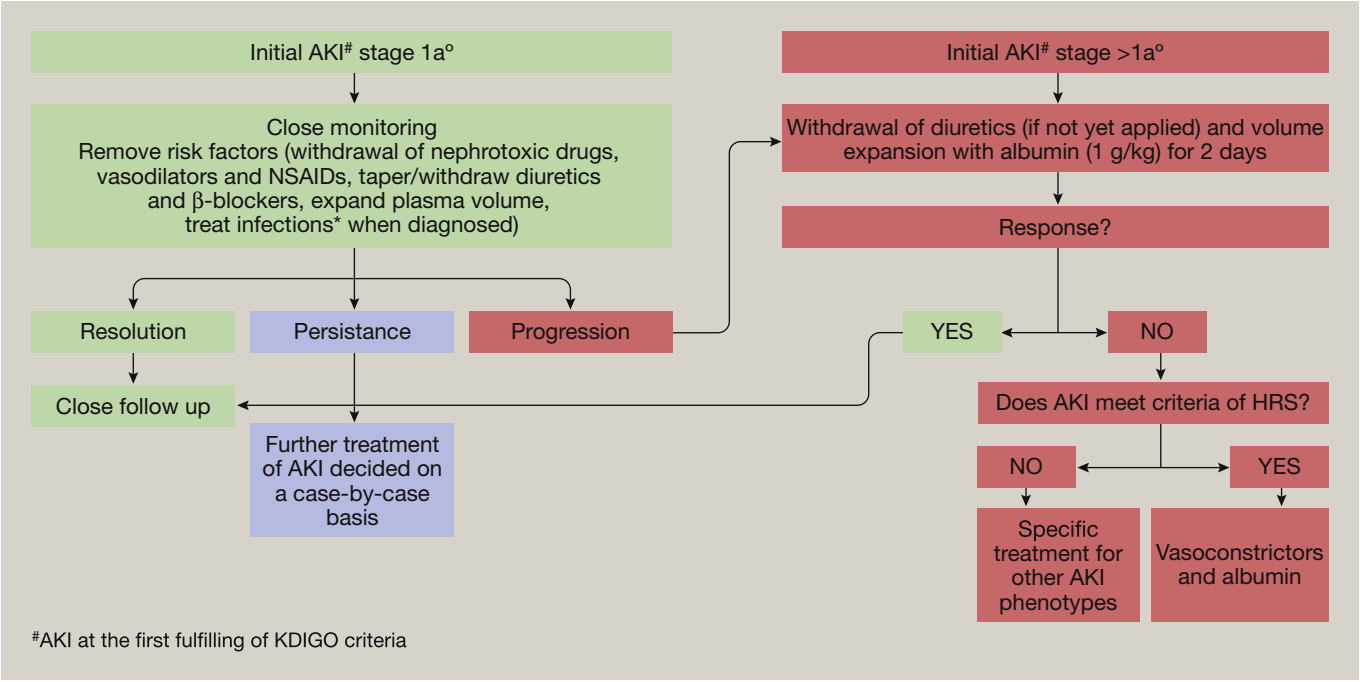

Figure 1 Algorithm for investigating AKI in patients with cirrhosis. Source: Reproduced from EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. European Association for the Study of the Liver. *J Hepatol* 2018; **69:** 406–60 with permission from Elsevier.

injury by mesangiocapillary glomerulonephritis with cryoglobulinaemia. The presence of cryoglobulins or rheumatoid factor can be indicative of this, and the definitive diagnosis is made on renal biopsy. With the advent of new directly acting antiviral therapy, HCV can be cured in almost all patients. Eliminating the virus prevents further renal parenchymal injury, thus preventing progression of CKD.

Hepatorenal syndrome

HRS, the end result of the vicious cycle of circulatory dysfunction described above, describes renal impairment in patients with advanced cirrhosis and in some cases of acute liver failure. It is most commonly encountered as a form of AKI (AKI-HRS), although it can manifest as chronic kidney disease (CKD-HRS).

The diagnosis of AKI-HRS can be made only after excluding the other causes discussed above. It is necessary to confirm a lack of response to withdrawal of diuretics and nephrotoxic drugs and to volume expansion, an absence of post-renal obstruction and intrinsic kidney disease. AKI-HRS confers the poorest prognosis of types of AKI in cirrhosis. Although the criteria for defining AKI-HRS (Table 3) refer to a creatinine level >133 micromol/litre, it is important to bear in mind that serum creatinine can be falsely reassuring as a measure of renal function in patients with advanced liver disease, hence the utility of the KDIGO criteria.

Management of AKI-HRS

Management of HRS aims to restore the effective circulating blood volume by reversing the vasodilatation of the splanchnic circulation with vasoconstrictive medications (chiefly terlipressin) and administering colloid in the form of albumin to prevent worsening of the condition by third space loss of fluid (Table 4). Median survival is 1 month without specific therapy; such therapy is effective in 40–50% of cases (Ginès & Schrier, 2009 in Further reading).

