Hypothesis

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Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis

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Summary

The peripheral arterial vasodilation hypothesis has been most influential in the field of cirrhosis and its complications. It has given rise to hundreds of pathophysiological studies in experimental and human cirrhosis and is the theoretical basis of life-saving treatments. It is undisputed that splanchnic arterial vasodilation contributes to portal hypertension and is the basis for manifestations such as ascites and hepatorenal syndrome, but the body of research generated by the hypothesis has revealed gaps in the original pathophysiological interpretation of these complications. The expansion of our knowledge on the mechanisms regulating vascular tone, inflammation and the host-microbiota interaction require a broader approach to advanced cirrhosis encompassing the whole spectrum of its manifestations. Indeed, multiorgan dysfunction and failure likely result from a complex interplay where the systemic spread of bacterial products represents the primary event. The consequent activation of the host innate immune response triggers endothelial molecular mechanisms responsible for arterial vasodilation, and also jeopardizes organ integrity with a storm of pro-inflammatory cytokines and reactive oxygen and nitrogen species. Thus, the picture of advanced cirrhosis could be seen as the result of an inflammatory syndrome in contradiction with a simple hemodynamic disturbance.

Keywords: Cirrhosis; Peripheral arterial vasodilation hypothesis; Ascites; Bacterial translocation; Pro-inflammatory cytokines; Cardiovascular dysfunction; Renal dysfunction; Systemic inflammation.

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Abbreviations: PAVH, peripheral arterial vasodilation hypothesis; HRS, hepatorenal syndrome; PRA, plasma renin activity; SNS, sympathetic nervous system; ACLF, acute-on-chronic liver failure; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TLR(s), toll-like receptors; DAMPs, danger-associated molecular patterns; ECM, extracellular matrix; C-RP, plasma C-reactive protein; ROS, reactive oxygen species; TNF, tumor necrosis factor; IL, interleukin; HE, hepatic encephalopathy; BT, bacterial translocation; MLNs, mesenteric lymph nodes; NO, nitric oxide; CO, carbon monoxide; VEGFs, vascular endothelial growth factors; K_{ATP}, adenosine triphosphate-sensitive potassium channels; GMP, guanosine 5′ monophosphate; NOS, nitric oxide synthase; HSP, heat shock protein; BH4, tetrahydrobiopterin; RTKs, receptor tyrosine kinases; LPS, lipopolysaccharide; GTP, guanosine 5′ triphosphate; AKI, acute kidney injury; HPS, hepatopulmonary syndrome; IPVD, intrapulmonary vasodilatation; CX3CL1, fractaline chemokine; RAI, relative adrenal insufficiency; PICD, paracentesis-induced circulatory dysfunction; SBP, spontaneous bacterial peritonitis; SIH, systemic inflammation hypothesis.

Revisiting the peripheral arterial vasodilation hypothesis

The "peripheral arterial vasodilation hypothesis" (PAVH) [1] was proposed because prior theories were not compatible with modern concepts on circulatory and renal pathophysiology. According to Starling's "vascular underfilling hypothesis", portal hypertension and hypoalbuminemia lead to ascites because hepatic and splanchnic lymph formation exceeds the drainage capacity of the thoracic duct. Renal dysfunction would be secondary to decreased plasma volume. Contrariwise, the "overflow theory" [2] considered sodium retention a "primary event", possibly related to signaling pathways between liver and kidney as shown in experimental cirrhosis [3,4]; ascites was thought to be secondary to blood volume expansion.

PAVH relied on three principles (Fig. 1A): 1. The "core" factor is a progressive splanchnic arterial vasodilation inducing

abnormalities in splanchnic and systemic hemodynamics. In the splanchnic circulation, arterial vasodilation increases portal venous inflow contributing to portal hypertension. In the systemic circulation, arterial vasodilation decreases arterial pressure due to effective hypovolemia. In this setting, arterial hypotension occurs despite a marked activation of endogenous vasoconstrictor systems, due to reduced vascular responsiveness to vasoconstrictors. Hemodynamic studies in human and experimental cirrhosis supported this concept. 2. In pre-ascitic cirrhosis, a moderate circulatory dysfunction can be compensated by increased plasma volume and cardiac output. However, as vasodilation intensifies with disease progression, cardiac output cannot increase further, leading to arterial hypotension, activation of vasoconstrictors and continuous renal sodium and water retention, accumulating as ascites. 3. Refractory ascites, hyponatremia and hepatorenal syndrome (HRS) are extreme manifestations of this process.

Some of these concepts have not been confirmed, and further knowledge in the pathogenesis of decompensated cirrhosis has been gained. Therefore, we believe the PAVH should be reviewed in the light of new knowledge.

PAVH proposes that splanchnic arterial vasodilation precedes ascites formation. Subsequent studies, however, found that arterial vasodilation in pre-ascitic cirrhosis is evident in the supine but not upright position [5]. Moreover, no evidence of vascular underfilling emerged in supine patients, as plasma renin activity (PRA) is suppressed and natriuresis increased [6,7]. Finally, sodium retention only occurs in the upright position [6], when arterial vasodilation is not observed. Thus, it can be postulated that pre-ascitic renal sodium retention occurs in the upright posture, favoring venous splanchnic pooling secondary to portal hypertension, while the supine position promotes blood volume redistribution to the systemic circulation, cardiac output increase and "secondary" shear stress-induced arterial vasodilation [8].

