Acute kidney injury (AKI) is one of the most common and morbid complications of decompensated cirrhosis. Management of AKI is dictated by cause: prerenal AKI is treated with volume resuscitation; hepatorenal syndrome (HRS), with intravenous albumin and vasoconstrictors; and acute tubular necrosis, with supportive care. However, differentiating between causes is difficult using creatinine-based definitions of AKI alone. The use of novel kidney biomarkers in AKI and cirrhosis provides an opportunity to improve both the diagnosis and prognosis of this vulnerable population. This review examines the challenges of AKI in cirrhosis and the research experience around novel kidney biomarkers in cirrhosis. Specific focus is paid to the tubular injury marker neutrophil gelatinase-associated lipocalin (NGAL), which has been the most studied in liver disease and has demonstrated the strongest performance in differentiating the cause of AKI (acute tubular necrosis vs functional injury such as prerenal AKI or HRS), as well as improving the prognostic performance of mortality prediction models such as the model for end stage liver disease (MELD) score. We advocate for the discussion of incorporating markers such as NGAL in the next iteration of HRS guidelines and identify areas for future research in this clinical condition.

Background

Hepatorenal Syndrome and Acute Kidney Injury in Cirrhosis

Acute kidney injury (AKI) is a common and morbid complication of decompensated cirrhosis and is associated with tremendous costs and health care burdens. AKI in cirrhosis is defined by change in serum creatinine level. Similar to other conditions of multisystem organ dysfunction, mortality in AKI in cirrhosis directly correlates with the relative increase in creatinine level, with the highest short-term mortality seen in stage 3 AKI (>60% at 3 months) and among those requiring kidney replacement therapy (>80% at 3 months). However, even relatively small increases of 0.3 mg/dL (stage 1 AKI) are associated with worsening outcomes.

Not surprisingly, one of the primary clinical challenges in this population lies in persistent AKI. Persistent AKI is defined as the absence of recovery of serum creatinine level by 50% from peak value or within <0.3 mg/dL of baseline. However, defining AKI in cirrhosis by the relative change in serum creatinine level does not fully inform the clinical picture. The cause of AKI also plays an important role in both the treatment and prognosis of AKI in cirrhosis. Not surprisingly, cirrhotic patients with reversible AKI largely have prerenal injury, which by definition resolves with volume administration and discontinuation of diuretic therapy.

Persistent AKI in cirrhosis consists predominantly of hepatorenal syndrome (HRS) and acute tubular necrosis (ATN). Differentiating between HRS and ATN remains one of the most challenging aspects of caring for this population and has important therapeutic implications. HRS pathophysiology was initially described in 1988 by Schrier et al. First, blood pools in the splanchnic/portal circulation, leading to decreased effective arterial blood volume. To compensate, there are increases in renin, aldosterone, catecholamine, and vasopressin levels, resulting in systemic vasoconstriction and retention of sodium and water in the kidneys. Later, decompensated cirrhotic patients develop ascites, reflecting their extremely sodium-avid state. Finally, when these mechanisms fail to provide adequate end-organ perfusion, the prototypical “functional” kidney injury is observed, in which there is little or no parenchymal kidney damage, though levels of serum creatinine and other markers of decreased glomerular filtration rate (GFR) are elevated. Hyperdynamic cardiac compensation is another hallmark of early cirrhosis, the loss of which is also noted in more advanced cirrhosis and likely contributes to HRS.

HRS is defined by the International Club of Ascites (ICA), whose updated 2015 guidelines lean heavily on this understanding of pathophysiology, as well as clinicians’ ability to rule out other causes of AKI (Box 1). In brief, these guidelines include confirming the presence of cirrhosis and ascites (requisite biological precursors to HRS, as above), ruling out prerenal AKI through a 48-hour volume challenge with intravenous albumin and withholding diuretic therapy, and demonstrating the absence of ATN (including nephrotoxic medications and shock) or glomerular injury (hematuria/proteinuria). Infamously, HRS lacks a single sensitive and specific diagnostic test, leading to the frequently quoted (and accurate) aphorism that “HRS is a diagnosis of exclusion.” The ICA guidelines also recommend replacing the term “HRS-1” (the acute and more severe AKI in cirrhosis that meets these criteria) with “HRS-AKI.” Although the 2 terms are nearly synonymous, we use HRS-AKI throughout this review.

