Acute Kidney Injury in Acute on Chronic Liver Failure: Where does Hepatorenal Syndrome Fit?

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Word count

Abstract	194
Body	5345
References	137
Figures	4
Tables	6

Key words acute kidney injury cirrhosis ACLF

hepatorenal syndrome

Short title – acute kidney injury in patients with cirrhosis

Disclosures

Rajiv Jalan has research collaborations with Ocera, and Yaqrit, consults for Ocera and Yaqrit and has received speaking fees from Sequana. Rajiv Jalan is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis.

Abstract

Renal dysfunction occurs in 25-50% of patients with cirrhosis admitted to hospital with an acute episode of hepatic decompensation and may be due to underlying chronic kidney disease, an acute deterioration or both. An acute deterioration in renal function in cirrhotic patients is now collectively referred to as acute kidney injury (AKI), which has been sub-classified into different grades of severity that identifies prognostic groups. Acute on chronic liver failure (ACLF) is characterised by acute hepatic and or extrahepatic organ failure driven by a dysregulated immune response and systemic inflammatory response. AKI is also one of the defining features of ACLF and a major component in grading the severity of ACLF. As such, the pattern of AKI now observed in patients admitted to hospital with acutely decompensated liver disease is likely to be one of inflammatory kidney injury including acute tubular injury (referred in this review as non-HRS-AKI) rather than hepatorenal syndrome (HRS). As the management and supportive treatment for non-HRS-AKI potentially differs from HRS, then from the nephrology perspective it is important to distinguish between non-HRS-AKI and HRS-AKI when reviewing patients with ACLF and AKI, so that appropriate and early management can be instituted.

Introduction

The onset of renal dysfunction in patients with cirrhosis is a frequent occurrence, which as a consequence of its association with increased morbidity and mortality poses clinicians with a distinct set of intricate challenges from precise recognition and diagnosis through to optimal management and treatment paradigms. The recent changes in the classification and nomenclature have started to stratify renal dysfunction into distinct subgroups defined by the underlying pathophysiology and prognosis. The recently published International Club of Ascites (ICA) guidelines have suggested that all acute renal dysfunction in patients with cirrhosis be classified under the broad heading, acute kidney injury (AKI). [1]

The archetypal scenario recognised for several decades is the development of renal dysfunction in patients with ascites and advanced cirrhosis,[2] a phenomenon subsequently termed hepatorenal syndrome (HRS). HRS-AKI is a functional syndrome in that the kidneys are typically devoid of parenchymal damage, and pathophysiologically the decline in renal function stems from the systemic hemodynamic effects of advanced portal hypertension and circulatory dysfunction. However, this represents only one aspect of the spectrum of AKI observed in cirrhosis. The kidneys can be subject to a multitude of insults in cirrhotic patients ranging from pre-renal insults such as hypovolemia to inflammatory tubular injury characteristic of sepsis, bile acid nephropathy, drug induced tubular damage; collectively now referred to as non-HRS-AKI. Intrinsic renal disease associated with the underlying causes of cirrhosis, such as glomerulopathies associated with

hepatitis B and C, alcohol and co-morbid conditions of diabetes and hypertension are grouped under the term chronic kidney disease (CKD).

Acute on Chronic Liver Failure (ACLF) is a recently recognised clinical entity,[3] distinct from acute decompensation and is characterised by hepatic and one or more extrahepatic organ failures associated with increased short term mortality within a period of 28 days and up to 3 months from onset (Figure 1).[4] Pathophysiologically, ACLF stems from a dysregulated immune response to a recognised or unrecognised precipitating event.[5] AKI is also one of the defining features of ACLF and a major component in grading the severity of ACLF.[3] The pathophysiological mechanisms underlying AKI are poorly characterised in ACLF. This review aims to provide an up to date evaluation of the aetiology, pathogenesis and treatment of AKI in ACLF.

Defining AKI

Old definitions of HRS, its limitations and new definitions

HRS has often been utilised as an all-encompassing term indicating AKI in patients with cirrhosis but with the development of precise criteria to delineate HRS, it now only accounts for a small but significant minority of cases of renal dysfunction rendering its incidence much less common than traditionally thought. Historically, HRS was classified into two types, type 1 and type 2; Type 1 HRS was defined as rapid progressive renal failure over two weeks with SCr >2.5mg/dL, whereas type 2 was associated with a steady progressive course of moderate renal failure (SCr from 1.5 to 2.5 mg/dL) in patients with refractory ascites.[6] It has been widely recognised

that in cirrhotic patients, creatinine levels may remain low despite advanced renal failure due to sarcopenia and that these criteria are very restrictive in terms of allowing earlier institution of therapy. The ICA has more recently proposed new diagnostic criteria for HRS in 2015[1] (Table 1) and the sub-classification of Type 1 and Type 2 has been withdrawn. In addition, the limiting threshold SCr>2.5mg/dL essential to diagnosis has also been removed and HRS is now recognised as a form of AKI (HRS-AKI). Similarly, the two-week threshold for diagnosing type 1 HRS has also been removed; thus HRS-AKI may now be diagnosed in the context of lack of response to plasma volume expansion in a patient who meets ICA-AKI criteria, has no recent exposure to nephrotoxic drugs or evidence of shock or signs of structural kidney disease. AKI represents a complex multifactorial syndrome encompassing different phenotypes of disease, which may be due to a number of pathological mechanisms that can overlap and exist concurrently. The definitions of AKI subtypes such as HRS-AKI and non-HRS-AKI are, at present, primarily clinical definitions based on clinical criteria rather than pathological diagnoses. Thus, they are likely to represent phenotypes of AKI where certain pathological mechanisms are more prominent.

