Sepsis-induced acute kidney injury in patients with cirrhosis

Paolo Angeli¹ · Marta Tonon¹ · Chiara Pilutti¹ · Filippo Morando¹ · Salvatore Piano¹

Received: 12 March 2015 / Accepted: 19 May 2015 / Published online: 4 July 2015
© Asian Pacific Association for the Study of the Liver 2015

Abstract  Acute kidney injury (AKI) is a common and life-threatening complication in patients with cirrhosis. Recently, new criteria for the diagnosis of AKI have been proposed in patients with cirrhosis by the International Club of Ascites. Almost all types of bacterial infections can induce AKI in patients with cirrhosis representing its most common precipitating event. The bacterial infection-induced AKI usually meets the diagnostic criteria of hepatorenal syndrome (HRS). Well in keeping with the “splanchnic arterial vasodilation hypothesis”, it has been stated that HRS develops as a consequence of a severe reduction of effective circulating volume related to splanchnic arterial vasodilation and to an inadequate cardiac output. Nevertheless, the role of bacterial infections in precipitating organ failures, including renal failure, is enhanced when their course is characterized by the development of a systemic inflammatory response syndrome (SIRS), thus, when sepsis occurs. Sepsis has been shown to be capable to induce “per se” AKI in animals as well as in patients conditioning also the features of renal damage. This observation suggests that when precipitated by sepsis, the pathogenesis and the clinical course of AKI also in patients with cirrhosis may differentiate to a certain extent from AKI with another or no precipitating factor. The purpose of this review is to describe the features of AKI precipitated by bacterial infections and to highlight whether infection and/or the development of SIRS may influence its clinical course, and, in particular, the response to treatment.

Keywords  Acute kidney injury · Hepatorenal syndrome · Acute on chronic liver failure · Albumin · Terlipressin · Sepsis · Bacterial infections · Biomarkers

Introduction

Acute kidney injury (AKI) is a severe complication of advanced cirrhosis as well as of acute liver failure and acute on chronic liver failure (ACLF) [1]. Different types of AKI can occur in these patients, namely, pre-renal, intrinsic and post-renal AKI (Fig. 1). Pre-renal AKI often meets the diagnostic criteria of hepatorenal syndrome (HRS) in these patients. According to the former diagnostic criteria of HRS proposed by the International Club of Ascites (ICA) in 1996, two different types of HRS had to be considered [2]. Type 1 HRS was classified as a rapid progressive renal failure defined by a doubling of the initial serum creatinine (sCr) concentrations to a level greater than 226 mmol/L (2.5 mg/dL) in less than 2 weeks. Over the last 20 years, type 1 HRS has, according to the “splanchnic arterial vasodilation theory”, been thought to develop as a consequence of a marked reduction of effective circulating volume due to both splanchnic arterial vasodilation and an inadequate cardiac output (Fig. 2) [3, 4]. Furthermore, it has been associated with an extreme over-activation of the endogenous systemic vasoconstrictor systems, namely, the renin-angiotensin system, the sympathetic nervous system, and the non-osmotic release of vasopressin [3]. Splanchnic arterial vasodilatation is thought to be mainly the consequence of an increased release of endogenous vasodilators due to portal hypertension and/or hepatic failure [3]. The inadequate cardiac output
can be the extreme manifestation of the systolic dysfunction, which represents one of the components of cirrhotic cardiomyopathy [4]. Such a pathophysiological background represents the rationale behind the use of vasoconstrictors in the treatment of type 1 HRS, to counteract splanchnic arterial vasodilation and improve effective circulating volume as well as reducing portal pressure.

