Acute kidney injury and hepatorenal syndrome in cirrhosis

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Key words
acute kidney injury, acute-on-chronic liver failure, adrenal insufficiency, cirrhosis, cirrhotic cardiomyopathy, hepatorenal syndrome.

Abstract
Cirrhosis is the eighth leading cause of “years of lost life” in the United States and accounts for approximately 1% to 2% of all deaths in Europe. Patients with cirrhosis have a high risk of developing acute kidney injury. The clinical characteristics of hepatorenal syndrome (HRS) are similar to prerenal uremia, but the condition does not respond to volume expansion. HRS type 1 is rapidly progressive whereas HRS type 2 has a slower course often associated with refractory ascites. A number of factors can precipitate HRS such as infections, alcoholic hepatitis, and bleeding. The monitoring, prevention, early detection, and treatment of HRS are essential. This paper reviews the value of early evaluation of renal function based on two new sets of diagnostic criteria. Interventions for HRS type 1 include terlipressin combined with albumin. In HRS type 2, transjugular intrahepatic portosystemic shunt (TIPS) should be considered. For both types of HRS patients should be evaluated for liver transplantation.

Introduction
Cirrhosis is a chronic liver disease that accounts for approximately 1% to 2% of all deaths in Europe. In the United States, the number of deaths caused by cirrhosis has increased over the last 20 years and cirrhosis is responsible for more than 1.23 million years of lost life. This makes cirrhosis the eighth leading cause of “years of lost life” in the United States. Cirrhosis is a global burden and was the cause of 493 300 alcohol-related deaths in 2010. In the United Kingdom, hospital admissions due to liver disease are expected to increase to 2 million per year by 2020. The increasing mortality rate from chronic liver disease combined with falling hospital admissions and mortality rates from other chronic diseases, such as stroke and heart disease, calls for increased focus on complication of chronic liver diseases.

Within a period of 10 years following the diagnosis of cirrhosis, around 60% will develop ascites. Cirrhosis and ascites are associated with high morbidity and mortality. Renal failure is one of the most severe complications. More than 50% of patients with renal failure and cirrhosis die within 1 month after the diagnosis. Twenty percent of hospitalized patients with cirrhosis and ascites develop acute kidney injury. Twenty percent of these patients have hepatorenal syndrome (HRS), a condition that occurs mainly in patients with cirrhosis and ascites. The clinical characteristics of HRS are similar to prerenal uremia, but the condition does not respond to volume expansion. Other causes of kidney injury must be excluded to make the diagnosis, for example nephrotoxic medications. In recent years, progress has been made in the understanding of the underlying pathophysiology of HRS leading to a number of new diagnostic, therapeutic, and prophylactic options. The purpose of this paper is to review the diagnostic criteria, pathophysiology, and interventions for HRS and the latest findings on acute kidney injury.

Definition of hepatorenal syndrome
The diagnostic criteria for HRS were defined in 1996 and revised in 2007 (Table 1). Based on the course of the disease, HRS is divided into two types:

• HRS type 1 is characterized by acute renal impairment with doubling of serum creatinine to > 226 μmol/L within 2 weeks. The condition usually develops secondary to a decrease in blood pressure as part of an inflammatory response caused by for example spontaneous bacterial peritonitis (SBP), sepsis, severe alcoholic hepatitis, or gastrointestinal bleeding. The median survival without treatment is a few weeks.
• HRS type 2 is characterized by a slow increase in serum creatinine from 133 to 226 μmol/L. It is an expression of a moderate reduction of renal function as a complication to end-stage liver disease and refractory ascites. The median survival is 6 months.