New definitions of AKI

Increasing knowledge of the epidemiology of AKI and improved understanding of the underlying pathophysiological mechanisms coupled with the critical observation that even small changes in renal function can be associated with patient mortality has led to redefining criteria for AKI.[7] The Acute Kidney Injury Network (AKIN) proposed guidelines to define AKI in 2007,[8] which was the basis on which AKI defining criteria

in cirrhotic patients was recommended by the Acute Dialysis Quality Initiative (ADQI) and ICA in 2011.[9] AKIN criteria aimed to improve the sensitivity of AKI diagnosis by allowing for the diagnosis of AKI to be made by detecting a change in absolute serum creatinine (SCr) level of ≥ 0.3 mg/dL (26.5μmol/L) or by a rise in SCr ≥ 50% from baseline within a 48 hour period. Several studies have subsequently been performed as a means of assessing the utility and performance of the AKIN criteria in the cirrhotic population.[10-15] The results of these studies validated the AKIN criteria as being independently associated with mortality in a stage-dependent manner and served as the evidence base on which the ICA proposed their new criteria defining AKI in cirrhotic patients (Table 2).[1] More recently, it has been proposed that AKI, stage 1 patients can be divided into 2 sub-groups, defined by whether their serum creatinine is greater or less than 1.5mg/dl. Those patients with AKI stage 1 but a serum creatinine of >1.5mg/dl were reported to have mortality rates similar to the mortality of patients with AKI stage 2 and it is proposed that these patients be referred to as having AKI stage 1B.[16] It is however, not clear from this study whether the latter patients, i.e. those proposed to have Type 1B AKI have greater underlying chronic kidney disease or more severe liver dysfunction, as AKI staging is descriptive based on changes in serum creatinine and not underlying pathophysiology. Further validation of these criteria is needed before altering the current guidelines.

Epidemiology and classification

AKI occurs in 25-50% patients with cirrhosis admitted to hospital with an episode of acute decompensation.[11, 17-19] It is a strong predictor of poor survival in both the short

and longer term, 25-31% of hospitalized cirrhotics with AKI do not survive their admission[10, 20] with a one and twelve month mortality rates of 58% and 63%, respectively.[21] Worsening severity of AKI correlates with higher rates of mortality and cirrhosis specific complications including ascites and encephalopathy.[10, 22] AKI is typically characterized as either pre-renal, renal parenchymal or obstructive in origin. Pre-renal causes of AKI such as hypovolaemia (for example due to upper gastrointestinal haemorrhage, diuretics or diarrhoea from purgatives), HRS-AKI and infection account for 60-70% of AKI.[23-26] Infection and or severe systemic inflammation, as observed in patients with acute alcoholic hepatitis may additionally cause non-HRS-AKI. Intrinsic renal causes such as ischaemic injury resulting in non-HRS-AKI, acute interstitial nephritis, or glomerulonephritis account for up to 30% of AKI with post-renal AKI being a relatively uncommon cause (<1%).[23, 25, 27] HRS accounts for around 15-20% of AKI in hospitalised patients with cirrhosis.[23, 26]

Pathophysiology

HRS-AKI pathogenesis

A figure describing possible pathophysiological mechanism of HRS-AKI is outlined in Figure 2.

Role of Splanchnic Vasodilation: Traditional pathophysiological explanations of HRS-AKI are that it is a functional disorder secondary to systemic haemodynamic effects of advanced portal hypertension leading to marked renal vasoconstriction. Early evidence for its functional nature include resolution in renal function after liver transplantation,[28] successful transplantation of cadaveric kidneys from patients with HRS[29] and post mortem examination of the kidneys.[29] Cirrhosis disrupts the liver

architecture giving rise to an increase in intra-hepatic vascular resistance leading to a raised portal pressure, which in turn leads to vasodilatation of the splanchnic vascular bed through a number of mediators including nitric oxide and endogenous cannabinoids.[30] In advanced cases of cirrhosis an increased cardiac output can no longer compensate for the decreased systemic vascular resistance caused by progressive splanchnic vasodilatation, resulting in a reduced effective circulating volume. This in turns lead to activation of the sympathetic nervous system and vasoconstrictor systems including Renin-Angiotensin-Aldosterone System (RAAS) and later vasopressin, to help maintain circulating volume[31] resulting in renal vasoconstriction and hypo-perfusion of the kidneys. Vasopressin levels are difficult to measure accurately but Copeptin, a fragment of the vasopressin precursor molecule which is more easily measured, has shown to be elevated in decompensated cirrhosis more than in compensated cirrhosis.[32] Higher Copeptin levels correlate with haemodynamic derangement in cirrhosis and are predictive of development AKI and associated with worse outcomes.[32, 33] Renal vasoconstriction has been demonstrated on angiography in the cirrhotic patient with renal failure[34] and Doppler studies of renal blood flow in cirrhotic patients with ascites have shown raised resistive indices predictive of the development of AKI and HRS.[35, 36] Also, renal blood flow autoregulation is lost in patients with HRS, implying less renal perfusion with the same perfusion pressure.[37] Certainly the current treatment concepts of HRS-AKI are founded on expanding circulating volume using albumin and splanchnic vasoconstrictors and have shown success in improving renal function.[38, 39] However, reversal of the syndrome may not occur in up to 40% of patients[40] indicating the role of additional pathophysiological mechanisms,[41] or the development of renal tubular injury.[42]