PAVH proposes that splanchnic arterial vasodilation and vasoconstrictor activation progressively increase. However, two observations challenged this view: first, sodium retention in "early" ascites is frequently associated with normal PRA, plasma aldosterone and norepinephrine (Fig. 1B). Second, no major

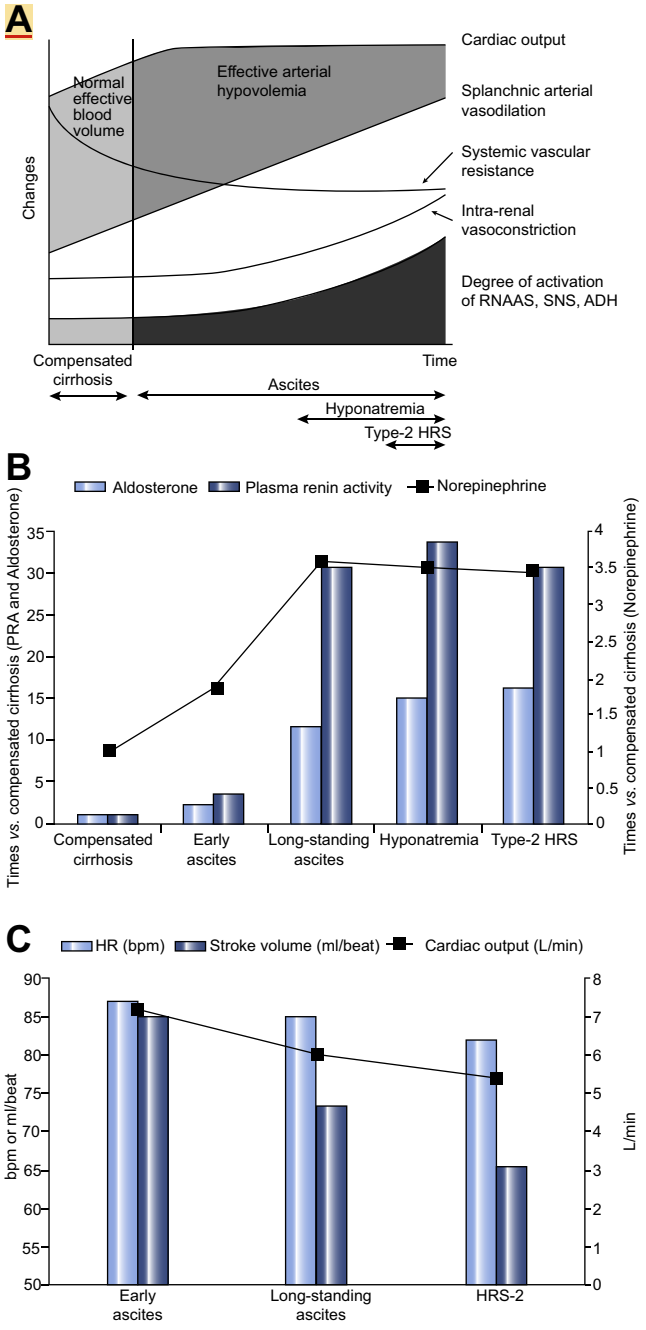

Fig. 1. Main principles of peripheral arterial vasodilation hypothesis (PAVH) and reasons justifying its appraisal. (A) The central event of the PAVH is progressive splanchnic arterial vasodilation. At the initial phase it is compensated by an appropriated response in cardiac inotropic and chronotropic functions. The secondary increase in cardiac output maintains the effective arterial blood volume, arterial pressure, the activity of the renin-angiotensin aldosterone system (RAAS), and sympathetic nervous system (SNS), antidiuretic hormone (ADH) release, and renal function within normal limits. As splanchnic vasodilation progresses, however, cardiac output can no longer increase and effective arterial hypovolemia develops leading to a compensatory increase in the RAS, SNS and ADH activity, water and sodium retention and ascites formation. Dilutional hyponatremia due to severe ADH hypersecretion and impaired free water excretion is a sign of a more advanced circulatory dysfunction. Finally, when splanchnic arterial vasodilation is extreme an intense intrarenal vasoconstriction develops leading to reduced perfusion and low glomerular filtration rate (type-2 HRS). (B) Plasma renin activity (PRA) and plasma aldosterone and norepinephrine concentration are sensitive markers of circulatory dysfunction. Their levels at different stages of decompensated cirrhosis suggests that circulatory dysfunction is not progressive. Circulatory function worsens markedly from early ascites with moderate sodium retention and low diuretic requirements to long-standing ascites with intense sodium retention and high diuretic requirements. However subsequent development of dilutional hyponatremia and HRS is not associated with further impairment in circulatory function (Data represent mean values obtained from 527 patients included in several prospective investigations assessing circulatory and renal dysfunction in cirrhosis; V. Arroyo unpublished). (C) Cardiac function in patients with early and long-standing ascites and HRS studied by Ruiz-del-Arbol *et al.* [9]. Cardiac inotropic and chronotropic function and cardiac output decrease with the progression of renal dysfunction.

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differences in PRA and plasma norepinephrine emerge between patients with long-standing ascites, with and without hyponatremia, and those with HRS, indicating that factors other than arterial vasodilation are involved in the development of renal dysfunction.

PAVH considers splanchnic arterial vasodilation as the unique cause of circulatory dysfunction. This has also been challenged. Cardiac output, once increased in "early" ascites, gradually declines with the progression of cirrhosis, being frequently normal in type-2 HRS [9,10] (Fig. 1C). Therefore, circulatory dysfunction results from both progressive arterial vasodilation and impaired cardiac function.