Recently, new ICA criteria for the diagnosis of AKI in patients with cirrhosis have been proposed [5]. This implies that AKI in patients with cirrhosis is defined either by an increase in sCr ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 h or by a percentage increase sCr ≥ 50% from the baseline, which is known, or presumed, to have occurred within the previous 7 days. Any previous final cut-off value for sCr has been removed from the definition of AKI and, consequently, from that of HRS in the context of AKI in these patients. Accordingly, type 1 HRS is now defined as HRS-AKI. Meanwhile, the former type 2 HRS is now considered to be a type of chronic kidney disease (CKD) in patients with cirrhosis (HRS-CKD). Thus, beyond this point of the manuscript we will refer to the previous type 1 HRS using the new term “HRS-AKI”. Precipitating events such as infections, bleeding and large-volume paracentesis without albumin administration can trigger HRS-AKI [1]. Bacterial infections are the most important precipitating events underlying HRS-AKI. In the past, the role of spontaneous bacterial infections (SBP) was highlighted in this clinical context on the basis of one observation that has since been partially revised [6]. In fact, initially it appears that only SBP was able to precipitate HRS-AKI, in spite of an effective antibiotic therapy in patients with cirrhosis, while it has now been recognized that almost all types of bacterial infections can do the same [7]. The precipitating role of bacterial infections is enhanced when their course is characterized by the development of a systemic inflammatory response syndrome (SIRS), thus, when sepsis...
occurs. There is increasing evidence from experimental and clinical data that the degree of inflammation and/or the tolerance to inflammation are crucial in the pathogenesis of organ failures, including renal failure, in cirrhosis [8]. More specifically, it has been shown that inflammation may influence the development of particular footprints of damage in the renal tissue. These observations suggest that when precipitated by a bacterial infection, the pathogenesis of HRS-AKI may be different from HRS-AKI with another or no precipitating factor.

Therefore, the purpose of this review is to describe the features of HRS-AKI precipitated by bacterial infections, and to highlight whether the development of SIRS may influence its clinical course and, in particular, its response to treatment.