Cardiac Dysfunction: More than 50% of patients with cirrhosis have abnormal or blunted cardiac responsiveness to physiological and pathological stress, termed cirrhotic cardiomyopathy, and a lower cardiac output has been reported to predict both the development of HRS-AKI and worse prognosis.[43] Prescription of non-selective beta-blockers to patients with ascites may pre-dispose to HRS-AKI and worsen prognosis,[44, 45] particularly in those with associated Spontaneous Bacterial Peritonitis (SBP). The dose of these agents should be titrated to maintain mean arterial pressure to avoid HRS-AKI development.

Adrenal Insufficiency: Relative Adrenal Insufficiency (RAI) is reported in 25% of decompensated cirrhotics and is more common with advancing disease.[46] RAI may contribute to cirrhotic cardiomyopathy by down regulation of the number of beta-adrenergic receptors in the heart and modulating the effect of catecholamines on cardiac contractility and vascular tone.[47]

Inflammation: Systemic Inflammation is an additional critical aspect in the pathogenesis of decompensated cirrhosis and plays an important role in organ dysfunction associated with ACLF.[48] Patients with SBP developing renal impairment showed significantly higher levels of the pro-inflammatory cytokines TNFα and IL-6 at diagnosis of SBP compared to those with normal renal function.[49] In a further study of cirrhotic patients with renal failure the in-hospital mortality rate was more than twice as high in those with the systemic inflammatory response syndrome (SIRS) than in those without.[50] It is in this group of patients who have evidence of

AKI that is precipitated by infection or alcoholic hepatitis, that are more likely to have non-HRS-AKI rather than HRS-AKI.

Pathogenesis of non-HRS-AKI

In order to better understand the pathophysiology on non-HRS-AKI, the concept of ACLF is described below.

Acute on Chronic Liver Failure

Renal function forms a key criterion in the stratification of ACLF severity (Table 3), and by definition the majority of patients with grade 1 ACLF have renal dysfunction. In the seminal CANONIC study[3] of 303 patients with ACLF, 209 (69%) had either renal dysfunction or renal failure signifying that renal impairment is a key component, and is the most single common organ failure observed in ACLF. The serum creatinine cut off >1.5mg/dL used to define renal dysfunction in ACLF probably leads to an under appreciation of the true incidence of renal dysfunction in ACLF patients (Table 3). However, in a study of 510 hospitalized patients with acute decompensation, the development of ACLF using the CLIF– OF score was found to more reliably predict 90-day mortality than AKI using the AKIN criteria (area under the receiving operating characteristic curve=0.72 vs. 0.62, respectively).[51] This may explained, in part by the CLIF-OF score including measures of non-renal organ failure and systemic inflammation,[3] and systemic inflammation as measured by white cell count and C-reactive protein (CRP) is an independent predictor of mortality in ACLF.[52] Whereas, changes in serum creatinine concentrations alone do not accurately match the severity of AKI , as they are affected by underlying pre-existing

kidney damage, changes in volume and creatinine generation rates, and do not take into account the underlying pathophysiology.

Currently, there are no epidemiological data in the literature reporting the proportion of ACLF patients with HRS-AKI but conversely it is likely that most of the patients with HRS-AKI will by definition have ACLF. In all HRS studies prior to the recent ICA HRS-AKI diagnostic criteria,[1] a serum creatinine >1.5mg/dL was required for the diagnosis of HRS, which is also required for ACLF grade 1 with additional organ dysfunction. HRS-AKI may therefore be present at the onset of ACLF or indeed develop as an additional organ failure during ACLF. Thus, HRS-AKI currently remains uncharacterized in ACLF but these terms are not mutually exclusive and are likely to share some underlying pathophysiological mechanisms. Pathogenic mechanisms involved in non-HRS-AKI associated with ACLF are described in Figure 3.

Specific Mechanisms involved in non-HRS-AKI

Role of Inflammation and bacterial translocation: AKI in ACLF is best characterised as a heterogeneous condition with variety of initiating factors including infection, with the severity of systemic inflammation and additional organ failures all influencing outcomes.[53] In the CANONIC study single organ renal failure was associated with 20% mortality, but mortality was significantly higher when renal failure, defined as a serum creatinine ≥1.5 mg/dL) was associated with additional organ failure.[3] Similarly lack of reversibility of HRS with albumin and terlipressin is associated with higher CLIF-OF scores, higher serum bilirubin and non-resolution of infection.[54-56] Further

evidence for systemic inflammation driving ACLF and organ dysfunction came from a study measuring 29 different cytokines and an oxidised form of albumin (human non-mercaptalbumin 2 [HNA2]), a marker of systemic oxidative stress. Patients with ACLF demonstrated higher levels of systemic inflammation markers than non-ACLF patients and severity of ACLF at enrolment was strongly associated with systemic inflammation as was the course of ACLF.[57] Specifically, the presence of renal dysfunction in ACLF correlated with IL-6, IL-8, and HNA2 and not with measured plasma renin concentrations, a marker for systemic circulatory disturbance, suggesting that the deleterious effects of systemic inflammation in the pathogenesis of ACLF is mediated predominantly by non-haemodynamic mechanisms.