The two types of HRS have different clinical courses and pathophysiology. While HRS type 1 often develops after an acute reduction in the effective arterial blood volume, HRS type 2 develops due to the hemodynamic derangement seen in end-stage liver disease with refractory ascites.
Pathophysiology

The pathophysiology leading to renal dysfunction includes several factors associated with cirrhosis (Fig. 1). The main factors are the hemodynamic changes seen in patients with cirrhosis, ascites, and portal hypertension. Portal hypertension causes an increased production and release of endogenous vasodilatation agents such as nitric oxide, carbon monoxide, and cannabinoids mainly into the splanchnic arterial circulation. The consequence is vasodilation, increased plasma volume, and blood flow in the splanchnic circulation leading to a reduction in the effective arterial blood volume and a drop in mean arterial pressure (MAP).15 To maintain sufficient perfusion of vital organs, compensation is initiated by increased cardiac output (CO) and activation of the endogenous vasoconstrictors including the renin-angiotensin-aldosterone system, the sympathetic nervous system, and release of arginine vasopressin.16 In severe cases, the heart cannot longer provide a sufficient CO to maintain an adequate MAP and circulation. The increased activity of the endogenous vasoconstrictors lead to renal vasoconstriction and sodium and water retention. Renal vasoconstriction combined with a reduced MAP may lead to hypoperfusion of the kidneys and renal impairment. Fluid retention leads to the development of ascites in the majority of the patients.17 The translocation of bacteria and bacterial products from the gut is likely to be a main factor in the progression of disease.18 Translocation increases with the severity of the underlying liver disease leading to a chronic inflammatory state, spontaneous infections, and complications including HRS.18,19

Understanding the circulatory dysfunction. The circulatory changes in cirrhosis and portal hypertension affect several organs and compromise the organism’s resistance to hemodynamic instability due to infection, bleeding, or surgery. Cardiomyopathy and relative adrenal insufficiency (AI) predict renal impairment and death and might be important for the understanding of the pathophysiology and future treatment of HRS. Cardiac hypertrophy, diastolic dysfunction, and impaired response to inotropic and chronotropic stimuli are frequent subclinical observations in cirrhosis.20–24 Renal failure in cirrhosis is associated with reduced CO.20 HRS type 1 is associated with a reduced CO and a decreased cardiopulmonary pressure under hyperactive vasoconstriction systems and reduced MAP.21 Cardiac dysfunction is closely related to a poor outcome including in particular renal impairment.22,24 These findings suggest a cardio renal link in advanced cirrhosis.25 In theory, renal failure and decreased effective blood volume in HRS type 1 are the consequences of an arterial vasodilatation and an impaired cardiac contractility that compromise an increased CO in response to stress. Relative adrenal insufficiency is a common subclinical condition in patients with cirrhosis diagnosed as an inadequate production of cortisol in response to stimulation with synthetic adrenocorticotropic hormone.26–28 It is seen in approximately 10% of all cases of cirrhosis and frequency increases with the severity of the liver disease.29 Cirrhotic patients with adrenal insufficiency increase the risk of bacterial infection, septic shock, and HRS.24 Cortisol plays an important role in the hemodynamic homeostasis. The heart’s and blood vessels’ response to catecholamines and angiotensin-II is increased by cortisol. Low levels of cortisol lead to an inadequate increase in CO and inadequate vasoconstriction in response to stress.30 Accordingly, adrenal insufficiency could be involved in the development of cardiomyopathy and HRS.25,26,29 Treatment with hydrocortisone in patients with cirrhosis and sepsis has been investigated, but the results are equivocal and it can only be recommended in selected patients with documented AI.31,32

Acute-on-chronic liver failure

Patients who develop HRS or other types of acute kidney dysfunction often present with acute deterioration of their chronic liver disease. Acute-on-chronic liver failure (ACLF) is associated with a high risk of sequential organ failure and increased mortality.33,34 A large-scale observational study was conducted to describe

Table 1  Current diagnostic criteria of hepatorenal syndrome, acute kidney injury and kidney dysfunction in cirrhosis