Finally, PAVH did not consider that decompensated cirrhosis involves multiorgan dysfunction. Indeed, acute-on-chronic liver failure (ACLF) [11], a syndrome characterized by systemic inflammation, organ failure(s) and poor short-term survival, was unknown at that time.

The new hypothesis we propose is based on data supporting PAVH and new features reported thereafter. As with any hypothesis, many, but not all, concepts have been demonstrated. Some are indirectly supported by clinical or experimental data in cirrhosis, others derive from investigations in other diseases, such as sepsis. Our proposal aims to promote research in new directions and treatments based on new concepts. Therefore, it should be taken as the beginning of a new scientific pathway that awaits confirmation.

Key points

- The peripheral arterial vasodilation hypothesis (PAVH) identifies effective hypovolemia secondary to splanchnic arterial vasodilation as the primary pathogenetic mechanism responsible for the cardinal manifestations of cirrhosis, such as ascites formation and renal dysfunction
- The PAVH neither fully accounts for the mechanisms underlying the progressive stages of decompensation in cirrhosis, nor does it recognize other factors impairing effective volemia. Moreover, the pathogenesis of vasodilation remains ill-defined
- The afferent signal triggering pre-ascitic renal sodium retention is splanchnic venous pooling due to portal hypertension in the upright posture, rather than primary splanchnic arterial vasodilation, which only appears in the supine position as a result of hemodynamically effective redistribution of volume overload
- Cardiac dysfunction contributes to the reduction of effective volemia in advanced cirrhosis, as the cirrhotic heart fails to compensate arterial vasodilation
- Progression in renal dysfunction occurs even without progression of circulatory dysfunction. In addition to impaired circulation, other factors are required for progression of renal dysfunction

Key points

- In advanced cirrhosis, translocation of Gram-negative bacteria across the intestinal barrier may lead to infection. Most often bacteria are killed, but bacterial byproducts known as pathogen-associated molecular patterns (PAMPs, such as lipopolysaccharide) are released
- PAMPs are spontaneously recognized by pattern recognition receptors (PRRs) expressed in immune and other cells. PRRs engagement may result in the release of pro-inflammatory cytokines/chemokines leading to systemic inflammation
- PAMPs themselves and/or systemic pro-inflammatory cytokines/chemokines, via their respective locally expressed receptors, may have two main targets involved in circulatory homeostasis: splanchnic arterioles and heart. In arteriole walls, bacterial-derived cues and/or cytokines/chemokines stimulate production of vasorelaxant molecules (the prominent being nitric oxide) causing marked vasodilation. In the heart, extracellular stimuli induce cardiomyocyte dysfunction. Overproduction of reactive oxygen and nitrogen species are also involved in cardiac dysfunction. These abnormalities contribute to a decrease in effective arterial blood volume and to a subsequent homeostatic neurohumoral activation that is involved in decreasing the perfusion of kidneys and brain
- There is also evidence that PAMPs themselves and/or systemic pro-inflammatory cytokines/chemokines play a role in kidney and brain dysfunctions and the development of hepatopulmonary syndrome

Key points

- The clinical ground has convincingly shown that renal as well as cardiac, cerebral, pulmonary and adrenal failures, is often precipitated by bacterial infections, particularly when a severe inflammatory response syndrome develops
- In the pathogenesis of organ failure(s), inflammation can trigger pathophysiological pathways more complex than those hypothesized by the peripheral arterial vasodilation hypothesis
- Peripheral arterial vasodilation hypothesis has not only been a powerful stimulus for research on ascites and HRS, but also the basis of several treatments with great impact in the management of decompensated cirrhosis such as i.v. albumin alone or associated with vasoconstrictors
- However, there is increasing evidence that albumin acts not only as a plasma expander but, also, as an anti-inflammatory agent, as it has a great capacity to bind and inactivate many pro-inflammatory molecules

What we learnt from immunologists

Before discussing new pathophysiological perspectives in cirrhosis, major immunological concepts on inflammation deserve consideration. Bacteria express components (pathogen-associated molecular patterns [PAMPs]) [12,13], recognized by pattern recognition receptors (PRRs) expressed in innate immune cells and epithelia. PRRs may be located on the cell surface (e.g. Toll-like receptor 4, TLR4), endolysosome (e.g. TLR9) or cytosol (e.g. nucleotide-binding oligomerization domain 1, NOD1). PAMP(s) recognition stimulates intracellular signaling pathways and transcription factors to induce a battery of genes encoding inflammatory molecules (Table 1). PAMP-induced inflammatory response is indispensable for combating invading bacteria. However, an excessive or chronic response may cause collateral tissue damage (immunopathology) and evoke a marked compensatory anti-inflammatory response ultimately leading to immune suppression and increased risk of secondary infections and delayed mortality [14].

Interestingly, TLRs recognize not only PAMPs, but also host molecules released by dying cells [12] (danger-associated molecular patterns [DAMPs]) (Table 2), such as extracellular matrix (ECM) components or proteases cleaving ECM. Other endogenous molecules activating TLRs are oxidized low-density lipoproteins (e.g. oxidative stress in atherosclerosis), oxidized phospholipids or antimicrobial β-defensin 2 (during infections). Recognition of all these molecules stimulates inflammation and tissue repair.

Self-derived nucleic acids (DNA or RNA) do not activate innate immune responses under normal conditions because they are degraded by serum nucleases before recognition by endolysosomal PRRs. However, there are examples of inappropriate

Table 1. Innate pathogen recognition receptors (PRRs) and their corresponding bacterial pathogen-associated molecular patterns (PAMPs), key intracellular adaptors and effectors.

