CHAPTER 45

Acute Kidney Injury in Cirrhosis

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OBJECTIVES

This chapter will:

1. Discuss the basis of pathophysiology of renal impairment in cirrhosis.
2. Describe the management of acute kidney injury (AKI) in cirrhosis, including treatment of hepatorenal syndrome.
3. Identify the indication for liver transplantation in the context of AKI: liver alone or simultaneous liver and kidney.

Acute kidney injury (AKI) is a common complication of end-stage liver disease and is one of the criteria that define acute-on-chronic liver failure.[1] AKI has been reported to occur in up to 50% of hospitalized patients with cirrhosis[2–4] and is thought to be due to the combination of an impaired effective arterial blood volume secondary to arterial vasodilation, with increased intrarenal vasoconstriction and impaired renal autoregulation. AKI can be precipitated by factors that further impair circulatory status and reduce renal perfusion, such as gastrointestinal bleeding and bacterial infections.[5–8] The development of AKI increases the risk of mortality,[9] affects short and long-term mortality, and reduces kidney function after liver transplantation.[10–12] In liver transplant candidates, identification of the cause of AKI is crucial because hepatorenal syndrome type 1 (HRS-1) is reversible after liver transplantation.[10,13,14] Kidney biopsy is difficult to perform in this population because of coagulation abnormalities; therefore there is a need for noninvasive tools to accurately determine the cause of kidney dysfunction, to better assess the prognosis, to target therapy, and to determine the potential for reversibility. There is currently no specific blood or urine biomarker that can reliably identify the cause of AKI in cirrhotic patients. Traditional diagnostic criteria focused particular attention to hepatorenal syndrome (HRS)[15] with criteria based on elevation in serum creatinine (SCr) > 1.5 mg/dL. However, the strict SCr cutoff and exclusion of other forms of AKI and chronic kidney disease (CKD) have led to new definitions that suggest a broader look at AKI in cirrhosis.[16,17]

PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY IN CIRRHOSIS

Several mechanisms contribute to the development of AKI in patients with cirrhosis, including circulatory changes, intrinsic kidney factors, and systemic inflammation (Fig. 45.1).[5,7] Cirrhosis is characterized by hyperkinetic state with splanchnic and systemic vasodilation. At the early stage, decreased systemic vascular resistance results in a mild reduction in mean arterial pressure, which is balanced by increased cardiac output that maintains adequate kidney perfusion. At this stage, glomerular filtration rate (GFR) is preserved. In more advanced stages, systemic vasodilation increases, leading to a state of decrease in effective blood volume that induces systemic vasoconstriction systems, namely renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), arginine vasopressin (AVP), and renal sodium and water retention. This stage is characterized by a switch from preserved to reduced kidney

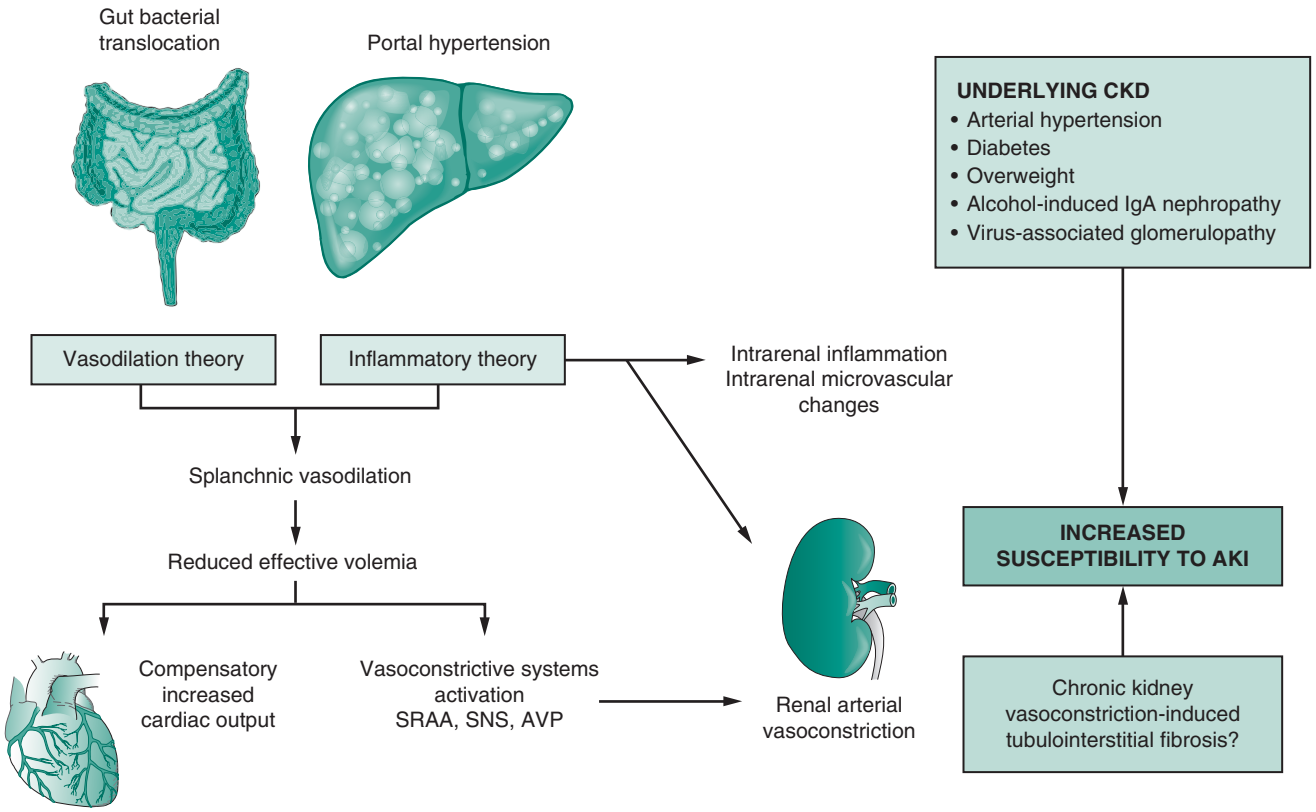

FIGURE 45.1 Mechanisms contributing to impaired kidney function in cirrhosis. Figure reproduction with permission. In end-stage liver disease, several factors contribute to increase susceptibility of the kidney to acute kidney injury (AKI). Vasodilation secondary to portal hypertension and systemic inflammation induced by gut bacterial translocation tend to induce renal arterial vasoconstriction because of the activation of vasoconstrictive systems in response to decreased effective blood volume. *AVP,* Arginine vasopressin; *CKD,* chronic kidney disease; *IgA,* immunoglobulin A; *RAS,* renin angiotensin system; *SNS,* sympathetic nervous system.

blood flow. At the most advanced stages of cirrhosis, renal vasoconstriction can no longer be balanced by increased cardiac output and renal blood flow markedly decreases.[18] In addition to changes in systemic hemodynamics, alterations of intrarenal hemodynamics along with abnormal autoregulation of renal blood flow contribute to decreased GFR.[8] Decreased cardiac output, characterizing the so-called "cirrhotic cardiomyopathy," may contribute to decreased renal perfusion and altered GFR.[18] However, circulatory changes associated with portal hypertension and kidney factors do not explain all the changes observed during HRS and other causes of AKI.

