

Sepsis in alcohol-related liver disease.

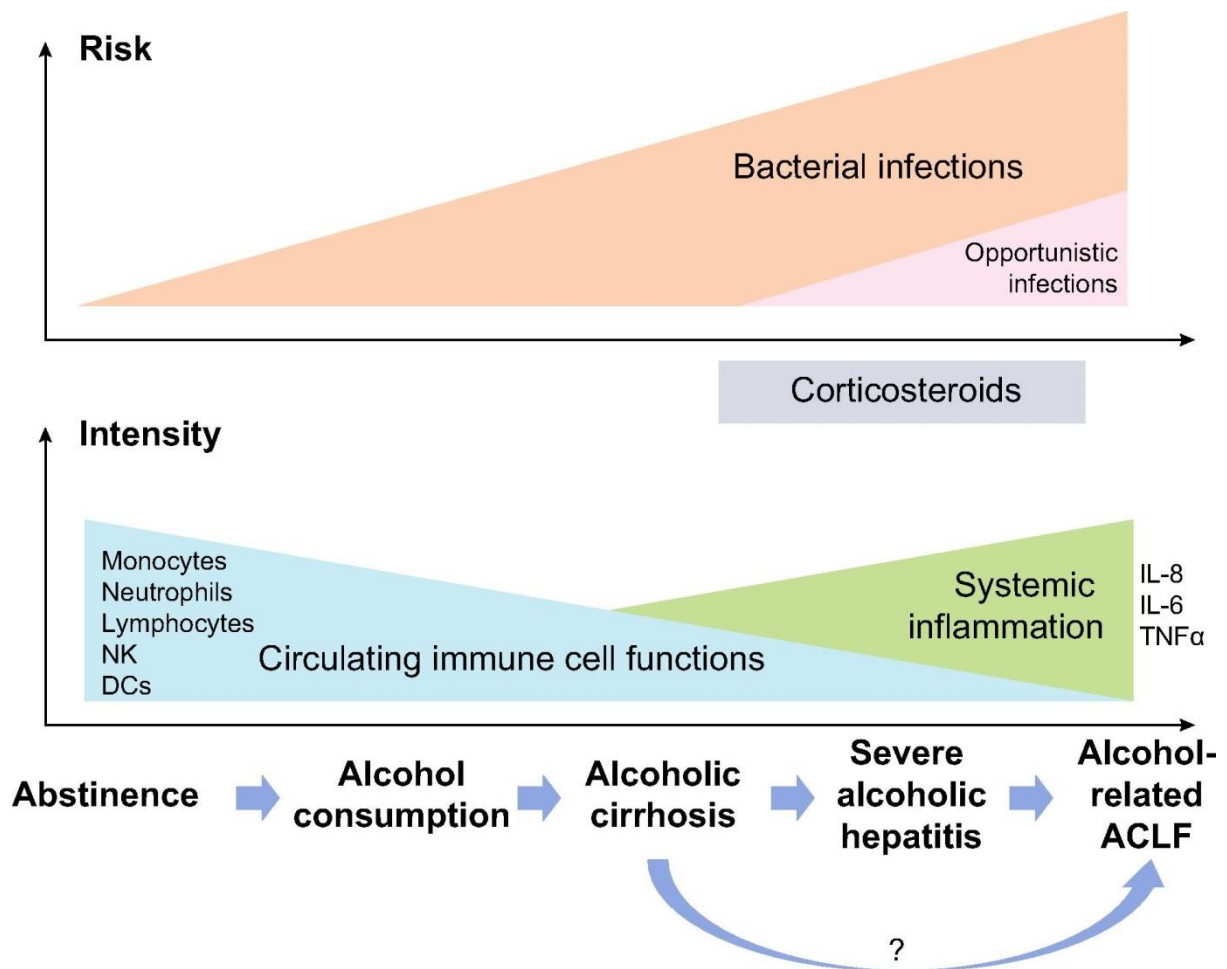
Dr Thierry Gustot et al. Published in Journal of Hepatology Volume 67, Pages 1031-1050 (November 2017).

Excessive alcohol consumption is a major public health problem. In 2012, over three million deaths were attributed to alcohol consumption, corresponding to 5.9% of total deaths worldwide. Alcohol is the most frequent cause of cirrhosis and accounts for approximately 40% of all liver transplants in Europe. Although mortality from alcohol-related liver disease (ALD) has declined over the last few decades in most Western European countries, ALD remains the most important cause of death due to alcohol.