Innate PRRs	Cellular localization	Bacterial PAMPs	Key adaptors	Effectors
Toll-like receptors (TLRs)				
TLR1	Cell surface	Triacylated lipopeptide	MyD88	IL-6, TNF-α
TLR2	Cell surface	Di/triacylated lipopeptides, peptidoglycan	MyD88, TIRAP	IL-6, TNF-α, IL-8, MCP-1, RANTES
TLR4 (co-receptor MD2, CD14, LBP)	Cell surface	Lipopolysaccharides	MyD88, TRIF, TIRAP, TRAM	IL-6, TNF-α, IFNβ, IP-10
TLR5	Cell surface	Flagellin	MyD88	TNF-α
TLR6	Cell surface	Diacylated lipopeptides, lipoteichoid acid	MyD88, TIRAP	TNF-α, IL-6, IL-8, MCP-1, RANTES
TLR7	Endolysosome	Single-stranded RNA	MyD88	IFN-α, IL-6, TNF-α
TLR9	Endolysosome	DNA containing the unmethylated phosphate-guanine (CpG) dideoxynucleotide motif (CpG-DNA)	MyD88	IFN-α, IL-6, TNF-α
Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)				
NOD1	Cytosol	γ-D-glutamyl-mesodiaminopimelic acid	RIP2	IL-6, TNF-α
NOD2	Cytosol	Muramyl dipeptide	RIP2	IL-6, TNF-α
NLRP1 (alias NALP1)	Cytosol	Muramyl dipeptide	?	IL-1β, IL-18
NLRP3	Cytosol	Bacterial RNA	ASC	IL-1β, IL-18
NLRC4 (alias IPAF)	Cytosol	Flagellin	ASC?	IL-1β, IL-18
Cytosolic DNA sensors				
Absent in melanoma (AIM) 2 (AIM2)	Cytosol	Double-stranded DNA	ASC	IL-1β, IL-18
IFI16	Cytosol	Double-stranded DNA	STING	IFN-β, IP-10, IL-6, IL-1β
Z-DNA binding protein 1 (ZBP1 also known as DAI)	Cytosol	Double-stranded DNA	STING	IFNβ
Cyclic GMP-AMP synthase (cGAS)	Cytosol	Double-stranded DNA	STING	IFNβ
LRRFIP1	Cytosol	Double-stranded DNA, single-stranded DNA	β-catenin	IFNβ
STING	Cytosol	Cyclic-di-GMP		IFNβ
HMGB	Cytosol	Double-stranded DNA, single-stranded DNA	?	IFN-β, IL-6, RANTES

Table 2. Examples of endogenous ligands that can be recognized by pattern recognition receptors (PRRs).

Ligands	PRRs
Danger-associated molecular patterns	
High mobility group box 1 (HMGB1)	TLR2, TLR4 and/or TLR9
Heat-shock proteins (HSP60, HSP70, HSP22, GP96)	TLR2, TLR4 or TLR2-TLR4
Extracellular matrix components (biglycan, hyaluronic acid, extradomain A of fibronectin and surfactant protein)	TLR2 or TLR4 or both
Oxidized low-density lipoproteins	TLR4-TLR6 along with the coreceptor CD36
Oxidized phospholipids	TLR4
Antimicrobial peptide β-defensin 2	TLR4
Other endogenous ligands	
Self DNA in complex with cathelicidin LL37	TLR9
Self RNA in complex with cathelicidin LL37	TLR7
HMGB1-self DNA complex internalized via RAGE	TLR9
Self DNA incompletely digested during apoptosis	Unknown cytosolic DNA receptor

TLR-mediated recognition of self-nucleic acids (Table 2) leading to inflammation [12].

Systemic inflammation: A new "core" factor in the development of decompensation and organ dysfunction in cirrhosis

Cirrhosis is associated with systemic inflammation, as white blood cell count, activated circulating neutrophils and monocytes, plasma C-reactive protein (C-RP), pro-inflammatory cytokines, markers of macrophage activation [15] and systemic oxidative stress [16,17] are increased. The grade of inflammation parallels the severity of liver, circulatory and renal dysfunction [18], hepatic encephalopathy (HE) [19] and ACLF [11]. Its deleterious effect on organ function may derive from reduced organ perfusion and/or the effects of cytokines and reactive oxygen species (ROS) on cell function and apoptosis.

The main mechanism of systemic inflammation in cirrhosis is the translocation of viable bacteria (BT) and/or PAMPs from intestinal lumen into intestinal mucosa [20,21] without overt bacterial infection. Viable bacteria are killed by the intestinal immune system, but PAMPs are released into the systemic circulation. PAMPs may also translocate directly from the intestinal lumen. Once translocated, PAMPs interact with PRRs in gut-associated lymphoid tissue and mesenteric lymph nodes (MLNs). This leads to the expression of genes encoding molecules responsible for inflammation of the intestinal mucosa [22], ultimately extending to the systemic circulation and peripheral organs. This endogenous "sterile" (unrelated to bacterial infections) systemic inflammation is common in decompensated cirrhosis and is the rule in ACLF. Increased circulating lipopolysaccharide (LPS) and bacterial DNA have been shown in cirrhosis, but other bacterial components are probably involved, given the diversity of PAMPs released by intestinal bacteria (Table 1).

A second "sterile" inflammation may derive from acute hepatic inflammatory processes [23]. The spread of immune cells activated within the liver and DAMPs released by dying hepatocytes would ultimately cause systemic inflammation. Identification of DAMPs and other endogenous PRRs ligands involved in these processes is needed.