There is only limited renal biopsy data available in cirrhotic patients, due to the risk of bleeding arising from coagulation defects. A retrospective French study assessed renal biopsy specimens in 65 cirrhotic patients with unexplained renal impairment (defined by serum creatinine >1.5mg/dl).[58] 18 patients with a with raised serum creatinine but with no proteinuria or haematuria demonstrated a variety of renal lesions, including chronic tubulointerstitial injury, glomerular injury and vascular injury such as endarteritis,[58] suggesting that patients deemed as having “functional renal failure” will also have renal parenchymal pathology. Renal biopsies in five patients with (non-HRS) AKI (and ACLF) caused by alcoholic cirrhosis revealed evidence of tubular damage with evidence of increased tubular expression of Toll like receptor (TLR)4, and caspase-3.[59] This increased TLR4 expression in the kidneys was reflected in increased urinary excretion of TLR4 protein. In contrast, patients with HRS-AKI (some of who also had ACLF by definition) did not show the same changes suggesting that they were likely to be pathophysiologically different and the

fundamental characteristic of non-HRS-AKI in ACLF patients is likely to be acute tubular injury. To an extent, this was further explored in animal models.

Although animal models of ACLF are limited, the application of lipopolysaccharide (LPS) to a rat model of cirrhosis (bile-duct ligated) demonstrated renal tubular injury with an increased renal expression of TLR4 and caspase-3.[60] Pro-inflammatory cytokines and LPS can directly cause renal tubular cell apoptosis through caspase mediated pathways,[61] and it was hypothesised that bacterial gut translocation could drive this inflammatory injury (Figure 4). Treatment with norfloxacin in cirrhotic rats prior to being given LPS demonstrated attenuation in the renal injury both biochemically and histologically.[60] Use of norfloxacin in humans as primary prophylaxis for SBP delayed the onset of HRS-AKI and improved one-year survival.[62] Long term use of Rifaximin (>3 months) was also shown to reduce the incidence of AKI including HRS-AKI.[63, 64] Rifaximin exerts its clinical effects by modulation of the metabolic function of the gut microbiota.

Role of Bile acids: Patients with ACLF have elevated serum bilirubin levels compared to patients with just acute decompensation without ACLF[3] and raised concentrations of bilirubin and bile acids may contribute to renal injury through direct toxic renal effects and by tubular obstruction.[65] A clinic-pathological study of renal biopsies in jaundiced patients showed that tubular bile casts were present in 11 of 13 patients with HRS-AKI[65] and were thought to be involved in pathogenesis of renal injury rather than being bystander phenomena. This is as yet a little explored mechanism of AKI in ACLF but could potentially explain observations of why high

bilirubin levels are predictors of poor response to vasoconstrictor therapy in HRS-AKI.[55, 56] Recently, the concept of bile acid nephropathy has been further characterised in animal models.[66]

Role of worsening portal hypertension: ACLF patients have been shown to have markedly increased intrahepatic intravascular resistance resulting in increased portal pressure, [67] which may contribute to further AKI through the hepatorenal reflex.[68]

Role of Cardiac dysfunction and renal hypoperfusion: ACLF patients show evidence of severe cardiovascular dysfunction that can manifest both with increased and decreased cardiac output that may result in worsening of renal perfusion and ischemia.[67] Patients with more advanced stages of ACLF also require inotropes which may further limit renal perfusion.[2,3]

Overlap of pathogenic mechanisms of HRS-AKI and non-HRS-AKI in ACLF

Although, the pathogenic mechanisms described above suggest that HRS-AKI and non-HRS-AKI are distinct sub-types, in reality it is likely that pathogenic mechanisms of AKI in ACLF patients have overlapping features (Table 4). It is possible that HRS-AKI evolves to non-HRS-AKI in the majority of cases. This contention is supported by the observations that only about 40% patients respond to terlipressin and albumin, and the duration of HRS increases unresponsiveness to these agents with time; mortality rates of over 80% despite evidence of temporary resolution in about

40% and lack of recovery of kidney function if HRS-AKI persists for over 6-weeks (see later).

The most common causes of liver disease such as non-alcoholic fatty liver disease, which is associated with diabetes and hypertension; Hepatitis B or Hepatitis C can be associated with nephropathy independent of the severity of liver disease. In most instances, serum creatinine levels may be within the normal reference range in these patients but they have reduced glomerular filtration rate and so are more susceptible to acute renal insults. Although these patients have, by definition, acute on chronic kidney dysfunction, they are considered to have AKI, by current staging criteria. It is also unclear as to whether increasing severity of liver disease and therefore, renal hypoperfusion, will result in greater risk of non-HRS-AKI.

