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Editorial

Infection and inflammation in liver failure: Two sides of the same coin☆

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Acute deterioration in the clinical condition of a cirrhotic patient due to the effects of a precipitating illness leading to hospital admission is associated with widely variable clinical outcomes. A proportion of patients makes an appropriate response to treatment of the precipitating event and can be discharged relatively quickly from hospital. There are a second group of patients, who despite treatment of the precipitating event progress to organ dysfunction, developing complications of cirrhosis and this is the group that is associated with high mortality rates and is referred to broadly as 'Acute on Chronic Liver Failure' (ACLF) [1]. The underlying mechanisms that determine which patient will recover and which patient will progress to multiple organ dysfunction despite similar precipitating events is not clear. The paper by Cazzaniga et al. in the present issue of the Journal addresses this important question and suggests that a systemic inflammatory response may be important in determining outcomes [2].

Multi-organ failure in cirrhosis

The term ACLF is not well defined but the syndrome it describes is known to all hepatologists [1]. ACLF refers to an acute deterioration in liver function in a patient with previously stable cirrhosis which results in 'organ failure' most commonly hepatic encephalopathy and renal dysfunction. Interestingly, the superimposed liver insult can be categorized as being primary or secondary. The primary insult can be due to the direct effects of a hepatotoxic factor including hepatotrophic viruses, a drug reaction or ingestion of hepatotoxins such as alcohol. Alternatively, the liver insult may be indirect as is seen in sepsis, in which case it is secondary end organ damage affecting the liver [3].

The underlying central theme in multi-organ dysfunction of cirrhosis is a profound disturbance in systemic hemodynamics. The cirrhotic patient has an increased or decreased cardiac output and a dilated, hyporesponsive peripheral circulation. There is increased portosystemic shunting, portal pressure with a reduction in renal blood flow [4]. The involvement of nitric oxide, a profound vasodilator, has gained considerable interest as an important mediator in this process [5]. In addition, to these systemic changes there are microvascular changes affecting capillary beds including disseminated intravascular coagulation. The acute hepatic insult in cirrhosis patients produces a pro-inflammatory milieu that exacerbates the circulatory changes seen in cirrhosis resulting in inadequate tissue perfusion and multi-organ failure. Hence, it has been shown that liver function is not the main determinant of outcome in cirrhotic patients with multi-organ dysfunction, thus the classical scores of hepatic function (Childs Pugh/MELD) are not able to accurately predict survival. Organ failure scores such as APACHE 11 and SOFA are more helpful in predicting outcome as was also shown by Cazzaniga [1,3,6–8].

The role of the systemic inflammatory response (Fig. 1)

The important role of the systemic inflammatory response (SIRS), which is a conglomeration of very

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simple and relatively crude clinical and hematological measure using heart and respiratory rates, temperature and white cell count, in determining the outcome of patients with liver failure was first fully described in the acute liver failure patient population, where the presence of SIRS, was associated with more severe encephalopathy, associated infection, renal failure and poor outcome [9–11]. More recently, the mortality of patients presenting with renal dysfunction of cirrhosis was significantly higher in the group with SIRS [12,13]. The study by Cazzaniga and colleagues confirms and extends these data in 141 patients with cirrhosis [2]. The group shows the presence of SIRS predicts a poor outcome in patients with cirrhosis presenting to the hospital with an episode of decompensation. The initial level of the SIRS response and persistent presence of SIRS during hospital stay have also been shown to be independent predictors of poor outcome in other studies [3,6–8].