Although the ICA guidelines provide a solid diagnostic framework for HRS, several key limitations remain. First, given that creatinine is derived from muscle and the sarcopenia commonly found in this population, creatinine level may not estimate GFR accurately enough in cirrhosis. To help address this, the 2015 guidelines...
replaced the absolute creatinine threshold with a more sensitive definition based on relative change in creatinine level.

Second, HRS exists on a clinical spectrum rather than as a concrete clinical entity. In a patient with portal hypertension and “at-risk” physiology, there is potential for superimposed prerenal AKI or ATN, as well as elements of underlying organic chronic kidney disease (CKD). Again, guidelines were updated to incorporate an iterative evaluation process of AKI in cirrhosis, acknowledging the dynamic nature of this population (Fig 1).3

Third, in the absence of a clear objective test for HRS, 48 hours of empirical volume challenge is required, which serves as both a diagnostic and therapeutic maneuver. However, there is not clear evidence that a “one size fits all” approach to AKI in cirrhosis benefits all patients. A fluid-first treatment algorithm may delay the initiation of vasoconstrictors in those with HRS19,20 or exacerbate clinical volume overload in those who are unlikely to respond, as in ATN.

Finally, as technologies have improved and our ability to characterize microvascular inflammatory changes has expanded, we have discovered additional mechanisms that may contribute to HRS. Our understanding of HRS has expanded to include aspects of disruption of gut permeability, increased bacterial translocation, and upregulation of systemic inflammatory mediators, which ultimately may contribute to the impaired circulatory function that defines HRS (Fig 2).21-25

Although GFR is represented by serum creatinine level in tools such as model for end stage liver disease (MELD) or MELD sodium (MELD-Na) scores,26-28 the mortality of patients with HRS is higher than what would otherwise be predicted with such prognostic models.29 Historically, cirrhotic patients with HRS have had worse outcomes than those with other types of AKI.5,7 However, changes in practice patterns and variability around liver transplant availability suggest that ongoing research into this issue is warranted.

Regardless, there is a great need for a reliable biomarker that can accurately distinguish persistent functional AKI (HRS) from parenchymal kidney damage (ATN) and simultaneously provide prognostic information. Fortunately, recent progress in the study of novel kidney biomarkers in AKI and cirrhosis holds the potential to close these gaps. In this article, we review the ability of kidney

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**Box 1. 2015 ICA Guidelines for the Diagnosis of Hepatorenal Syndrome**

- Diagnosis of cirrhosis and ascites
- AKI by ICA-AKI criteria (increase in Scr ≥ 0.3 mg/dL within 48 h or 50% increase from baseline presumed to have occurred within 7 d)
- Lack of response after 48 h of diuretic withdrawal and plasma expansion with 1 g/kg of intravenous albumin
- Absence of shock
- No recent nephrotoxic drug use
- Absence of macroscopic signs of structural kidney injury (ie, proteinuria < 500 mg/d, <50 RBCs/high-power field, and normal kidney ultrasound)

Abbreviations: AKI, acute kidney injury; ICA, International Club of Ascites; RBCs, red blood cells; Scr, serum creatinine.

*Guidelines specifically highlight the need for future research into urinary kidney biomarkers to differentiate between hepatorenal syndrome and acute tubular necrosis.*

Based on Angeli et al.3

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**Figure 1.** Suggested approach to the diagnosis and management of acute kidney injury in cirrhosis. Resolution is defined as a decrease in serum creatinine level to within 0.3 mg/dL of baseline value. Stage 1 acute kidney injury (defined as an increase in serum creatinine ≥ 0.3 mg/dL from baseline) is stratified in stage 1A (serum creatinine < 1.5 mg/dL) and stage 1B (serum creatinine ≥ 1.5 mg/dL). Stage 1A has a higher chance of resolution with supportive measures (90%), compared with stage 1B (52%).29 Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drug. Adapted from Huelin et al81 (itself adapted from Angeli et al3) with permission of John Wiley and Sons; original graphic © 2019 by the American Association for the Study of Liver Diseases.
biomarkers to improve the diagnosis and prognosis of HRS, as well as their future implications in the management of this vulnerable population.

