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**Hepatosplanchnic circulation in cirrhosis and sepsis**

Prin M *et al*. Splanchnic circulation in cirrhosis

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**Abstract**

Hepatosplanchnic circulation receives almost half of cardiac output and is essential to physiologic homeostasis. Liver cirrhosis is estimated to affect up to 1% of populations worldwide, including 1.5% to 3.3% of intensive care unit patients. Cirrhosis leads to hepatosplanchnic circulatory abnormalities and end-organ damage. Sepsis and cirrhosis result in similar circulatory changes and resultant multi-organ dysfunction. This review provides an overview of the hepatoplanchnic circulation in the healthy state and in cirrhosis, examines the signaling pathways that may play a role in the physiology of cirrhosis, discusses the physiology common to cirrhosis and sepsis, and reviews important issues in management.

**Key words:** Liver cirrhosis; Sepsis; Splanchnic circulation; Hepatic circulation; Hepatic artery buffer response

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**Core tip:** The prevalence of cirrhosis in critically ill patients is increasing worldwide. Cirrhosis leads to hepatosplanchnic circulatory abnormalities and end-organ damage, which resemble the clinical syndrome of patients with sepsis. The pathophysiology of cirrhosis can both predispose patients to, and exacerbate, sepsis. An understanding of this pathophysiology may assist critical care providers in the development and application of treatment modalities.

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**Introduction**

The prevalence of severe liver disease among intensive care unit (ICU) patients ranges from 1.35%-3.3%[[1-3](#_ENREF_1)] and is increasing worldwide. A study of 174 ICUs in the United Kingdom reported that the number of patients admitted to ICU with alcoholic liver disease tripled from 1995 to 2005[[1](#_ENREF_1)]. The ICU mortality for patients with liver disease is high, ranging from 36.6% to 73.6%[[4-8](#_ENREF_4)], and the one-year mortality for ICU survivors is as high as 68%[[6](#_ENREF_6)].

Liver disease exacerbates coexisting diseases. Hepatic cirrhosis is associated with an increased risk for ICU-associated pneumonia, respiratory failure, and death[[9](#_ENREF_9),[10](#_ENREF_10)]. In both the UK and the United States the proportion of sepsis in the setting of liver disease is increasing and patients with cirrhosis are more likely to die from sepsis[[11](#_ENREF_11),[12](#_ENREF_12)]. The systemic effects of cirrhosis also increase the morbidity and mortality of surgery[[13](#_ENREF_13),[14](#_ENREF_14)].

Given the high morbidity of severe liver disease in critical care, an appreciation of hepatosplanchnic physiology may help guide intensivists, particularly those who care for patients with sepsis. This review provides an overview of the hepatic and splanchnic circulatory anatomy, examines the factors that contribute to the circulatory changes of cirrhosis, reviews the pathophysiology common to cirrhosis and sepsis, and discusses clinical management in the ICU.

***Epidemiology of Cirrhosis in the ICU***

Cirrhosis may be the result of infectious, autoimmune, vascular, hereditary, or toxic factors. In Europe and the US it is primarily caused by either alcohol use or infection with Hepatitis C virus (HCV), while in Asia and sub-Saharan Africa the most common cause is infection with Hepatitis B virus (HBV)[[15](#_ENREF_15)]. Observational studies in the UK and France showed that the most common cause of cirrhosis among patients admitted to ICUs was alcoholic hepatitis (43%-78%) followed by viral hepatitis (10%-19%)[[4](#_ENREF_4),[6](#_ENREF_6),[16](#_ENREF_16)].

Although the precise global prevalence is unknown because compensated disease can remain undetected for many years, up to 1% of populations worldwide may have histological cirrhosis[[17](#_ENREF_17)]. In the United States the prevalence of cirrhosis is estimated at 0.15%[[18](#_ENREF_18)].

***Hepatic circulation***

The liver receives 20% of cardiac output[[19](#_ENREF_19)]. Total liver blood flow is approximately 100 mL/min per 100 g liver tissue, or 800-1200 mL/min[[20](#_ENREF_20)]. The liver has a dual blood supply with blood from the hepatic artery and portal vein, which together with the bile duct form the hepatic triad. The hepatic artery is a branch of the celiac artery, with a pressure similar to aortic pressure (mean 60-80 mmHg). It carries well-oxygenated blood to the liver, providing approximately 30% of hepatic blood flow. The valveless portal vein is a low-pressure/low-resistance system that provides partially deoxygenated blood from the intestinal bed to the liver, accounting for 70% of hepatic blood supply. Normal mean portal pressures range from 5-10 mmHg[[21](#_ENREF_21)] (Figure 1). Oxygen delivery to hepatocytes does not depend on the proportion of portal versus arterial blood flow[[22](#_ENREF_22)]. Animal models have demonstrated that normal hepatocyte oxygen supply is approximately 16 mL/min per 100 g liver tissue with an extraction ratio of 35%[[22](#_ENREF_22)]. Oxygen extraction changes with variations in demand; as oxygen supply decreases the extraction can approach 100%[[22](#_ENREF_22)].