Recently, the concept of systemic inflammatory in multiorgan disease has emerged and challenged the vasodilation theory.[19] Sepsis is a common trigger of AKI in patients with cirrhosis. In patients without cirrhosis, hemodynamic changes and inflammatory response clearly are involved in the mechanisms leading to sepsis-associated AKI.[20] In severe sepsis, AKI may develop in the absence of decreased renal blood flow.[21–23] In patients with preserved renal blood flow, intrarenal microvascular changes resulting in decreased GFR may include an imbalance between preglomerular and postglomerular resistance (which corresponds to preglomerular and post glomerular vascular tone) as well as impaired renal microcirculation affecting tubular and glomerular function.[23] Finally, it has been hypothesized that sepsis could lead to intrarenal redistribution of blood flow out of the cortex, thus inducing corticomedullary junction ischemia with subsequent tubular injury.[23] In most clinical situations, hemodynamic changes are associated with systemic and/or renal inflammatory responses leading to microcirculatory changes and a significant reduction of perfused capillaries.

Even in the absence of overt bacterial infection, cirrhosis is characterized by a state of systemic inflammation, correlated to the severity of liver disease and portal hypertension.[19] Translocation of bacteria and/or pathogen-associated molecular patterns (PAMPs) from the lumen of the gut to the bloodstream is probably the main mechanism leading to inflammation. Translocation induces a wide spectrum of genes encoding molecules responsible for inflammation via specific receptors called pattern recognition receptors (PRR).[19] Proinflammatory mediators then may extend to the systemic circulation and peripheral organs leading to extrahepatic organ dysfunction, including the kidney. For instance, patients with bacterial translocation have increased levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]) as well as increased levels of vasoactive factors (such as NO) as compared with patients without translocation.[24,25] A substantial proportion of patients with HRS have bacterial infection as a precipitating factor and/or systemic inflammatory response syndrome (SIRS).[26] However, about 30% of patients with HRS have SIRS without documented bacterial infection.[26]

Toll-like receptor 4 (TLR4) is the main PPR that has been studied in this field. In an experimental model of cirrhosis, inflammatory insult induced by lipopolysaccharide resulted in increased expression of TLR4 in proximal renal tubules

and eventually, tubular cell injury.[27] In experimental models, digestive decontamination reduces expression of TLR4 and protects against tubular damage.[27] A similar overexpression of tubular TLR4 has been described in patients with cirrhosis and renal dysfunction.[28] Interestingly, a subset of patients with a diagnosis of HRS showed overexpression of TLR4 in tubular cells and evidence of tubular cell damage. These findings suggest that a diagnosis of HRS does not exclude some degree of structural changes.

Overall, the pathophysiology of AKI in decompensated cirrhosis is complex with various factors being involved, including hypovolemia, administration of nephrotoxic agents, infection, and/or SIRS that may precipitate renal hypoperfusion and intrarenal circulatory changes, which are a hallmark of cirrhosis-associated AKI, regardless of the cause.

ASSESSMENT OF KIDNEY FUNCTION

Evaluation of kidney function in patients with cirrhosis remains a critically important and challenging problem. Although SCr remains the most commonly used clinical index of kidney function, in the setting of cirrhosis, SCr tends to overestimate kidney function as a result of the combination of decreased creatine production by the liver, protein calorie malnutrition, muscle wasting, reduced physical activity and large volume of distribution in the setting of fluid overload.[29] In patients with AKI, SCr can lag by days despite a decrease in GFR, especially in the setting of fluid overload.[30,31] In addition, in patients with high serum bilirubin, SCr can be inaccurate if colorimetric-based Jaffe assays are used because bilirubin interferes with the color reaction, and thus enzymatic assays are preferred. Other indirect markers of kidney function, such as serum cystatin C, are costly and have not been shown to be superior to SCr in patients with cirrhosis.[29,32]

GFR is considered the best estimate of kidney function, although there is no universally accepted gold standard for measurement of GFR, especially in patients with cirrhosis. GFR measurement using isotopes and radiocontrast methods are confounded by changes in volume of distribution because of ascites and extracellular volume expansion and are not used routinely in clinical practice because of reasons of cost, convenience, and availability. GFR can be measured by creatinine clearance with timed urinary collection; however, in addition to inherent limitations related to incomplete urine collection, increased tubular secretions of creatinine may bias creatinine clearance as GFR declines in cirrhosis.[33,34]

The Modified Diet in Renal Disease 6 (MDRD-6) has been shown to be the most accurate creatinine-based equation in cirrhosis.[34–36] Equations based on cystatin C, with or without SCr (i.e., CKD-EPI creatinine-cystatin C equation) may be superior to creatinine-based equation[37,38]; however, all equations tend to overestimate the true GFR. In addition, all the estimating equations for GFR were based on study populations with CKD with stable SCr. In a recent study in critically ill patients with AKI, estimating equations performed poorly when estimating GFR.[39] Therefore, during non–steady-state conditions, using creatinine-based equations to estimate GFR can result in inaccurate assessment of kidney function.

Despite the many limitations of SCr, its widespread use and access makes it the most practical method of GFR assessment. In addition, SCr remains the basis of existing clinical definitions of AKI in patients with without kidney disease and is a key component in the Model for End-Stage Liver Disease (MELD) score, which is used to prioritize patients for liver transplantation.

DEFINITION OF ACUTE KIDNEY INJURY

The definition of AKI in cirrhosis has undergone significant changes over the past several years (Table 45.1). In 2010 the Acute Dialysis Quality Initiative (ADQI) recommended adaptation of the Acute Kidney Injury Network (AKIN) criteria[40] to define AKI in patients with cirrhosis instead of the traditional definition using a fixed SCr cutoff value of greater than 1.5 mg/dL.[16] These recommendations also were endorsed by the International Club of Ascites (ICA).[41] These criteria were irrespective of the cause of AKI and as such, type 1 HRS was categorized as a specific type of AKI. In addition, the term hepatorenal disorders was proposed to encompass the full range of conditions in which liver and kidney disease coexist.[16] Since then, the use of AKIN criteria in predicting mortality has been validated in numerous studies of hospitalized patients with cirrhosis, including those in the intensive care units (ICUs).[2,9,42,43] Recently, the definition of HRS and AKI in patients with cirrhosis was modified by the ICA.[17] Although oliguria is not included in the current definition of AKI in patients with cirrhosis and has yet to be validated, urine output has been found to be a sensitive and early marker for AKI in ICU patients and to be associated with adverse outcomes.[44–46]

There remains some debate as to the most appropriate reference SCr to use to diagnose and stage AKI.[47–49] The ICA recently suggested that a baseline SCr result within the previous 3 months should be used as the reference, if available, or if no baseline exists, then the admission SCr can be used as the reference.[17] If more than one baseline value of SCr is available in the previous 3 months, a recent International Consensus Meeting recommended that the value closest to the event be used as the reference SCr.[50]

CAUSE OF ACUTE KIDNEY INJURY

The most common cause of AKI in hospitalized patients with cirrhosis is prerenal AKI, accounting for approximately 68% of the cases.[51,52] Prerenal causes are classified according to response to volume expansion. In patients who are volume-responsive, AKI can be the consequence of hypovolemia (gastrointestinal hemorrhage, aggressive diuresis, or diarrhea) or large volume paracentesis. Type 1 HRS, by contrast, is defined by the absence of response to volume expansion and constitutes approximately 17% of cases of AKI in hospitalized patients with cirrhosis. Acute tubular necrosis (ATN) is the most common cause of intrarenal AKI and may be precipitated by sepsis, which is a common complication during advanced cirrhosis.[52]