**Kidney Biomarkers**

**Scope of Challenges**

The discovery and validation of novel kidney biomarkers has focused on addressing serum creatinine’s limitations, identifying markers specific to parenchymal kidney damage, and aiding in kidney-centric management and prognosis. Current guidelines that define AKI based on a relative change in serum creatinine level are unable to distinguish causes of AKI, most notably between functional/prerenal injury and parenchymal/tubular damage, and lack tissue diagnosis for confirmation. Such definitions also rely on a baseline creatinine value for comparison, which may not always be available. Creatinine has several confounders that can lead to acute changes in serum levels without actual kidney injury, including drug interference with tubular creatinine secretion, changes in dietary intake, and fluid administration that dilutes serum levels. Furthermore, creatinine is insensitive at detecting mild parenchymal damage in patients with adequate kidney functional reserve and demonstrates a slow kinetic increase in AKI (on the order of 8-12 hours), which may lead to delays in diagnosis. Taken together, these features result in major statistical limitations when using serum creatinine as a reference or gold standard to evaluate novel kidney biomarkers. Especially in populations with a low prevalence of AKI, apparent diagnostic errors of novel biomarkers may be attributed to faults in an imperfect reference test, rather than poor performance of the biomarker itself. As such, caution should be taken when interpreting areas under the curve (AUCs) of biomarker performance in any population, including in studies of liver disease.

**Goals of Novel Kidney Biomarkers**

Emerging technologies, specifically proteomic platforms, have led to the discovery of several classes of kidney biomarkers, both in serum and urine. These biomarkers are
often used in preclinical models of drug development, facilitating early identification of prohibitively nephrotoxic compounds, thus helping to streamline more promising candidates toward clinical trials. As biomarker discovery has moved from preclinical to clinical studies, specific populations have emerged as groups of interest. The majority of clinical studies of kidney biomarkers occur in the intensive care unit (ICU), which enriches the target population by increasing AKI prevalence, thereby addressing some of the mentioned statistical limitations. In particular, cardiac surgery populations have been used here extensively, given that the initial timing of kidney injury is known (cardiac bypass/aortic cross-clamping) and the mechanism of AKI is more homogeneous than ICU populations at large.

Kidney biomarkers have the potential to address several knowledge gaps around AKI. First, large prospective studies have demonstrated that multiple kidney biomarkers can detect AKI within hours of injury. This allows for more timely identification of AKI and potentially affects the timing of kidney replacement therapy and triage of patients to more appropriate levels of care. Second, certain biomarkers can distinguish prerenal AKI from ATN, thus limiting volume resuscitation to those with fluid-responsive kidney injury. Third, kidney biomarkers can predict AKI severity by identifying those who will progress to a more severe AKI stage. Combined with the earlier detection of AKI, this has the potential to improve triage by illness severity even further. Fourth, multiple kidney biomarkers have been associated with long-term clinical outcomes, including renal recovery rates, cardiovascular outcomes, and overall mortality.

**Classes of Kidney Biomarkers**

Novel kidney biomarkers can generally be categorized in 3 groups: (1) markers of kidney function, (2) tubular injury markers, and (3) markers of cell-cycle arrest (Table 1). For this review, we limit discussion to biomarkers that are approved for clinical use and/or have a substantial literature in AKI and cirrhosis.

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Testing Location</th>
<th>Time to Expression</th>
<th>Function</th>
<th>Nonrenal Expression and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Cystatin C&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Serum (urine)</td>
<td>12-24 h</td>
<td>Structural protein of cysteine protease inhibitor family</td>
<td>Similar to Scr, ↑ in CKD</td>
</tr>
<tr>
<td>Tubular injury</td>
<td>NGAL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Urine (serum)</td>
<td>1-12 h</td>
<td>Innate immune regulation via iron sequestration</td>
<td>Infection (UTI), liver disease</td>
</tr>
<tr>
<td></td>
<td>IL-18</td>
<td>Urine</td>
<td>1-12 h</td>
<td>Immune regulation</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>KIM-1</td>
<td>Urine</td>
<td>1-12 h</td>
<td>Activates T&lt;sub&gt;H&lt;/sub&gt; cells, promotes apoptotic cell clearance</td>
<td>Clear cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>L-FABP</td>
<td>Urine</td>
<td>1-12 h</td>
<td>Free fatty acid transporter</td>
<td>Liver disease, PKD, sepsis</td>
</tr>
<tr>
<td>Cell cycle arrest</td>
<td>[TIMP-2] × [IGFBP-7]&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Urine</td>
<td>&lt;12 h</td>
<td>Regulate cell injury repair</td>
<td>Little evidence in cirrhosis</td>
</tr>
</tbody>
</table>

