Review

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# Renal and circulatory dysfunction in cirrhosis: Current management and future perspectives

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Chronic liver diseases are amongst the top leading causes of death in Europe as well as in other areas of the world [1–3]. Chronic liver diseases are characterized by unrelenting progression of liver inflammation and fibrosis over a prolonged period of time, usually more than 20 years, which may eventually lead to cirrhosis [4]. Advanced cirrhosis leads to a complex syndrome of chronic liver failure which involves many different organs besides the liver, including the brain, heart and systemic circulation, adrenal glands, lungs, and kidneys [5]. The high morbidity and mortality secondary to chronic liver failure is due to complications related to the dysfunction of these organs, either alone or, more frequently, in combination. Understanding the mechanisms leading to organ dysfunction is crucial to the development of strategies for treatment and prevention of complications of cirrhosis. This article reviews our current knowledge, as well as future perspectives, on the management of circulatory and renal dysfunction in chronic liver failure.


## A brief review of the current understanding of renal and circulatory dysfunction in cirrhosis

A wealth of evidence indicates that impairment in circulatory function is the main cause of renal dysfunction in cirrhosis. The dysfunction in the systemic arterial circulation is largely characterized by a reduction in systemic vascular resistance due to primary arterial vasodilation of the splanchnic circulation triggered by portal hypertension [6–9]. The relationship between liver disease, portal hypertension, and abnormalities in splanchnic circulation is discussed in detail in several recent reviews [4,10,11]. The vasodilation of the splanchnic arterial circulation is due to an increased production/activity of vasodilator factors, particularly nitric oxide, carbon monoxide, and endogenous cannabinoids [7–13].

At the early stages of cirrhosis, when patients are usually asymptomatic and with normal physical status, the increase in hepatic vascular resistance, mainly due to fibrosis, is moderate and therefore the increase in portal pressure is also moderate. In this context, there is a slight reduction in systemic vascular resistance due to moderate splanchnic arterial vasodilation which is compensated by an increase in cardiac output, thus permitting arterial pressure and effective arterial blood volume to remain within normal limits [6,7]. In advanced stages of cirrhosis, when patients are usually symptomatic and have already developed some complications of the disease, the reduction in systemic vascular resistance is marked and cannot be compensated by further increases in cardiac output; therefore, underfilling of the arterial circulation develops, there being a disarrangement between the intravascular blood volume and a very enlarged intravascular arterial circulation [7]. Moreover, evidence indicates that at this stage of the disease there is a reduction in the cardiac output that contributes to the arterial underfilling [14]. In this context of marked underfilling of the arterial circulation, arterial pressure must be maintained by the activation of vasoconstrictor systems, including the renin–angiotensin-system, the sympathetic nervous system, and, at late stages, a non-osmotic hypersecretion of arginine vasopressin (the antidiuretic hormone) [7]. These systems help maintain effective arterial blood volume and arterial pressure but have important effects on kidney function, particularly sodium and solute-free water retention with accumulation of ascites and edema. If the activation of these systems is extreme, renal vasoconstriction leading to markedly reduced glomerular filtration rate may occur, a condition known as hepatorenal syndrome (HRS) [7,8]. Other factors that may contribute to the development of HRS are vasoactive mediators acting on the intrarenal circulation. An increased synthesis of several vasoactive factors in the intrarenal circulation, which may affect renal blood flow or glomerular filtration rate, such as cysteinyl leukotrienes, thromboxane A2, $F_2$-isoprostanes, and endothelin-1, has been reported, yet the role of these factors in the pathogenesis of HRS remains poorly understood [6]. Nonetheless, a role for endothelin-1 is unlikely since the administration of the endothelin antagonist tazosentan does not improve renal function in patients with type 2 HRS [15]. Recent data indicate that impairment in the cardiac function, likely due to cirrhotic cardiomyopathy, is a risk factor for the development of HRS and likely further contributes to the impairment of the arterial blood volume that is related to splanchnic vasodilation [16,17]. A summary of the pathogenesis of ascites and functional renal abnormalities with possible therapeutic interventions are shown in Figs. 1–3.

A wealth of evidence indicates that altered splanchnic hemodynamics is related to the development of portal hypertension [11]. On the other hand, studies in both experimental animals and patients with cirrhosis suggest that bacterial translocation, the