Pathogenesis of sepsis induced-AKI

According to the revised “splanchnic arterial vasodilation hypothesis”, the pathogenesis of HRS-AKI in patients with cirrhosis involves two main factors: (1) arterial vasodilation and (2) reduction in cardiac output (Fig. 2). Splanchnic arterial vasodilation and the consequent reduction in effective circulating volume induce the extreme over-activation of the systemic vasoconstrictor systems which are responsible for the severe arterial vasoconstriction which is thought to be the pathophysiological basis of HRS-AKI [3]. Nitric oxide (NO) and carbon monoxide (CO) are the main vasodilators involved in arterial splanchnic vasodilation. In the context of bacterial infections and particularly in that of sepsis, circulating endotoxins and proinflammatory cytokines further impair portal hypertension and liver function, further increasing their negative effect on the cardiovascular dysfunction in patients with cirrhosis [9] (Fig. 3). In addition, they stimulate per se inducible NO synthase (iNOS), and heme oxygenase type 1, leading to an increased production of NO [10] and CO [11], respectively. Therefore, the combined increase in production of CO and NO results in a further enhancement of splanchnic vasodilation in patients with cirrhosis. In addition, the impairment of cardiac output is a well-known factor underlying the pathogenesis of HRS-AKI. In patients with SBP, a lower cardiac output was found to be a strong predictor of the development of HRS-AKI [12]. The activation iNOS and NO are also involved in the development of cardiac dysfunction in patients with cirrhosis and bacterial infections. Interestingly, the negative inotropic effects of NO mediated by cGMP production have been observed in cirrhosis [13]. Moreover, innate immune system and inflammation play a key role in the development of AKI during sepsis. Bacteria and bacterial products are recognized by monocytes through the bond with pattern recognition receptors such as toll-like receptors 4 (TLR4) and 2 (TLR2). This bond activates monocytes to release proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β). TNF-α and IL-6 concentrations turn out to be strong predictors of AKI development in patients with SBP [13]. TNF-α stimulates iNOS synthesis via nuclear factor kappa B, resulting in a reduced cardiac contractility and enhanced peripheral arterial vasodilation. Patients with HRS-AKI frequently show failure of organs other than the kidney. It is well known that high baseline values of serum bilirubin, as well as a lower rise in mean arterial pressure, were identified as negative predictors of response to terlipressin plus albumin [14]. It seems, therefore, that the coexistence of a severe degree of other organ failures such as liver failure or cardiovascular failure can influence the response of HRS-AKI to medical treatment. These observations have been strongly supported by the data on acute-on-chronic liver failure (ACLF). In spite of a variety of its definitions [8, 15], ACLF is a recently recognized syndrome characterized by acute decompensation (AD) of cirrhosis and organ failure(s) and extremely poor survival (28-day mortality rate 30–40 %). ACLF occurs in relatively young patients. It is especially frequent in alcoholic- and untreated hepatitis B associated-cirrhosis. It may develop at any time during the course of the chronic liver disease. The development of ACLF occurs in the setting of a systemic inflammation whose degree correlates with the number of organ failures and the 28-day mortality rate [15]. According to the data of the Canonic study, bacterial infections are often a precipitating event of ACLF and renal failure, and even a mild renal dysfunction is important for defining ACLF [8]. When renal failure fulfilled the criteria for type 1 HRS in patients with ACLF, the rate of response to terlipressin plus albumin, the most effective treatment of HRS, was found to be negatively affected by the severity of ACLF [16]. Non-responders had significantly higher values of CLIF-SOFA score compared to responders, thereby indicating a greater severity of ACLF. A CLIF-SOFA score ≥11 had 92 % sensitivity and 100 % specificity in predicting no response to therapy [16]. There are two possible explanations for this finding. Multiple organ failures may simply affect the effectiveness of therapy, but the presence of multiple organ failure may be the expression of a more complex pathophysiological background, other than the severe renal arterial vasoconstriction, able to induce the development of renal damage. The most striking difference between patients with ACLF and patients without ACLF seems to be the development of a more severe degree of inflammation and/or a reduced tolerance to inflammation in the former group [8]. In agreement with the data of the Canonic study, even if inflammation develops
independently of bacterial infections, there is no doubt that they play a relevant role in its occurrence. Putting these observations together, like a jigsaw puzzle, the missing piece becomes the following: can a more severe degree of inflammation and/or lesser tolerance to it affect the development of a type of kidney damage other than that of HRS? It has been observed in clinical [17] as well as in experimental studies [18] that in cirrhosis and superimposed infection/inflammation, an up-regulation of renal tubular TLR4 may occur, associated with the development of florid renal dysfunction with tubular damage and apoptosis. Renal dysfunction in these patients is associated with significant tubular injury and apoptosis and with increased renal expression and urinary excretion of the TLR4, suggesting a potential role of TLR4 as mediator of renal injury [17]. Although the mechanism of up regulation of tubular TLR4 is not entirely clear, it seems likely to be a consequence of the continuous exposure to gut bacterial translocation [17] and may be prevented by gut decontamination with norfloxacin [18]. These data suggest that increased bacterial translocation may exert a priming effect in the kidney through the up regulation of tubular TLR4, making the kidneys more susceptible to the effect of superimposed inflammation. The matter is made even more complex by the fact that ACLF and, therefore, AKI can also occur in a patient with previously compensated cirrhosis or even in a patient with a previous diagnosis of a chronic liver disease without clinical, laboratory and/or instrumental signs of cirrhosis. This is important because it is possible to imagine that inflammation induced by bacterial infections could precipitate the AKI in decompensated cirrhotic patients by exacerbating the pre-existing degree of portal hypertension and/or liver failure. However, following the steps provided by the “splanchnic arterial vasodilation” theory, this would be more difficult to achieve in cirrhotic patients without a history of previous episodes of decompensation or in patients with non-cirrhotic chronic liver disease. In the latter two types of patients, it is worth considering that inflammation per se might be entirely responsible for the development of AKI. Stretching this concept, the pathophysiology of AKI in these patients could deviate from the one traditionally theorized for the HRS. In a new hypothesis on its pathogenesis proposed recently, sepsis-induced AKI has been defined as the early clinical and biochemical manifestation of an adaptive response of the tubular cells to an injurious, inflammatory danger signal [19] (Fig. 4). The interplay of inflammation and microvascular dysfunction characterize and amplify this signal, and in response to this, mitochondria within tubular cells orchestrate a complete metabolic down-regulation and reprioritization which favors individual cell survival processes (such as the maintenance of membrane potential and cell cycle arrest), at the expense of “kidney function”. All these features develop in the context of normal or even increased renal blood flow and provide the framework of the clinical phenotype characterized by a dramatic decrease in glomerular filtration rate and the development of uremia [19]. This may explain why patients with a more severe grade of ACLF and HRS-AKI had a lower rate of response to treatment with terlipressin and albumin than those with less severe ACLF. These observations seem to be confirmed by preliminary data on the use of biomarkers of tubular damage in patients with cirrhosis. Among them, urinary neutrophil-gelatinase associated lipocalin (uNGAL) was found to be the one with the highest value for the early prediction of outcome of renal function in patients with cirrhosis and bacterial infections [20, 21]. Indeed, uNGAL was high in patients with persistent AKI, whereas patients with transient AKI had