The unique interaction between the hepatic artery and portal vein flow, termed the Hepatic Artery Buffer Response (HABR)[[23](#_ENREF_23)], is essential to maintenance of hepatic blood flow. The hepatic artery flow increases in response to decreases in portal venous flow[[24](#_ENREF_24),[25](#_ENREF_25)]. This relationship is unilateral; portal vein flow does not change in response to alterations of hepatic artery flow. The HABR is capable of offsetting a 25%-60% decrease in portal vein flow[[26](#_ENREF_26),[27](#_ENREF_27)].

The HABR is the primary regulator of hepatic artery flow. Flow does not change in response to metabolic activity or blood oxygen content[[28](#_ENREF_28)] and myogenic autoregulation plays a relatively small role[[29](#_ENREF_29)]. The physiologic purpose of HABR is unclear, as hepatic oxygen supply exceeds demand and oxygen extraction can increase in response to metabolic changes or decreased blood supply. Further, the underlying physiology remains unclear. The role of nitric oxide synthase (NOS) has been investigated but animal models have not shown a major contribution to the HABR[[30](#_ENREF_30)]. The HABR is likely regulated by washout of adenosine, mediated through P1-purinoceptors[[26](#_ENREF_26),[31](#_ENREF_31),[32](#_ENREF_32)].

***Splanchnic circulation***

The splanchnic vasculature, comprised of gastric, small intestinal, colonic, pancreatic, and splenic vessels arranged in parallel, receives approximately 25% of cardiac output at rest[[33](#_ENREF_33)] and more during digestion. The major supplying arteries are the celiac, superior and inferior mesenteric. The capillary beds of this system form extensive anastamoses. Human studies of splanchnic blood flow are scarce because direct measurement of splanchnic vasculature is almost impossible without surgery. Most studies rely on indirect measurements and extrapolation from experimental models.

Splanchnic blood flow is regulated by a combination of local and systemic factors including paracrine and endocrine signaling, vasoactive substances, and sympathetic innervation. Autonomic regulation is a weak contributor, although it is enhanced in the fed state compared to the starved state[[34](#_ENREF_34)]. In a low-flow state, splanchnic blood flow decreases in order to maintain vital cardiac and cerebral blood supply[[35](#_ENREF_35)]. This response occurs even after small-volume hemorrhage[[36](#_ENREF_36)]. The splanchnic organs do not produce lactate early in low-flow states because oxygenation is preserved due to high baseline supply[[35](#_ENREF_35)]. However, recovery of splanchnic flow is protracted even after adequate volume resuscitation[[37](#_ENREF_37)].

The hepatosplanchnic vasculature’s active response to systemic bloodflow contributes to its role as a blood volume reservoir, and its anatomic position just distal to the inferior vena cava (IVC) make it a significant component of cardiovascular preload. As a capacitance vessel, it has been shown to pool 2.5% or mobilize up to 5%-6% of total blood volume (TBV) in response to physiologic challenges[[38-40](#_ENREF_38)].

***Circulatory changes of cirrhosis***

Liver cirrhosis is the end-stage of chronic liver disease characterized by replacement of hepatic tissue with fibrosis and regenerative nodules (structurally abnormal areas of attempted tissue repair), and impaired liver function. The altered hepatic architecture in cirrhosis leads to circulatory abnormalities, namely portal hypertension, splanchnic vasodilation, and hyperdynamic circulation.

***Portal hypertension***

Portal hypertension is a pathognomic feature of liver cirrhosis, defined as an increase in the hepatic venous pressure gradient (HVPG) (an indirect reflection of the portocaval gradient in patients with cirrhosis) of more than 10 mmHg[[41](#_ENREF_41)]. Portal hypertension can also be diagnosed ultrasonographically: hepatic vein pulsatility flattens from triphasic to monophasic secondary to histologic reductions in hepatic vein compliance. This is accompanied by a decrease in portal vein flow and an increase in the hepatic artery pulsatility index, due to the HABR[[42](#_ENREF_42)]. Portal hypertension can be diagnosed clinically by the presence of esophageal varices, patency of the umbilical vein, and the presence of portocaval shunts (*e.g.,* splenorenal shunts).