Abbreviations and definitions: CKD, chronic kidney disease; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; L-FABP, liver-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; PKD, polycystic kidney disease; Scr, serum creatinine; [TIMP-2] × [IGFBP7], combination of urine concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7; T<sub>H</sub>, T helper; UTI, urinary tract infection.

<sup>a</sup>Approved for clinical use in North America.
<sup>b</sup>Approved for clinical use in Europe.
IL-18 is a pro-inflammatory cytokine that is expressed ubiquitously by systemic immune cells. Its level in urine increases after acute ischemic injury to the proximal tubule, a pattern that does not seem to be confounded by urinary infections, sepsis, or CKD. In studies of humans, urine IL-18 level performs moderately at predicting the development of AKI, as well as predicting clinical outcomes such as mortality. KIM-1 is a transmembrane protein that is upregulated in the proximal tubule after ischemic kidney injury, has few extrarenal confounders, and can differentiate ATN from prerenal AKI and CKD. L-FABP is a free fatty acid transporter that is expressed in the proximal tubule and released into urine in response to sepsis and AKI and may be confounded by infection as well as liver disease.

Insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases 2 (TIMP-2), a 2-component urinary biomarker of cell-cycle arrest, represents the final subgroup of kidney biomarkers. It was discovered through an unbiased proteomic screen in human populations of AKI and performs well at detecting AKI and predicting clinical outcomes. Although [TIMP-2] \times [IGFBP7] is FDA approved to aid in risk assessment for moderate to severe AKI in the adult ICU, there is only 1 small study describing an unclear role for this marker in cirrhosis and it is not discussed further.

Kidney Biomarkers in Cirrhosis

Unlike other populations in which kidney biomarkers have been studied, cirrhosis is the only disease that has an AKI-directed therapy—the vasoconstrictor terlipressin—which is approved for the treatment of HRS in Europe and is under evaluation by the FDA. The vasopressor norepinephrine, which can be used as an alternative in settings in which terlipressin is not available, has performed similarly to terlipressin in a small number of randomized trials. The availability of such vasoconstrictors increases the likelihood that improved diagnosis and prognosis in this population will translate into meaningful improvements in patient outcomes.

Diagnosis of HRS Versus ATN

Current definitions of AKI in cirrhosis remain grounded in change in serum creatinine level. When comparing multiple eGFR formulas using iothalamate clearance as a reference, the CKD-EPI creatinine–cystatin C equation outperformed all others in cirrhotic patients. Likely owing to the poor muscle mass of cirrhotic patients, formulas based on creatinine level alone overestimate GFR in this group. However, eGFR formulas provide only a point estimate and have a limited clinical role when kidney function is not in steady state, as is the case in AKI. There are minimal data examining relative changes in cystatin C level to define AKI in cirrhosis, though what is published suggests, similarly to creatinine, that increased cystatin C level is associated with the development of AKI. Based on current evidence, we believe that a change in serum creatinine level remains the most appropriate test to define AKI in cirrhosis.

Tubular injury biomarkers have shown promise in differentiating the cause of AKI in cirrhosis. Current guidelines suggest withdrawal of diuretic therapy and volume expansion with albumin in the initial management of AKI, which essentially eliminates reversible prerenal AKI from diagnostic consideration if serum creatinine level improves. Distinguishing between the remaining persistent causes of AKI—HRS and ATN—presents the biggest challenge in this clinical condition. Urinary tubular marker levels increase predictably across the different AKI causes, with prerenal AKI lowest, followed by slightly higher levels seen in HRS, and significantly elevated levels seen in ATN. This pattern reflects the spectrum of physiology seen in cirrhosis. Functional AKI types, such as prerenal injury and HRS, are not expected to result in significant tubular damage; thus, biomarkers levels are low. Although experimental evidence is not conclusive, HRS may theoretically result in some tubular injury as the phenotype of renal vasoconstriction worsens to the eventual point of ischemic injury.

