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Development of Acute Kidney Injury in a Patient With Alcohol-Related Cirrhosis: The Importance of Diagnosing the Cause of Acute Kidney Injury

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After obtaining patient's consent, this clinical case was discussed in a multidisciplinary panel consisting of 2 hepatologists (AJ and ATM), a transplant hepatologist (GC), a pathologist (MPA), a nephrologist (ASA), and a hepatologist (PG) as moderator. A summary of the case history and discussion are presented here.

Case History

A 52-year-old patient with a history of at-risk alcohol consumption and no other relevant past medical conditions was admitted to the hospital because of recent appearance of progressive abdominal distention and peripheral edema, without fever, other symptoms, or recent medications. On physical examination, grade 3 ascites and peripheral edema were noted, along with stigmata of chronic liver disease and abdominal venous collateral circulation. Blood pressure was 107/63 mm Hg.

Initial laboratory workup revealed aspartate aminotransferase/alanine aminotransferase levels of 39/20 U/L (reference, <40 U/L), total bilirubin of 1.0 mg/dL (reference, 0.3–1.0 mg/dL), international normalized ratio (INR) of 1.3 (reference, <1.1), platelet count of 114,000/μL (reference, 130,000–400,000/μL), albumin 29 g/L (reference, 34–48 g/L), hemoglobin 11 g/dL (reference, 13–15 g/dL), and impaired renal function with a serum creatinine level of 3.4 mg/dL (reference, 0.3–1.3 mg/dL), with the most recent previous value of 0.8 mg/dL four months before admission. Sodium and potassium levels were 141/4.9 mEq/L (reference, 135–145/3.5–5.5 mEq/L, respectively), and the acid–base balance was within normal limits. A diagnostic paracentesis revealed ascitic fluid consistent with transudate (12 g/L total protein; 8 g/L of albumin; serum ascites albumin gradient of >1.1 g/L and meeting the criteria for spontaneous bacterial peritonitis (SBP; 1,160 white blood cells/mm^3 with 80% neutrophils). Additionally, urinalysis showed abundant leukocytes and hematuria. Blood, urine, and ascitic fluid cultures were collected.

An ultrasound examination was performed, which revealed a liver with heterogeneous parenchyma and nodular contour, no space-occupying lesions, and patent portal vein and hepatic veins. The ultrasound examination also showed homogeneous splenomegaly and abundant ascites. The kidneys were of normal size and morphology, with adequate corticomedullary differentiation and no dilation of the urinary tract.

The patient was diagnosed with a first episode of decompensation of alcohol-related liver cirrhosis, presenting with ascites, SBP, urinary tract infection (UTI), and acute kidney injury (AKI) grade 3. The patient was started on empirical antibiotic therapy (ceftriaxone 1 g every 24 hours) and albumin in accordance with clinical guidelines (1.5 g/kg at admission (total dose of 120 g) and 1 g/kg at 48 hours from diagnosis (total dose of 80 g).

After 48 hours of treatment, the ascitic fluid still met the criteria for SBP without signs of improvement (1,500 white blood cells/mm^3, 92% neutrophils), prompting an escalation of antibiotic therapy in line with guidelines (ampicillin 2 g every 6 hours was added). Repeat blood test revealed a serum creatinine level of 3.2 mg/dL, sodium/potassium levels of 139/4.1 mEq/L, and albumin of 26 g/L. Protein electrophoresis indicated polyclonal hypergammaglobulinemia, with an increase in immunoglobulin A (IgA) levels. A 24-hour urine study showed >1,000 erythrocytes/field, proteinuria of 1.7 g/24 hours, and urine sodium of 69 mEq/L. The urine culture identified the presence of *Escherichia coli*. No bacteria were isolated from blood or ascitic fluid cultures.

The medical team was concerned about the patient's kidney dysfunction and wanted to initiate treatment; however, it was first necessary to establish the etiology of AKI.

Question: Which of the following is the most likely cause of the AKI in this patient?

A. The cause of AKI in this patient is hepatorenal syndrome associated with SBP. The patient should be treated with terlipressin (or norepinephrine) plus albumin as soon as possible, in conjunction with antibiotic therapy for SBP and UTI.

B. The cause of AKI in this patient is acute tubular necrosis related to sepsis; antibiotic therapy and maintaining adequate fluid balance are essential to the management of AKI in this patient.

C. The presence of proteinuria and hematuria raise the suspicion of glomerular disease. However, the presence of *E coli* in the urine may alter these results. Urinary analysis should be repeated to confirm the presence of proteinuria and hematuria when the UTI is solved. Additionally, a kidney biopsy may be needed to confirm the diagnosis of glomerular disease.