Because of a better understanding of the pathophysiology of cirrhosis, new concepts challenge the classical view of AKI. For instance, it has been suggested that type 1 HRS does not exclude tubular lesions and that ATN may result from unrecognized and/or untreated prerenal failure with prolonged hypoperfusion leading to ischemic injury. In some patients, type 1 HRS and ATN may be a continuum rather than two distinct entities. In addition, in patients with decompensated cirrhosis and AKI corresponding to the definition of HRS, there are often precipitating factors

TABLE 45.1

Definition and Staging of Acute Kidney Injury

AKI DEFINITION	DEFINITION OF BASELINE SERUM CREATININE		AKI STAGE SERUM CREATININE CRITERIA			AKI STAGE URINE OUTPUT CRITERIA		
			1	2	3	1	2	3
AKIN[40] (2007)	Increase SCr ≥ 0.3 mg/dL within 48 hours; or increase SCr ≥1.5 × baseline within 48 hr; or UO <0.5 mL/kg/hr × 6 hrs	First SCr measured	Increase ≥0.3 mg/dL within 48 hr or ≥1.5–2 × baseline	Increase 2–3 × baseline	Increase 3 × baseline or SCr >4 mg/dL with an acute rise >0.5 mg/dL or on RRT	<0.5 mL/kg/hr × 6–12 hr	<0.5 mL/kg/hr × 12 hr	<0.3 mL/kg/hr × 24 hr or anuria × 12 hr
AKI in Cirrhosis								
ADQI[16] (2010)	Increase SCr ≥ 0.3 mg/dL within 48 hr; or increase SCr ≥ 1.5 × baseline HRS-1 is a specific form of AKI		Increase ≥0.3 mg/dL within 48 hr or ≥1.5–2 × baseline	Increase 2–3 × baseline	Increase 3 × baseline or SCr > 4 mg/dL with an acute rise >0.5 mg/dL or on RRT	-	-	-
ICA[17] (2015)	Increase SCr ≥0.3 mg/dL within 48 hours; or increase SCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days	SCr within 3 months can be used as baseline. In patients with more than one SCr value, value closest to hospital admission should be used. In patients without previous SCr, SCr on admission should be used.	Increase ≥0.3 mg/dL within 48 hr or ≥1.5–2 × baseline	Increase 2–3 × baseline	Increase 3× baseline or SCr > 4 mg/dL with an acute rise >0.5 mg/dL or on RRT	-	-	-

ADQI, Acute dialysis quality initiative; *AKI,* acute kidney injury; *AKIN,* acute kidney injury network; *ICA,* international club of ascites; *RRT,* renal replacement therapy; *SCr,* serum creatinine; *UO,* urine output.

of AKI, such as hypovolemia, infection, and/or SIRS that precipitate renal hypoperfusion.

The prevalence of underlying CKD in patients with cirrhosis who develop AKI ("acute-on-chronic kidney disease") is unknown. However, it can be reasonably assumed that patients with advanced cirrhosis frequently have chronic kidney changes resulting from comorbidities (e.g., diabetes and hypertension) and/or specific causes of CKD (e.g., IgA nephropathy, viral-induced glomerulopathy).[53] The combination of acute and chronic kidney changes makes it even more difficult to predict reversibility in the absence of biopsy. Finally, evidence for close interconnections between AKI and CKD emerged recently in the general population.[54] These interconnections are likely to exist in patients with cirrhosis. Patients with underlying CKD are at 10 times higher risk of developing AKI compared with patients without CKD.[55] In parallel, the risk of developing CKD is higher in patients with severe or repeated episodes of AKI.[54] The rate of CKD after one episode of AKI is as high as 8 per 100 patient-years.[56] Maladaptive repair after tubule cell necrosis is one of the main mechanisms leading to progression from AKI to CKD.[57,58] Because patients with end-stage cirrhosis are prone to develop repeated episodes of AKI as a consequence of events such as sepsis, hypovolemia, paracentesis-induced circulatory changes, and HRS, it can be suspected that these patients with repeated episodes AKI eventually develop irreversible chronic kidney changes.

PREVENTION OF ACUTE KIDNEY INJURY

Prevention of AKI is a key issue in the management of patients with end-stage cirrhosis (Table 45.2).[52,59] Drugs may exert a direct nephrotoxic effect by intrarenal blood flow impairment (e.g., nonsteroidal antiinflammatory drugs, renin–angiotensin–aldosterone system blockers), direct renal tubule toxicity (e.g., radiocontrast dye, aminoglycosides, vancomycin, amphotericin B), or by allergic interstitial injury (e.g., β-lactam antibiotics, diuretics). Changes in drug distribution because of volume overload and altered pharmacokinetics resulting from changes in renal and hepatic blood flow and function can affect the concentration and half-life of medications and their metabolites leading to nephrotoxicity. It has been suggested that cirrhosis may not be a predisposing factor for contrast media–induced nephropathy.[60] However, contrast imaging should be performed only when needed.

The prevention of infections and hypovolemia is crucial in the prevention of AKI. Spontaneous bacterial peritonitis (SBP) prophylaxis with daily antibiotics,[61–63] intravenous albumin use in patients with[64] or without[65,66] SBP and in patients undergoing large volume paracentesis (>5 L),[5] and prompt replacement of gastrointestinal blood loss along with antibiotic prophylaxis[67–69] have been shown to decrease the incidence of AKI, specifically HRS.

TABLE 45.2

Prevention of Acute Kidney Injury in Patients With Cirrhosis

RISK FACTORS	PREVENTIVE APPROACHES
Hepatorenal syndrome development	Judicious use of diuretics and lactulose to avoid dehydration Antibiotic prophylaxis following GI bleedings Albumin administration during large volume paracentesis (6 to 8 gm/L of ascitic fluid removed) Spontaneous bacterial peritonitis (SBP) prophylaxis in patients with low-protein ascites Early recognition and treatment of SBP with antibiotics and albumin at the dose of 1.5 g per kg of body weight at the time of diagnosis of SBP and 1 g per kg of body weight at the third day of treatment
Nephrotoxic medication exposure	Avoid nephrotoxic medications if possible Appropriate drug dosing based on pharmacokinetics and close monitoring of drug toxicity and early recognition of drug-induced AKI and discontinuation of offending agent if possible Use of lipid formulations of amphotericin B rather than conventional formulations of amphotericin B Use of azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed
Radiocontrast exposure	Consider alternative imaging methods or avoidance of intravenous (IV) contrast if possible Use of low or isoosmolar agents with lowest volume possible Use of N-acetylcysteine use in combination with IV hydration
Intraabdominal hypertension	Paracentesis, with coadministration of albumin, in patients with tense ascites

Similarly, it has been proposed that N-acetyl-cysteine may prevent HRS in patients with alcoholic hepatitis.[70] Although nonselective beta blockers are used to prevent gastrointestinal bleeding and improve survival, they have been shown to be associated with reduced survival in patients with refractory ascites.[71,72] In these patients, beta blockers may be associated with more pronounced paracentesis-induced circulatory dysfunction and, possibly, AKI. In addition, because the reduction in cardiac output could precipitate AKI and decrease survival in patients with end-stage liver diseases, Baveno VI recommendations propose to stop beta blockers.[73]

Abdominal compartment syndrome (defined as increased intraabdominal pressure to >20 mm Hg), which could occur from tense ascites, may lead to AKI by increasing venous pressure.[74] Improvement in renal function has been shown in these patients after paracentesis with albumin.[75,76]

EVALUATION AND MANAGEMENT OF ACUTE KIDNEY INJURY

Patients with cirrhosis may develop AKI resulting from many causes and should be suspected in the presence of increased SCr and/or decreased Urine output (UO) (Fig. 45.2). The cause of AKI should be investigated quickly to prevent further worsening of AKI, because progression to advanced stage AKI has been associated with a higher mortality rate.[9] The diagnosis of type 1 HRS is particularly important because early initiation of treatment increases the likelihood of HRS resolution and has been shown to improve survival.[77] Vasoconstrictive agents such as terlipressin, which are detailed in another section, are the reference in the treatment of type 1 HRS with more than 50% experiencing response.[78–80]

Recently, algorithms have been developed to help with the evaluation and the management of AKI (Fig. 45.3).[17,50,59] Briefly, the general principles are (1) rapid diagnosis of AKI, (2) control of precipitating factors (withdrawal of nephrotoxic drugs, NSAIDs, and diuretics; treatment of infections), and (3) plasma volume expansion.