The development of portal hypertension is multifactorial. Hepatic fibrosis plays a role by disrupting hepatocyte architecture and increasing resistance to bloodflow. Hepatic sinusoidal pressure is negatively correlated with the percentage of un-fibrosed portal spaces, or “residual portal spaces”[[43](#_ENREF_43)]. Hepatic fibrosis is largely caused by hepatic stellate cell injury. When injured by toxins (*e.g.,* alcohol, hepatitis virus, infection, acetaminophen) or exposed to platelet activating factor (PAF), hepatic stellate cells transform into myofibroblast-like cells, releasing collagen I and III[[44](#_ENREF_44)]. Other cell types implicated in fibrosis include myofibroblasts derived from portal vessels[[45](#_ENREF_45)] and hematopoietic stem cells[[46](#_ENREF_46)].Fibrosis is also stimulated by inflammatory cytokines and vasoactive molecules, including chemotactic protein 1, transforming growth factor (TGF)-β1, nitric oxide, endothelin-1 and angiotensin II[[47](#_ENREF_47),[48](#_ENREF_48)]. These mediators are increased in liver disease and can further upregulate their own release, thereby accelerating an inflammatory cycle.

Circulatory system changes may also contribute to the development of portal hypertension. Direct intraoperative measurements have demonstrated that, in cirrhosis, a basal HABR is continuously activated but the acute HABR is impaired[[49](#_ENREF_49)]. While recent data suggests that angiotensin II is a primary mediator of the progression from hepatic inflammation to fibrosis[[48](#_ENREF_48)], the entire renin-angiotensin-aldosterone system (RAAS) may also play a role[[50](#_ENREF_50)].

***Splanchnic vasodilation***

Splanchnic arteriolar vasodilation with hyperdynamic flow has been demonstrated in liver disease by observation of shortened albumin transit times through the splanchnic circulation[[51](#_ENREF_51)], increased splenic and mesenteric bloodflow[[52](#_ENREF_52)], and decreased measured superior mesenteric artery impedance[[53](#_ENREF_53)]. Decreased mesenteric artery impedance begins early in liver disease and worsens with the progression to cirrhosis[[53](#_ENREF_53)]. Splanchnic vasodilation is multifactorial and not completely understood. The pathogenesis is partly explained by increased resistance to portal outflow, but activation of other mediators including the RAAS, nitric oxide, platelet activating factor, vasopressin, and inflammatory molecules likely plays a role.

Early in liver disease, total blood volume increases but is largely sequestered in the splanchnic vascular bed, leading to “splanchnic steal” and systemic hypovolemia[[54-56](#_ENREF_54)]. Animal models have shown that this occurs before the development of portal hypertension or splanchnic vasodilation[[57](#_ENREF_57)]. Splanchnic steal is likely mediated by the RAAS[[58](#_ENREF_58)], a hormone cascade which leads to volume loading through modulation of renal sodium retention. Recently an alternate RAAS pathway, angiotensin-converting-enzyme-2 (ACE-2) has also been investigated for its role in liver disease. ACE-2 levels are upregulated in cirrhosis, and expression is directly related to hepatocyte hypoxia[[59](#_ENREF_59),[60](#_ENREF_60)]. The ACE-2 system acts downstream at the Mas receptor, which vasodilates splanchnic vessels. In cirrhosis, blockade of this receptor reduces portal pressure[[60](#_ENREF_60)].

Nitric oxide (NO) is an endothelial-derived relaxing factor. Cirrhotic patients not only have increased expression of NO, but also show increased sensitivity to NO-mediated vasodilation[[61](#_ENREF_61)]. NO causes vasodilation by stimulating soluble guanylate cyclase to generate cyclic guanosine monophosphate (cGMP) in vascular smooth muscle[[62](#_ENREF_62)]. It also decreases vascular response to vasoconstrictors[[63](#_ENREF_63)]. In animal models this vasoplegia is completely reversed by removal of the endothelium[[64](#_ENREF_64)]. The constitutively expressed endothelial isoform of NOS has been implicated as a major contributor to splanchnic vascular overexpression of NO and its activity precedes splanchnic vasodilatation in rats[[65](#_ENREF_65)].Neuronal NOS is also upregulated in experimental models of cirrhosis[[66](#_ENREF_66),[67](#_ENREF_67)]. In addition to nitric oxide, other vasodilators suggested to play a role in splanchnic dilation include carbon monoxide[[68](#_ENREF_68)], plasma calcitonin gene related peptide (CGRP)[[69](#_ENREF_69)], eicosanoids, bile salts, adenosine and substance P[[41](#_ENREF_41)].

PAF is a pro-inflammatory molecule that affects platelet aggregation, vascular permeability, and vascular tone. Hepatic concentrations of PAF are increased in cirrhosis[[70](#_ENREF_70)]. The effect of PAF on vasculature tone is regional, and exogenous PAF increases portal pressure but decreases systemic arterial blood pressure[[71](#_ENREF_71)]. PAF is also neoangiogenic, and may play a role in the development of the arteriovenous and portocaval shunts common to cirrhosis.