However, we have found no differences in urinary NGAL levels in patients with persistent versus reversible HRS-AKI (E. Solà et al, unpublished data, 2020). In a study of 112 patients with cirrhosis and either prerenal AKI, HRS, or ATN, Belcher et al examined urinary NGAL, IL-18, KIM-1, and L-FABP and found that each marker differentiated ATN from nontubular causes of kidney injury, with NGAL performing best (AUC of 0.79). Additionally, the likelihood of having ATN increased with an increasing number of positive biomarkers. In a meta-analysis of 8 studies of 1,129 patients, urine NGAL and IL-18 demonstrated good discrimination between ATN and other types of AKI (AUCs of 0.89 and 0.88, respectively). NGAL has both serum and urine assays available, but the serum test is not as well studied as urinary NGAL. There is insufficient evidence comparing the performance of serum versus urinary NGAL to determine the cause of AKI in cirrhosis.

Kidney Outcomes

Success of HRS-directed medical therapy, such as terlipressin and intravenous albumin, is defined by a durable improvement in serum creatinine level, to within 0.3 mg/dL of baseline and/or <1.5 mg/dL (complete response) or regression of AKI stage but still above this creatinine threshold (partial response). Therefore, kidney biomarkers that predict progression to higher AKI stage or dialysis dependence are of great clinical interest. In a North American cohort in which terlipressin was not available, higher urinary NGAL, IL-18, KIM-1, and L-FABP level were each independently associated with progression of AKI stage, with urinary IL-18 performing best. In a European cohort of prerenal AKI, ATN,
and HRS in which terlipressin was used as part of a protocol-based treatment algorithm, AKI progression was most associated with high urinary NGAL level checked on hospital day 3, after 48 hours of volume expansion. Day 3 urinary NGAL level also predicted the eventual need for kidney replacement therapy, but was not associated with response to terlipressin.81

As in other AKI populations, urinary tubular biomarker levels may increase earlier than serum creatinine level in response to injury and thus could improve early detection of AKI.85,86 However, there are insufficient data to draw firm conclusions on their role in cirrhosis in this area.

There is a small literature around the use of kidney biomarkers in predicting native kidney recovery after liver transplant. This has dramatic potential clinical implications in determining whether simultaneous liver-kidney transplant is indicated. However, in large part due to small sample sizes, evidence is conflicting on whether such markers improve the prediction of kidney recovery after liver transplant.89,90 It may be that a combination of novel biomarkers and clinical characteristics work best in this regard.91 Currently, the 2017 United Network for Organ Sharing/Organ Procurement and Transplantation Network guidelines use creatinine-based eGFR and time on kidney replacement therapy as the sole determining factors of dual-organ transplantation.92

**Patient Outcomes**

There is a range of evidence that novel kidney biomarkers can predict mortality in cirrhosis and AKI. In a 2017 meta-analysis of 5 studies, elevated urinary NGAL and urinary IL-18 excretion were associated with short-term mortality (AUC of 0.76 for both).86 Four of these studies had consistent conclusions, and in the fifth, urinary NGAL excretion was associated with mortality in univariate but not multivariable analysis.85 Since this meta-analysis, additional groups have shown similar associations between kidney biomarker levels and mortality, including 1 study in which serum NGAL alone performed similarly to MELD score in mortality prediction, whereas cystatin C level did not.92

Interestingly, tubular injury biomarkers have demonstrated prognostic strength for mortality in wider populations of decompensated cirrhosis both with and without AKI.63,80,84,94 In one analysis of the multicenter European CANONIC study population, in which all patients were hospitalized for acute-on-chronic liver failure (ACLF) and 34% had baseline decreased kidney function (as defined by serum creatinine > 1.5 mg/dL), cystatin C and plasma NGAL levels independently predicted 90-day mortality (hazard ratios of 3.1 [95% CI, 2.1-4.7] and 1.9 [95% CI, 1.3-2.4], respectively).27