The study by Cazzaniga et al. [2] does not throw light on the mechanisms of this inflammatory response or the mechanism of how SIRS leads to increased multi-organ dysfunction and exacerbated mortality. Studies in our group have focused on this question and we have observed evidence of severe hemodynamic derangements manifested by accentuation of the severity of portal hypertension and reduction in hepatic blood flow when there is superimposed inflammatory stress on the background of existing cirrhosis [14]. We observed that this was associated with an increase in the concentration asymmetric dimethylarginine, which is an endogenous inhibitor of nitric oxide synthase [4,15]. The role of SIRS in the development of renal failure of cirrhosis can be explained by a shift in the renal autoregulation curve towards the left as shown recently [16]. Infection/inflammation is a well-known precipitant of hepatic encephalopathy in cirrhotic patients [17]. Recent studies in experimental models suggest that inflammation may alter cerebral blood flow [18], increase peroxynitrite formation and also lead to activation of inflammatory response in the brain [19,20]. More recently, patients with SIRS on the background of cirrhosis have been shown to have a marked reduction in the functional capacity of the circulating albumin with evidence of oxidative modification of albumin [21]. The question of the mechanism of whether cirrhosis predisposes to the effects of the precipitating illness and in some ways exacerbates the inflammatory response is unclear.

Inflammation and infection

From the pathophysiological perspective, it is expected that SIRS should be associated with increased pro-inflammatory cytokine response and possibly positive clinical outcomes with the use of anti-inflammatory interventions. This is clearly not the case with very

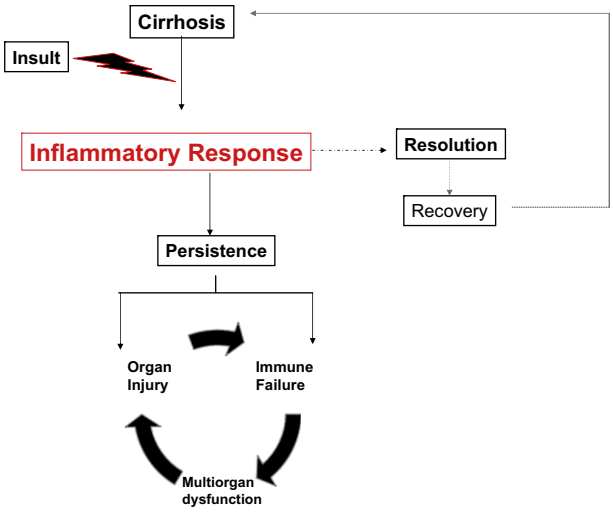

Fig. 1. This figure illustrates the possible outcomes of a patient with cirrhosis who is admitted to the hospital depending upon the occurrence and/or resolution of a systemic inflammatory response. In the patients in whom the systemic inflammatory response persists, it is likely they will progress to the organ injury/immune dysfunction pathway leading to a high probability of developing acute on chronic liver failure with a self-perpetuating vicious cycle. [This figure appears in colour on the web.]

widely variable values in the literature [22] for the measured cytokines and the observation that use of anti-TNF alpha strategies in the patients with severe alcoholic hepatitis who are defined by SIRS, was associated with increased risk of infection and poorer outcome in the treated group compared with the placebo treated group [23,24]. However, the use of anti-TNF antibodies in these patients was associated with an immediate and sustained improvement in the hemodynamic status with a reduction in portal pressure, and an increase in hepatic and renal blood flow highlighting that in principle, interventions dealing with SIRS have the potential to be effective [4]. However, the limiting factor to using any intervention that has the potential to further reduce the function of the immune system is likely to be deleterious. This is well illustrated in the Cazzaniga study, where 57% of patients with SIRS had associated infection.

It is likely that it is not necessarily the SIRS itself but the cause of a SIRS response that may be important. This hypothesis is highlighted by the observation that the outcome in patients with decompensated alcoholic cirrhosis was better when the precipitating event was superimposed alcoholic hepatitis rather than sepsis [25]. In fact, bacterial infection is the major cause of death in patients with decompensated cirrhosis. The cyclical relationship between the SIRS response and infection cannot be overstated and appears to be central to the pathophysiology of the condition [8]. A SIRS response leads to immune deregulation predisposing to infection, whilst at the same time infection initiates a pro-inflammatory response resulting in SIRS. This

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