<table>
<thead>
<tr>
<th>Diagnostic criteria of hepatorenal syndrome</th>
<th>Acute Kidney Injury Networks classification of acute kidney injury</th>
<th>Classification of kidney dysfunction in cirrhosis</th>
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<tbody>
<tr>
<td>• Cirrhosis with ascites</td>
<td>Grade I Increase in serum creatinine</td>
<td>Grade I Increase in serum creatinine ≥ 50% compared with baseline or ≥ 26.4 μmol/L within 48 h</td>
</tr>
<tr>
<td>• S-creatinine &gt; 133 μmol/L</td>
<td>Grade II Increase in serum creatinine &gt; 100–200% from baseline</td>
<td>Grade II Increase in serum creatinine ≥ 26.4 μmol/L within 48 h</td>
</tr>
<tr>
<td>• No improvement in serum creatinine (i.e. S-creatinine &lt; 133 μmol/L) after at least two days pausing of diuretics and volume expansion therapy with albumin. The recommended dose of albumin is 1 /kg of body weight per day (maximum 100 /day)</td>
<td>Grade III Increase in serum creatinine to &gt; 200% from baseline or acute increase of ≥ 44 μmol/L to ≥ 354 μmol/L</td>
<td>Grade III Increase in serum creatinine ≥ 50% compared with baseline or ≥ 26.4 μmol/L within 48 h in a patient with CKD</td>
</tr>
<tr>
<td>• Absence of shock</td>
<td></td>
<td></td>
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<tr>
<td>• No current or recent treatment with nephrotoxic drugs</td>
<td></td>
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<tr>
<td>• Absence of parenchymal kidney disease which is proteinuria &lt; 500 mg/dl, microhematuria (&lt; 50 erythrocytes/field) and/or pathology by ultrasound of the kidney and urinary tract</td>
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ACKD, acute-on-chronic kidney disease; AKI, acute kidney injury; CKD, chronic kidney injury; HRS, hepatorenal syndrome; MDRD6, modification of diet in renal disease.
The study evaluated the severity of the organ dysfunction based on a composite score known as the Chronic Liver failure-Sequential Organ Failure Assessment (CLIF-SOFA) score. The score is based on the SOFA score which predict mortality in intensive care unit patients. The SOFA score was modified to make it a liver specific score. Based on the observational study, patients with ACLF were classed into four groups, which reflect the underlying mortality: no ACLF or grade 1, grade 2, or grade 3 (Table 2). The study showed that acute kidney failure with serum creatinine > 177 μmol/L and kidney dysfunction with serum creatinine 133 μmol/L to 177 μmol/L were strong predictors of mortality.

Classification of acute kidney injury in cirrhosis

The diagnostic criteria for HRS include a serum creatinine above 133 μmol/L. However, patients with cirrhosis often have reduced levels of serum creatinine due to malnutrition and decreased muscle mass. Serum creatinine may therefore overestimate the renal function. A revised strategy that is more sensitive to changes in creatinine rather than the absolute creatinine level may improve early detection of HRS and other types of acute kidney injury in patients with severe liver disease. In 2007, the Acute Kidney Injury Network (AKIN) established new criteria for the classification of acute renal failure (Table 1). The classification is more sensitive to small changes in serum creatinine and may improve the assessment of kidney injury in cirrhosis. The Acute Dialysis Quality Initiative Group proposes a new classification of kidney dysfunction in cirrhosis based on the AKIN criteria (Table 1). Several observational studies of patients with cirrhosis and renal insufficiency have evaluated the usefulness of the AKIN classification. The main conclusion in most studies is that the AKIN criteria predict mortality, infection, and potentially the risk of progression to HRS (Table 3). Although the AKIN criteria are useful, it has been argued that the criteria specific to HRS are more accurate. A classification that combines the AKIN criteria with the classic HRS criteria may provide a better prediction than the AKIN criteria alone. Consensus on this issue is not yet reached. In addition, no studies have investigated if the use of the AKIN criteria improves patients’ overall prognosis.
Prevention and treatment of the triggering event

Volume depletion due to infection, severe alcoholic hepatitis, and gastrointestinal bleeding can trigger HRS type 1. SBP is the predominant infection leading to HRS. It is defined as an infection in the ascites fluid with >250 neutrophils/mm³ ascites fluid. Patients with cirrhosis and ascites have a compromised immune system and an increased risk of translocation of intestinal bacteria. This leads to HRS in approximately 30% of the patients. SBP is often associated with Gram-negative aerobic bacteria. Several antibiotics have been recommended for the initial treatment of SBP including cefotaxime or other third-generation cephalosporins, amoxicillin-clavulanic acid, or quinolones. Ascites puncture should be repeated after 2–3 days to assess the effect of treatment on neutrophil count if a lack of response is suspected. A meta-analysis found that albumin infusion combined with antibiotics reduces the incidence of renal impairment and mortality. Patients with low ascites protein (<15 g/L) combined with advanced disease or with a history of SBP should be treated prophylactically with norfloxacin (400 mg daily, orally) to prevent SBP.

