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REVIEW

Update on acute-on-chronic liver failure☆

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Abstract Acute-on-chronic liver failure (ACLF) is a recently defined syndrome characterised by acute decompensation of chronic liver disease, associated with organ failures and high mortality. ACLF is a common condition and may affect up to 30% of patients admitted to hospital for cirrhosis complications. Bacterial infections, alcoholism and reactivation of viral hepatitis are the most common precipitating factors in ACLF, although in up to 40% of patients no precipitating factor can be identified. Although the pathophysiology of ACLF is not completely understood, the presence of an excessive inflammatory response appears to play a key role. There is no specific treatment for patients with ACLF and management is based on organ support and liver transplantation. New treatment strategies based on liver support systems and immunomodulatory treatments are being evaluated but existing data are still limited.

PALABRAS CLAVE
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Actualización en la insuficiencia hepática aguda sobre crónica

Resumen La insuficiencia hepática aguda sobre crónica (ACLF, *acute-on-chronic liver failure*) es un síndrome definido recientemente y caracterizado por una descompensación aguda de una hepatopatía crónica, asociada al fallo de diferentes órganos y a una elevada mortalidad. La ACLF es frecuente, y afecta al 30% de los pacientes ingresados por complicaciones de la cirrosis. Las infecciones bacterianas, el alcoholismo y la reactivación de hepatitis virales representan los factores precipitantes más frecuentes, aunque hasta en un 40% de los pacientes no se identifica ningún factor precipitante. La fisiopatología no es completamente conocida, pero se considera que la existencia de una respuesta inflamatoria excesiva juega un papel clave en su desarrollo.

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No existe ningún tratamiento específico para la ACLF y su manejo se basa en el tratamiento de soporte y el trasplante hepático. Actualmente se están evaluando nuevas estrategias de tratamiento, como mecanismos de soporte hepático y tratamientos inmunomoduladores, pero los datos son todavía limitados.

Introduction

Liver cirrhosis evolves from compensated cirrhosis until the onset of decompensated cirrhosis, characterised by the development of the typical complications of the disease (ascites, hepatic encephalopathy, bacterial infections and gastrointestinal bleeding) and is associated with a poorer prognosis.[1,2] Patients with acute decompensated cirrhosis with no other associated factors are identified in daily clinical practice, while other patients present with acute decompensation associated with the rapid onset of multiple organ failure and a poor short-term prognosis. Traditionally, this concept has been called *acute-on-chronic liver failure* (ACLF). To summarise, and based on clinical experience, ACLF has been defined as acute decompensation in a patient with chronic liver disease, associated with the failure of organs other than the liver and a high mortality rate. However, this has been and continues to be a heterogeneous concept since, until recently, there was no established definition and the existing definitions were based on consensus rather than data from prospective studies.

In 2009, the Asian Pacific Association for the Study of the Liver (APASL) established the first agreed-upon definition for ACLF: ''acute liver damage manifested as jaundice (bilirubin $\geq$5 mg/dL) and clotting (INR $\geq$1.5), complicated in the space of 4 weeks with ascites or encephalopathy''.[3] More recently, two prospective studies aimed at establishing a definition for ACLF were published. The first study was conducted by the North American Consortium for the Study of End-Stage Liver Disease (NASCELD) in the United States and Canada, and included only patients with cirrhosis and bacterial infections; thus, it did not consider the remaining patients.[4] The second study was the CANONIC study conducted by the EASL-Chronic Liver Failure (EASL-CLIF) Consortium, which included 1343 consecutive patients with liver cirrhosis admitted to 21 European hospitals for acute decompensation of the disease.[5] Therefore, the CANONIC study is currently the prospective study conducted with the largest number of patients, which includes all patients admitted for cirrhosis-related complications, of any aetiology, and is aimed at establishing a definition for ACLF.

Definition and diagnosis

According to the results of the CANONIC study, ACLF is defined as a syndrome characterised by acute decompensated cirrhosis, associated with the failure of various organs and a high short-term mortality rate (mortality at 28 days $\geq$15%). In that study, the existence of organ failure was evaluated using a modified version of the Sequential Organ Failure Assessment (SOFA) score, an index that is widely used to evaluate organ failure in critical patients. In that case, the SOFA index was adapted to the characteristics of patients with cirrhosis and was called CLIF-SOFA, or its simplified version, *CLIF-C Organ Failure score* (CLIF-C OF) (Table 1).[5,6] The presence of ACLF was identified according to the number and type of organ failure, while its severity was classed into 3 stages (Table 2).[6]

Although the prospective studies only included patients with liver cirrhosis, it should be noted that in reality ACLF can appear in patients with both compensated and decompensated cirrhosis, as well as in patients with chronic liver disease without cirrhosis. In this regard, and in an attempt to clarify the concept, in a recent consensus meeting aimed at unifying the diagnostic criteria for ACLF, it was suggested that ACLF should be defined as ''a syndrome that occurs in patients with chronic liver disease, with or without previously diagnosed cirrhosis, which is characterised by acute liver decompensation that leads to liver failure (jaundice and clotting) and is associated with the failure of one or more extrahepatic organs''.[7] It was suggested that ACLF be classified into 3 types according to the stage of the underlying chronic liver disease: Type A ACLF (patients with chronic liver disease without cirrhosis); Type B ACLF (patients with compensated cirrhosis); and Type C ACLF (patients with decompensated cirrhosis). The CANONIC study included patients with type B and type C ACLF.[5,7] Patients with type A ACLF are patients with underlying chronic liver disease, without cirrhosis, and which typically occurs as acute hepatitis associated with chronic liver disease or as the reactivation of viral hepatitis. As described in the previous section, bearing in mind that viral hepatitis is the most common precipitating factor for ACLF in Asia, type A ACLF would be the most common in this region. However, this classification and the concept of type A ACLF should be validated in future prospective studies to confirm whether type A ACLF truly has characteristics similar to those of patients with type B ACLF and type C ACLF.

Epidemiology

ACLF is a common complication in patients with liver cirrhosis, which is a common reason for hospital admission and one of the most common causes of death in these patients. Overall, the prevalence of ACLF is approximately 30%. Studies