The finding of hematuria, proteinuria, and/or abnormalities of kidney morphology point toward the existence of underlying parenchymal kidney disease, and patients may develop AKI, including HRS, on the background of preexisting kidney disease.[16] Parenchymal kidney disease requires confirmation by appropriate diagnostic tests, preferably including kidney biopsy, although this rarely is performed because of abnormal coagulation.

Volume expansion is the main step not only in the treatment but also in the differential diagnosis of the cause of AKI. The type of fluid needed for resuscitation should be tailored based on the cause of AKI. Patients with intravascular volume loss because of diarrhea or diuretics should be treated with crystalloids, whereas patients with gastrointestinal bleeding should be given packed red blood cells to maintain a hemoglobin value between 7 and 9 g/dL.[81] Patients without an obvious cause for hypovolemia should be given an initial trial of plasma expansion with 20% to 25% albumin (1 g/kg up to a maximum of 100 g). Because patients with cirrhosis and AKI have reduced renal sodium and water excretion, caution should be used with the administration of crystalloids or albumin to avoid development of significant fluid retention. Patients in whom other causes of AKI have been ruled out should receive treatment for type 1 HRS with vasoconstrictors, which in combination with albumin constitute the main therapy for type 1 HRS.[77,82]

Absence of response to plasma volume expansion does not make it possible to distinguish type 1 HRS from ATN. Differentiation between the two entities is not currently possible, because this would require a kidney biopsy. Urine biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1) in addition to urine microalbuminuria or fractional excretion of sodium may be helpful in not only diagnosing AKI earlier and more accurately but also potentially shedding light on the cause of AKI (i.e., differentiating ATN vs HRS).[9,83–88] These tubular biomarkers potentially may help identify patients who are less likely to benefit from volume resuscitation and vasopressor therapy.

The initiation of renal replacement therapy (RRT) should be made on clinical grounds, including electrolyte disturbances (hyperkalemia, metabolic acidosis, hyponatremia not

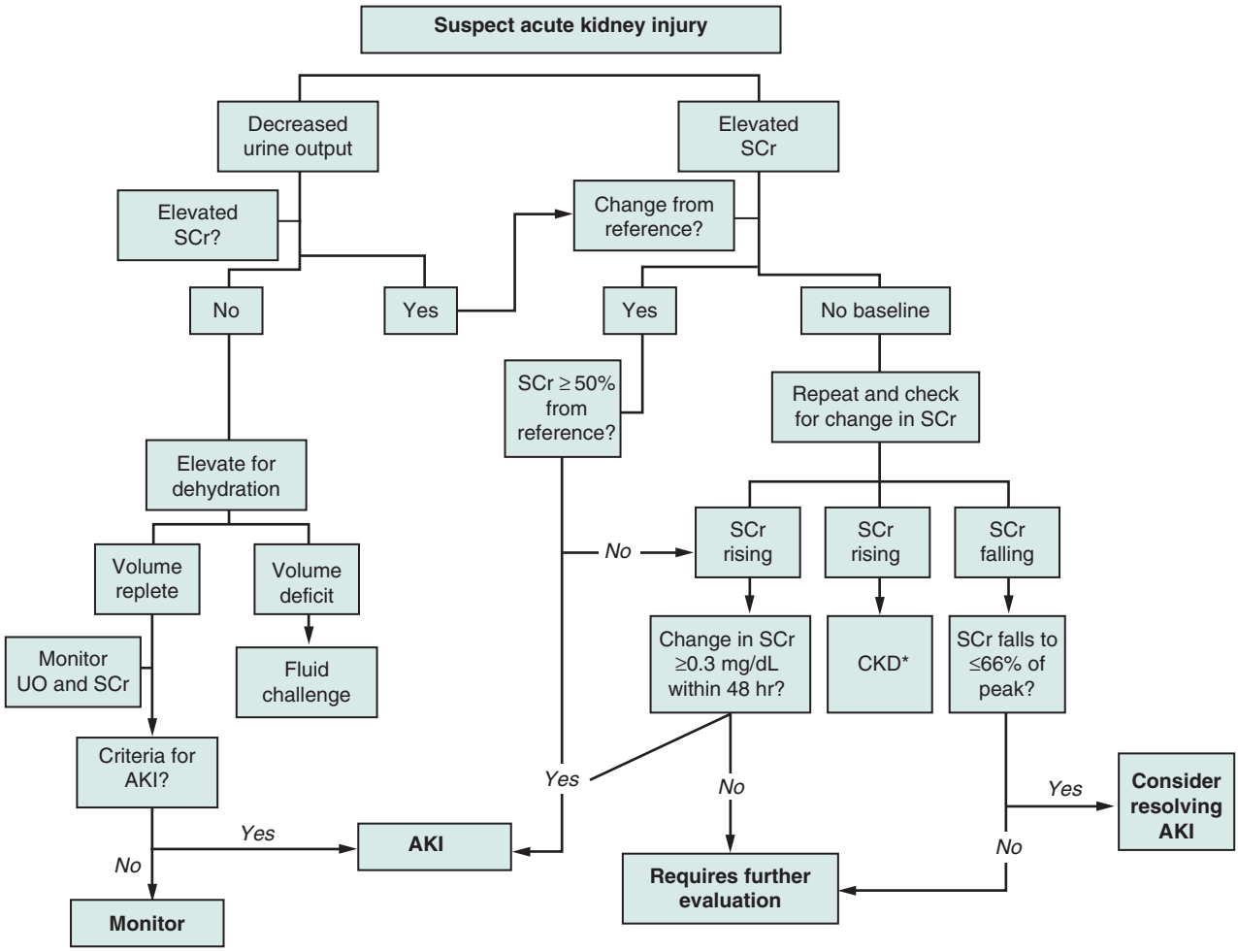

FIGURE 45.2 Diagnostic algorithm to evaluate acute kidney injury in the hospitalized patient with decompensated cirrhosis. Fluid overload may mask serum creatinine increases. CKD based on 6-variable MDRD equation eGFR < 60 mL/min. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *MDRD,* Modification of Diet in Renal Disease; *SCr,* serum creatinine; *UO,* urine output.

responding to medical management), oliguria with increasing volume overload, and diuretic intolerance/resistance. RRT may be required to prevent fluid accumulation and should be considered in patients if the daily fluid balance cannot be maintained as even or negative regardless of their urine output. The ideal timing for initiation of RRT has not been studied in patients with cirrhosis; however, recent data from AKI studies in critically ill patients without liver disease suggest that early RRT initiation[89,90] and maintenance of negative fluid balance[30,31,91–93] improves survival. In patients receiving RRT, continuous renal replacement therapy (CRRT) allows for the slower correction of serum sodium over time and provides greater cardiovascular stability compared with standard intermittent hemodialysis.