Finally, bacterial infections are a third mechanism of systemic inflammation. Interestingly, BT-induced pre-activation of the innate immune system leads to an exaggerated inflammatory response to bacterial infections and other pro-inflammatory stimuli [24,25]. This is a critical feature of cirrhosis, where infections are common, as the exaggerated inflammatory response frequently precipitates HE, type-1 HRS, ACLF, and death.

Molecular mechanisms underlying arterial vasodilation in cirrhosis. Role of excessive inflammatory response

In the 1990s, numerous endogenous vasodilators, including nitric oxide (NO), carbon monoxide (CO), glucagon, prostacyclin, adrenomedullin, vascular endothelial growth factors (VEGFs), endocannabinoids, neuropeptides, endogenous K_{ATP} channel "openers", and β_2-adrenoceptor agonists [26,27] were proposed to explain the arterial vasodilation in cirrhosis. However, measuring cyclic-GMP levels and using potent NO-synthase (NOS) inhibitors, it became clear that NO had a preeminent role [27]. Subsequent studies aimed to identify whether the "constitutive", Ca^{2+}/calmodulin-dependent endothelial NOS (eNOS) or inducible NOS (iNOS) promoted NO overproduction. The hemodynamic response to portal vein stenosis was measured in mice deleted for *Nos3* (encoding eNOS), *Nos2* (encoding iNOS) or both [28,29]. Genetic studies in *Nos2*$^{-/-}$ mice did not support a role of iNOS, while discrepant results emerged from *Nos3*$^{-/-}$, as portal vein ligation led to a systemic hyperdynamic circulation in one study [28], but not in another [29]. The reasons for these differences are unclear. However, global *Nos3* deletion is not entirely appropriate to address the role of eNOS in the development of portal hypertensive hyperdynamic circulation.

In contrast to genetic studies, the role of eNOS in hyperdynamic circulation was clarified by combining biochemical and pharmacological studies. In the mesenteric vasculature from cirrhotic rats, eNOS hyperactivity but not iNOS induction caused NO overproduction [30]. Such hyperactivity resulted from several mechanisms, including interaction with heat shock protein 90 (HSP90) [31], increased availability of tetrahydrobiopterin (BH4, an essential cofactor of eNOS) [30] and eNOS phosphorylation by serine-threonine kinase AKT [32]. Moreover, vessel eNOS expression was increased in portal hypertensive animals [30].

In systemic arteries (e.g. aorta) from cirrhotic rats, eNOS protein was also overexpressed and hyperactive in relation to HSP90 activation and AKT-dependent eNOS phosphorylation [33]. Interestingly, eNOS activity closely paralleled the intensity of shear stress forces sensed by endothelia [26]. Therefore, arterial NO overproduction in cirrhosis would seem a "mechanical" result of primary hyperdynamic circulation [33]. However, overproduction of eNOS-derived NO may precede hyperdynamic splanchnic circulation in portal hypertensive rats [34]. Thus, hyperdynamic circulation and increased shear stress forces would represent a feed-forward mechanism maintaining or further enhancing eNOS activity.

Cues other than mechanical stimuli are involved in NO-induced portal hypertensive hemodynamic abnormalities. TNF-α activates phosphatidylinositol-3-OH kinase and its downstream target AKT [35]. In portal hypertensive animals, anti-TNF-α therapies, such as anti-TNF-α antibodies [36,37] or thalidomide [38], attenuate hyperdynamic circulation. Moreover, anti-TNF-α antibodies reduce *in vivo* TNF-α-induced AKT-mediated eNOS upregulation in gastric mucosa [22,39]. Tyrphostin AG 126, which inhibits receptor tyrosine kinases (RTKs), decreased hyperdynamic circulation, serum NO levels, and TNF-α levels in MLNs [40]. Since RTKs contain 20 subfamilies not including receptors for TNF-α [41], these findings suggest that one or more RTK control NO and TNF-α production in advanced cirrhosis. Interestingly, VEGFs, whose circulating levels may be increased in cirrhosis [27], have cognate receptors belonging to the RTK family [41]. As RTK engagement activates AKT [41], its inhibition may explain the tyrphostin-induced decline in NO production. Together, these findings indicate that pro-inflammatory cytokines contribute to NO-mediated vasodilation in cirrhosis.

Patients or animals with cirrhosis and ascites have abnormal Gram-negative BT across the intestinal barrier. Selective intestinal decontamination with norfloxacin decreases vascular NO production [42] and systemic hyperdynamic circulation [43] in patients, suggesting a link between BT and hemodynamic alterations. Most of the translocated bacteria are killed and this results in the systemic release of PAMPs, such as LPS (Table 1). LPS may stimulate innate immune cells to produce cytokines [22] and induce the BH4-producing enzyme GTP-cyclohydrolase 1 directly *via* TLR4 [22,44] or indirectly *via* TNF-α [30]. Interestingly, circulating endotoxin and TNF-α, as well as GTP-cyclohydrolase 1 activity in mesenteric vessels, are higher in cirrhotic rats with BT than in those without [30,44]. Therefore, BT *via* PAMPs and/or systemic TNF-α may explain the increased eNOS activity in mesenteric arterioles. Interestingly, aortic walls from cirrhotic rats overexpress pro-inflammatory cytokines, contributing to both iNOS induction and eNOS hyperactivity [45]. Importantly, the aortic wall pro-inflammatory phenotype is abolished after five-day norfloxacin therapy. Moreover, norfloxacin dramatically reduces aortic NO production [45,46]. These findings suggest that BT *via* PAMPs induces systemic and local pro-inflammatory responses that increase arterial NO production. This response is harmful because it disrupts vascular homeostasis, a crucial perturbation in the development of complications like ascites and HRS. Therefore, systemic hemodynamic abnormalities in cirrhosis should be considered at least partially the result of an excessive inflammatory response to BT.

