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Editorial

Acute on chronic liver failure and prognostic factors: time for reevaluation

Our present knowledge on the management of cirrhotic patients in specialized critical care units has significantly rised in recent years because of an increase —however insufficient— in the number of those units (1). Nevertheless, the concept of liver failure has become somewhat blurry due to the various definitions in use. *Acute liver failure* is currently defined as a sudden, serious impairment of liver function in the form of coagulopathy and encephalopathy in patients with no previous liver disease (2,3). *Chronic liver failure* develops only in patients with cirrhosis and is characterized by a progressive deterioration of the different liver functions in an irreversible, usually slow manner, often associated with increased portal pressure and related complications. The recently coined term *acute on chronic liver failure* (ACLF) refers to a sudden impairment of liver function in a patient with previous chronic liver disease, by definition potentially reversible with therapy and always with a trigger factor, even though the latter may not always be identified (4). In ACLF the patient may occasionally survive on conventional therapy, but most often than not will need multiple organ support including mechanical ventilation, inotropic support or kidney replacement therapy, among others. The study by Freire et al. included in this issue of the journal examines a high number of the latter two types of liver failure (5) in subjects admitted on several grounds in a gastroenterology intensive care unit. Another study by these same authors assessed the usefulness of these prognostic models in patients with all sorts of serious digestive conditions (6).

The primary differences between chronic liver failure and ACLF include the fact that the former is progressive, results from the natural history of cirrhosis, and —while manageable with drug or instrumental therapy— is irreversible by definition until the patient either dies or undergoes a liver transplant. The latter, however, may be a chronic liver condition with or without cirrhosis, with an acute deterioration of liver function as a result of a noxa unrelated to the natural history of the liver disorder, and most often considered reversible no matter the severity of functional impairment (4).

ACLF remains a little known condition mainly because of its highly variable definitions as used in different studies. These are patients with well compensated chronic liver disease in which liver function is decompensated by an acute factor such as sepsis, gastrointestinal bleeding, ischemia, or added liver damage including viral hepatitis, alcohol, or toxics (6). The most relevant characteristic is reversibility when the trigger factor is managed before it is too late.

Factors that may impair liver function in patients with prior chronic liver disease are categorized in two major groups: hepatotoxic factors and systemic factors. The former group refers to alcohol ingestion, exposure to drugs or hepatotoxic substances, and infection with hepatotropic viruses. The latter group, which includes

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gastrointestinal variceal bleeding and sepsis, has a significant impact on multiple organs including an already damaged liver that will lead the clinical picture (7).

The most common *triggers* of acute on chronic failure include sepsis and digestive bleeding (4). Sepsis may worsen liver function via the release of bacterial lipopolysaccharide (LPS) (8) and ischemia resulting from hemodynamic changes (9). LPS may induce liver cell apoptosis via tumor necrosis factor alpha (TNFa) (10-12). Some studies have shown improved liver function and a potential benefit on the survival of patients with severe alcoholic hepatitis using anti-TNFa antibodies (13,14). LPS may also upregulate nitric oxide (NO) formation and increase cell damage due to the production of free radicals (15).

Gastrointestinal bleeding may also impair liver function. Many cirrhotic patients die not from bleeding but from its metabolic consequences. Logically, bleeding results in an ischemic injury that may eventually worsen liver function (9). In addition, due to red blood cell ingestion and hemoglobin's specific composition, there is a massive delivery of low-quality proteins. Hemoglobin is poor in isoleucine but rich in valine and leucine (16,17). These amino acids are degraded in the intestine to yield ammonium, which enters the portal circulation and results in encephalopathy (18-20). Furthermore, the relative isoleucine deficiency gives rise to a catabolic status where proteins are degraded in order to deliver the missing amino acid (21). This catabolic situation increases ammonium formation as described above (hence increasing encephalopathy), decreases DNA synthesis, which impairs epithelial and immune cell division (thus increasing the risk for infection), and reduces low-half-life proteins including some coagulation factors (resulting in risk for re-bleeding) (22). ACLF liver manifestations include severe hyperbilirubinemia and jaundice, acutely reduced coagulation factors, and multifactorial worsening of thrombopenia.

