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INVITED EDITORIAL

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Editorial: infections and hepatic encephalopathy–does the chicken or the egg come FIRST? A novel perspective at the horizon

Cirrhotic patients are at risk for bacterial infections, mainly due to gut dysbiosis, loss of intestinal integrity, bacterial translocation, cirrhosis-associated immune dysfunction and portal-systemic shunting.[1] Infections occur in almost 46% of hospitalised patients, are the most frequent cause of death, particularly in those with decompensated disease[2] and are the most frequent precipitating factor for the development of acute-on-chronic liver failure (ACLF).[3,4] Acute decompensation (AD) is initiated by acute worsening of stable cirrhosis through different pathophysiological mechanisms considered as precipitants. CANONIC[3] and PREDICT[5] studies modify this view suggesting that AD manifests mainly because of systemic inflammation, inducing multiple organ dysfunction and presents with different clinical phenotypes. Recently, the PREDICT study group[6] demonstrates that bacterial infections, severe alcoholic hepatitis, gastrointestinal bleeding and hepatic encephalopathy (HE) were related to AD. Therefore, bacterial infections and systemic inflammation play a key role on the course of cirrhosis by precipitating or aggravating decompensation and organ failure, particularly with circulatory, renal and central nervous system involvement.

In the traditional view, infections have been considered as a major risk factor for HE.[7] Merli demonstrated that HE was frequent in cirrhosis with infection without SIRS (79%) and with sepsis (90%). Infection was the only independent predictor of cognitive impairment (OR 9.5) at multivariate analysis. Minimal HE was also related to infections and reversible after resolution.[8]

Alabsawy[9] proposed a different view from such well-established paradigm: namely that HE represent an important determinant for infections. In fact, the authors introduce an innovative concept according to which HE plays a decisive role in the pathogenesis of infections. The association appears substantiated by statistical analysis. On multivariate analyses, overt HE (OR 1.532), and admission to intensive care (OR 2.303) were independent risk factors for de-novo infection. The association between overt HE and de-novo infection may be a putative mechanism explaining the higher 28-day mortality.

In modern medicine, any statistical association should stimulate research not only to confirm it in larger, independent populations but also to identify the underlined pathophysiology and possibly a target therapy. The authors speculate about several possible explanation of these findings because some mechanisms underlying the interaction between the immune and nervous systems are still not entirely clear but are possibly mediated by neural pathways able to modulate the immune system. Moreover, also the role of ammonia, a well-known toxin involved in HE pathogenesis, should be further clarified.

Rifaximin has entered in the drug armamentarium for HE long-term secondary prophylaxis. Its specific mechanism of action is still not fully understood but reduces circulating gut-derived endotoxins and modulate gut microbiota. Patel et al[10] showed that rifaximin not only resolve HE, but also reduces the likelihood of infection and systemic inflammation. Moreover, rifaximin plays a role in gut-barrier repair which could be the mechanism by which it ameliorates bacterial translocation and systemic endotoxemia typical of cirrhosis. Therefore, a such preventive pharmacological approach is not only useful for HE prophylaxis but could also be promising for infection prevention and might have, long term, a beneficial effect on prognosis.

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LINKED CONTENT

This article is linked to Alabsawy et al papers. To view these articles, visit https://doi.org/10.1111/apt.16790 and https://doi.org/10.1111/apt.16829

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