Biomarkers of AKI

Biomarkers are being investigated and assessed in order to discriminate between differing phenotypes of AKI, to allow earlier diagnosis of AKI and to aid in prognostication. Biomarkers of tubular injury may allow differentiation of functional from ischaemic injury which is important in managing AKI and determining which patients should be considered for certain therapies. Following volume expansion those with HRS-AKI should receive a trial of vasopressors,[69] whereas those with non-HRS-AKI should be considered for support if required and when appropriate with Renal Replacement Therapy (RRT).[53]

Using Serum Creatinine to define AKI in cirrhotic patients

The use of Scr in cirrhosis is affected by several factors which hinder its utility as a marker of renal function. The amount of creatinine produced each day is related to the muscle mass and physical activity, which are often reduced in patients with cirrhosis,[70] thus creatinine values in cirrhotics are lower and smaller rises are likely to reflect a larger degree of renal dysfunction. Tubular secretion of creatinine is increased in cirrhotics,[71] rendering SCr a less accurate measure of renal function. Scr is measured as a concentration so is affected by volume status, such as in those with significant fluid shifts or fluid overload,[72] this is especially relevant in decompensated cirrhotics who often have ascites and or peripheral oedema.

In practice, both chemical and enzymatic methods are used to measure creatinine in body fluids, with most clinical laboratories in the US and UK currently using variations of the Jaffe reaction; a method of which there are multiple variations. Many of the modifications have been undertaken to improve the specificity of the reaction, as the Jaffe reaction is not specific for creatinine: other compounds that may produce a Jaffe-like chromogen include proteins,[73, 74] glucose, ascorbic acid[75] ketone bodies,[76] pyruvate, guanidine, haemoglobin F, blood-substitute products[77] and cephalosporins.[78] The degree of interference varies between individuals but collectively may account for 20% of measured ‘creatinine’ at physiological concentrations.[79-81] More importantly for patients with cirrhosis bilirubin may interfere with laboratory creatinine assays due to spectral effects or reaction with assay reagents. Bilirubin is generally a negative interferent, with 5.8mg/dL (100 µmol/L) bilirubin reducing measured serum creatinine by 0.11-0.15mg/dL (10-15 µmol/L) in

three widely used commercial assays.[74] An alternative approach has been to measure creatinine by enzymatic methods. The degree of interference with bilirubin is generally lower than that observed with Jaffe based assay.[74] Although attempts to standardise measurements have been attempted, differences remain between assays and laboratories and these may contribute to differences in reporting AKI, and may lead to changes in clinical management.[82-84] Relying on measurement of serum creatinine as a surrogate for renal function although practical and universally available, most likely provides an under appreciation of renal dysfunction in patients with cirrhosis.

Biomarkers of AKI to help determine severity and distinguish subtypes

Urinary Sodium

Urinary sodium excretion is typically reduced in HRS, and the fractional excretion of sodium < 1%. However, sodium excretion can be affected by diuretic administration. As such the fractional excretion of urea of ≥35 has been suggested to be more indicative of HRS and provide greater discrimination.[53]

Novel biomarkers

A number of biomarkers associated with AKI have been recently described, including serum cystatin C, urinary and serum Neutrophil Gelatinase Associated Lipocalin (NGAL), urinary IL-18, kidney Injury Molecule (KIM-1), liver type fatty acid binding protein, insulin like growth factor (IGFBP7) and tissue inhibitor metalloproteinase (TIMP2) (Table 5).[85-87] NGAL has been the most widely studied of these novel

biomarkers. It is a small protein whose renal expression is upregulated following ischaemic or nephrotoxic insult resulting in higher concentrations in urine and serum. Although urinary NGAL levels demonstrated utility in differentiating between pre-renal azotemia, HRS and intrinsic acute kidney injury,[87-89] there remain limitations because of significant overlap between NGAL values and the types of AKI. The phenotype of AKI in the NGAL studies are based on clinical criteria not renal biopsy data, so correlation with NGAL relates not necessarily to differing underlying pathophysiology but to current clinical definitions of disease phenotypes.

Studies to date have shown that these novel biomarkers increase with severity of liver injury and are predictive of outcomes.[90, 91] Biomarkers are increased in both cases of HRS-AKI and non-HRS AKI. However, levels tend to be greater for non-HRS AKI compared to HRS, but with a marked degree of overlap reported in most studies. In addition, urinary infection, which is more prevalent in patients with ACLF, also potentially increases urinary biomarker excretion. As such further study is required before biomarkers, and changes in biomarker levels can aid in differentiating HRS from AKI and lead to change in clinical outcomes.[92]

Treatment

Management of AKI in ACLF requires a multifaceted approach, providing support to failing organs, preventing further deterioration or progression of ACLF or AKI, whilst ensuring that any precipitant is promptly identified and treated. ACLF is associated with high mortality, thus management in a critical care setting is recommended as the optimal setting.[93] Assessing intra-vascular volume status is an initial key step

with a view to ensuring any hypovolaemia is adequately treated. Volume status is challenging when managing patients with cirrhosis because of the hyperdynamic circulation, low systemic vascular resistance coupled with the common finding of ascites with or without peripheral oedema. There is only a limited role for central venous pressure (CVP) monitoring given the poor relationship with intravascular volume or response to fluid challenge.[94] In addition, the presence of ascites results in a higher CVP without a corresponding increase in ventricular preload. Crystalloids may be used as initial fluid resuscitation but the use of hydroxethyl starch is contraindicated as its use has been associated with increased risk of AKI and mortality.[95] In the general ICU setting volume resuscitation with albumin compared to crystalloids does not reduce mortality or risk of AKI,[96] however in cirrhotic patients albumin is likely to have several theoretical advantages given the additional anti-oxidant and anti-inflammatory properties of albumin over and above the oncotic pressure it exerts as a plasma protein.[97] Treatment of SBP with albumin infusions at 1.5g per Kg on day 1 and 1g per kg on day 3 in addition to antibiotics has been shown to reduce the occurrence of both AKI and mortality.[98] Cirrhosis associated immune dysfunction is in part mediated by prostaglandin E2, which suppresses macrophage pro-inflammatory cytokines and bacterial killing in vitro, and albumin reduces Prostaglandin E2 bioavailability in vitro and attenuates prostaglandin E2 mediated immunosuppression.[99]