At the renal level an *hepatorenal syndrome* (HRS) (23,24) may develop from extreme renal parenchymal hypoperfusion as a result of increased renal vascular resistance because of a disbalance between vasodilating and vasoconstrictive factors with the latter predominating (25). Hepatorenal syndrome is likely overdiagnosed in patients with liver disease when any renal dysfunction occurs, on occasion due to a poor understanding of acute renal injury. Many classic triggers of hepatorenal syndrome, including gastrointestinal bleeding, sepsis, high-dose diuretics, nephrotoxic contrast agents, hypovolemia, and non-steroidal anti-inflammatory drugs, may induce acute renal injury because of toxicity, hypoperfusion, or overt ischemia. Therefore, these may not be strictly defined as HRS but are included in the clinical spectrum of acute on chronic failure. The pathogenesis of HRS is complex and poorly understood. Vasoconstrictive factors such as angiotensin and catecholamines are known to play a significant role in an early stage. Then, it is endothelin-1, produced in liver sinusoids, that delivers vasoconstriction (26) while local nitric oxide secretion induces vasodilation in other territories. Furthermore, renal perfusion self-regulation is impaired so that small decreases in blood pressure result in large renal perfusion reductions. Vasodilating stimuli such as sepsis may induce a greater renal vasoconstriction response in patients with acute on chronic liver failure (27,15).

Hepatic encephalopathy is a most apparent manifestation. Ammonium production remains a core feature in this syndrome's origin. The correlation between serum ammonium and liver disease outcome is highly controversial with studies both for and against it. However, it seems clear that serum ammonium levels are associated with uncal herniation and death in acute liver failure (28). Other factors include blood-brain barrier impairment, which allows the passage of modified amino acids, as well as brain perfusion and both oxygen and glucose consumption deficiencies.

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Some studies also suggest that patients with acute on chronic liver failure may, as is the case with patients with acute liver failure, develop brain edema and intracranial hypertension. However, most experts do not endorse such hypotheses (1,3,4).

Any vascular change, both general or local, may bring about changes in a previously damaged liver. In these patients hemodynamic changes are similar to those of cirrhotic patients, only more severe. There is high cardiac output, peripheral vascular dilation, and scarcely reactive vessels. There is also collateral circulation, increased portal pressure, and decreased renal blood flow. Nitric oxide seems particularly involved in the pathogenesis of circulatory and cardiovascular changes. NO, when synthesized from L-arginine by the constitutive enzyme nitric oxide-synthase (NOS), which depends on the presence of calcium, seems to exert a protective effect on microcirculation in animal endotoxemia models (29).

However, NO production by the inducible, calcium-independent NOS, which occurs within hours after an injury with release of endotoxins or proinflammatory cytokines, results in deep vasodilation that is no longer beneficial but harmful (30,31). This high-dose NO is thought to justify the poor response of these patients to vasoconstrictor drugs (32), and may also initiate the endothelial damage that is characteristic of early multiple organ failure (32). Despite all this, most of these hypotheses must be confirmed by more extensive research.

In this type of patients, as in any cirrhotic subject but to a higher extent, there is *hyperreninemic hyperaldosteronism* as a result of severe vasodilation and relative hypovolemia. Various studies demonstrated that inducible NOS inhibition reduces hyperreninemia, and improves hemodynamic changes, renal function, and sodium excretion (33,34). Both in vitro and in vivo studies show compartmentalized inducible NOS production, which may account for systemic vasodilation and selective vasoconstriction in renal, hepatic, and cerebral territories (35-38).

Understanding these patients' prognosis is key for their proper clinical care. Acute on chronic failure manifests with hepatic, cardiovascular, renal, and cerebral changes, but differs from acute liver failure in many clinical features. Its prognosis cannot be established with the criteria used to determine whether a patient with acute liver failure needs a transplant or can live on with only multiple organ support, including King´s College criteria (39), the recently introduced BiLE criteria (40), or Beaujon criteria (41), since a defining characteristic of ACLF is its reversibility, and as a result the clinical picture itself should not be a determining factor when deciding on a transplant, being there an absolute contraindication in some instances, including sepsis. The Child-Turcotte-Pugh (CTP) classification is believed to be insufficient in patients with ACLF as it only takes liver variables into account, and cardiovascular, renal, respiratory, or neurological dysfunction too often determine prognosis. Furthermore, this classification does not seem sensitive enough to detect subtle liver function changes, which may vary from one day to the next. Therefore, this classification should be reserved for chronic liver failure. However, the study by Freire et al. shows that the CTP model is useful for prognosis prediction in both patient types overall (5).

Many models have been suggested to establish a prognosis, including the Acute Physiology And Chronic Health Evaluation II and III (APACHE II and APACHE III), Simplified Acute Physiology Score II (SAPS II), or Sequential Organ Failure Assessment (SOFA), which are used in intensive care units (42) to assess a condition's severity and often prognosis, or Mayo Clinic's Model for End stage Liver Disease (MELD) (43), associated with serum sodium (MELD-Na) (44) or indocyanine green clearance (MELD-ICG) (45,46). MELD was initially designed to estab-