Endothelin is a paracrine vasoconstrictor, released by vascular endothelial cells, which is increased in cirrhosis[[72](#_ENREF_72)]. It stimulates hepatic sinusoidal macrophages to produce platelet activating factor (PAF)[[73](#_ENREF_73)], particularly in the setting of cirrhosis[[74](#_ENREF_74)]. There are least four endothelin receptors (ETA, ETB1, ETB2, ETC). Endothelin-1 mediated vasoconstriction occurs through the activation of the ETA receptor, and the ETB1 receptor stimulates the release of nitric oxide[[75](#_ENREF_75)]. Endothelin-1 also stimulates catecholamine release[[76](#_ENREF_76),[77](#_ENREF_77)] which may contribute to the elevated levels seen in cirrhosis. In vitro models have shown a direct relationship between ETA and ETB expression and portal pressure[[78](#_ENREF_78)]. It is unclear if endothelin is increased in cirrhosis as a consequence or pathogenic response to splanchnic dilation.

Vasopressin is a neurohypophyseal hormone that regulates plasma osmolality and increases vascular resistance in vasodilated states. Cirrhotic patients are vasopressin deficient, but respond to exogenous vasopressin (and its analogues terlipressin or ornipressin) with increased blood pressure[[79](#_ENREF_79)]. It is unclear if vasopressin deficiency precedes or causes splanchnic dilation.

***Hyperdynamic circulation***

The hyperdynamic circulation associated with cirrhosis is characterized by increased heart rate, increased cardiac output, and systemic hypotension[[80](#_ENREF_80)]. The etiology of hyperdynamic circulation is unclear but may include (1) desensitization of myocardial β-receptors in the setting of an activated sympathetic nervous system[[81](#_ENREF_81),[82](#_ENREF_82)]; (2) splanchnic steal that decreases the effective circulating volume; (3) anemia[[83](#_ENREF_83)]; and (4) cardiodepressants such as nitric oxide[[84](#_ENREF_84),[85](#_ENREF_85)] and endogenous cannibinoids[[86](#_ENREF_86)]. Hyperdynamic circulation is exacerbated by systemic and intrahepatic angiogenesis, which is mediated by hypoxia, PAF, vascular endothelial growth factor, and transforming growth factor[[87](#_ENREF_87)]. Portal hypertension-mediated engorgement of collateral veins (*i.e.,* esophageal varices, hemorrhoids, caput medusae) also increases the circulatory surface area.

Observational echocardiographic studies of cirrhotic patients have noted normal baseline cardiac contractility but attenuated stress-response, with disturbances of left diastolic function[[88](#_ENREF_88),[89](#_ENREF_89)]. This dysfunction is termed cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is distinct from alcoholic cardiomyopathy which is characterized by reduced left ventricular contractility at baseline[[90](#_ENREF_90)]. Overt heart failure is rare in cirrhotic cardiomyopathy. The splanchnic sequestration of blood volume reduces the cardiac workload and disguises the symptoms of heart failure; these can be unmasked by physical or pharmacologic stress (*e.g.,* surgery). The pathophysiology of cirrhotic cardiomyopathy is not completely understood but endocannibinoid-receptor antagonists have improved cardiac contractility in animal models, suggesting a role for endocannibinoids in the pathogenesis of cardiac dysfunction[[91](#_ENREF_91)].

***Cirrhosis and sepsis***

The circulatory changes in cirrhosis lead to a clinical syndrome that resembles sepsis (Table 1). Both sepsis and cirrhosis feature a vasodilated state despite high levels of endogenous catecholamines, a compensatory hyperdynamic state with the possibility of cardiac dysfunction, and splanchnic hyperemia with systemic hypovolemia. Both cirrhotic and septic patients frequently present with signs of systemic inflammatory response syndrome (SIRS) including elevated heart rate, elevated respiratory rate, and blunted temperature regulation.

Bacterial infections are a common complication of cirrhosis[[92](#_ENREF_92),[93](#_ENREF_93)], and are the most common independent risk factor for death[[94](#_ENREF_94),[95](#_ENREF_95)]. A multicenter prospective cohort study found the highest case fatality rate was from infections with *Clostridium dificile* (40%), respiratory infections (37.5%), and spontaneous bacteremia (37%)[[94](#_ENREF_94)]. In a large epidemiologic survey, Foreman *et al*[[9](#_ENREF_9)] noted that cirrhosis more than doubles both the risk of being hospitalized with sepsis and the risk of death from sepsis.

The increased risk for sepsis may be attributed to bacteremia, particularly from intestinal bacterial translocation. Bacteremia increases the risk of spontaneous bacterial peritonitis (SBP) which is found in up to 15% of hospitalized cirrhotic patients[[96](#_ENREF_96)] and 3%-3.5% of asymptomatic outpatients with cirrhosis[[97](#_ENREF_97),[98](#_ENREF_98)], and it increases the risk of variceal hemorrhage[[99](#_ENREF_99)]. Bacterial translocation occurs in the setting of splanchnic vasodilation (which increases intestinal mucosal permeability)[[100](#_ENREF_100)], bacterial overgrowth secondary to delayed intestinal transit time[[101](#_ENREF_101),[102](#_ENREF_102)] and structural damage of intestinal epithelial cells[[103](#_ENREF_103)] (Figure 2). iNOS knockout mice are resistant to bacterial translocation, suggesting a link between NO and bacterial translocation[[104](#_ENREF_104)] (Figure 3). Bacterial translocation also stimulates the release of inflammatory mediators, and severity of liver disease correlates with levels of these mediators, including interleukin (IL)-1β, IL-2R, IL-6, IL-8 and IL-10[[105](#_ENREF_105),[106](#_ENREF_106)].