Intestinal dysbiosis and bacterial translocation initiate and sustain systemic inflammation in cirrhosis

The host and intestinal bacteria reside in a symbiotic state during health. Any disruption of intestinal homeostasis might cause quantitative (overgrowth) and/or qualitative changes in the microbiota (dysbiosis). Cirrhosis is associated with both intestinal bacterial overgrowth, [47,48] and dysbiosis, as autochthonous bacteria are decreased and potentially pathogenic bacteria increased [49–51]. On the phylum level, there are fewer Bacteroidetes, but more Proteobacteria and Fusobacteria; on the species level, *Streptococcus* spp. and *Veillonella* spp. prevail [51].

Gut microbiome changes comprise not only altered taxonomics, but also functional changes, as shown by metagenomics [51]. Several causes underlie such abnormalities in cirrhosis, including impaired gut motility, reduced bile flow, impaired gastric acid secretion, and altered IgA secretion and antimicrobial molecules [52–55]. These abnormalities might primarily contribute to dysbiosis by facilitating the oral microbiome transition to small and large intestine, as bacterial species of buccal origin are enriched in the fecal microbiome of cirrhotic patients [51].

While etiology mainly influences microbiome changes in pre-cirrhotic liver disease, the consequences of cirrhosis (e.g. reduced bile flow) prevail in end-stage liver disease [56,57].

A second common intestinal feature of cirrhosis is a disrupted gut barrier [57,58] leading to pathological BT. Dysbiosis is causatively linked to these abnormalities and their consequences, such as intestinal and systemic inflammation [59].

Small intestinal bacterial overgrowth in cirrhosis is associated with pathological BT and endotoxemia [48]. Conversely, antibiotic intestinal decontamination reduces endotoxemia and liver disease severity [60,61]. Dysbiosis induces intestinal inflammation and gut leakiness in pre-cirrhotic animal models of non-alcoholic steatohepatitis and alcoholic liver disease [62,63]. Similarly, both experimental and human cirrhosis show features of intestinal inflammation [64–67].

Therefore, dysbiosis-induced intestinal inflammation may contribute to pathological BT. The mechanism triggering intestinal inflammation in cirrhosis is unknown, but hitherto unidentified microbial products/metabolites might be involved. Conversely, a compromised intestinal defense might contribute not only to dysbiosis, but also to enhanced pathological BT. In rats with cirrhosis, ascites, and translocation of viable bacteria to MLNs, Paneth cells produce lower levels of defensins and Reg3 molecules than those without BT, accompanied by decreased antimicrobial activity against *Enterobacteriaceae* [55]. Moreover, intestinal immune surveillance might not adequately clear translocated bacteria in the lamina propria [68]. Because antibiotic intestinal decontamination restored immune surveillance in experimental cirrhosis [68], the intestinal microbiome might exhaust the mucosal immune response. Thus, cirrhosis-associated dysbiosis contributes to intestinal homeostasis disruption by altering the intestinal immune system.

Increased intestinal permeability allows microbial products/bacteria to translocate from the intestinal lumen to extraintestinal organs and spaces including MLNs, portal and systemic circulation. While microbial products likely escape from the intestinal lumen to the lamina propria *via* a paracellular route through disrupted tight junctions, living bacteria translocate *via* a transcellular route (transcytosis) [21]. Intestinal permeability is already increased in pre-cirrhotic stages in experimental

alcoholic steatosis, cholestatic and toxin-induced liver fibrosis [57,63]. Similarly, patients with pre-cirrhotic liver disease show a disrupted gut barrier [69–71]. However, translocation of viable bacteria is a hallmark of cirrhosis, in particular during decompensation [21].

In cirrhosis, impaired liver clearance contributes to an accumulation of PAMPs, and bacteria in the systemic circulation [47,72,73]. DAMPs originating from damaged liver tissue also increase during acute and chronic liver diseases [23]. Microbial products and DAMPs activate receptors of the innate immune system contributing to liver disease progression and causing a systemic inflammatory response. Persistent stimulation of circulating immune cells increases plasma pro-inflammatory cytokines including IL-6, TNF-α and NO [74,75]. Several of these molecules, namely TNF-α, can disrupt intestinal tight junctions augmenting gut leakiness. During decompensated cirrhosis, a further increase in intestinal permeability could contribute to enhanced translocation of PAMPs and viable bacteria [21], possibly leading to overt infections. As antibiotic intestinal decontamination normalizes the number of activated immune cells and their production of pro-inflammatory cytokines in experimental and human cirrhosis [76,77], the intestinal microbiota likely represents a driving force for systemic inflammation. However, bacteria and bacterial products translocation is not exclusively detrimental. The commensal microbiota is protective in experimental liver fibrosis. Hepatotoxins cause more liver injury and fibrosis in germ-free than in wild-type mice [78]. Consistently, a mouse model of primary sclerosing cholangitis shows exacerbated hepatobiliary damage under germ-free conditions [79]. These results suggest that the intestinal microbiota has a beneficial role in chronic liver disease.

Cirrhosis as a systemic inflammatory multiorgan disease (Fig. 2)

Extrahepatic organ dysfunctions are common in advanced cirrhosis. Although the underlying mechanisms have been only partially elucidated, inflammation and oxidative stress may be involved favoring cell death and tissue injury as in sepsis [80].