Fig. 3 Pathogenesis of hepatorenal syndrome (HRS) in patients with cirrhosis and sepsis: role of inflammation. NO nitric oxide, CO carbon monoxide

<table>
<thead>
<tr>
<th>Inflammation/Portal hypertension/liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further increase in the release of NO, CO and other vasoactive molecules</td>
</tr>
<tr>
<td>Splanchnic arterial vasodilation</td>
</tr>
<tr>
<td>Reduction in effective circulating volume</td>
</tr>
<tr>
<td>Maximal activation of endogenous vasoconstrictor systems</td>
</tr>
<tr>
<td>Severe renal arterial vasoconstriction</td>
</tr>
<tr>
<td>HRS</td>
</tr>
</tbody>
</table>
significantly lower levels, which were similar to those in patients without AKI [20]. As far as the differential diagnosis of AKI is concerned, uNGAL was found to be useful in differentiating acute tubular necrosis (ATN) from functional types of AKI, including pre-renal AKI and HRS-AKI [20]. Nevertheless, patients with HRS associated with bacterial infections had levels of uNGAL higher than those of patients with classical HRS, and similar to those of patients with ATN [20]. These results support the hypothesis of the existence of some degree of tubular injury in patients with HRS associated with bacterial infections, compared to patients with HRS not associated with active infections. Currently, it is still uncertain whether patients with AKI due to bacterial infections and/or with ACLF can develop a phenotype of renal dysfunction other than HRS, characterized by a significant tubular injury and which can explain the failure of treatment with vasoconstrictors plus albumin. However this represents an exciting working hypothesis (Fig. 5) that should be addressed in the future. The previously mentioned finding, that baseline uNGAL concentration was not significantly different between responders and non-responders to the treatment, should not be considered a definitive argument against this hypothesis since it should be confirmed in a larger cohort of patients.

**Differential diagnosis of sepsis induced-AKI**

The prevalence of AKI is 27–49 % in patients with cirrhosis and bacterial infections [7, 22]. Among patients with cirrhosis and bacterial infections, those with ascites have a threefold higher risk of developing AKI than those without ascites (23 vs. 60 %) [7]. According to published data, in these patients AKI is reversible in 50–70 % of cases. In the remaining cases, AKI is progressive and has the characteristics of HRS-AKI [7]. Those observations led ICA to introduce new diagnostic criteria for HRS, removing an ongoing bacterial infection as an exclusion criterion [23]. Indeed, according to recently published data, ~70 % of HRS-AKI episodes are not reversible despite the treatment of the infection [24]. The differential diagnosis of AKI in patients with cirrhosis and bacterial infection should follow the new ICA-AKI criteria [5] (Table 1). Patients with AKI stage 1 should be managed as soon as possible with the following measures: early treatment of the bacterial infection, tapering or withdrawal of diuretics, withdrawal of nephrotoxic drugs, and plasma volume expansion in case of hypovolemia (with crystalloids or albumin according to clinical judgment). In the case of progression towards a higher AKI stage diuretics should be withdrawn and expansion of plasma volume with albumin at a dose of 1 g per kg of body weight per day for two consecutive days should be performed to treat pre-renal-AKI. Patients without response should be checked for the other HRS-AKI criteria (normal renal ultrasound, 24 h proteinuria <500 mg/dL, red blood cells <50 per high power field, absence of septic shock, and absence of the recent use of nephrotoxic drugs). The differential diagnosis of AKI is crucial both for the treatment and for prognostic assessment. It has been clearly shown that the different phenotypes of AKI have a different impact on prognosis, HRS AKI having the worst [25]. As mentioned above, HRS has been defined as a functional renal failure without detectable signs of renal parenchymal damage. It is time to ask whether this statement is still valid, since the criteria for excluding parenchymal damage in patients with AKI and, therefore, for diagnosing HRS-AKI are scant and inaccurate. This statement is based on the findings of (a) the application of renal biopsy in patients with cirrhosis