ACUTE KIDNEY INJURY IN CANDIDATES FOR LIVER TRANSPLANTATION

The important issues in candidates for liver transplantation are to predict reversibility of impaired renal function and, in those with a potential for reversibility, to predict to which extent renal function may improve after liver transplantation alone. The treatment of choice in patients with type 1 HRS is liver transplantation and, in theory, renal function is fully reversible after transplantation.[10,13,78,94,95] However, several reports have shown that mean SCr after liver transplantation is higher in patients transplanted for type 1 and type 2 HRS as compared with patients without HRS at transplantation.[13,14,94]

In patients with AKI, several consensus meeting have proposed criteria on the indications to perform simultaneous liver-kidney (SLK) transplantation rather than liver transplantation alone, based on a high probability of nonrenal recovery posttransplantation.[96–98] However, neither center nor national guidelines predict kidney recovery with a high level of certainty[10,95,99,100]; therefore the current allocation system allows listing for SLK transplantation based on subjective clinical judgment. Therefore alternative criteria for predicting the reversibility or irreversibility of AKI after transplantation, such as biomarkers, clearly are needed to allow more accurate allocation of kidney grafts and avoid "futile" kidney transplantation in patients with a high potential for renal recovery.[99]

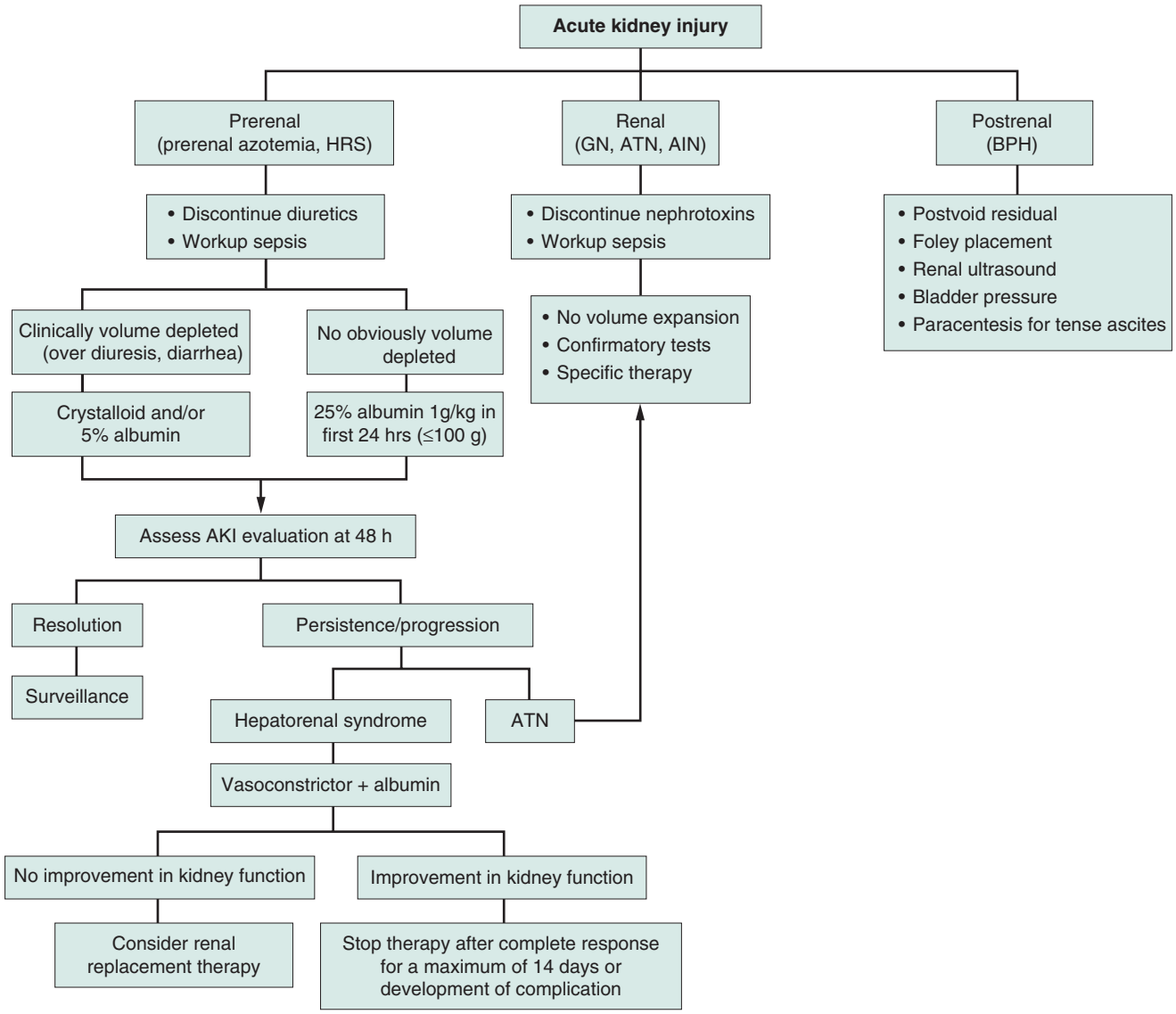

FIGURE 45.3 Algorithm for management of acute kidney injury (AKI). *AIN,* Acute interstitial nephritis; *ATN,* acute tubular necrosis; *BPH,* benign prostatic hypertrophy; *FeNa,* fractional excretion of sodium; *GN,* glomerulonephritis; *HRS,* hepatorenal syndrome.

BIOMARKERS

In the general population, conventional tools used to diagnose and determine the cause of AKI include SCr, UO, fractional excretion of sodium or urea, and proteinuria. However, all of these tools have limitations, especially in patients with advanced cirrhosis. In addition, neither absolute values nor changes in SCr help differentiate functional impairment from structural changes. In candidates for liver transplantation, it has been shown that there is a poor correlation between conventional markers and biopsy findings.[53,101] In the last decade, several innovative biomarkers of AKI have been assessed in patients with cirrhosis.[102] Markers of acute tubular injury have been the most extensively studied because they typically reflect the earliest markers of ischemia-related events. Within the kidney, the proximal tubule is located in an area that is especially exposed to hypoxic injury after hypoperfusion. Whatever the cause, hypoxia leads to proximal tubule dysfunction, resulting in an increase in excreted low molecular weight proteins into urine. The most promising biomarkers of tubular injury in AKI are (1) NGAL, (2) IL-18, and (3) KIM-1.