D. This is prerenal AKI. Fluid administration should be increased while carefully monitoring the patient's volume status.

Look on page 223 for the answer and see the *Gastroenterology* website (www.gastrojournal.org) for more information on submitting to *Gastro* Grand Rounds.

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Conflicts of interest
These authors disclose the following: Giuseppe Cullaro reports consulting fees from Ocelot Bio and Retro Sciences. Andrew S. Allegretti reports consulting fees from Mallinckrodt Pharmaceuticals, Ocelot Bio, Bioporto, Motric Bio, Sequana Medical and DSMB committee service for Astrazeneca. Pere Ginès has received research funding from Gilead & Grifols; has consulted or attended advisory boards for Gilead, RallyBio, SeaBeLife, Merck, Sharp and Dohme (MSD), Ocelot Bio, Behring, Roche Diagnostics International, Boehringer Ingelheim, and Astra-Zeneca; and has received speaking fees from Pfizer. The remaining authors disclose no conflicts.

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Answer (Page 221): The presence of proteinuria and hematuria raise the suspicion of glomerular disease. However, the presence of *E coli* in the urine may alter these results. Urinary analysis should be repeated to confirm the presence of proteinuria and hematuria when the UTI is solved. Additionally, a kidney biopsy may be needed to confirm the diagnosis of glomerular disease.

The correct answer is C.

Multidisciplinary Case Discussion

PG: One question that frequently arises in patients with cirrhosis and high serum creatinine found at admission to the hospital is whether the patient has an AKI or chronic kidney disease (CKD). Could you comment on how the differential diagnosis is made between these 2 conditions?

AJ: The main difference between AKI and CKD is the time of onset of the increase in serum creatinine. According to the International Club of Ascites (ICA)—European Association for the Study of the Liver (EASL) definition, AKI is defined as an increase in serum creatinine of $\geq$0.3 mg/dL (26.5 μmol/L) within 48 hours, or an increase of $\geq$50% from baseline, known or presumed to have occurred within the prior 7 days. In contrast, patients with an estimated glomerular filtration rate (eGFR) of $<$60 mL/min/1.73 m^2 and/or markers of kidney damage such as proteinuria or hematuria, or structural abnormalities identified by imaging technique, present for more than 3 months, are considered to have CKD.[1]

The challenge in this scenario is to establish a baseline serum creatinine value, which, according to guidelines, should be the value closest to the current date within the previous 3 months. In the current case, only a serum creatinine from 4 months before admission was available, which was normal. In contrast, some patients may not have a known baseline value. In such cases, clinical guidelines rely on clinical judgment and the patient's clinical course to determine whether the patient has AKI or CKD. In the current scenario, the diagnosis of kidney function impairment in the context of SBP and UTI led the clinicians consider that the increase of serum creatinine had occurred over a short time period; thus, the impairment of kidney function was considered to be an AKI.

PG: What examinations should be done in patients with cirrhosis presenting with AKI? How fast should these examinations be performed?

AJ: Patients with decompensated cirrhosis and AKI should undergo a complete physical examination, with particular attention to volume status assessment (signs of dehydration, volume overload, etc) and looking for potential infections, which are the most common trigger of AKI. Blood tests should include serum creatinine, electrolytes, and complete cell blood count, as well as liver enzymes (serum transaminases, gamma-glutamyl transferase, alkaline phosphatase) and liver function tests (bilirubin, prothrombin time/INR, and albumin).

Bacterial infections should be investigated thoroughly, with blood, ascites fluid, and urine cultures, and spot urine analysis to check for the presence of bacteria, hematuria, or leukocytes. Finally, a chest radiograph should be performed to rule out pneumonia and assess for possible signs of cardiopulmonary overload or heart failure.

Within the first 24 hours of AKI, a 24-hour urine collection should be performed, focusing on proteinuria, albuminuria, and hematuria, to rule out structural kidney damage. If possible, an ultrasound examination should be performed to evaluate the kidneys and urinary tract and rule out structural abnormalities. Table 1 summarizes all recommended tests that should be performed in patients with AKI and decompensated cirrhosis.

Overall, these investigations are crucial for (1) evaluating whether the patient has hypovolemia, the most common cause of AKI in patients with decompensated cirrhosis, which would benefit from fluid administration, (2) ruling out bacterial infections, which are involved in a significant percentage of AKI episodes, and (3) assessing structural kidney damage.

PG: Ann, you have recently reported a study on the validation of the EASL algorithm for the diagnosis and management of AKI in cirrhosis. One of the key steps in the EASL algorithm, as well as in that of American Association for the Study of Liver Diseases (AASLD) is the administration of albumin for 48 hours. Could you comment on which patients should be given this albumin challenge and what is the proportion of patients who respond to this challenge?