Considerations when using terlipressin relate mainly to its vasoconstrictive properties. The authors recommend that an electrocardiogram is recorded in at-risk patients to rule out ischaemic changes as terlipressin can precipitate cardiovascular events; the BASL Decompensated Cirrhosis Care Bundle defines this specifically for those >65 years of age. Other common side effects of terlipressin include abdominal pain and diarrhoea. Adverse effects can be minimized by gradual uptitration of terlipressin with careful patient monitoring. Given the need for intensive monitoring to prevent fluid overload and progressive hyponatraemia, patients with HRS may be better managed in the critical care setting and as such should be discussed early with these teams.

There is little high-quality evidence on the use of renal replacement therapy in AKI-HRS so decisions regarding this should be discussed on a case-by-case basis.

Chronic kidney disease in chronic liver disease

CKD in cirrhosis is defined as an eGFR of <60 ml/min/1.73m^2 for more than 3 months.[4] This definition encompasses CKD as a result of renal parenchymal damage together with functional renal impairment from altered haemodynamics in advanced liver disease, CKD-HRS.

A recent prospective study of 2346 cirrhotic hospital inpatients demonstrated the presence of CKD in 46.8% of this population. CKD in cirrhosis increases morbidity and mortality,[5] has a negative impact on liver transplant assessment and can restrict treatment options for hepatocellular carcinoma. As a result, the presence of CKD should be actively sought out in

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Criteria for the diagnosis of HRS

- Cirrhosis with ascites
- Serum creatinine >133 micromol/litre
- Absence of shock
- Absence of hypovolaemia as defined by a lack of sustained improvement in renal function (creatinine decreasing to <133 micromol/litre) after at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, a lack of microhaematuria (<50 red cells per high-powered field) and normal renal ultrasonography

Source: Reproduced from EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. European Association for Study of the Liver. J Hepatol 2010; 53: 397–417 with permission from Elsevier.

Table 3

Management of AKI-HRS

General measures	Close monitoring of vital signs and biochemistry (LFTs, U&Es, coagulation screen, FBC, CRP) in a critical care setting if available Removal or treatment of precipitating and exacerbating factors • Screening for and treatment of sepsis • Withdrawal of nephrotoxic medications and those that can worsen haemodynamic status, such as diuretics and β-adrenoceptor blockers Careful fluid management to avoid volume overload and hyponatraemia Limited paracentesis with albumin cover to relieve discomfort in tense ascites
Volume replacement with 20% human albumin solution	1 g/kg on day 1 followed by 40 g/day to improve circulatory function
Vasoconstrictive drugs to counteract splanchnic arterial vasodilation and improve renal perfusion	Terlipressin 1 mg IV four times daily, titrated up to a maximum of 2 mg four times daily in the absence of at least a 25% reduction in creatinine at day 3
Treatment maintenance	Continue the above treatment until either there is a complete response (serum creatinine reduced to <133 micromol/litre) or a maximum of 14 days has elapsed with partial or non-response

CRP, C-reactive protein; FBC, full blood count; IV, intravenous; LFT, liver function test; U&Es, urea and electrolytes.

Source: Adapted from EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. European Association for Study of the Liver. J Hepatol 2010; 53: 397–417.

Table 4

cirrhotic individuals, so they can be closely monitored and treatment initiated to reduce risk factors for progression of renal dysfunction.

Common causes of renal parenchymal damage in cirrhotic patients include hypertensive and diabetic nephropathy, particularly in those with cirrhosis related to non-alcoholic fatty liver disease (NAFLD). NAFLD and CKD share a number of risk factors, in particular features of the metabolic syndrome. A systematic review and meta-analysis by Musso et al.[6] demonstrated that the prevalence (odds ratio (OR) 2.12, 95% confidence interval (CI) 1.69–2.66) and incidence (HR 1.79, 95% CI 1.65–1.95) of CKD in patients with NAFLD was almost double that in those without. A large cohort study of 41,430 adults undergoing comprehensive health check-ups in South Korea identified NAFLD as an independent risk factor for the development of CKD (hazard ratio 1.22, 95% CI 1.04–1.43) (see Sinn et al. 2017 in Further reading).

Furthermore, the presence of NAFLD has also been identified as an independent risk factor for decline in eGFR in CKD (see Jang et al. 2018 in Further reading); this association was stronger in patients with more advanced NAFLD, as measured by a higher fibrosis score. Consequently, it is important to recognize and consider treatment for CKD in patients with NAFLD cirrhosis. Other causes include glomerulonephropathies, in particular those associated with chronic viral hepatitis infection, adult polycystic kidney disease with associated liver cysts and immunoglobulin (Ig)A nephropathy in alcoholic liver disease. ◆

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