The risk for developing sepsis may also be secondary to impaired cellular immunity. In a single-center study, decreased levels of tumor necrosis factor (TNF-α) and human leukocyte antigen-DR (HLA-DR) were found in patients with acute liver failure and patients with sepsis, in comparison to patients with stable cirrhosis[[106](#_ENREF_106)]. Changes in cellular immunity may alter the secretion of inflammatory mediators and the vulnerability to infection.

Liver disease increases the susceptibility for sepsis, but sepsis also aggravates liver disease. In animal models of sepsis, portal vein and overall hepatic flow decreases and angiotensin II has been implicated[[107](#_ENREF_107),[108](#_ENREF_108)]. Up to one third of patients with late septic shock have depleted vasopressin levels[[109](#_ENREF_109)] resulting in hypotension, vasoplegia, and catecholamine resistance. These circulatory changes may affect hepatic blood flow and function. In septic patients with no previous history of liver disease, postmortem histopathologic hepatic changes were found, including portal inflammation, centrilobular necrosis, and hepatocellular apoptosis[[110](#_ENREF_110)]. Human studies of hepatosplanchnic flow in sepsis remain scarce and it is important to note that animal studies do not always include volume-resuscitated arms, which would increase their clinical relevance.

***Critical care considerations***

Patients with cirrhosis may be admitted to the ICU with decompensated disease, after surgery, or with infection and sepsis. Although the Child-Turcotte-Pugh score[[111](#_ENREF_111),[112](#_ENREF_112)] has traditionally been used for risk assessment, the Model for End Stage Liver Disease (MELD) score[[113](#_ENREF_113)] is now commonly used to assess liver disease and rank-list patients for liver transplantation. While the MELD score is an excellent tool for predicting short-term mortality amongst cirrhotic patients awaiting liver transplantation[[114](#_ENREF_114)], data regarding its predictive power for mortality in hospitalized cirrhotic patients has been inconsistent. Teh *et al*[[115](#_ENREF_115" \o "Teh, 2007 #203)] retrospectively demonstrated increased mortality in postoperative cirrhotic patients with MELD greater than 20, while Oberkofler *et al*[[[115](#_ENREF_115),[116](#_ENREF_116)] found no mortality prediction in a cohort of liver transplant recipients.

ICU scoring systems (*e.g.,* Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II) have demonstrated superior mortality prediction in cirrhotic patients in the ICU[[117](#_ENREF_117),[118](#_ENREF_118)]. Recently, two new scores have been developed for mortality prediction: a modified SOFA score for Chronic Liver Failure (CLIF-SOFA) and the Royal Free Hospital Score[[119](#_ENREF_119),[120](#_ENREF_120)]. Single biomarkers have also shown prognostic value. In developing the CLIF-SOFA score, Moreau *et al* demonstrated that leukocyte count was independently associated with acute-on-chronic liver failure and associated 28-day mortality. Furthermore, in an effort to identify patients at risk for imminent decompensation, Lopez-Velazquez *et al* found that bilirubin concentration alone was an independent predictor of 7-day mortality[[121](#_ENREF_121)].

Beyond scoring systems, multiorgan dysfunction in cirrhosis has been correlated with hospital mortality: a prospective study of ICU patients with cirrhosis found that coma and acute renal failure were independent predictors of mortality[[8](#_ENREF_8)]. While organ dysfunction is reflected in scoring systems, these findings highlight the importance of assessing patients for clinical markers of dysfunction other than those included in scores. Recently a novel method of transient elastography has been used to measure liver stiffness, a metric associated with hepatic fibrosis. In a prospective study of ICU patients, liver stiffness was highest in patients with decompensated cirrhosis (compared to other critical illnesses or comorbidities), and was associated with increased ICU- and post-discharge-mortality[[122](#_ENREF_122)]. Transient elastography may serve as a useful triage tool for critically ill patients with liver disease.

As noted, the circulatory abnormalities of cirrhosis predispose patients to multiorgan dysfunction including heart failure, renal dysfunction, and hemodynamic instability. Monitoring to predict or prevent this morbidity has not been identified, nor has the optimal treatment regimen. Notably, a prospective study of ICU patients with cirrhosis demonstrated 100% mortality for those with pulmonary artery catheters, 84% mortality for patients requiring mechanical ventilation, and 89% mortality for those requiring renal replacement therapy[[8](#_ENREF_8)]. These mortality rates likely reflect a high severity of disease rather than adverse effects of the monitors themselves. Studies are needed to determine the most appropriate monitoring and interventions for ICU patients with cirrhosis.