ATM: Both the EASL and AASLD algorithms recommend administering albumin at 1 g/kg/day for 48 hours in patients with more severe AKI stages.[2,3] The main difference between the 2 algorithms is that albumin is recommended at AKI stage $\geq$1B in the EASL algorithm (defined as an increase in serum creatinine of $>$0.3 mg/dL from baseline, but a $<$2-fold increase, with an absolute value of $\geq$1.5 mg/dL), and at AKI stage $\geq$2 in the AASLD one (defined as a $\geq$2-fold increase in baseline serum creatinine). Moreover, the EASL guidelines specify that, if a patient has evidence of acute gastrointestinal bleeding or hypovolemia from diarrhea or excessive diuresis, clinicians should administer with the most appropriate fluid, such as blood products and crystalloids, respectively.

Table 1. Clinical Evaluation Checklist for Patients With AKI and Decompensated Cirrhosis

AKI criteria and severity classification	Baseline SCr Increase in serum creatinine of ≥0.3 mg/dL, or ≥50% from baseline. Presumed to have occurred within the prior 7 days Define AKI severity. AKI 1A: AKI criteria with SCr < 1.5 mg/dL (132.6 μmol/L) AKI ≥ 1B: AKI criteria with SCr ≥1.5 mg/dL (132.6 μmol/L)
Physical examination	Volume status Dehydration (dry mucous membranes, decreased skin turgor…) Volume overload (jugular venous distension, orthopnea and pulmonary crackles…) Signs of Infection (fever, ↑HR, ↑leukocyte count, ↑CRP…) Suspected source: _ _ _ _ _ _ _ _
Laboratory tests	Blood tests (complete cell blood count, creatinine and electrolytes, liver enzymes and liver function tests) Urine spot Diagnostic paracentesis Cultures Blood Urine Ascitic fluid 24-hour urine analysis Urinary NGAL, if available (preferably after 48 hours of AKI diagnosis and albumin administration)
Radiological techniques	Chest radiograph Renal and urinary tract ultrasound

AKI, acute kidney injury; CRP, C-reactive protein; HR, heart rate; NGAL, neutrophile gelatinase associated lipocalin; SCr, serum creatinine; US, ultrasound.

In our prospective cohort study, we sought to validate the EASL algorithm, and therefore administered albumin at 1 g/kg/day for 48 hours in hospitalized patients with cirrhosis and AKI stage ≥1B, unless another type of fluid replacement was indicated. We found that 34% of patients responded to albumin by 48 hours, which is quite high considering this is a fairly straightforward intervention.[4]

Nevertheless, clinicians should remember that, even with a short albumin challenge of 48 hours, pulmonary edema is possible, although uncommon, which we encountered in 1% of albumin-treated patients in our study.[4] Patients should therefore be monitored for this condition, and those who already have evidence of pulmonary edema or circulatory overload may not be good candidates for the albumin challenge.

PG: Recently, a consensus paper has been published that recommends the administration of albumin to be restricted to 24 hours instead of 48 hours.[5] Could you please comment on the duration of albumin therapy in patients with cirrhosis and AKI?

ATM: Shortening the duration of albumin administration from 48 to 24 hours has the theoretical advantage of diagnosing hepatorenal syndrome (HRS)-AKI earlier, at a lower serum creatinine, which could be associated with better response to terlipressin.[6] However, the time difference is relatively short, and there are some implications to this proposed change.

After this consensus was published,[5] we examined the patients with cirrhosis and AKI who had responded to the 48-hour albumin challenge in our prospective cohort study.[4,7] Response was defined as a decrease in AKI stage to stage 1A, or resolution of AKI (serum creatinine that returns to within 0.3 mg/dL of baseline). Of these albumin responders, we found that 61% had indeed responded by the 24-hour mark, but the remaining 39% required 48 hours of albumin treatment to respond. Only 1 patient had progression of AKI stage and then responded by 48 hours. Based on the new definition of HRS-AKI, these 39% of patients could have been labelled as having HRS-AKI and been treated with vasoconstrictors, potentially exposing them to important side effects, when in fact another 24 hours of albumin treatment would have been sufficient for AKI reversal.

Thus, I would favor 48 hours over 24 hours of albumin administration in patients with AKI stage ≥1B.

PG: How is the diagnosis of HRS-AKI vs parenchymal nephropathy made in this algorithm? Which criteria are used?

ATM: In the EASL algorithm, the diagnosis of HRS-AKI is made following the 2015 ICA definition.[1] That definition includes straightforward, clinical criteria, such as a lack of response to 48 hours of albumin administration (to rule out hypovolemic component to AKI), absence of nephrotoxic drugs and absence of significant proteinuria and hematuria (to rule out parenchymal nephropathy). A recent consensus conference has proposed some modifications to the definition of HRS-AKI (Supplementary Table 1), including the possibility of mixed kidney injury, which will be discussed elsewhere in this report.