---

**Fig. 4** Pathogenesis of hepatorenal syndrome acute kidney injury (AKI) in sepsis; a new theory. PAMPs pathogen associated molecular patterns, DAMPs damage associated molecular patterns, + potentiating effect, GFR glomerular filtration rate
and AKI and (b) the development of new biomarkers of renal tubular damage. The latter has already been discussed in the previous section. As for renal biopsy, it should be outlined that it has been clearly shown that in patients with cirrhosis and renal dysfunction, the absence of a significant proteinuria and hematuria do not rule out the presence of renal lesions [26]. More specifically, in one out of two among 18 patients with sCr \( >1.5 \text{ mg/dL} \), with proteinuria \( <500 \text{ mg/day} \) and no hematuria, the analysis of renal biopsy specimens revealed chronic tubule-interstitial injury in 13, acute tubule-interstitial injury in 12, glomerular injury in ten, and vascular in 12 patients. Therefore, due to the limitation of the current criteria for the exclusion of a renal parenchymal damage, some degree of parenchymal damage may occur even in patients who develop a HRS-AKI. This concept should be taken into account in further research for the validation of new biomarkers in the differential diagnosis of AKI in patients with cirrhosis. This process must go hand in hand with the development of our knowledge about the nature of the HRS and subsequently, with an update of its definition.

### Prevention and treatment of sepsis induced-AKI

Several studies have shown that the onset of AKI in patients with cirrhosis and bacterial infection is associated with a poor prognosis, with a probability of in-hospital survival and 3-month survival rates of 67 and 44 %, respectively [7]. The presence of SIRS, with or without infection, was found to be a major independent prognostic factor in patients with cirrhosis and AKI suggesting that prevention and treatment of SIRS is an important target in order to reduce mortality in these patients [27]. However, taking into account HRS-AKI episodes, the prognosis is even worse, with 1- and 3-month probabilities of survival of 35 and 21 %, respectively [25]. For these reasons, every effort should be made to prevent HRS-AKI in patients with

---

**Table 1** Diagnostic criteria of hepatorenal syndrome (HRS) according to ICA criteria

<table>
<thead>
<tr>
<th>HRS-AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of cirrhosis and ascites</td>
</tr>
<tr>
<td>Diagnosis of AKI according to ICA criteria</td>
</tr>
<tr>
<td>No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight</td>
</tr>
<tr>
<td>Absence of shock</td>
</tr>
<tr>
<td>No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)</td>
</tr>
<tr>
<td>No macroscopic signs of structural kidney injury, defined as:</td>
</tr>
<tr>
<td>- Absence of proteinuria (&gt;500 mg/day)</td>
</tr>
<tr>
<td>- Absence of microhaematuria (&gt;50 RBCs per high power field)</td>
</tr>
<tr>
<td>Normal findings on renal ultrasonography</td>
</tr>
</tbody>
</table>

ICA International Club of Ascites, AKI acute kidney injury, NSAIDs nonsteroidal anti-inflammatory drugs, RBC red blood cells

* Modified from Angeli et al. [5]
cirrhosis and bacterial infections. Currently, two strategies have been found to be effective in preventing HRS-AKI and improving survival in these patients: (1) plasma volume expansion with albumin and (2) primary prophylaxis of SBP with norfloxacin. In a randomized controlled trial, the administration of albumin at the dose of 1.5 g per kg of body weight at the time of diagnosis of SBP and 1 g per kg of body weight at the third day of treatment was able to reduce the incidence of AKI and to improve survival in patients with SBP [28]. However, in the context of bacterial infections other than SBP, results are conflicting. Guévara et al. [29] found a significant improvement in renal and circulatory function with albumin administration and a trend towards an improvement in survival. Conversely, Thevenot et al. [30] found albumin able to delay the onset of renal failure, even though the 3-month renal failure rate and survival rate were not different between the two groups. Currently, in order to address this issue, a large multicenter randomized controlled trial is ongoing in Europe. The mechanisms underlying the therapeutic effects exerted by albumin are not fully understood, but they are more complex than the simple plasma volume expansion. Albumin is endowed with an array of non oncotic properties beyond its role as plasma volume expander. Albumin prevents AKI in patients with SBP through an improvement in peripheral vascular resistance and in cardiac function. The mechanism by which albumin ameliorates the peripheral arterial circulation is probably related to its scavenger effect on proinflammatory cytokines and vasodilator molecules released during infection [31]. The most likely mechanism for the improvement in left ventricular function may still be the increased venous return and cardiac preload. However, in an experimental study, it has been shown that albumin exerts an anti-oxidative and anti-inflammatory action capable of restoring cardiac contractility [32]. As far as primary prophylaxis of SBP is concerned, in a randomized placebo-controlled trial, Fernandez et al. found that the administration of norfloxacin (400 mg/day) in patients with advanced cirrhosis [Child-Pugh score ≥9 points with serum bilirubin level ≥3 mg/dL or impaired renal function (serum creatinine level ≥1.2 mg/dL, blood urea nitrogen level ≥25 mg/dL, or serum vsodium level ≤130 mEq/L)] and low ascites protein levels (<15 g/L) were able to reduce the incidence of HRS-AKI and to improve 3-month survival [33].