After excluding obstruction, then if renal function does not improve following simple volume expansion, the differential diagnosis of volume-unresponsive AKI can be classified into one of two groups; HRS-AKI or non-HRS-AKI. If AKI is associated with hypotension such as in sepsis or critically ill patients vasopressors may be utilised,

as they are conventially thought to improve mean arterial pressure (MAP) and hence renal blood flow. However, it is now recognised that sepsis associated AKI may be associated with increased renal blood flow and low urine output, which is thought to occur due to maldistribution or shunting of intra-renal blood flow. [100] Ensuring adequate renal perfusion is essential; however, targeting higher MAPs of 80-85 mmHg compared to lower target MAPs 65-70mmHg in an ICU setting has been shown to have similar outcomes including rates of AKI.[101]

The principal treatment strategy in HRS-AKI is to raise the low cardiac output and mean arterial pressure (MAP)[102] by increasing the effective circulating volume through use of intravenous albumin combined with systemic vasoconstrictors to counter arterial vasodilatation and pooling in the splanchnic circulation. Albumin has been used successfully with a number of different vasoconstrictors; vasopressin analogues (terlipressin), alpha-adrenergic agonists (norepineprine) and a combination of somatostatin analogue (octeotride) and the alpha adrenergic agonist (midodrine), successfully to reverse HRS-AKI (Table 6). Although albumin doses have varied between studies, a recent meta-analysis indicates a key aspect of successful albumin therapy in HRS appears to be the cumulative dose.[39] This meta-analysis included 19 studies totalling 574 patients and observed a dose response relationship between the amount of infused albumin and survival, with significant improvement in survival associated with 100g increments in cumulative albumin dose over the range of cumulative albumin doses between 200g and 600g independent of treatment duration, vasoconstrictor type or MAP.[39] In HRS-AKI patients with large volume ascites, abdominal paracentesis followed by albumin infusion improves creatinine clearance likely through reduction in intra-abdominal

pressure and improved renal blood flow as indicated by decreased renal resistive indices.[103]

Several studies have shown that an improvement in systemic haemodynamics through a raised MAP in response to systemic vasoconstrictor therapy is associated with and predictive of HRS-AKI and the degree of improvement in MAP correlated with improvement in renal function.[104] The early studies of vasoconstrictor use for HRS-AKI were limited by retrospective design and small numbers of patients,[105-112] with the same confounders also affecting the vast majority of randomised controlled trials (RCTs) (table 6). Terlipressin has been the vasoconstrictor most studied, and has greater affinity for V1 receptors in the splanchnic bed than V2 receptors in the kidney, leading to greater splanchnic vasoconstriction than renal.[113] Terlipressin is not available in the USA or Canada for the treatment of HRS, thus norepinephrine or combination of octeotride and midodrine are used as alternatives. Two meta-analyses have demonstrated that norepinephrine is equally as efficacious as terlipressin for reversal of HRS with no difference in 30-day survival.[114, 115] Although some studies reported a benefit of octeotride and midodrine in conjunction with albumin for HRS-AKI,[69, 116] a randomised controlled trial (RCT) of terlipressin versus a combination of octeotride and midodrine demonstrated that terlipressin was a superior treatment with a significantly higher rate of recovery of renal function (70.4%) versus (28.6%).[117] Recently the largest RCT of terlipressin for HRS-AKI (n=196)[118] showed benefit for terlipressin over placebo but this did not reach statistical significance either for complete reversal of HRS-AKI (19.6 % vs. 13.1 %, P= 0.22) or partial HRS-AKI reversal (23.7% vs. 15.2%, P=0.13). The rate of HRS-AKI reversal was significantly less than that in earlier RCTs[119-121] which may be due

to a shorter duration of terlipressin treatment, up to 1/3 patients had ≤3 days of terlipressin administration, and relatively higher use of renal replacement therapy and liver transplantation compared to earlier studies.[122] Nevertheless as most HRS-AKI occurs in the setting of ACLF, the results of this study should serve as a catalyst to shift the treatment paradigm from solely haemodynamics to targeting systemic inflammation, the hallmark of ACLF.[122]

