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Nowlan Selvapatt
Arjuna Singanayagam
Julia Wendon
Charalambos Gustav Antoniades

Understanding infection susceptibility in patients with acute-on-chronic liver failure

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N. Selvapatt (✉) · C. G. Antoniades
Department of Hepatology, St Mary's Hospital, London, UK
e-mail: nowlan.selvapatt@imperial.nhs.uk

A. Singanayagam · J. Wendon
Liver Intensive Care Unit, King's College Hospital, London, UK

Introduction

Infection accounts for over 50 % of admissions of cirrhotic patients to hospital and is the main precipitant for the development of multiple organ dysfunction syndrome (MODS), including hepatic encephalopathy, renal, respiratory and circulatory failure, a syndrome referred to as acute-on-chronic liver failure (AoCLF) [1]. Once established, AoCLF carries a prohibitively high 30-day mortality rate in excess of 25 % [2]. In recent census studies from Europe and USA [1, 2], 35 % of patients admitted with AoCLF require organ support, posing a significant burden on critical care services and resources. Despite advances in organ support, little progress has been made in understanding the pathogenesis and treatment of infections in patients with liver disease.

Infection in liver failure

Bajaj et al. have shown that gram-positive and gram-negative organisms from the urinary tract and ascites (spontaneous bacterial peritonitis) constitute the commonest causes of infections in patients with AoCLF [1]. It is, however, the failure of clearance of infection and superimposed secondary infections that are associated with refractory organ dysfunction and death. Secondary infections are an independent predictor of 30-day mortality, where a causative organism is undetected in up to 30 % of patients with AoCLF—termed culture-negative sepsis [2].

In this review, we propose that infection in AoCLF is due to systemic translocation of microbes from gut-derived organisms, impaired hepatic clearance mechanisms and an ability of circulating immune cells to combat infectious cues (peripheral immune paresis).

Gut translocation

Gastrointestinal dysfunction in critically ill septic patients is common and proposed to be the consequence of acute reduction and dysfunction of enterocytes and loss of gut barrier function [3]. Recent data indicates that this phenomenon is of pathogenic significance in liver failure where the immune system is perpetually stimulated by gut-derived bacterial products [4]. The pathogenesis of bacterial translocation in liver failure is multifactorial, resulting from increased intestinal permeability, intestinal dysmotility and small bowel bacterial overgrowth [5]. These changes culminate in increased bacterial translocation of gut-derived organisms into the portal and lymphatic circulations and increase the risk of infections in liver failure.

Immune dysfunction in AoCLF

Immune dysfunction in AoCLF is multifactorial and can be broadly categorised as being due to (1) structural changes resulting from variations in portal haemodynamics, (2)

impaired synthetic function and (3) immune cell dysfunction, as demonstrated in Fig. 1.

Impaired innate response due to variation in portal haemodynamics

The presence of portal hypertension results in splanchnic vasodilation and increased flow into the portal circulation [6]. Hepatic inflammation in cirrhosis results in increased vascular resistance in the intrahepatic circulation that results in increased arterio-venous shunting [7]. Although yet unexplored, the combination of increased gut translocation, increased intrahepatic vascular resistance and portal hypertension would facilitate systemic translocation of gut-derived organisms into the circulation during the evolution of organ dysfunction in AoCLF.

AoCLF is associated with upregulation of pro-inflammatory cytokines (IL-1, IL-6, IL-17, TNF-α, IFN-γ) and anti-inflammatory cytokines (IL-10, IL-13, TGF-β1). The liver represents a vital first-line defence to bacterial infections. Kupffer cells, which represent 80–90 % of tissue macrophages [7], are increased in number and exhibit an activated phenotype, characterised by increased CD163 expression [8]. CD163 is a specific marker for macrophage activation that is produced within and released from the liver, and is increased during liver inflammation.

In the context of organ failure in AoCLF, there is some evidence emerging to suggest that changes in intrahepatic blood flow and hepatic perfusion activate intrahepatic inflammatory responses [9]. We propose that this hepatic recruitment and pooling of circulating immune effector cells during AoCLF further aggravates the susceptibility to infection. This is supported by recent findings showing an expanded hepatic immune infiltrate rich in macrophages, $CD4^+$ T cells, $CD8^+$ T cells and NK cells with a concomitant depletion of these immune cells in the peripheral circulation [10].

Impaired hepatic defence and peripheral immune paresis

A number of defects in innate immune responses have been demonstrated and are believed to confer an