Interestingly, in our cohort study, the use of the EASL algorithm (and by extension the 2015 ICA definition of HRS-AKI) still allowed for the rapid identification of patients with HRS-AKI.[4] The median time from AKI diagnosis to terlipressin

initiation was only 2.5 days. In fact, we started terlipressin at a lower serum creatinine than reported in recent trials (2.4 mg/dL vs 3.5 mg/dL in the CONFIRM trial[8]), and found a very good response to terlipressin, at 61%. Considering that the ICA 2015 definition of HRS-AKI has been validated and is associated with good response to terlipressin therapy, it seems reasonable to use this definition in clinical practice, at least until more data emerge to support the newer definition.

PG: The differential diagnosis between HRS-AKI and acute tubular necrosis (ATN) is often difficult. Could you comment on the possible use of kidney biomarkers, particularly urinary NGAL?

AJ: According to the ICA-EASL algorithm, the differential diagnosis between HRS-AKI and ATN should be made after 48 hours of albumin administration, if there is no resolution of AKI stage $\geq$1B.[3] As mentioned, HRS-AKI should be diagnosed in patients with cirrhosis and ascites if there is no evidence of structural kidney damage (such as hematuria, proteinuria, or morphological alterations of the kidneys).

Several studies have looked at the role urinary biomarkers to improve the diagnostic accuracy of these 2 conditions.[9,10] The biomarker with the largest body of evidence in this regard is urinary neutrophil gelatinase-associated lipocalin (uNGAL).[10] Furthermore, NGAL is produced via gene up-regulation following kidney tubular cell injury. Several studies have reported that patients with ATN have higher levels of uNGAL compared with other causes of AKI, including HRS-AKI. Patients with uNGAL levels of >220 ng/mL are likely to have ATN (area under the receiver operating characteristic curve, 0.87; sensitivity, 88%; specificity, 85%).[11–13] In the current patient case, the levels of urinary NGAL measured after resolution of UTI were of 184 ng/mL, which suggests that the patient did not have ATN.

An algorithm summarizing the diagnostic approach to patients with cirrhosis and AKI is shown in Figure 1.

PG: The peak serum creatinine in this patient was 3.4 mg/dL. Physicians caring for this patient decided to wait for a possible improvement of kidney function instead of an early use of renal replacement therapy (RRT). Could you comment on the indications for RRT in patients with cirrhosis and AKI and whether indications are identical to or different from those of patients with AKI without liver disease? In this patient, would the approach have been different if either the clinical suspicion is of ATN or possible glomerulopathy?

ASA: The approach to RRT in a patient with AKI and cirrhosis is similar to the approach in the general population, with a few important liver-specific additions. We can extrapolate from high-quality evidence in the ESRD and critical care literature that there is equipoise in the timing of initiation, although cirrhosis is underrepresented in these studies.[14,15] We lack an objective number or eGFR cutoff that defines optimal timing, though most would agree an eGFR of <5–10 mL/min/m^2 would commonly support RRT. In the absence of a life-threatening concern with acidosis, electrolytes (particularly hyperkalemia), volume overload, dialyzable intoxicants, or uremic symptoms, careful clinical judgement must be used as to whether symptoms could be managed medically or require RRT. Cirrhosis-specific indications include hyperammonemia refractory to medical management, as RRT can be used as an adjunct therapy to lower plasma ammonia levels, and transplant-specific indications. For listed patients who have severe acidosis or volume overload that may impede successful liver transplantation, clinicians should have a lower threshold for initiating RRT to optimize the patient for surgery.

When considering the etiology of kidney injury in approach to RRT in cirrhosis, the most important factor is whether the patient has AKI or CKD. Most of the data examining RRT in cirrhosis are around acute hemodynamic injuries, such as HRS and ATN, both of which portend a poor short-term prognosis once initiating RRT.[16] Patients with CKD and glomerular diseases were not well-represented in these studies and, in general, do better than the AKI population. More studies are needed about the role of RRT in patients with CKD and glomerular disease and cirrhosis; there are few comparisons of outcomes between patients with hemodynamic/nephrotoxic injuries like HRS and ATN compared with glomerulopathy in this population.

PG: IgA glomerulopathy may occur in patients with alcohol-related decompensated cirrhosis. Could you comment on the frequency and management of IgA nephropathy in patients with cirrhosis?