Alcoholic hepatitis occurs after an excessive use of alcohol over a longer period (>100 g/day) and usually after withdrawal of alcohol intake. Symptoms include jaundice, fever, ascites, and proximal loss of muscles. Severe cases are often associated with
increased serum creatinine and the development of HRS type 1. Standard treatment is prednisolone or pentoxifylline. A double-blind randomized controlled trial (RCT) on 270 patients with alcoholic hepatitis found no difference in mortality between patients allocated to prednisolone and pentoxifylline versus prednisolone and placebo. The trial found a potential benefit on HRS in the pentoxifylline group, which is consistent with the results of a meta-analysis on pentoxifylline. Thus pentoxifylline may be the preferred first-line treatment for patients with alcoholic hepatitis and high risk of HRS, which is in line with a recent multiple treatment comparison meta-analysis.

Gastrointestinal bleeding may result in blood loss and infections both of which may lead to HRS. Variceal bleeding is treated according to clinical guidelines including resuscitation, antibiotic prophylaxis, vasoactive drugs, and endoscopic therapy. For bleeding oesophageal varices, the administration of terlipressin and antibiotics reduces bleeding, mortality and the risk of HRS. Oral quinolones are the antibiotic recommended for most patients. Intravenous cephalosporins should be considered in patients with severer cirrhosis and patients in previous quinolone prophylaxis.

Paracentesis with large volume (>5 liters) may affect hemodynamics and thereby result in post-paracentesis circulatory dysfunction (PCD). This condition is characterized as a reduction in the effective blood volume and may lead to HRS. A meta-analysis found that approximately 73% develops PCD after undergoing large volume paracentesis (LVP) if the procedure is not combined with volume supportive treatment. This meta-analysis shows that administration of albumin reduces the incidence of post-PCD, HRS type 1, and mortality. Therefore albumin should be administered to all patients undergoing LVP (8 g/L of drained ascites fluid).

Management of patients with cirrhosis, ascites, and renal impairment

Renal impairment in patients with cirrhosis and ascites should be evaluated quickly. Correct handling of renal impairment is required to avoid further deterioration and reduce the risk of renal failure and death. Table 4 describes a proposal for primary investigation of patients with cirrhosis, ascites, and renal impairment. The initial evaluation should include volume expansion by infusion of human albumin and discontinuation of diuretics and nephrotoxic drugs (Table 5). Other causes that can lead to renal impairment (e.g. obstructive uropathy) should also be excluded.

Evidence-based intervention for treatment of HRS

Vasoconstrictors and albumin. Terlipressin and albumin is the recommended treatment for patients with HRS type 1. The treatment improves the MAP and thereby the renal perfusion. Terlipressin, which is an analogue of vasopressin, induces vasoconstriction by stimulating vasopressin receptors in the smooth muscle cells in the vessel wall. Intravenous administration of albumin combined with terlipressin increases the effective arterial blood volume and thereby preload to the heart. This improves the circulation and stabilizes MAP as a result of an increased preload and CO. The treatment of HRS type 1 should be initiated rapidly, as early diagnosis and treatment improves the prognosis. The effect of terlipressin and albumin has been assessed in several randomized clinical trials. When the results are combined in a meta-analysis, terlipressin and albumin reduce the mortality and improve renal function in patients with HRS type 1. There is little evidence for this treatment of HRS type 2. A few small studies have compared the effect of terlipressin with norepinephrine or other vasoconstrictors. Since the trials have low statistical power, it is not possible to assess whether other vasoconstrictors are as effective as terlipressin. There is no standardized dose of terlipressin, but the efficacy in HRS has been established in studies using an initial bolus injection of 1 mg four to six times daily and titrated to a maximum of 2 mg six times daily based on the effect on creatinine (Table 6). Terlipressin is considered effective if S-creatinine is reduced >25% after 3 days of intervention. Treatment should be continued until S-creatinine is below 133 μmol/L. The treatment is effective in up to 40% of the patients using current the diagnostic criteria and dose regime.