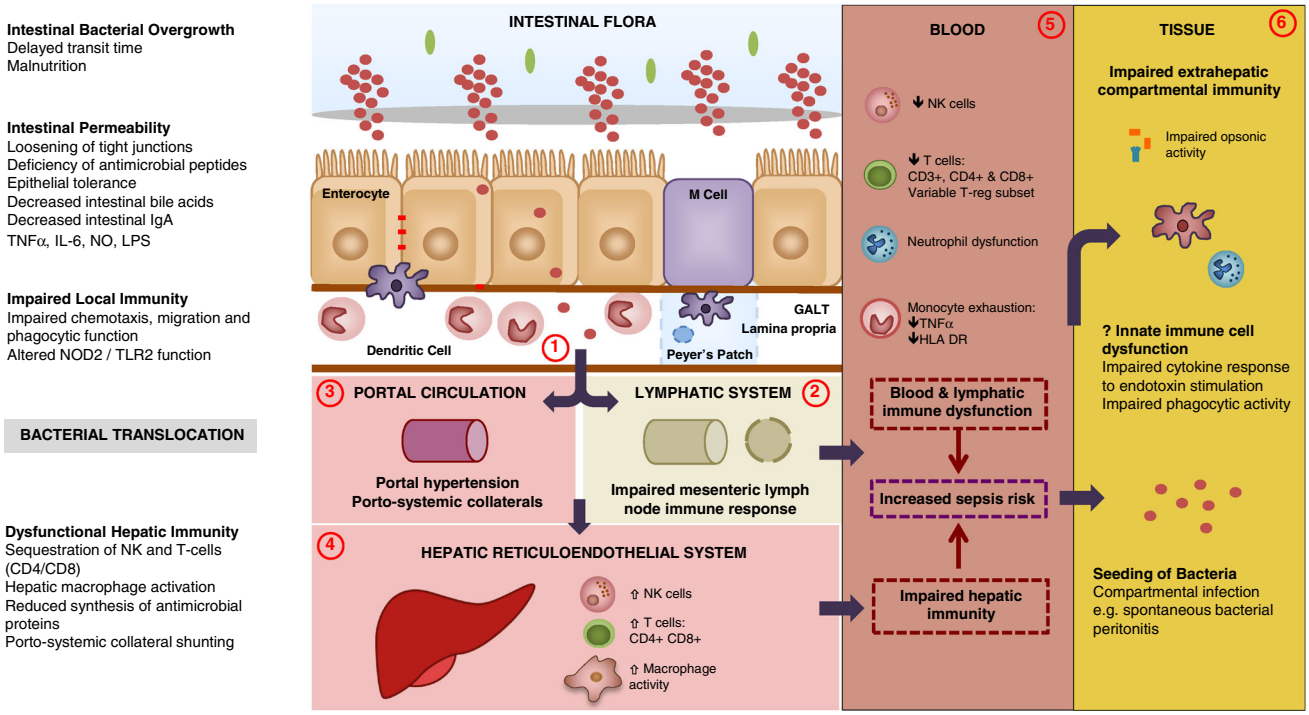

Fig. 1 Proposed model of infection susceptibility in acute-on-chronic liver failure (AoCLF): *1* intestinal bacterial overgrowth, enhanced intestinal permeability and impaired gut immunity lead to increased translocation of gut-derived bacteria into the portal circulation; *2* pathogens are inadequately eliminated at regional mesenteric lymph nodes; *3* systemic translocation of gut-derived bacteria is promoted following entry into portal circulation and shunting via porto-systemic collaterals; *4* relative hepatic ischaemia and higher titres of translocated pathogens lead to intrahepatic macrophage activation, recruitment and sequestration of NK and $CD4^+$/$CD8^+$ T cells increasing systemic susceptibility to systemic infection; *5* immune dysregulation in peripheral blood propagates infection via lack of adequate immune responses and pathogen elimination; and *6* seeding of infection to mucosal/tissue-specific compartments leading to increased predisposition to infection

increased susceptibility to failure of clearance of infections in liver failure. Elevated circulating levels of ammonia in AoCLF have been shown to impair neutrophil phagocytic capacity [11]. Pathogen clearance by the reticuloendothelial system is reduced in proportion to the severity of hepatic dysfunction. Reduced hepatic synthesis of antimicrobial proteins, such as albumin and complement, lead to impaired free radical and lipopolysaccharide binding and opsonisation, respectively [7].

Both innate and adaptive immune responses within AoCLF are impaired, independent of the underlying aetiology of cirrhosis, which bears striking similarities to septic shock [12]. Our group and others have previously described AoCLF as a state of cellular immune depression [12, 13]. TNF-α production by monocytes and HLA-DR expression are both significantly depleted in AoCLF, independent of aetiology, compared to stable cirrhotics and healthy controls. These changes may reflect a state of immune exhaustion as a consequence of uncontrolled immune activation in AoCLF. However, from these findings it is not yet clear if this state of immune dysfunction is causal or consequential in the progression from cirrhosis to AoCLF and needs more work to address this in more detail.

Similar to septic shock subjects, appreciable reductions in $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes are detected in AoCLF [14]. However, effects of T lymphocytes in AoCLF are more complicated than analysis of simple numerical depletion. $CD4^+$ T cell subsets in AoCLF are of varying prevalence. Regulatory T lymphocyte populations appear resistant to apoptosis and are upregulated in correlation to severity of AoCLF [15]. Regulatory T lymphocytes have regulatory properties that affect signalling downstream of various innate and adaptive immune cells and play an important role in maintaining immunological tolerance to self and foreign antigens. Their immunosuppressive effects are possibly important in further perpetuating impaired immune response in AoCLF.

Conclusions

Infection plays a major role in the pathogenesis and mortality in AoCLF. The mechanisms conferring the susceptibility to infection are numerous and share similarities with other systemic inflammatory pathologies. Further research is required to explore the exact immunological mechanisms that lead to the increased predisposition to infection in patients with cirrhosis in order to develop targeted immunotherapeutic strategies to improve the outcome in this increasingly prevalent and devastating disease.

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