NGAL is a small protein (25 KDa) produced by several organs including kidney, lung, stomach, and colon.[103] In animal models, NGAL expression is increased markedly in the kidneys and released in urine after ischemic or nephrotoxic insults. Urinary concentration increases very rapidly (within 2 hours) after ischemia.[103,104] Human studies have shown that NGAL measurement in either urine or serum may be useful to detect AKI at an early stage in numerous clinical situations (sepsis, septic shock, contrast-induced nephropathy, cardiac surgery, polytrauma, and hypothermia).[105–111] In addition, NGAL may be useful in monitoring some kidney diseases such as delayed kidney graft function,[112,113] kidney allograft rejection,[114] lupus nephritis,[115] and IgA nephropathy.[116] Recently, it has been suggested that NGAL may help identify the cause of AKI in patients with liver disease, especially in differentiating ATN from HRS.[56,85–87] In average, urinary NGAL is higher

in patients with cirrhosis and AKI compared with patients without AKI[86] and is significantly higher in patients with persistent AKI as compared with patients with transient AKI.[87] Among patients with AKI, urinary NGAL was found to be markedly higher in those with a diagnosis of ATN as compared with those with a diagnosis of type 1 HRS, pre-renal azotemia, or CKD.[83,86] Among patients with type 1 HRS, urinary NGAL was significantly higher in those with concomitant infections. Interestingly, two studies suggest that elevated urinary NGAL is predictive of early mortality in cirrhotic patients with AKI.[85,87] However, initial enthusiasm for NGAL has been tempered by some limitations.[117] Urinary NGAL level increases during AKI but also during other conditions such as chronic and acute inflammation as well as CKD.[118] The performance of NGAL in patients with cirrhosis should be interpreted with caution for several reasons. First, recent studies have shown an increase in NGAL liver synthesis during sepsis.[119,120] Second, even though urinary NGAL level is higher in ATN as compared with HRS and other causes of AKI, there is a significant overlap between groups, which is more pronounced with plasma NGAL levels.[85,86] Finally, in studies exploring NGAL, a diagnosis of ATN was based on clinical criteria without a definitive gold standard because biopsy cannot be reached in the majority of patients with cirrhosis.

IL-18 is a proinflammatory cytokine overexpressed in proximal tubule and released in urine after AKI.[88,121] Human studies have shown that urinary IL-18 levels are increased in AKI and/or ischemic kidney changes,[122] whereas levels remain low in nephrotoxic AKI, CKD, and urinary tract infections. In ICU patients with AKI, urinary IL-18 may predict a poor outcome.[123] In patients with cirrhosis, significantly higher urinary IL-18 levels have been observed in patients with a clinical diagnosis of ATN as compared with non-ATN AKI.[124] However, similar to urine NGAL, there was overlap between groups.

KIM-1 is a transmembrane protein that is upregulated by ischemic kidney injury. It is a marker of proximal tubule injury.[125] Urinary KIM-1 is increased in patients with ATN, whereas no increase is observed in those with prerenal azotemia, urinary tract infections, or CKD.[126,127] Few studies have explored KIM-1 in patients with cirrhosis and AKI.[56,128] These studies have suggested that urinary KIM-1 levels are increased in ATN compared with other causes of AKI and that high levels of KIM-1 could predict progression of AKI. However, substantial overlap in urinary KIM-1, similar to that observed with NGAL and IL-18, has been observed between patients with a diagnosis of ATN as compared with patients with other causes of AKI.[56]

Serum osteopontin has been shown to be predictive of early mortality in ICU patients with AKI independent of the cause of AKI.[129,130] Osteopontin is a broadly expressed cytokine that is upregulated during inflammation. In animal models of AKI, osteopontin expression and mRNA levels are increased in proximal and distal tubular cells.[131] Although osteopontin is supposed to be upregulated by inflammation, in critically ill patients with AKI, sepsis was not associated with a significant increase in circulating osteopontin. Urinary osteopontin level seems markedly higher in patients with cirrhosis and AKI.[88] Urinary osteopontin level was also higher in patients with a clinical diagnosis of ATN as compared with other causes of AKI but with overlap between groups.[88] A recent study suggests that the combination of elevated plasma osteopontin and TIMP-1 levels, age younger than 57 years, and absence of diabetes pretransplantation are relatively accurate at differentiating patients with reversible AKI from patients with irreversible AKI posttransplantation.[132]

Activation of TLRs may play a role in interstitial fibrosis, renal involvement in systemic immune disorders, and more generally in AKI.[133] In AKI, irrespective of the initial trigger that leads to tubular cell injury, necrotic tubular cells release potential TLR ligands, which could activate other tubular cells or resident immune cells in the kidney.[133] High levels of urinary TLR-4 have been found in patients with cirrhosis and AKI.[28] Further studies clearly are needed to determine if urinary TLR-4 could help determine the cause of AKI.

Overall, several urinary or plasma biomarkers may help to (1) recognize impaired renal function at an earlier stage as compared with SCr, (2) identify the mechanisms involved in AKI and (3) improve prognostication. However, all the studies comparing ATN to other causes of AKI have been performed without histologic confirmation of ATN, which is a potential source of bias. All of these markers are increased in tubular injury, but none of them is specific of any part of the nephron. In addition, overlap between groups still represents a limitation. Sequential assessment and/or combinations of biomarkers should be tested because it could help determine the AKI and also predict the outcome.

Key Points

1. In patients with end stage liver disease, renal vasoconstriction resulting from several factors including portal hypertension, gut bacterial translocation and systemic inflammation represent a predisposing factor for AKI.
2. Underlying CKD resulting from associated comorbidities, the prevalence of which is unknown, eventually increases the risk for AKI.
3. The impact of prolonged kidney vasoconstriction is not elucidated clearly but may induce tubular interstitial fibrosis and CKD and further increases the risk of AKI.
4. AKI is common in hospitalized patients with end-stage cirrhosis and has a poor prognosis.
5. An important issue in clinical practice is to differentiate hepatorenal syndrome (HRS) from acute tubular necrosis (ATN) as outcome and management differ (including indication for liver transplantation). However, no reliable tool is currently available and, although invasive and challenging in patients with end-stage liver disease, kidney biopsy theoretically remains the gold standard (1) to determine the phenotype of AKI and (2) to identify underlying CKD.
6. Neutrophil gelatinase-associated lipocalin (NGAL) is the most studied biomarker in the field, but NGAL is a tubular biomarker of AKI, whatever the phenotype.
7. Future challenge includes development of noninvasive biomarkers for early identification of kidney fibrosis before irreversible kidney injury.

Key References

7. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279-1290.

16. Nadim MK, Kellum JA, Davenport A, et al. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2012;16:R23.
17. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968-974.
50. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepatol*. 2016;64:717-735.
102. Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. *J Hepatol*. 2016.