ASA: IgA nephropathy is the most common primary glomerular disease worldwide, so it is not surprising that it is also the most common glomerular disease in alcohol-related liver disease.[17] The pathogenesis of IgA nephropathy is thought to be due to autoantibody formation in the presence of increased circulating IgA1 (a molecule important in gut mucosal immunity) with reduced O-link glycosylation, which ultimately leads the production of circulating immune complexes that deposit and inflame the glomerulus. IgA antibodies are cleared hepatically, so it stands to reason that cirrhosis would increase the risk of the first step of this pathogenesis. The management of IgA nephropathy focuses on reducing the gut burden of IgA (through systemic steroids or more gut-specific budesonide), reduction of intraglomerular pressure via angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ARB) and/or sodium-glucose transport protein 2 inhibitor therapy to slow CKD progression, and nonimmune inhibition of renal endothelin type A receptors to slow renal fibrosis.[17] These medical therapies should be used with caution in cirrhosis owing to increased side effect profiles, particularly the combination endothelin receptor antagonist/ARB sparsentan, which carries a warning for hepatotoxicity and requires close liver tests monitoring. I tend to have a high threshold to initiate immunosuppression for glomerular disease in decompensated cirrhosis for fear of side effects, especially in patients with high Model for End-stage Liver Disease scores and listed for transplant, to avoid negatively affecting their candidacy. For patients with stable kidney function and an eGFR of >20–30 mL/min/m^2 and >500–1000 mg/day proteinuria, I do consider the nonimmune therapies for IgA nephropathy such as angiotensin-converting enzyme inhibitors/ARB and sodium-glucose transport protein 2 inhibitors.