HRS-AKI, the new definition of type 1 HRS [81] in the setting of acute kidney injury (AKI) [82], is often precipitated by bacterial infections [83–85], particularly when a severe inflammatory response develops [86]. This suggests a more complex pathophysiology [87] than hypothesized by PAVH, which connected HRS-AKI to intrarenal arterial vasoconstriction secondary to severe effective hypovolemia. Indeed, both in clinical [88] and experimental [89] cirrhosis infection/inflammation leads to renal tubular TLR4 upregulation associated with tubular damage, suggesting that TLR4 mediates renal injury. The mechanism underlying these abnormalities is undefined, but likely results from sustained exposure to PAMPs. Indeed, LPS-induced renal dysfunction in experimental cirrhosis is prevented by gut decontamination with norfloxacin [90]. Thus, BT may upregulate tubular TLR4, increasing kidney susceptibility to inflammatory injury. TLR4 stimulation increases the transcription of pro-inflammatory cytokines by upregulating nuclear factor κB-p65, ultimately leading to apoptotic tubular damage. Therefore, inflammation may represent an important pathogenic factor for organ failures including AKI.

Systolic cardiac dysfunction, a feature of "cirrhotic cardiomyopathy" [90], is also involved in the pathogenesis of HRS-AKI [10]

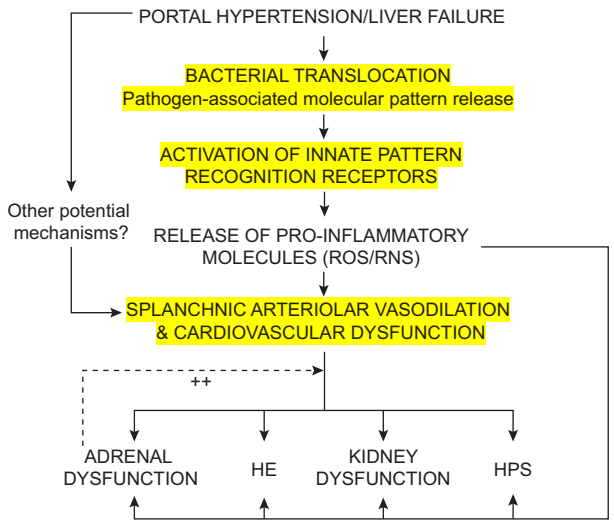

Fig. 2. Potential mechanisms leading to the major clinical manifestations of advanced cirrhosis. Along with the pathway promoting splanchnic arteriolar vasodilation and cardiovascular dysfunction secondary to portal hypertension, the sustained activation of innate host immunity brought about by abnormal gut translocation of bacteria and bacterial products (known as pathogen-associated molecular patterns) is responsible for persistent activation of innate pattern recognition receptors (e.g., Toll-like receptors) and subsequent inflammation. Pro-inflammatory cytokines and oxidative/nitrosative stress impair effective hypovolemia by enhancing arterial vasodilation (mainly mediated by NO) and preventing cardiac output to fulfill the needs of peripheral circulation. Moreover, direct effects on kidney and other organs worsen their dysfunction. HE, hepatic encephalopathy; HPS, hepatopulmonary syndrome; ROS / RNS, reactive oxygen / nitrogen species.

because it cannot sustain sufficient cardiac output to compensate the extreme vasodilation characterizing this condition. The pathophysiology of systolic dysfunction in cirrhosis is complex [90] and not well understood. Hyperdynamic circulation is involved, but there is growing experimental evidence highlighting the role of inflammation. Oxidative stress- and TNFα-induced activation of the NF-κB-iNOS pathway and oxidative stress-induced alteration of β-receptor signaling accounted for impaired left ventricular contractility [91]. Interestingly, such molecular abnormalities were reversed and contractility restored by the anti-oxidant and scavenging effect of human albumin [91]. However, other potential mechanisms should be investigated to explain cardiac dysfunction in advanced cirrhosis, particularly in sepsis. Enhanced expression of the C5a cardiomyocytes receptor is involved in experimental septic cardiomyopathy [92], but its role in cirrhosis is unknown.

Systemic inflammation could also be implicated in the pathogenesis of hepatopulmonary syndrome (HPS) caused by intrapulmonary vasodilatation (IPVD) and, less commonly, pleural and pulmonary arteriovenous communications resulting in functional and anatomic shunts [93–95]. IPVD pathophysiology is likely multifactorial, but the involvement of BT-induced systemic inflammation is supported by evidence that norfloxacin improves HPS in rats with cirrhosis [96].

HPS is strongly related to increased NO release in pulmonary circulation [95]. BT-related endotoxemia and the pro-inflammatory response induce macrophage accumulation in lung microvasculature [97], where the activation of fractalkine (CX3CL1) chemokine enhances monocyte adherence [98]. Monocytes express iNOS and produce heme oxygenase-1 that

promotes CO production, augmenting vasodilation [99]. CX3CL1 and VEGF-A produced by circulating monocytes also contribute to angiogenesis, an IPVD pathogenetic factor [100,101]. Other factors, such as eNOS activation through endothelin-B receptor overexpression in the pulmonary endothelium [102–104] and a reduced production of alveolar surfactant proteins [105], should be considered. Although the role of inflammation in HPS pathogenesis is not as evident as in ARDS, all previous features suggest a role of BT-induced inflammatory response.

Evidence for systemic inflammation triggering resident brain immune cells (microglial cells) to produce pro-inflammatory cytokines, which exacerbate ammonia-elicited astrocyte swelling, has also been provided in cirrhosis [19]. This may contribute to HE pathophysiology, since astrocyte swelling likely represents a crucial event [106].