The spectrum of ALD includes steatosis, steatohepatitis, progressive liver fibrosis, and cirrhosis and its complications. At any stage, patients can develop a severe form of ALD called alcoholic hepatitis (AH). Although most heavy drinkers develop steatosis, only a small subset of them will develop AH, and 10–20% progress to cirrhosis. Current management of ALD focuses on alcohol abstinence, nutritional support, and primary and secondary prevention of cirrhosis complications.

AH is a clinical entity (which typically presents abruptly) characterised by recent onset (<3 months) of jaundice and typical histological lesions in a patient with on-going alcohol consumption (minimal threshold for women ≥ 40 g per day [3 drinks], for men ≥ 50 –60 g per day [4 drinks]). The true prevalence of AH is currently unknown, owing to the lack of systematic biopsy-driven diagnosis, but it has been reported to be as high as 20% in alcoholic hospitalised patients. Its severe form (severe alcoholic hepatitis [sAH]; defined by a Maddrey discriminant function [mDF] ≥ 32) is associated with a high risk of mortality in the short-term (about 30% at one month). Although treatment for sAH remains a topic for debate, corticosteroids (prednisolone 40 mg per day) have been reported to result in a 14% reduction in 1-month mortality in patients with sAH, in a meta-analysis of five randomised controlled trials (RCT). A recent large RCT (STOPAH study) confirmed that corticosteroids significantly improved survival at 28 days compared to placebo and after adjustment for different severity factors, but at a lower level than expected. This survival benefit was not maintained at 90 days and one year.

Individuals who chronically drink excessive amounts of alcohol are usually subclinically “immunocompromised”. This immune dysfunction becomes clinically significant only when a secondary insult occurs. Clinical evidence indicates that chronic alcohol consumption increases the risk of viral and bacterial infections. For example, the combined immunosuppressive effects of alcohol and human immunodeficiency virus (HIV) infection are well described. Excessive alcohol use is associated with increased risk of chronic hepatitis C infection and immunologic studies have found that alcohol and hepatitis C virus (HCV) are synergistic in inhibition of antigen-specific immune responses and activation of non-specific pro-inflammatory responses.



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Bacterial infections constitute a major complication of alcoholic and non-alcoholic cirrhosis and are associated with high mortality rates. Infections can occur in compensated and decompensated cirrhosis, frequently precipitate clinical decompensations (variceal haemorrhage, hepatic encephalopathy), and may further deteriorate decompensated patients (variceal rebleeding and hepatorenal syndrome). Therefore, it is not surprising that bacterial infection is associated with increased in-hospital mortality (4/5-fold), and risk of death from sepsis (2-fold). Well-known clinical risk factors for the development of bacterial infections are poor liver function, upper gastrointestinal bleeding, low protein ascites, prior spontaneous bacterial peritonitis, and hospitalisation (especially if associated with invasive procedures and intensive care unit admission). Alcoholic cirrhosis, active alcohol consumption and poor nutritional status have also been suggested as predisposing factors to infection.

SUMMARY

Alcoholic cirrhosis and sAH are recognised as risk factors for infections. The immune defect seems to increase gradually with the severity of ALD. The leaky gut and intestinal dysbiosis, particularly described in ALD, contribute to this immune defect and infectious complications. Infection in patients with sAH is a major driver of

mortality. Systematic screening for infection should be performed at admission, before the initiation of corticosteroids. The controversy surrounding the contribution of corticosteroids to patients' susceptibility to infections remains. Although one study observed an increased risk of infection in patients treated with corticosteroids, this was not confirmed in a recent meta-analysis and the higher risk in the STOPAH trial was conversely associated with a lower risk of death in patients treated with prednisolone. Opportunistic infections become an emergent problem, particularly in patients with SAH treated by corticosteroids. High levels of suspicion, with systematic screening and prompt, adequate treatment are warranted to improve outcomes in those patients. Prophylactic or preemptive strategies in this high-risk population might be a preferable option, because of the high short-term mortality rate despite adequate therapies. However, these strategies should be assessed in well-designed trials before clinical implementation.