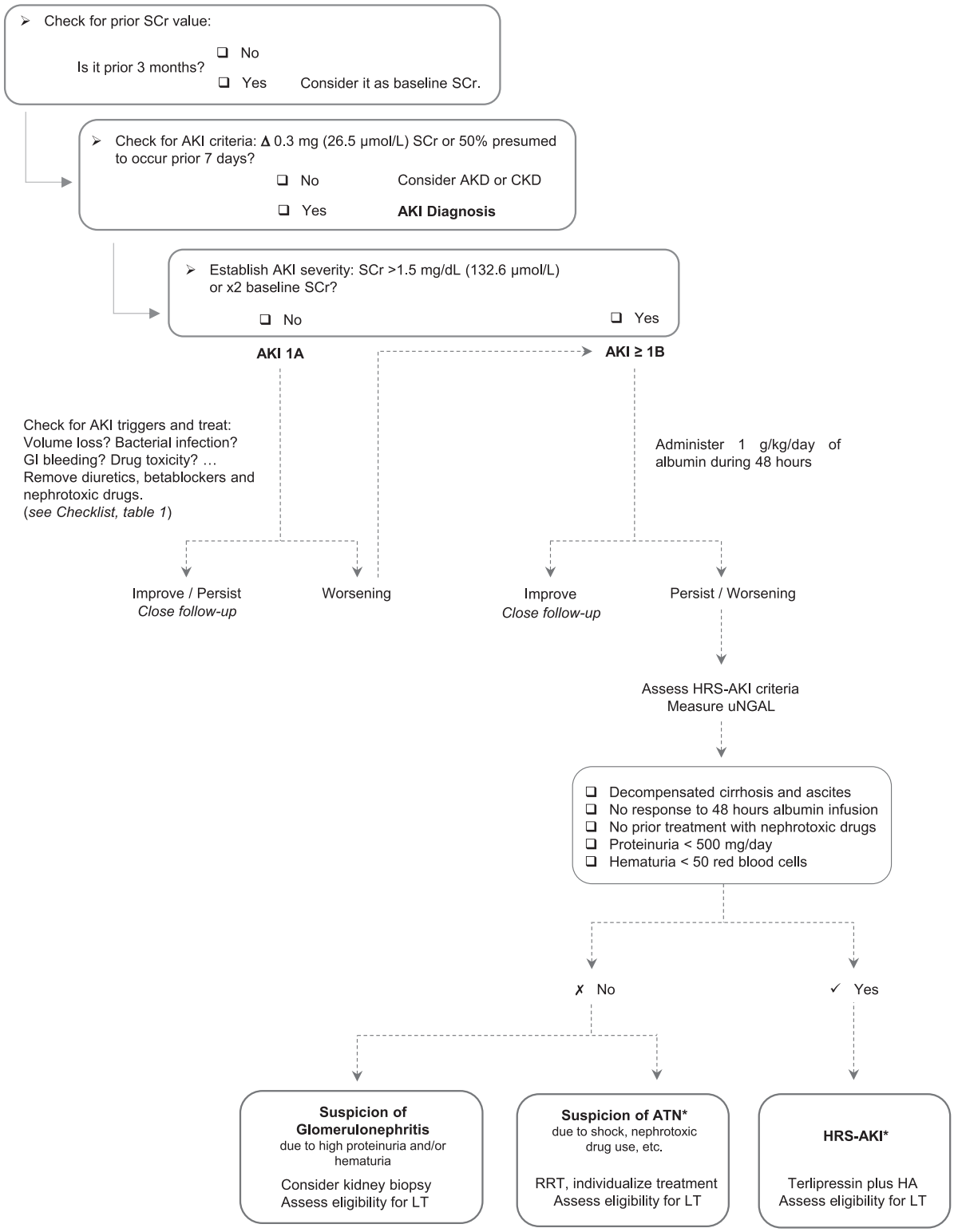

Figure 1. Expanded algorithm for AKI diagnosis and management. *The assessment of NGAL levels in the urine helps in the differential diagnosis between ATN and HRS-AKI. Values higher than 220 ug/g of creatinine are highly suggestive of ATN, whereas values lower than 220 ug/g of creatinine are highly suggestive of HRS-AKI in patients meeting the diagnostic criteria of this syndrome. AKD, acute kidney disease; AKI, acute kidney injury; ATN, acute tubular necrosis; CKD; chronic kidney disease; HA, human albumin; HRS, hepatorenal syndrome; LT, liver transplant; SCr, serum creatinine.

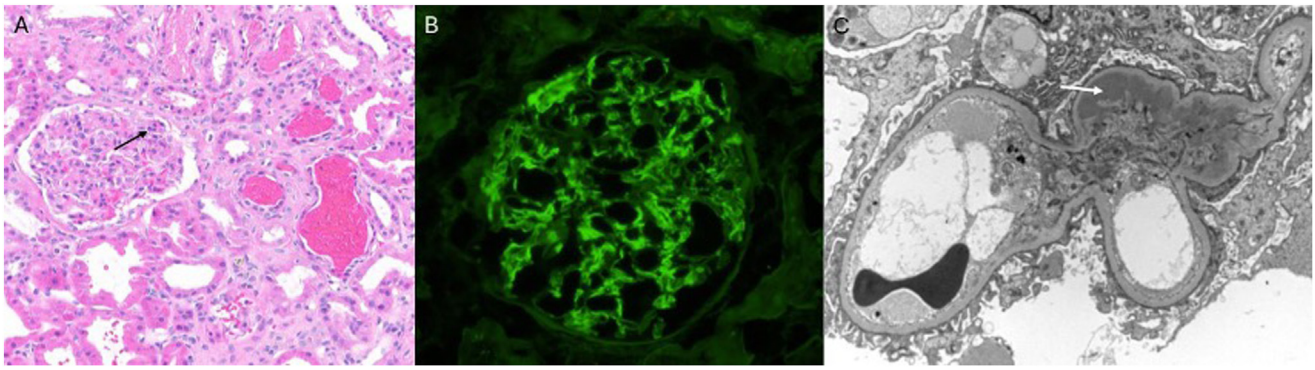

Figure 2. IgA nephropathy: findings from kidney biopsy. The glomerulus shows mild mesangial proliferation (*black arrow*). The biopsy in addition shows acute tubular injury with a few prominent red cell casts. (*A*) Hematoxylin and eosin, original magnification ×200. (*B*) Immunofluorescence microscopy highlights IgA deposits predominantly localized to the mesangium, original magnification ×400. (*C*) Electron microscopy, ultrastructural studies highlight prominent granular electron dense mesangial deposits (*white arrow*), original magnification ×6000.

PG: Some authors suggest that treatment with terlipressin be started as soon as possible in patients with cirrhosis and AKI to prevent progression of possible HRS-AKI, even if the existence of parenchymal nephropathy has not been fully ruled out with all diagnostic tools (kidney ultrasound, 24-hour urine protein, etc). Do you agree with this approach?

ASA: This is an excellent question with some level of equipoise in the current literature. It is clear from both clinical trial and real-world observational data that earlier administration of terlipressin (ie, with a lower serum creatinine) results in high rates of HRS reversal.[8,9] Therefore, in patients with classically defined HRS, waiting for a complete diagnostic workup may delay therapy initiation, and theoretically decrease the chances of reversal. In contrast, forsaking an algorithm-based approach using guideline from societies like EASL[3] and AASLD[2] can lead to the potential overuse of terlipressin, resulting in increased health care costs and side effects.[5,7] Furthermore, patients with evidence of parenchymal injury, including ATN and proteinuria, were not included in terlipressin trials. It is not clear how terlipressin performs in states of mixed injury, where some underlying hepatorenal physiology may be present, on top of tubular or glomerular damage. Because HRS is a complicated and multifaceted syndrome, rather than a discrete or uniform clinical entity, there is likely a subgroup of patients with mixed injury who would benefit from terlipressin, but as of yet, we are not able to define this group. Treatment approaches and the use of terlipressin in these nonstandard cases should be individualized, incorporating drug labeling guidance, societal recommendations, and clinical judgment. In short, in patients with HRS-AKI, treatment with terlipressin plus albumin should be initiated immediately after diagnosis. The starting terlipressin dose is 1 mg every 6 hours if administered as boluses or 2 mg/day if given via continuous infusion. Albumin should also be administered at a dose of 40 g/day, as it has been shown to improve response rates compared with terlipressin alone. If there is no reduction in serum creatinine of $\geq$25% within 48 hours, the terlipressin dose should be increased. Treatment should be continued until serum creatinine decreases to $\geq$0.3 mg/dL from baseline, for a maximum of 14 days, or until significant side effects occur.