Severity of ACLF predicts poor response to terlipressin and albumin in HRS-AKI,[54-56] thus therapies which potentially ameliorate the severity of ACLF by modulating the immune system such as mesenchymal stem cell therapy,[123] Granulocyte Colony–Stimulating Factor[124] or plasmapheresis may potentially have a future role. Severity of ACLF is also strongly predictive of mortality, grade 3 ACLF (3 organ failure) is associated with 75% 28 day mortality,[3] and maybe useful if prognostic decisions regarding treatment utility such as us the use of renal support in cases of HRS-AKI and multi-organ failure. Renal replacement in HRS-AKI is controversial[125] with a consensus statement from the ADQI group recommending withholding renal support unless there is an acute reversible component or plan for liver transplantation given the lack of evidence showing any survival benefit of RRT in HRS-AKI.[53, 126] The use of extra corporeal albumin dialysis such as Molecular Adsorbent Recirculation System (MARS) has been trialled in HRS-AKI on the basis that clearance of albumin bound vasodilators may improve outcomes, but clinical studies have so far failed to confirm any survival advantage.[127]

Currently liver transplantation affords the only therapeutic modality, which cures end stage liver disease and leads to reversal of AKI.[128, 129] Overall one and five year outcomes of liver transplantation in the context of pre-transplantation AKI have been reported as 77% and 69%, respectively.[130] A retrospective study of liver transplantation in patients with ACLF and AKI found one and five year survival of 75% and 72% in those without renal dysfunction compared to 61% at one and five years with HRS.[131] Pre- transplant renal function is predictive of post- transplant renal dysfunction with shorter duration of HRS (<4 weeks) associated with better outcomes[128, 132] but in those with a higher risk of renal non-recovery such as sustained AKI greater than 6 weeks simultaneous liver kidney transplant should be considered.[53]

Conclusion and future perspectives

ACLF is a relatively newly recognised syndrome marked by systemic inflammation, which is altering our understanding of the pathogenesis of organ failure, especially renal failure. Current diagnostic criteria do not allow accurate distinction between HRS-AKI and non-HRS-AKI in ACLF patients and the available urinary biomarkers are limited in their ability to do so. Earlier diagnosis of the cause of AKI may help treatment of HRS. Prevention of progression of HRS to acute tubular injury remains an unmet need and despite the ability of terlipressin and albumin to reverse HRS in about 40% patients, mortality rates are not influenced significantly. Therefore, strategies for renal protection need to be developed. Inflammation is increasingly recognised as an important driver of AKI, particularly in patients with associated infection and multiorgan failure. Novel therapies are needed as terlipressin and

albumin are ineffective in this situation. As AKI that is persistent, rapidly becomes irreversible, then novel approaches are required to allow tubular regeneration to avoid the need for combined liver and kidney transplantation.

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Table 1. International Club of Ascites (ICA) Diagnostic criteria for hepatorenal syndrome (HRS)

HRS-AKI Diagnosis

• Diagnosis of cirrhosis and ascites
• Diagnosis of acute kidney injury (AKI) according to ICA-AKI criteria
• No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
• Absence of shock
• No current or recent use of nephrotoxic drugs
• No macroscopic signs of structural kidney injury*,
defined as:
- absence of proteinuria (>500 mg/day)
- absence of microhaematuria (>50 RBCs per high power field),
- normal findings on renal ultrasonography

Table 2 – International Club of Ascites (ICA) definition and grading of acute kidney injury (AKI) in patients with cirrhosis

Stage of AKI	Definition
1	Increase in Serum Creatinine ≥0.3 mg/dl (26.5 µmol/L) or an increase in Serum Creatinine ≥1.5-fold to 2-fold from baseline
2	Increase in Serum Creatinine >2-fold to 3-fold from baseline
3	Increase of in Serum Creatinine >3-fold from baseline or in Serum Creatinine ≥4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy

Table 3. Diagnostic Criteria for Acute on Chronic Liver Failure (ACLF)

A. Definition of organ failure for the diagnosis of ACLF

Organ System	**Score = 1**	**Score = 2**	**Score = 3**
Liver (bilirubin mg/dl)	Bilirubin < 6	6 ≤ Bilirubin ≤ 12	Bilirubin >12
Kidney (creatinine mg/dl)	Creatinine <2	Creatinine ≥2 <3.5	Creatinine ≥3.5 or renal replacement
Brain (West-Haven criteria)	Grade 0	Grade 1-2	Grade 3-4
Coagulation INR	INR < 2.0	2.0 ≤ INR < 2.5	INR ≥ 2.5
Circulation Mean arterial pressure mmHg	MAP ≥70	MAP <70	Vasopressors
Respiratory: PaO_2/FiO_2 or SpO_2/FiO_2	>300 >357	≤300 - > 200 >214- ≤357	≤200 ≤214

Values obtained at hospital admission. Shaded area represents organ failure. International normalised ratio (INR), arterial oxygen tension mmHg (PaO2), inspired oxygen concentration (FiO2), pulse oximetry oxygen saturation (%) (SpO2).

B. Diagnostic criteria and Grading of Acute on Chronic Liver Failure (ACLF)

ACLF Grade	**Definition**
No ACLF	(a) Patients with no organ failure (b) Patients with single hepatic, coagulation, circulation or respiratory failure, serum creatinine <1.5 mg/dl and no HE (c) Patients with cerebral failure and creatinine <2mg/dl
ACLF Grade 1	(a) Patients with renal failure (b) Patients with other single organ failure with (a) serum creatinine ≥1.5 and<2 mg/dl and/or (b) HE grade 1-2.
ACLF Grade 2	Two organ failures
ACLF Grade 3	Three organ failures or more

Table 4. Hepatorenal syndrome-acute kidney injury (HRS-AKI) and non-HRS-AKI as causes of AKI in Acute on Chronic Liver Failure (ACLF) patients.