In another analysis of the CANONIC study by Ariza et al95 that included patients both with and without ACLF, urinary NGAL excretion was elevated in ACLF and significantly improved the accuracy of MELD to predict mortality, especially at higher MELD scores.95 For example, for a MELD score of 30, the 28-day mortality was only 5% in patients with urinary NGAL-creatinine ratios < 15 μg/g compared to 41% in those with urinary NGAL-creatinine ratios > 105 μg/g (Fig 3). In a more focused population of patients with hepatitis B–associated ACLF from China, serum NGAL level incrementally improved MELD score’s mortality prediction, whereas cystatin C level did not.96

Among all these biomarkers, NGAL should be highlighted as the most well-studied prognostic tool in cirrhosis.77,80,81,86,94-96 In 2 studies looking at panels of multiple biomarkers (1 European and 1 American cohort), NGAL level demonstrated the highest statistical performance in predicting mortality when compared with IL-18, KIM-1, L-FABP, cystatin C, and others.82,87 Perhaps the most definitive study examining urinary NGAL in cirrhosis and AKI was by Huelin et al81 in 2019. These authors approached 320 consecutive cases of AKI in cirrhosis using a standard algorithm (Fig 1) and measured urinary NGAL on days 1, 3, 7, and 14 of admission. They found day 3 urinary NGAL level (post–volume challenge) best distinguished ATN from other AKI (AUC of 0.87 at a cutoff NGAL-creatinine ratio of 220 μg/g), predicted AKI stage progression, and predicted 28-day mortality. When used in the context of a diagnostic algorithm, Huelin et al81
suggest that NGAL may be useful in the differential diagnosis of AKI and outcome prediction in cirrhosis.

There is one notable unanswered question about the role of novel kidney biomarkers in predicting mortality in ACLF, both with and without AKI: how much of their predictive value is driven by the AKI itself? Naturally, levels of kidney biomarkers such as NGAL are elevated in AKI, and AKI is associated with increased mortality in cirrhosis, so there is some collinearity between the two. Because AKI is so common in ACLF, it is difficult to exclude those patients from analysis. This can be somewhat addressed statistically by including a diverse spectrum of liver and kidney disease in biomarker studies. Additionally, mechanistic studies that strengthen the biological link between biomarkers and liver disease can further justify the importance of their clinical role. For example, in the 2016 study by Ariza et al, a subanalysis of patients with liver biopsies demonstrated that hepatic expression of lipocalin 2, which regulates NGAL production, is significantly increased in ACLF. NGAL’s expression in response to liver injury further strengthens its biological link to AKI, ACLF, and cirrhosis.

Conclusions and Future Directions

Creatinine is the standard test used to quantify the morbidity and mortality associated with AKI in cirrhosis. However, emerging evidence suggests that novel kidney biomarkers can improve both the diagnosis and prognosis of this vulnerable population. The tubular injury biomarker NGAL is the most well studied in cirrhosis and we believe is the closest to making a meaningful impact on clinical practice. It is a single objective test that has the ability to differentiate ATN from functional AKI such as HRS, as well as improve mortality prediction models, especially at high MELD scores, for which further prognostic accuracy has tremendous implications in organ allocation.

Although progress has been made in recent years, there are several areas of need that warrant further research effort. Some of the previously evaluated novel kidney biomarkers used older definitions of HRS and AKI in cirrhosis and thus should be studied further in the context of the definitions in the 2015 ICA-HRS guidelines. Tubular injury markers such as NGAL are not approved for clinical use worldwide, which limits evaluation of these tests in real-world clinical practice. Additional studies of these biomarkers in cirrhosis are needed, especially in North American populations, because most of the data are from European studies. These tests also lack defined cut points or accepted normal ranges in cirrhotic populations, which is another barrier to wider adoption. A consensus around whether to normalize urinary biomarker levels for concurrent urine creatinine levels should be reached to limit variability in methodologies between studies.

Overall, novel kidney biomarkers can be integrated into overall treatment approach for AKI in cirrhosis (Fig 4). We believe there is sufficient evidence behind tubular injury biomarkers such as NGAL to warrant discussion about their incorporation into the next iteration of ICA-HRS guidelines.
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