Given the morbidity and mortality attributable to sepsis for cirrhotic patients in the ICU, intensivists should maintain a high index of suspicion for infection. Early prophylactic antibiotics for patients with cirrhosis may reduce the incidence of bacterial translocation, sepsis, and variceal hemorrhage[[123](#_ENREF_123)]. Studies focused on immune system function and inflammatory mediators may clarify the pathophysiology common to cirrhosis and sepsis, and suggest novel therapeutic interventions.

**Conclusion**

The hepatosplanchnic circulatory system is the largest blood reservoir in the human body and is essential to multiple aspects of homeostasis, including nutrient absorption, endocrine function, and toxin metabolism. Pathologic splanchnic vasodilation in cirrhosis leads to hyperdynamic circulation and blunting of the HABR. These alterations contribute to systemic disease and perioperative mortality, and resemble pathophysiologic changes seen in sepsis. Cirrhosis increases the risk of developing sepsis, and sepsis may exacerbate cirrhosis. A better comprehension of circulatory changes in cirrhosis may lead to therapeutic modalities that improve intensive care management.

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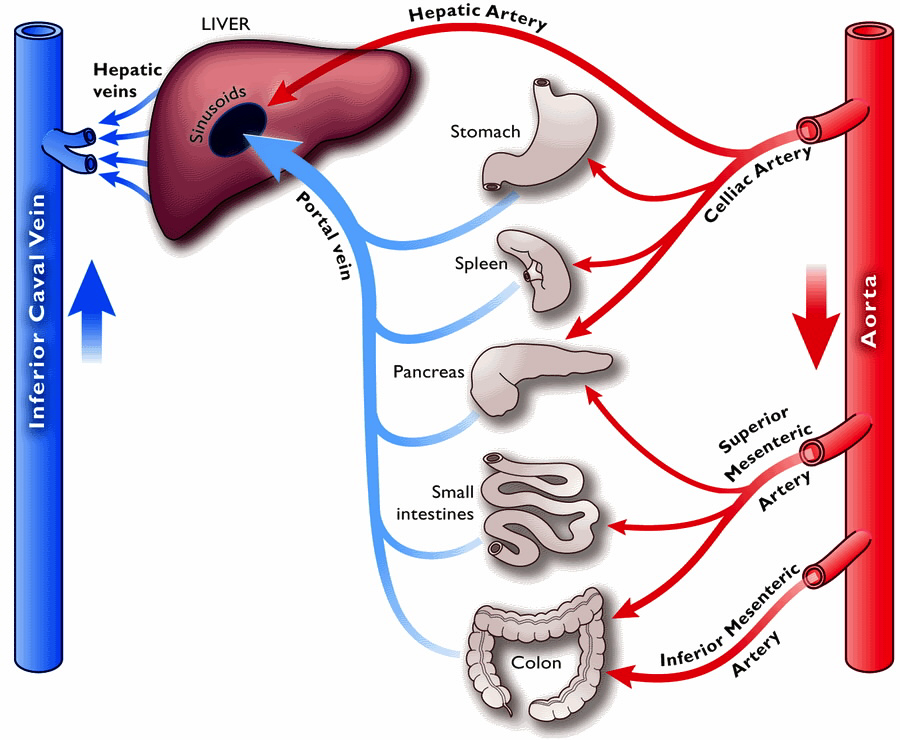
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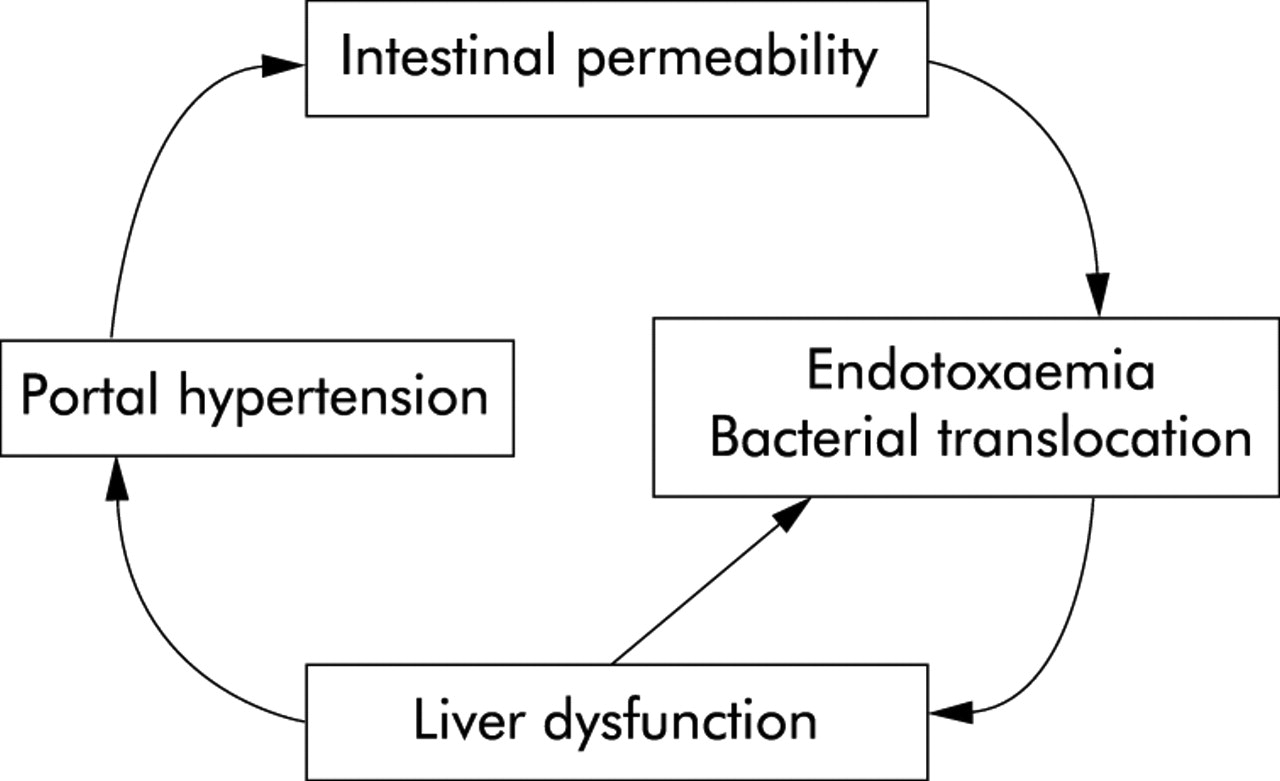
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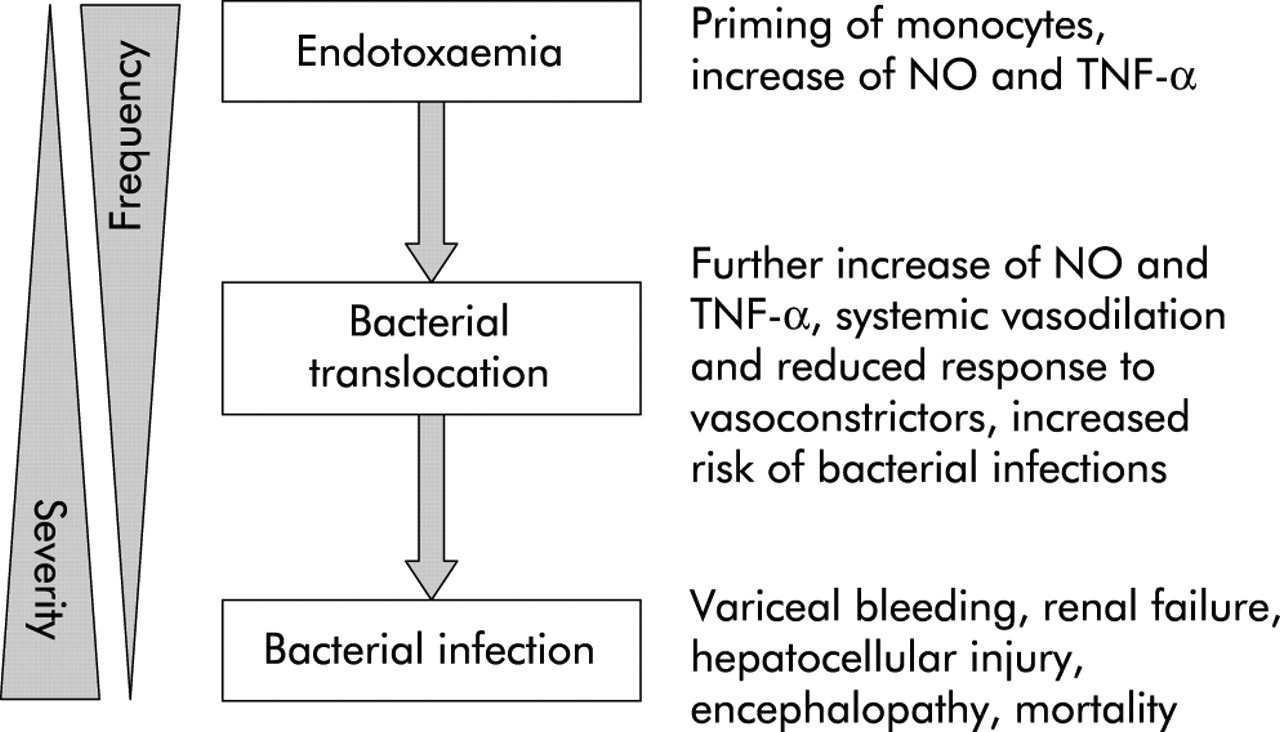
**P-Reviewer:** Carulli l, Cucchetti A, Kitade m, Reshetnyak VI **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**



**Figure 1 Anatomy of the splanchnic, portal and hepatic venous circulation.** (with permission: Gelman S, Mushlin PS: Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology* 2004, **100**: 434-439).