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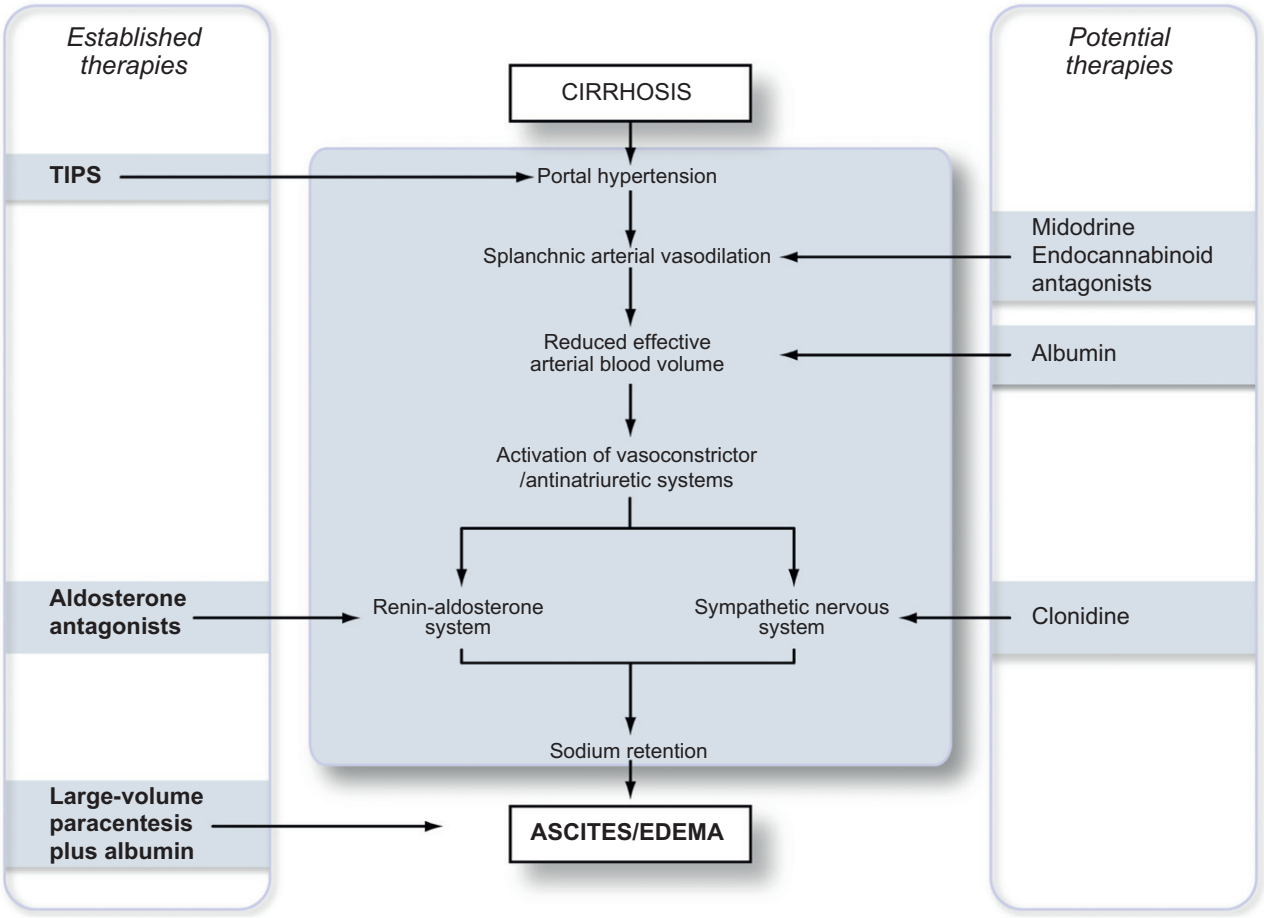


**Fig. 1. Schematic representation of the proposed pathogenesis of ascites and edema formation in cirrhosis**. Established therapies are given on the left side and potential new therapies on the right. TIPS, transjugular intrahepatic portosystemic shunt.

passage of bacteria from the intestinal lumen to mesenteric lymph nodes, may play an important role in circulatory dysfunction in advanced cirrhosis [18,19]. Bacterial translocation may elicit an inflammatory response with increased production of proinflammatory cytokines in the splanchnic area, which may in turn lead to vasodilatation of the splanchnic arterial vessels. Patients with cirrhosis and increased levels of lipopolysaccharide-binding protein or circulating levels of bacterial DNA, which are considered surrogate markers of bacterial translocation, have higher serum levels of cytokines, lower systemic vascular resistance, and higher cardiac output when compared to those who do not [20,21]. The important role of bacterial translocation in circulatory dysfunction is further supported by the observation that the administration of norfloxacin, an antibiotic that causes selective intestinal decontamination, improves circulatory function [22,23].

## The expanded extracellular fluid volume: ascites and edema

Sodium is the main determinant of the volume of the extracellular fluid (ECF). In healthy subjects the amount of sodium is maintained constant through a very precise equilibrium between sodium intake and sodium excretion by the kidneys [24,25]. In advanced cirrhosis, this equilibrium is lost because of an increased retention of sodium in the kidneys and positive sodium balance develops leading to expansion of the ECF [26,27]. The excess of ECF is mainly stored in the peritoneal cavity (because of the high pressure of the splanchnic capillaries due to portal hypertension) and in the interstitial tissue of the legs (because of the high pressure of the capillaries of the lower extremities), causing ascites and edema, respectively. Excessive ECF may also be stored in other locations, such as the pleural space, causing pleural effusion. Ascites and edema are the most frequent complication of patients with advanced chronic liver diseases.

### *Current management*

The current management of ascites and edema is based on dietary salt restriction together with diuretics to increase renal sodium excretion [28] (Table 1). The aim of the treatment is therefore to achieve a natriuresis higher than sodium intake that causes negative sodium and fluid balance with weight loss and reduction in the ECF volume. The diuretics of choice are aldosterone antagonists, because of the increased aldosterone secretion present in cirrhosis [29]. Administration of loop diuretics (mainly furosemide) in combination with aldosterone antagonists may be helpful in patients with recurrent ascites [28]. Diuretic treatment is effective in more than two thirds of patients with ascites. Doses of diuretics should be adjusted according to several factors, particularly whether the episode of ascites is the first or recurrent,