**Table 4** Proposal for primary investigation of patients with cirrhosis, ascites, and renal impairment

<table>
<thead>
<tr>
<th>Clinical examination</th>
<th>Checking of volume status/hydration</th>
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<tbody>
<tr>
<td>Hemodynamics/blood pressure and pulse</td>
<td>Signs of infection</td>
</tr>
<tr>
<td>Medical history</td>
<td>Examination of the medication list for nephrotoxic drugs</td>
</tr>
<tr>
<td>Paraclinical tests</td>
<td>Broad blood screening including hemoglobin, electrolytes, creatinine, CRP, and differential count</td>
</tr>
<tr>
<td>Radio diagnostic</td>
<td>Diagnostic ascites puncture with cell count, protein measurement and culture</td>
</tr>
<tr>
<td></td>
<td>Blood culture</td>
</tr>
<tr>
<td></td>
<td>Urine analyses and culture</td>
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<tr>
<td></td>
<td>Possible sputum culture</td>
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<table>
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<tr>
<th>Table 5</th>
<th>Drugs that should be avoided or used with caution in patients with cirrhosis and ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Should be avoided</td>
</tr>
<tr>
<td>ACE inhibitors, AT-II receptor antagonists and α1-adrenergic receptor blockers</td>
<td>Use with caution and avoid completely at elevated creatinine</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Caution should be taken by monitoring of creatinine, electrolytes and hydration</td>
</tr>
<tr>
<td>Laxatives</td>
<td>Pay attention to diarrhoea and dehydration</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Should be avoided</td>
</tr>
<tr>
<td>Contrast media</td>
<td>Use with caution and avoid completely at elevated creatinine</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Careful titration and caution at elevated creatinine and low blood pressure</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; AT, angiotensin; NSAID, non-steroid anti-inflammatory drug.
Table 6  Evidence-based treatment of hepatorenal syndrome

<table>
<thead>
<tr>
<th>Treatment of HRS</th>
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<tbody>
<tr>
<td>Liver transplantation should be considered in all patients with HRS and advanced liver disease</td>
</tr>
<tr>
<td><strong>HRS type 1</strong></td>
</tr>
<tr>
<td>Terlipressin: The recommended dose is 1 mg (\times) 4–6/day. The dose may be increased by lack of effect to a maximum of 2 mg (\times) 6/day. Treatment continues to the (\text{S-creatinine}) level is (&lt;) 133 (\mu\text{mol/L})</td>
</tr>
<tr>
<td>Albumin: The recommended dose is 1 g/kg human albumin on the first day of treatment followed by 20–40 g daily</td>
</tr>
<tr>
<td><strong>HRS type 2</strong></td>
</tr>
<tr>
<td>Therapeutic paracentesis: Should be offered to cirrhotic patients with refractory ascites who do not qualify for treatment with TIPS</td>
</tr>
<tr>
<td>TIPS: Should be considered in all patients with HRS type 2 and refractory ascites</td>
</tr>
</tbody>
</table>

HRS, hepatorenal syndrome; TIPS, transjugular intrahepatic portosystemic shunt.

ongoing RCT (NCT01530711) is currently evaluating terlipressin titrated according to the hemodynamic response. The dose of terlipressin is increased every 8 h until the arterial blood pressure is increased with more than 10 mmHg or \(\text{S-creatinine}\) is reduced with more than 25%.

Adverse events. Approximately 30% of patients develop adverse events on terlipressin. In 4% of patients, treatment with terlipressin has to be stopped due to adverse events. Most adverse events reflect vasoconstrictor effects with mild degrees of peripheral ischemia including cyanotic fingers and toes. Arrhythmias, most commonly bradycardia, are seen in approximately 7% of patients. Sixteen percent of patients develop abdominal pain and diarrhea probably due to splanchnic ischemia. There has been one case of intestinal ischemic necrosis. Rarely, ischemic necrosis is seen.