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References

1. Arroyo V, Moreau R, Jalan R, et al. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *J Hepatol*. 2015;62:S131-S143.
2. Tsien CD, Rabie R, Wong F. Acute kidney injury in decompensated cirrhosis. *Gut*. 2013;62:131-137.
3. Barreto R, Fagundes C, Guevara M, et al. Type-1 hepatorenal syndrome associated with infections in cirrhosis: natural history, outcome of kidney function, and survival. *Hepatology*. 2014;59:1505-1513.
4. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol*. 2013;59:482-489.
5. Durand F, Graupera I, Gines P, et al. Pathogenesis of hepatorenal syndrome: implications for therapy. *Am J Kidney Dis*. 2016;67:318-328.
6. Adebayo D, Morabito V, Davenport A, et al. Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. *Kidney Int*. 2015;87:509-515.
7. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279-1290.
8. Stadlbauer V, Wright GA, Banaji M, et al. Relationship between activation of the sympathetic nervous system and renal blood flow autoregulation in cirrhosis. *Gastroenterology*. 2008;134:111-119.
9. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology*. 2013;57:753-762.
10. Nadim MK, Genyk YS, Tokin C, et al. Impact of the etiology of acute kidney injury on outcomes following liver transplantation: acute tubular necrosis versus hepatorenal syndrome. *Liver Transpl*. 2012;18:539-548.
11. Bahirwani R, Campbell MS, Siropaides T, et al. Transplantation: impact of pretransplant renal insufficiency. *Liver Transpl*. 2008;14:665-671.
12. Hilmi IA, Damian D, Al-Khafaji A, et al. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. *Br J Anaesth*. 2015.
13. Boyer TD, Sanyal AJ, Garcia-Tsao G, et al. Impact of liver transplantation on the survival of patients treated for hepatorenal syndrome type 1. *Liver Transpl*. 2011;17:1328-1332.
14. Tan HK, Marquez M, Wong F, et al. Pretransplant type 2 hepatorenal syndrome is associated with persistently impaired renal function after liver transplantation. *Transplantation*. 2015;99:1441-1446.
15. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56:1310-1318.
16. Nadim MK, Kellum JA, Davenport A, et al. Hepatorenal syndrome: the 8th International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2012;16:R23.
17. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968-974.
18. Krag A, Bendtsen F, Henriksen JH, et al. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut*. 2010;59:105-110.
19. Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol*. 2015;63:1272-1284.
20. Alobaidi R, Basu RK, Goldstein SL, et al. Sepsis-associated acute kidney injury. *Semin Nephrol*. 2015;35:2-11.
21. Langenberg C, Wan L, Egi M, et al. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69:1996-2002.
22. Langenberg C, Wan L, Egi M, et al. Renal blood flow and function during recovery from experimental septic acute kidney injury. *Intensive Care Med*. 2007;33:1614-1618.
23. Prowle JR, Bellomo R. Sepsis-associated acute kidney injury: macrohemodynamic and microhemodynamic alterations in the renal circulation. *Semin Nephrol*. 2015;35:64-74.
24. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol*. 2014;60:197-209.
25. Albillos A, de la Hera A, Gonzalez M, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology*. 2003;37:208-217.
26. Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology*. 2007;46:1872-1882.
27. Shah N, Dhar D, El Zahraa Mohammed F, et al. Prevention of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol*. 2012;56:1047-1053.
28. Shah N, Mohamed FE, Jover-Cobos M, et al. Increased renal expression and urinary excretion of TLR4 in acute kidney injury associated with cirrhosis. *Liver Int*. 2013;33:398-409.
29. Davenport A, Cholongitas E, Xirouchakis E, et al. Pitfalls in assessing renal function in patients with cirrhosis–potential inequity for access to treatment of hepatorenal failure and liver transplantation. *Nephrol Dial Transplant*. 2011;26:2735-2742.
30. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care*. 2010;14:R82.
31. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39:2665-2671.
32. Xirouchakis E, Marelli L, Cholongitas E, et al. Comparison of cystatin C and creatinine-based glomerular filtration rate formulas with 51Cr-EDTA clearance in patients with cirrhosis. *Clin J Am Soc Nephrol*. 2011;6:84-92.
33. Proulx NL, Akbari A, Garg AX, et al. Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis. *Nephrol Dial Transplant*. 2005;20:1617-1622.
34. Francoz C, Glotz D, Moreau R, et al. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol*. 2010;52:605-613.
35. Francoz C, Nadim MK, Baron A, et al. Glomerular filtration rate equations for liver-kidney transplantation in patients with cirrhosis: validation of current recommendations. *Hepatology*. 2014;59:1514-1521.
36. Gonwa TA, Jennings L, Mai ML, et al. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl*. 2004;10:301-309.
37. Mindikoglu AL, Dowling TC, Weir MR, et al. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology*. 2014;59:1532-1542.
38. De Souza V, Hadj-Aissa A, Dolomanova O, et al. Creatinine- versus cystatine C-based equations in assessing the renal function of candidates for liver transplantation with cirrhosis. *Hepatology*. 2014;59:1522-1531.
39. Bragadottir G, Redfors B, Ricksten SE. Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury–true GFR versus urinary creatinine clearance and estimating equations. *Crit Care*. 2013;17:R108.
40. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
41. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*. 2011;60:702-709.
42. de Carvalho JR, Villela-Nogueira CA, Luiz RR, et al. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J Clin Gastroenterol*. 2012;46:e21-e26.
43. Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol*. 2013;59:474-481.
44. Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol*. 2015.

45. Macedo E, Malhotra R, Bouchard J, et al. Oliguria is an early predictor of higher mortality in critically ill patients. *Kidney Int*. 2011;80:760-767.
46. Macedo E, Malhotra R, Claure-Del Granado R, et al. Defining urine output criterion for acute kidney injury in critically ill patients. *Nephrol Dial Transplant*. 2011;26:509-515.
47. Siew ED, Matheny ME, Ikizler TA, et al. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. *Kidney Int*. 2010;77:536-542.
48. Zavada J, Hoste E, Cartin-Ceba R, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant*. 2010;25:3911-3918.
49. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? *Kidney Int*. 2015;87:46-61.
50. Nadim MK, Durand F, Kellum JA, et al. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. *J Hepatol*. 2016;64:717-735.
51. Moreau R, Lebrec D. Diagnosis and treatment of acute renal failure in patients with cirrhosis. *Best Pract Res Clin Gastroenterol*. 2007;21:111-123.
52. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology*. 2008;48:2064-2077.
53. Trawale JM, Paradis V, Rautou PE, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. *Liver Int*. 2010;30:725-732.
54. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371:58-66.
55. Khosla N, Soroko SB, Chertow GM, et al. Preexisting chronic kidney disease: a potential for improved outcomes from acute kidney injury. *Clin J Am Soc Nephrol*. 2009;4:1914-1919.
56. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Urinary biomarkers and progression of AKI in patients with cirrhosis. *Clin J Am Soc Nephrol*. 2014;9:1857-1867.
57. Bonventre JV. Maladaptive proximal tubule repair: cell cycle arrest. *Nephron Clin Pract*. 2014;127:61-64.
58. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. *Nat Rev Nephrol*. 2015;11:264-276.
59. O'Leary JG, Levitsky J, Wong F, et al. Protecting the kidney in liver transplant candidates Practice-Based Recommendations from the American Society of Transplantation Liver and Intestine Community of Practice. *Am J Transplant*. 2016.
60. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. *J Hepatol*. 2004;40:140-146.
61. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology*. 2007;133:818-824.
62. European Association for the Study of the L. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53:397-417.
63. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut*. 2012;61:297-310.
64. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol*. 2013;11:123-130.
65. Guevara M, Terra C, Nazar A, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol*. 2012;57:759-765.
66. Thevenot T, Bureau C, Oberti F, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol*. 2015;62:822-830.
67. Bendtsen F, Krag A, Moller S. Treatment of acute variceal bleeding. *Dig Liver Dis*. 2008;40:328-336.
68. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007;46:922-938.
69. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131:1049-1056, quiz 285.
70. Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1781-1789.
71. Serste T, Francoz C, Durand F, et al. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. *J Hepatol*. 2011;55:794-799.
72. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology*. 2010;52:1017-1022.
73. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743-752.
74. de Cleva R, Silva FP, Zilberstein B, et al. Acute renal failure due to abdominal compartment syndrome: report on four cases and literature review. *Rev Hosp Clin Fac Med Sao Paulo*. 2001;56:123-130.
75. Umgelter A, Reindl W, Franzen M, et al. Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. *Intensive Care Med*. 2009;35:152-156.
76. Umgelter A, Reindl W, Wagner KS, et al. Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial. *Crit Care*. 2008;12:R4.
77. Gluud LL, Christensen K, Christensen E, et al. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology*. 2010;51:576-584.
78. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology*. 2002;122:923-930.
79. Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. *Gastroenterology*. 2016.
80. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. *Hepatology*. 2015;62:567-574.
81. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368:11-21.
82. Gluud LL, Christensen K, Christensen E, et al. Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev*. 2012;(9):CD005162.
83. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Urinary biomarkers and progression of AKI in patients with cirrhosis. *Clin J Am Soc Nephrol*. 2014;9:1857-1867.
84. Belcher JM, Sanyal AJ, Peixoto AJ, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology*. 2014;60:622-632.
85. Verna EC, Brown RS, Farrand E, et al. Urinary neutrophil gelatinase-associated lipocalin predicts mortality and identifies acute kidney injury in cirrhosis. *Dig Dis Sci*. 2012;57:2362-2370.
86. Fagundes C, Pepin MN, Guevara M, et al. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol*. 2012;57:267-273.
87. Barreto R, Elia C, Sola E, et al. Urinary neutrophil gelatinase-associated lipocalin predicts kidney outcome and death in patients with cirrhosis and bacterial infections. *J Hepatol*. 2014;61:35-42.
88. Ariza X, Sola E, Elia C, et al. Analysis of a urinary biomarker panel for clinical outcomes assessment in cirrhosis. *PLoS ONE*. 2015;10:e0128145.
89. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the elain randomized clinical trial. *JAMA*. 2016;315:2190-2199.

90. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016.
91. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int*. 2009;76:422-427.
92. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008;12:R74.
93. Vaara ST, Korhonen AM, Kaukonen KM, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012;16: R197.
94. Wong F, Leung W, Al Beshir M, et al. Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. *Liver Transpl*. 2015;21:300-307.
95. Ruiz R, Barri YM, Jennings LW, et al. Hepatorenal syndrome: a proposal for kidney after liver transplantation (KALT). *Liver Transpl*. 2007;13:838-843.
96. Eason JD, Gonwa TA, Davis CL, et al. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). *Am J Transplant*. 2008;8:2243-2251.
97. Davis CL, Feng S, Sung R, et al. Simultaneous liver-kidney transplantation: evaluation to decision making. *Am J Transplant*. 2007;7:1702-1709.
98. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant*. 2012;12:2901-2908.
99. Levitsky J, Baker T, Ahya SN, et al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. *Am J Transplant*. 2012;12:2949-2957.
100. Ruiz R, Kunitake H, Wilkinson AH, et al. Long-term analysis of combined liver and kidney transplantation at a single center. *Arch Surg*. 2006;141:735-741, discussion 41-2.
101. Wadei HM, Geiger XJ, Cortese C, et al. Kidney allocation to liver transplant candidates with renal failure of undetermined etiology: role of percutaneous renal biopsy. *Am J Transplant*. 2008;8:2618-2626.
102. Francoz C, Nadim MK, Durand F. Kidney Biomarkers in Cirrhosis. *J Hepatol*. 2016.
103. Mishra J, Ma Q, Prada A, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol*. 2003;14:2534-2543.
104. Mishra J, Mori K, Ma Q, et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol*. 2004;15:3073-3082.
105. Wheeler DS, Devarajan P, Ma Q, et al. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. *Crit Care Med*. 2008;36:1297-1303.
106. Hirsch R, Dent C, Pfriem H, et al. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. *Pediatr Nephrol*. 2007;22:2089-2095.
107. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet*. 2005;365:1231-1238.
108. Wagener G, Jan M, Kim M, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology*. 2006;105:485-491.
109. Makris K, Markou N, Evodia E, et al. Urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early marker of acute kidney injury in critically ill multiple trauma patients. *Clin Chem Lab Med*. 2009;47:79-82.
110. Trachtman H, Christen E, Cnaan A, et al. Urinary neutrophil gelatinase-associated lipocalcin in D+HUS: a novel marker of renal injury. *Pediatr Nephrol*. 2006;21:989-994.
111. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med*. 2008;148:810-819.
112. Pianta TJ, Peake PW, Pickering JW, et al. Clusterin in kidney transplantation: novel biomarkers versus serum creatinine for early prediction of delayed graft function. *Transplantation*. 2015;99:171-179.
113. Lee EY, Kim MS, Park Y, et al. Serum neutrophil gelatinase-associated lipocalin and interleukin-18 as predictive biomarkers for delayed graft function after kidney transplantation. *J Clin Lab Anal*. 2012;26:295-301.
114. Kohei J, Ishida H, Tanabe K, et al. Neutrophil gelatinase-associated lipocalin is a sensitive biomarker for the early diagnosis of acute rejection after living-donor kidney transplantation. *Int Urol Nephrol*. 2013;45:1159-1167.
115. Torres-Salido MT, Cortes-Hernandez J, Vidal X, et al. Neutrophil gelatinase-associated lipocalin as a biomarker for lupus nephritis. *Nephrol Dial Transplant*. 2014;29:1740-1749.
116. Ding H, He Y, Li K, et al. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is an early biomarker for renal tubulointerstitial injury in IgA nephropathy. *Clin Immunol*. 2007;123:227-234.
117. Ostermann M, Joannidis M. Biomarkers for AKI improve clinical practice: no. *Intensive Care Med*. 2015;41:618-622.
118. Martensson J, Bellomo R. The rise and fall of NGAL in acute kidney injury. *Blood Purif*. 2014;37:304-310.
119. Macdonald SP, Stone SF, Neil CL, et al. Sustained elevation of resistin, NGAL and IL-8 are associated with severe sepsis/septic shock in the emergency department. *PLoS ONE*. 2014;9:e110678.
120. Otto GP, Busch M, Sossdorf M, et al. Impact of sepsis-associated cytokine storm on plasma NGAL during acute kidney injury in a model of polymicrobial sepsis. *Crit Care*. 2013;17:419.
121. Liu Y, Guo W, Zhang J, et al. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. *Am J Kidney Dis*. 2013;62:1058-1067.
122. Wu H, Craft ML, Wang P, et al. IL-18 contributes to renal damage after ischemia-reperfusion. *J Am Soc Nephrol*. 2008;19:2331-2341.
123. Siew ED, Ikizler TA, Gebretsadik T, et al. Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes. *Clin J Am Soc Nephrol*. 2010;5:1497-1505.
124. Belcher JM, Sanyal AJ, Peixoto AJ, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology*. 2014;60:622-632.
125. Han WK, Bailly V, Abichandani R, et al. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int*. 2002;62:237-244.
126. Nishida M, Kawakatsu H, Okumura Y, et al. Serum and urinary neutrophil gelatinase-associated lipocalin levels in children with chronic renal diseases. *Pediatr Int*. 2010;52:563-568.
127. Parikh CR, Devarajan P. New biomarkers of acute kidney injury. *Crit Care Med*. 2008;36:S159-S165.
128. Qasem AA, Farag SE, Hamed E, et al. Urinary biomarkers of acute kidney injury in patients with liver cirrhosis. *ISRN Nephrol*. 2014;2014:376795.
129. Lorenzen JM, Hafer C, Faulhaber-Walter R, et al. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26:531-537.
130. Nejat M, Pickering JW, Walker RJ, et al. Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. *Crit Care*. 2010;14:R85.
131. Verstrepen WA, Persy VP, Verhulst A, et al. Renal osteopontin protein and mRNA upregulation during acute nephrotoxicity in the rat. *Nephrol Dial Transplant*. 2001;16:712-724.
132. Levitsky J, Baker TB, Jie C, et al. Plasma protein biomarkers enhance the clinical prediction of kidney injury recovery in patients undergoing liver transplantation. *Hepatology*. 2014;60:2017-2026.
133. Anders HJ, Banas B, Schlondorff D. Signaling danger: toll-like receptors and their potential roles in kidney disease. *J Am Soc Nephrol*. 2004;15:854-867.