Although liver transplantation is the treatment of choice in patients with HRS-AKI, not all patients are eligible for liver transplantation, and the time needed to get a graft is unpredictable. Moreover, in the context of sepsis-induced HRS-AKI, the infection needs to be solved before liver transplant. Other medical strategies have been introduced in the last 10 years, in particular, the administration of vasoconstrictors and albumin have been effective in improving renal function and in resolving HRS AKI in patients with cirrhosis [34–37] (Table 2). Vasoconstrictors were used in order to counteract the splanchnic arterial vasodilation, to reduce the portal pressure, and to improve effective circulating volume. Albumin was introduced to further improve the effective circulating volume. The complex mechanism of the action of albumin in improving the effective circulating volume in patients with cirrhosis has been already discussed. The molecular mechanisms of terlipressin, the most widely investigated vasoconstrictr in the treatment of HRS-AKI, are only partially known. Nevertheless, it should be highlighted that the activation of smooth muscle V1a-vasopressin receptors by terlipressin induces arterial vasoconstriction, not only through an increase in intracellular calcium via the phosphatidyl-inositol-bisphosphonate cascade, but also by inhibiting the expression of the inducible nitric oxide synthase in the arterial wall [38]. In two randomized controlled trials, terlipressin given as intravenous boluses (starting from 1 mg/4–6 h to 2 mg/4–6 h) plus albumin (20–40 g/day) was more effective than albumin alone in the treatment of HRS-AKI [34, 35]. Midodrine (starting from 7.5 mg/8 h to 12.5 mg/8 h) plus octreotide (starting from 100 μg/8 h to 200 μg/8 h) and albumin were found to be effective in the treatment of HRS-AKI [36, 39]. However, in a recent multicenter randomized controlled trial, terlipressin (given as continuous intravenous infusion starting from 3 mg/24 h to 12 mg/24 h) and albumin were more effective than midodrine plus octreotide and albumin in the treatment of HRS-AKI [40]. Noradrenalin was shown to have a similar efficacy than terlipressin in a randomized controlled trial [37]. Nonetheless, in the latter, the sample size was too small to detect a difference between the two groups and further studies are warranted. As reported above, until 2007 active bacterial infections were considered to be an exclusion criterion for the diagnosis of HRS-AKI. Accordingly, most published data about the use of vasoconstrictors in HRS-AKI excluded patients with a bacterial infection. More recently, two studies reported that the rate of response of type 1 HRS to vasoconstrictors plus albumin was not affected by bacterial infection as a precipitating event of HRS [16, 40], provided that the infection was resolved by the antibiotic treatment [16]. Finally, it has very recently provided a preliminary evidence that the presence of SIRS is associated with a better response to terlipressin plus albumin in patients with type 1 HRS [41].

Conclusions and perspectives

When precipitated by bacterial infections, HRS-AKI can be treated effectively with terlipressin and albumin. Nevertheless, patients with HRS-AKI associated severe ACLF, a
Inflammation is the fingerprint of the pathogenesis of ACLF, organ failures, are unlikely to respond to this treatment. Since infections and which is characterized by the development of inflammation and/or of reduced tolerance to inflammation. Whether inflammation can influence a type of AKI other than HRS needs to be confirmed in future research. Likewise, further studies should be performed to investigate new treatment strategies for patients with sepsis-induced organ failures, including AKI, in the context of ACLF.

Compliance with ethical requirements and Conflict of interest This article does not contain any studies with human or animal subjects performed by any of the authors. Paolo Angeli, Marta Tonon, Chiara Pilutti, Filippo Morando and Salvatore Piano declare that they have no conflict of interest.

References


