Type-1 hepatorenal syndrome in patients with cirrhosis and infection vs. sepsis-induced acute kidney injury: What matters?

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Type-1 hepatorenal syndrome (HRS) is considered to be a specific complication of advanced cirrhosis characterized by an abrupt pre-renal like deterioration in renal function, unresponsive to volume expansion and associated with an especially poor prognosis [1]. With the aim of better reflecting the specificity of HRS, the original definition was very stringent with a number of exclusion criteria such as ongoing sepsis [2]. With increasing experience, it was felt that these diagnostic criteria were too restrictive since HRS is frequently triggered by precipitating factors. Accordingly, since revised guidelines have been proposed in 2007, bacterial infection is no longer considered to be an exclusion criterion for the diagnosis of HRS [3].

The main mechanism of HRS is an extreme renal vasoconstriction due to the activation of sodium-retaining and vasoconstrictor systems resulting in a major decrease in glomerular filtration rate (GFR) [4]. This cascade of events results from marked splanchnic vasodilatation and a state of low effective arterial blood volume. Insufficient cardiac output may also contribute to renal hypoperfusion. A paradox is that the reference treatment of HRS, where renal vasoconstriction is central, is based on a potent vasoconstrictor agent: terlipressin. Practically, this apparent paradox could be explained by the fact that terlipressin-induced vasoconstriction predominates in the splanchnic system. Terlipressin may reverse, at least in part, splanchnic arterial vasodilatation with redistribution to systemic vascular bed and reversal of reduced effective arterial blood volume. While only few data are available on type-2 HRS, several studies have shown that terlipressin improves renal function in up to 65% of patients with type-1 HRS with a significant improvement in survival [5–8]. Unfortunately, in the absence of transplantation, short term mortality remains very high. However, in all these studies patients with ongoing sepsis were excluded according to the original definition of HRS. In this issue of the Journal of Hepatology [9], Rodriguez E. and colleagues report on the results of a pilot study exploring the role of terlipressin and albumin in patients with type-1 HRS and sepsis. Interestingly, the authors found that in this subgroup, results similar to those previously reported in patients without sepsis could be achieved. Response to therapy (decrease in serum creatinine below 1.5 mg/dl or 133 μmol/L) was observed in 67% of patients. The response rate was higher as compared to a historical group of patients with type-1 HRS not treated by terlipressin and albumin even if the difference did not reach significance (67% vs. 40%, p = 0.06). Three-month survival rate was significantly higher in responders as compared to non-responders. These results strongly support the use of terlipressin and albumin in patients with type-1 HRS and bacterial infection. However, they should be interpreted with caution since the study population was relatively small and there was no control group. Even though controlled studies are unlikely to be performed in this uncommon condition, the results might be validated in other centers.

The results of this study also support the concept that, whatever patients with cirrhosis have bacterial infection or not, the mechanisms of type-1 HRS are similar. Indeed, in this population of patients with infection, response to terlipressin was characterized by an improvement of circulatory function along with a significant decrease in plasma renin activity and plasma norepinephrine concentration. However, these results should be interpreted in the light of the recently revisited mechanisms of sepsis-induced acute kidney injury (AKI) in non-cirrhotic patients, suggesting that many factors other than renal hypoperfusion are involved. An increasing body of evidence shows that sepsis-induced AKI is a complex process where several factors including microcirculatory changes, patchy areas of tubular cells with apical vacuolization but no necrosis or apoptosis and, finally, metabolic downregulation of tubular cells induced by inflammation and oxidative stress come into play [10]. Besides microcirculatory changes and extraglomerular shunting, these tubular changes may lead to decreased GFR through activation of the tubuloglomerular feedback, constriction of the afferent arteriole and decreased hydrostatic pressure in the glomerulus. These mechanisms may explain why sepsis-induced AKI can be observed in the absence of overt renal hypoperfusion [11]. Whether similar mechanisms are involved in type-1 HRS associated with infection is an important issue, especially in those who do not respond to terlipressin. The absence of significant increase...
in urinary neutrophil gelatinase associated lipocalin (a biomarker of acute tubular necrosis) in non-responders as compared to responders is consistent with the changes observed during sep-
sis-induced AKI, as described above. However, the respective role of renal vasoconstriction and hypoperfusion on the one hand and the mechanisms involved in sepsis-induced AKI other than hypo-
perfusion on the other hand needs to be further investigated. In
general efforts should be made in the development of tools to
monitor renal blood flow. Such tools may obviously help opti-
mize the management.