**Figure 2 Damage to the intestinal barrier leads to bacterial translocation and endotoxaemia and thus to impairment of liver function and increase in portal pressure, possibly causing further damage to the gut: a vicious circle.** (with permission: Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK: Infection, coagulation, and variceal bleeding in cirrhosis. *Gut* 2005; **54**: 556-563).



**Figure 3 Endotoxaemia, bacterial translocation, and bacterial infection may be different expressions of the same process at different degrees of severity, and are associated with increasingly severe complications.** NO: Nitric oxide; TNF-α: Tumor necrosis factor α. (with permission: Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK: Infection, coagulation, and variceal bleeding in cirrhosis. *Gut* 2005; **54**: 556-563).

**Table 1 Common features and difference of hepatic cirrhosis and sepsis**

|  |  |  |
| --- | --- | --- |
|  | **Cirrhosis** | **Sepsis1** |
| Prevalence in ICU population[[1-3](#_ENREF_1),[124-126](#_ENREF_124)] | 1%-3% | 11%-33 % |
| ICU mortality[[4-8](#_ENREF_4),[127](#_ENREF_127),[128](#_ENREF_128)] | 37%-74 % | 18%-61 % |
| Clinical presentation[[129](#_ENREF_129)] | * Jaundice * Enlarged collateral veins (*i.e.,* esophageal varices, hemorrhoids, caput medusae) * SIRS like presentation possible | * Systemic inflammatory response syndrome (SIRS):   Temp < 36 °C/> 38 °C  Heart rate > 90  RR > 20 or PaCO2 < 32  WBC < 4 k or > 12 k   * andinfection |
| Laboratory findings[[129](#_ENREF_129),[130](#_ENREF_130)] | * ↓ Polymorphonuclear cells * Thrombocytopenia * Hypoalbuminemia * Increased PT, INR * Hyperlactatemia * Hypoglycemia | ↓ or ↑ Polymorphonuclear cells  Thrombocytopenia  Increased PT, aPTT, INR  Decreased fibrinogen |
| Bacteremia[[94](#_ENREF_94),[131-134](#_ENREF_131)] | 32%-41 % | 27%-31% |
| Sources of infection[[6](#_ENREF_6),[128](#_ENREF_128),[135](#_ENREF_135),[136](#_ENREF_136)] |  |  |
| Respiratory | 9%-61% | 60%-64 % |
| Abdominal | 8%-30 % | 15%-19 % |
| Bloodstream | 17%-72 % | 13%-15 % |
| Renal/urinary | 7%-11 % | 11%-14 % |
| Skin | 7.1% | 7% |
| Catheter-related | 4%-5% | 5% |
| Microbiology[[6](#_ENREF_6), [128](#_ENREF_128), [135](#_ENREF_135), [136](#_ENREF_136)] |  |  |
| Gram-negative | 52.7%-64 % | 49%-63 % |
| Gram-positive | 30%-56 % | 40%-47 % |
| Fungi | 10%-25 % | 10%-19 % |
| Mediators associated with disease progression[[47](#_ENREF_47),[61](#_ENREF_61),[71](#_ENREF_71),[72](#_ENREF_72),[105](#_ENREF_105),[106](#_ENREF_106),[137](#_ENREF_137)] | Endothelin, angiotensin, PAF, NO, TNF-α and HLA-DR, bacterial DNA, IL-1β, IL-2R, IL-6, IL-8 and IL-10 | Endothelin, NO, LPS, LTA, lipoproteins, sTNF, bacterial DNA, peptidoglycans, IL-6, IL-8, IL-4, IL-10 |
| Endotoxin levels[[138](#_ENREF_138),[139](#_ENREF_139)] | ↑↑ | ↑↑ |
| Protein C activity[[140](#_ENREF_140),[141](#_ENREF_141)] | ↓↓ | Predicts outcome |
| Mesenteric lymph nodes[[95](#_ENREF_95),[142](#_ENREF_142)] | + | + |

1Sepsis includes patients without cirrhosis classified as having sepsis, severe sepsis, and septic shock. SIRS: Systemic inflammatory response syndrome; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; PAF: Platelet activating factor; NO: Nitric oxide; TNF: Tumor necrosis factor; HLA: Human leukocyte antigen; IL: Interleukin; LPS: Lipopolysaccharide; LTA: Lipoteichoic acid; sTNF: Soluble tumor necrosis factor.