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lish survival of cirrhotic patients following a transjugular intrahepatic portosystemic shunt (TIPS) procedure, but since February 27, 2002 is in use by the United Network of Organ Sharing in the United States, and later by many other countries, to determine priority on the transplant waiting list (47). One of the shortcomings found in MELD is its inability to detect minimal liver function changes potentially relevant in the clinical evolution of patients with acute on chronic failure. Unlike CTP, it does consider renal function by using serum creatinine. However, there has been harsh criticism regarding its ability to favor males versus females with the same disease and renal insufficiency grade simply because males have more muscle mass (48). On the other hand, patients with more advanced liver disease develop muscle wasting due to their catabolic status. Again, serum creatinine may not properly reflect that they may require a transplant or their renal function. On these and other grounds many authors suggested the use of glomerular filtration rate instead of serum creatinine for renal marker in MELD, but it is still pending. The study by Freire et al. (5) attempts to validate the usefulness of prognostic models as used in critical care units in a specific unit for gastroenterology patients.

A prognostic model has been recently reported for ACLF patients with chronic hepatitis B infection, but its usefulness remains to be validated by further studies (49). In the study by Freire et al. (5), as in other studies with similar populations, these prognostic models obtain good calibration and discrimination results, with the SOFA model emerging as the best overall. However, as the authors remark, the low mortality of their patients is outstanding, with relatively low APACHE II, SAPS II, and SOFA scores. Also, the development of problems common in critical care units such as acute kidney injury or need for intubation and mechanical ventilation is uncommon. Model applicability is possibly different for patients with the same diseases but higher severity, which suggests that the studied population is dependent on their hospital's organization.

Current treatment is based on multiple organ support and trigger correction. Commonly this consists of antibiotic therapy for infection or endoscopic and drug management for bleeding (50). Cardiovascular support requires special monitoring with central venous pressure measurement, invasive arterial pressure monitoring, and usually -though not always- the measurement of cardiac output and other parameters such as peripheral vascular resistance, lung water volume, and pulmonary capillary permeability. These parameters may be measured using thermodilution techniques or, more accurately, a Swan-Ganz catheter. There is no evidence of the usefulness of measuring the hepatic vein-portal gradient (HVPG) in these patients. When a patient shows a low mean blood pressure, below 60 to 65 mmHg, volume in the form of small saline boluses (250 mL) should be given to ascertain whether a response to volume is elicited. Measuring venous oxygen saturation or simply raising a patient's legs may be useful to predict the response to volume administration. If a patient does not respond to volume vasoconstrictor drugs must be administered, with noradrenaline being the drug of choice (51). Vasopressing will be dosed as a vasoconstrictor for patients who respond poorly to conventional vasoconstrictors (the effect of nitric oxide reduces the vascular response to these drugs) (52). In those with confirmed relative adrenal insufficiency steroids may be given (53). Only with reduced cardiac output will drugs such as dobutamine, levosimendan or milrinone be administered.

Neurological support is based on encephalopathy management and, when advanced (grades 3 and 4), on patient intubation, sedation, and ventilation. The presence of cerebral edema and intracranial hypertension in these patients is a contro-

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versial topic among different teams, with data for and against it as discussed above. Non-aggressive measures such as 30-degree head-of-bed elevation and a cranial CT scan when there is obvious neurological deterioration are recommended. However, current evidence is lacking in order to warrant invasive procedures such as intracranial pressure monitoring implants. Further studies are needed confirming or otherwise the presence of intracranial hypertension in acute on chronic liver failure to implement measures against it (54,55). Lactulose should be used with the greatest care because of the risk for intravascular depletion, abdominal distension, and water and electrolite imbalance (56). Respiratory support is implemented using intubation for airway protection, and mechanical ventilation as advised by patient status.

Finally, renal support requires attentive renal function monitoring using glomerular filtration rate and hourly urine production. Serum urea may not be useful because of changes in the urea cycle in association with liver dysfunction. Because of previously discussed reasons new renal function markers should be used in the future given the unreliable nature of creatinine and urea in patients with liver disease. If a patient develops impaired renal function not responding to improved hemodynamic and respiratory parameters, as well as improved intra-abdominal pressure, renal replacement therapy must be initiated in the form of continuous venovenous hemofiltration (52). It is also recommended that this therapy be initiated in case of volume overload or severe metabolic changes such as hypercalcemia, hyperkalemia or acidosis (4).

As it can be seen, the current management of patients with acute on chronic failure is particularly oriented to multiple organ support with little or no emphasis in the liver, to trigger factor elimination, and to maintaining patients alive while liver function improves on its own. A deeper understanding of the pathogenesis and mechanisms by which this syndrome develops may lead to the use of therapies that will specifically improve liver function with no need to wait for spontaneous recovery, including inducible NOS expression or local NO levels modulation, TNFa-mediated apoptosis blocking drugs (57), antioxidants (58) or isoleucine supplementation during bleeding (59), as well as improved artificial liver support systems (60-64) or hepatocyte transplantation (65).

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