Dealing with adverse events. There is no specific antidote to terlipressin. Careful selection of patients without contraindications, close surveillance of adverse events, and daily adjustments of the dose and duration of therapy is recommended to prevent serious adverse events and treatment withdrawals. Myocardial infarctions and malignant arrhythmias are absolute contraindications to continued therapy. The efficacy of terlipressin is established in studies with bolus infusion; however, continuous infusion may be as effective as bolus and have fewer adverse events. This is being examined in an ongoing equivalence trial (NCT00742690). Continuous low dose infusion can therefore, until further data document non-inferiority to bolus infusion, only be recommended in patients with an increased risk of adverse events (AEs) or in case of moderate AEs. Less severe side-effects such as skin cyanosis without necrosis can usually be managed by a reduction in dose and oxygen therapy or shifting from bolus to continuous infusion therapy. Abdominal pain and loose stools are usually self-limiting. In patients with mild to moderate atherosclerotic cardiovascular disease, terlipressin can be administered at a low dose or as continuous infusion with careful titration and monitoring.

Alternative vasoconstrictors. In some countries, including the United States, terlipressin is not available. The American Association for the Study of Liver Diseases’ guidelines on management of ascites suggests albumin infusion plus midodrine or octreotide or norepinephrine in the treatment of HRS type 1. Even though some studies found benefits in these treatments, additional randomized controlled trials are still needed as the evidence to support these recommendations are weak.

Transjugular intrahepatic portosystemic shunt. HRS type 2 develops in patients with ascites refractory to treatment with diuretics. Therapeutic paracentesis and Transjugular intrahepatic portosystemic shunt (TIPS) have been studied and both are considered effective treatments. Randomized controlled trials suggest that TIPS improves survival compared with therapeutic paracentesis. TIPS can cause heart failure and increases the risk of hepatic encephalopathy. Therefore, cardiac function should be examined and a history of hepatic encephalopathy should be included when assessing the treatment strategy. The model of end-stage liver disease (MELD) score predicts the survival in patients treated with elective TIPS. Therefore, the MELD score should be included in monitoring of patients to better select the patients who would benefit from TIPS placement.

Liver transplantation. Liver transplantation should be considered in all patients with advanced liver disease, if there are no obvious contraindications such as ongoing excessive use of alcohol or malignant disease. A successful liver transplantation will completely reverse HRS. The 5-year post-transplant mortality is 32% in patients with advanced liver disease and prerenal dysfunction. Simultaneous liver-kidney transplantation should be considered when renal failure reflects chronic kidney disease with glomerular filtration rate (GFR) < 30 mL/min or acute kidney injury with dialysis > 8 weeks.

Conclusion

Cirrhosis is a growing global problem. Worldwide death caused by cirrhosis is increasing. Acute kidney injury is an important prognostic marker in cirrhosis. HRS is seen in approximately 20% of cirrhotic patients hospitalized with renal impairment. A number of well-known factors can trigger HRS. The risk of developing HRS can be reduced by prevention of these events as well as adequate treatment. HRS type 2 is associated with end-stage liver disease and patients should be evaluated for TIPS or liver transplantation. For HRS type 1, the first-line treatment is the combination of terlipressin and albumin. This treatment is effective in up to 40% of the patients under current diagnostic criteria and dose regime, which is why a more aggressive dose titration as well as earlier detection of renal impairment is under evaluation. The SOFA-CLIF score is a prognostic tool to estimate the survival in patients with cirrhosis and acute deterioration. In this scoring system, kidney dysfunction is associated with very poor outcome. The
AKIN criteria is suggested to detect those patients earlier who have an increased risk of developing HRS and death by use of small changes in serum creatinine. However, there is not at this stage a consensus on the application of the criteria and more research is needed in this area.

Acknowledgment

Figure 1 is made in a collaboration of designer Jalte Windum and the authors.

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Acute kidney injury


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