Characteristic	**HRS**	**Non HRS-AKI**
History of decompensated Cirrhosis and ascites	Common and almost invariable	Not necessary
Systemic Haemodynamics	Reduction of Effective arterial blood volume +++	Reduction of Effective arterial blood volume +
Cardiac Output	Increased, rarely reduced	Variable
Requirement for vasopressors	Rare	Common
Renal Blood Flow	Reduced +++	Reduced +
Renal Blood Flow autoregulation	Shifted to the right +++	Unknown
Appearances of renal Histology	Normal	Evidence of renal tubular injury and cell death, inflammatory cell infiltration, increased expression of TLR4 in the tubules
Extra renal organ failure	Rare	Common
Bile acid nephropathy	Rare	Common
Systemic Inflammatory response	Rare	Common
Proteinuria (>500gr/day)	No	Usually present
Urinary Biomarkers NGAL IL-18 TLR4	May be increased	Typically increased
Response to Terlipressin and Albumin	Yes	Unknown
Need for Renal Replacement Therapy	Rare	Usual

neutrophil gelatinase associated lipocalin (NGAL), interleukin (IL), Toll like receptor (TLR4),

Table 5. Biomarkers that have been studied to differentiate acute kidney injury (AKI) caused by tubular injury compared to other causes of AKI

Biomarker	Origin	Limitations
Neutrophil gelatinase-associated lipocalin (NGAL)	Kidney – tubular protein, release caused by cell damage	- Increased levels in inflammation. - Significant overlap in values between AKI groups - Small quantities produced by the Llver
Interleukin 18 (IL-18)	Monocytes and macrophages (pro-inflammatory)	- Significant overlap in values between AKI groups - Increased in Sepsis and Systemic Inflammation of any cause - Pathophysiologically, inflammatory cell infiltration is not a major components of ATI in cirrhosis
Kidney Injury Molecule -1 (KIM-1)	Kidney - Tubular transmembrane protein upregulated by injury	- Significant overlap in values between AKI groups - Data do not allow distinction between HRS and ATI
Liver-type Fatty-acid binding protein (L-FABP)	Kidney – proximal tubule, upregulated by cell injury	- Increased in CKD and sepsis
Trefoil Factor 3 (TFF-3)	Epithelial cells	- Increased in CKD and inflammatory conditions, Limited data in cirrhosis
Glutathione-S-transferase-π (GST-π)	Kidney- tubular protein, release caused by cell damage to tubular epithelial cells	- Limited data in cirrhosis - Cannot distinguish between ATI and HRS
Urinary Toll Like receptor 4	Kidney tubular epithelium in cirrhosis	- The test is semi-quantitative - Limited data

Hepatrorenal syndrome (HRS)

Table 6 – Randomised controlled trials s of albumin and vasoconstrictors for treatment of hepatorenal syndrome (HRS) type 1

Author	Year	Treatment/comparative group	n (% HRS Type 1)	Albumin	HRS reversal %	Survival (%)
Solanki et al. [133]	2003	Terlipressin	24 (100%)	40 g/day to keep CVP 10–12	42	42
		Placebo			0	0
Alessandria et al. [134]	2007	Terlipressin	22 (41%)	To keep CVP 10 - 15	83	92
		Noradrenalin			70	80
Neri et al. [121]	2008	Terlipressin	52 (100%)	1 g/kg then 20 – 40 g/day	81	42
		Placebo			19	15
Martin-Llahi et al. [120]	2008	Terlipressin	46 (56%)	1 g/kg followed by 20-40 g/day	44	27
		Placebo			9	19
Sanyal et al.[119]	2008	Terlipressin	112 (100%)	1 g/kg then 25 g/day	34	13
		Placebo			13	9
Sharma et al. [135]	2008	Terlipressin	40 (100%)	To keep CVP 10–12	50	45
		Noradrenalin			50	45
Singh et al. [136]	2012	Terlipressin	46 (100%)	20g/day	39	39
		Noradrenalin			43	48
Cavallin et al. [117]	2015	Terlipressin	49 (92%)	1 g/kg followed by 20-40 g/day	70	70
		Midodrine and Octeotride			29	59
Srivastava et al. [137]	2015	Terlipressin	40 (100%)	20g /day	-	21
		Dopamine and furosemide			-	20
Boyer et al. [118] –	2016	Terlipressin	196 (100%)	20-40g/day	20	58
		Placebo			13	55

Figure legends

Figure 1 Proposed classification of acute-on-chronic liver failure.

Acute-on-chronic liver failure, which can develop after a precipitating insult in patients with non-cirrhotic chronic liver disease (type A) or compensated (type B) or decompensated (type C) cirrhotic liver disease.

Adapted from Jalan et al. (2014) [4].

Figure 2. Pathogenesis of Hepatorenal Syndrome in patients with Acute on Chronic Liver Failure (ACLF).

Figure 3. Pathogenesis of Acute Tubular Injury in Acute on Chronic Liver Failure (ACLF).

patients (modified from Jalan et al. J Hepatol 2014).

Figure 4. Evidence of ATI in patients with non-HRS associated renal failure and demonstration of apoptosis as a cause of cell death in patients with non-HRS renal failure (reproduced from Shah et al. Liver International 2013)