According to the definition proposed recently by the
EASL-CLIF Consortium [12], all patients in the study by Rodrí-
gez E. and colleagues [9] met the criteria for acute-on-chronic
liver failure (ACLF). Indeed, all patients had cirrhosis and serum
creatinine above 2 mg/dl (180 μmol/L). ACLF and the derived
CLIF-SOFA score [12] allow to categorize patients with cirrhosis
and acute deterioration according to the number and severity of
organ/system failures. The CLIF-SOFA score is a prognostic score
derived from the widely used SOFA score in general intensive
Care unit patients [13], with some modifications aimed at better
reflecting the impact of organ/system failures in the context of
cirrhosis. The higher the CLIF-SOFA score, the higher the mor-
tality rate in patients with ACLF. The study by Rodriguez E. and
colleagues offers an original approach allowing to analyze the
impact of type-1 HRS not only as a single event during the
course of cirrhosis but rather as one of the extra-hepatic complica-
tions that may occur during end stage cirrhosis. It is not sur-
prising that in this study, non-responders had a significantly
higher CLIF-SOFA score as compared to responders. Nor is it sur-
prising that the higher the CLIF-SOFA score, the higher the mor-
tality rate. Interestingly, the authors found that patients with
ACLF grade 3 as well as those with a CLIF-SOFA score over 11
had a very low probability of response to terlipressin and albu-
min. Since there was a strong interaction between resolution
of infection and severity of ACLF, the absence of resolution of
infection was also associated with a low probability of response
to therapy. Altogether, these findings illustrate the determining
impact of extra-hepatic organ failures on reversibility of type-1
HRS with terlipressin. Whether in this subgroup of patients,
terlipressin is ineffective because the mechanisms involved are
relatively independent of renal hypoperfusion (such as in
sepsis-induced AKI) or because patients relentlessly progress
to acute tubular necrosis needs to be clarified.

Finally, another factor that should be taken into account is
the presence or absence of underlying chronic kidney changes.
In advanced cirrhosis, indeed, normal baseline serum creatinine
does not exclude a major impairment in renal function [14,15].

In a series of patients with cirrhosis who had transvenous renal
biopsy for increased serum creatinine (>1.5 mg/dl) and no pro-
teinuria, some of whom met the criteria for HRS, none had nor-
mal histology [16]. Chronic kidney changes were found in 77%
of patients. In most patients injuries to different structures were
combined. Significant glomerular lesions could be observed in
the absence of proteinuria. Such lesions are likely to be related
to comorbidities. It is conceivable, although not clearly dem-
onstrated, that patients with end-stage cirrhosis, underlying
chronic kidney changes and a precipitating event such as sepsis
are at higher risk to develop “acute-on-chronic renal failure”
[17]. In those meeting the criteria for type-1 HRS, chronic
kidney changes may preclude improvement with terlipressin and
favor the occurrence of extra-hepatic organ failures.

Unfortunately, renal biopsy is impractical in these patients
and biomarkers that clearly differentiate acute (reversible) from
chronic (irreversible) kidney changes are missing.

In summary, the study by Rodriguez E. and colleagues [9]
suggests that the response rate to terlipressin and albumin of
type-1 HRS in patients with cirrhosis is similar whatever sepsis
is present or absent. There is no clear evidence that the
complex mechanisms involved in sepsis-induced AKI have a
significant impact on type-1 HRS associated with sepsis since
response to therapy and general course are similar to those
observed in cirrhotic patients without infection. These findings
suggest that renal macro and microvascular changes induced
by sepsis are different in cirrhotic patients as compared to
non-cirrhotic patients. However, not all patients with type-1
HRS and sepsis respond to terlipressin and albumin. In non-
responders, the prognosis remains especially poor. What
matters in this subgroup seems to be the number and severity of
organ failure(s).

Conflict of interest

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