PG: This patient had findings that could be compatible with IgA nephropathy and therefore a kidney biopsy was performed. Could you comment on the histological findings of this condition as well as on the clinicopathological spectrum of this disease in patients with cirrhosis?

PA: The biopsy is characterized by IgA dominant glomerular staining on immunofluorescence microscopy and by light microscopy the glomeruli show mesangial hypercellularity with a focal segmental scar (Figure 2). Active necrotizing lesions and/or cellular crescents are not seen. These findings support the diagnosis of IgA nephropathy. Additionally, there is evidence of acute tubular injury. The histological pattern of IgA nephropathy in general is variable, ranging from mesangio and/or endocapillary cellularity with or without sclerosing or crescentic lesions. These key lesions constitute the MEST_C score of the widely used Oxford classification of IgA nephropathy.[18] IgA nephropathy in the setting of liver disease is the most common cause of secondary IgA nephropathy and has been incidentally detected in as many as 9%–25% patients who undergo liver transplantation. Cirrhosis-associated IgA nephropathy may account for $\leq$14% of IgA nephropathy cases and in many cases are asymptomatic, although there is much variation in the reported frequency of hematuria and proteinuria, ranging from 10% to 90%. A recent study comparing biopsy-based pathology of cirrhosis-related IgA nephropathy and primary IgA nephropathy showed that mesangioproliferative pattern of glomerular injury was seen commonly in both groups of IgAN, but a more severe membranoproliferative pattern of glomerular injury was identified in cirrhosis-related IgA nephropathy.

PG: The patient had coexistence of findings of ATN with IgA nephropathy. How common is the coexistence of different histological findings in kidney biopsies of patients with cirrhosis?

MPA: The common pathology one encounters on kidney biopsies include ischemia-associated ATN, acute interstitial nephritis, and parenchymal nephropathy. Ischemia-associated ATN may be due to prolonged prerenal azotemia, abdominal compartment syndrome, cardiorenal processes, or hemorrhagic or septic shock. Another pathology one encounters is acute interstitial nephritis. This condition may be noted in the setting of proton pump blocker use, or antibiotics such as vancomycin or ciprofloxacin, among others. Vancomycin-associated cast nephropathy is a more recently described entity with a unique histological picture. Bile cast nephropathy characterized by tubular obstruction by bile casts is seen in the setting of marked hyperbilirubinemia. Hepatic glomerulosclerosis, characterized by mesangial expansion, with ultrastructural evidence of subendothelial lucency, and clusters of membranous vesicles that are distributed in the mesangium, subendothelial space and, occasionally, in the basement membrane may also be seen in patients with liver disease. Beside IgA nephropathy, other glomerular diseases in patients with cirrhosis included viral-associated (hepatitis B and hepatitis C) immune complex disease processes such as membranous nephropathy, membranoproliferative glomerulonephritis, and cryoglobulinemic nephropathy. Infection-associated glomerulonephritis, particularly secondary to staphylococcal infection, can pose a diagnostic dilemma, because these are IgA dominant. These are often associated with hypocomplementemia, have a dominant or co-dominant C3 staining, and have hump-like deposits on electron microscopy.

PG: Kidney biopsy is used infrequently as a diagnostic tool in patients with cirrhosis and AKI because of the fear of bleeding complications related to the procedure. Could you comment on the indications of the use of kidney biopsy in patients with cirrhosis and AKI?

ASA: Major bleeding is indeed the most feared complication of a kidney biopsy, with rates of approximately 1% in the general population, but >10 times higher in cirrhosis, with 1 study citing 12% of biopsies requiring transfusion or subsequent hemostatic procedure. Complications of kidney biopsy, particularly bleeding, are increased in patients with ascites because of the difficulties in the kidney access and in patients with coagulation disorders, even mild elevations of INR. Thus, kidney biopsy should be reserved for very narrow indications in cirrhosis, and should not be part of the routine evaluation of presumed hemodynamic injury. Kidney biopsy can be considered in patients with cirrhosis with a high pretest probability of glomerular disease where knowledge of the diagnosis will influence therapy (such as choice of immunosuppression) and the risk of bleeding is low enough to warrant the procedure. This cohort would include patients like ours, with seemingly preserved synthetic function, who hemodynamically stable, and with a high probability of glomerular disease based on hematuria and proteinuria. We also recommend optimization of coagulation parameters before the procedure, which may include administration of platelets, desmopressin acetate, cryoprecipitate, and proactive red blood cell transfusion.

PG: Could you comment on the indications of combined liver–kidney transplantation vs liver transplantation alone for patients with cirrhosis and AKI?

GC: The indications for combined liver–kidney transplantation (CLKT) are predicated on a set of well-defined criteria, which aim to identify liver transplant candidates with a low probability of renal function recovery following liver transplantation alone. In the United States, 3 specific criteria have been established to prioritize kidney allocation to liver transplant recipients (Table 2).[19]

PG: The indications of CLKT seem to be different in the United States vs other countries, particularly Europe, because CLKT is used more frequently in the United States than in other countries. Could you comment on this?

GC: It is an interesting observation that CLKT use varies significantly globally. Taking the last year for which there were comparative data—2012 —CLKT represented approximately 8% of liver transplants in the United States, but only 2% in the UK and 4% in Brazil. That said, if we look closer at the use of CLKT in the United States from 2022, approximately 90% of the 800 CLKTs performed were for a CKD indication. Understanding this, and assuming these global variations still persist, we would attribute this variation to (1) higher prevalence of comorbidities predisposing to CKD, such as obesity and diabetes, in the United States; (2) programmatic differences in organ allocation and CKD diagnosis, including varying CLKT thresholds; and (3) health care system resources and the access to CLKT. However, these hypotheses are based on limited comparative data, highlighting the need for further research to elucidate the precise drivers of this variation.

Table 2. Criteria for Prioritization of Kidney Allocation to Combined Liver–Kidney Transplantation

CKD, defined as an eGFR of ≤60 mL/min/1.73 m^2 persisting for >90 consecutive days, with the most recent eGFR ≤30 mL/min/1.73 m^2
Sustained acute kidney injury, characterized by an eGFR ≤25 mL/min/1.73 m^2 or the requirement for renal replacement therapy for ≥6 consecutive weeks
The presence of certain metabolic diseases: hyperoxaluria, atypical hemolytic uremic syndrome from mutations in factor H or factor I, familial non-neuropathic systemic amyloidosis, methylmalonic aciduria

NOTE. These criteria, while acknowledging their limitations, were developed through a consensus process involving the Organ Procurement and Transplantation Network and the United Network for Organ Sharing Kidney Transplantation Committee. The process incorporated valuable input from key stakeholders, including the American Society of Transplantation, the National Kidney Foundation, and the American Urological Association, to ensure a comprehensive and multidisciplinary approach to organ allocation in this complex patient population.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Clinical Course and Outcome

The patient was treated with prednisone at a starting dose of 90 mg/day, followed by a tapering regimen over 3 months. Serum creatinine gradually descended towards normal levels, reaching 1.19 mg/dL 6 months after the onset of the episode. After steroids treatment, urinalysis showed a low protein excretion rate (68 mg/24 hours), no microalbuminuria (11 mg/24 hours), and normal natriuresis (92 mEq/L). Ascites was resolved progressively with diuretic therapy, without any associated complications. Given the improvement in kidney function and effective ascites management, liver transplantation or CLKT was no longer indicated. The patient currently has recompensated alcohol-related cirrhosis with normal liver and kidney function.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2025.03.056.

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Supplementary Table 1. Comparison of the 2015 and 2024 Definitions of Hepatorenal Syndrome-AKI

Criteria	ICA 2015[1]	ADQI-ICA 2024[5]
Patient population	Cirrhosis and ascites	Cirrhosis and ascites
AKI diagnosis	Diagnosis of AKI as per ICA-AKI criteria	Diagnosis of AKI as per ICA-AKI criteria
Fluid challenge	No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg of body weight	Absence of improvement in serum creatinine and/or urine output within 24h following adequate volume resuscitation (when clinically indicated)
Exclusion of alternative causes of AKI	Absence of shock No current or recent use of nephrotoxic drugs No macroscopic signs of structural kidney injury (absence of proteinuria >500 mg/d, absence of microhematuria >50 RBC per HPF, normal kidney US)	Absence of strong evidence for an alternative explanation as the primary cause of AKI

ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; HPF, high-powered field; ICA, International Club of Ascites; RBC, red blood cells; US, ultrasound.