Finally, arterial vasodilation can contribute to relative adrenal insufficiency (RAI) by impairing adrenal perfusion. RAI is frequent (51–77%) in decompensated cirrhosis with severe sepsis or septic shock [107,108], but also occurs in 7–49% of non-critically ill patients [109,110]. However, other factors, like liver failure and systemic inflammation are likely involved as both impaired cholesterol synthesis and enhanced pro-inflammatory cytokine production can reduce adrenal steroidogenesis [111]. Adrenal dysfunction attenuates the vascular effect of angiotensin-II, norepinephrine and vasopressin in decompensated cirrhosis, further activating sympathetic tone [110]. Since sympathetic hyperactivity impairs intestinal motility and immunity, a vicious circle favoring bacterial overgrowth [112], BT, bacterial infections and/or systemic inflammatory response [113] can ensue. Finally, RAI may also be involved in the development of an excessive compensatory anti-inflammatory response following severe sepsis.

PAVH-based treatments: a new perspective

PAVH has not only been a powerful stimulus for research on pathophysiology, but has also had a major impact on the management of decompensated cirrhosis. The first PAVH-based treatment was the prevention of paracentesis-induced circulatory dysfunction (PICD), a complication due to accentuated splanchnic arterial vasodilation [114]. Indeed, the administration of human albumin lowered the incidence of PCD [115] and its complications, such as hyponatremia and mortality [116]. The second PAVH-inspired indication was the prevention of HRS-AKI following spontaneous bacterial peritonitis (SBP), a lethal complication due to enhanced arterial vasodilation and reduced cardiac output [117]. The prevalence of HRS-AKI and hospital mortality decreased by 60% in patients treated with antibiotics plus human albumin compared to patients receiving antibiotics alone [118]. Finally, the latest contribution of PAVH to therapy is the HRS-AKI treatment with vasoconstrictors (terlipressin) and albumin, which leads to renal function recovery in up to 60–70% of patients [119,120], reduces post-liver transplant need for ICU and renal replacement therapy and improves transplant-free survival [121,122]. Terlipressin counteracts splanchnic arterial vasodilation, and albumin expands blood volume.

The beneficial effects of these treatments could be related to improved effective volemia, indirectly supporting PAVH. However, evidence that other mechanisms are likely involved has emerged. Indeed, terlipressin induces arterial vasoconstriction not only through an increase in intracellular calcium via the phosphatidyl–inositol-bisphosphonate cascade, but also by inhibiting iNOS expression in the arterial wall [123]. A recent meta-analysis showed that albumin is superior to other volume expanders in preventing PICD and its consequences [116], implicating effects other than mere volume expansion. In SBP, human albumin, but not hydroxyethyl starch, increased peripheral vascular resistance and left ventricular stroke work index [124]. In addition, albumin increases cardiac contractility by counteracting oxidative stress and inflammation in the myocardium of cirrhotic rats [91]. These observations could contribute to explain why albumin is essential in the treatment of HRS-AKI, since the effect of terlipressin is drastically reduced without albumin [125].

Besides being a powerful plasma expander, human albumin also acts as an anti-inflammatory agent [91,126] able to bind and inactivate many pro-inflammatory bacterial molecules, such as LPS, lipoteichoic acid, and peptidoglycan. Moreover, albumin binds and blocks cytotoxic agents released during the inflammatory process, such as ROS and nitrogen species. These molecules cause microvascular coagulation and cell dysfunction, leading to organ hypoperfusion, cell necrosis and apoptosis and organ(s) dysfunction/failure. Finally, albumin binds endogenous vasodilators released during inflammation, such as NO and prostaglandins, and modulates their effects [91,127,128]. These findings would support the concept that, besides volume expansion, albumin affects the systemic circulation in decompensated cirrhosis due to its anti-inflammatory activity.

Finally, it could be argued that trans-jugular porto-systemic shunt (TIPS) is effective in the treatment of HRS-AKI by improving the effective volemia. Nevertheless, TIPS may limit BT by reducing portal pressure.

Beyond PAVH: the systemic inflammation hypothesis (SIH) of cirrhosis decompensation, HRS and ACLF (Fig. 3)

Based on the data presented in this review, we propose a change in our current view on the pathogenesis of decompensation and multiorgan failure in cirrhosis based on PAVH. The new hypothesis proposes that decompensation, HRS-AKI and ACLF develop from a progressive systemic inflammatory process that mainly originates in the intestine following translocation of viable bacteria and/or bacterial products from the lumen to the mucosa and submucosa. In some circumstances (i.e. acute alcoholic hepatitis), liver inflammation could also contribute. This inflammatory process would have two major consequences: first, splanchnic arterial vasodilation secondary to local release of endogenous vasodilators, a feature impairing systemic hemodynamics and organ perfusion; second, the extension of splanchnic inflammation to the peripheral blood and organs. The inflammation-induced release of cytokines and ROS within the liver, kidney and other organs may directly induce cell dysfunction and death. Therefore, the mechanism causing decompensation and multiorgan dysfunction/failure would be a combination of organ hypoperfusion and tissue/cell damage. Thus, SIH relies on the concept that BT, splanchnic and peripheral organ inflammation and arterial vasodilation increase progressively causing the clinical features and complications characterizing the different phases of cirrhosis.

In *early pre-ascitic cirrhosis*, there would be no viable bacterial translocation, splanchnic inflammation or sustained splanchnic arterial vasodilation. With disease progression, however,

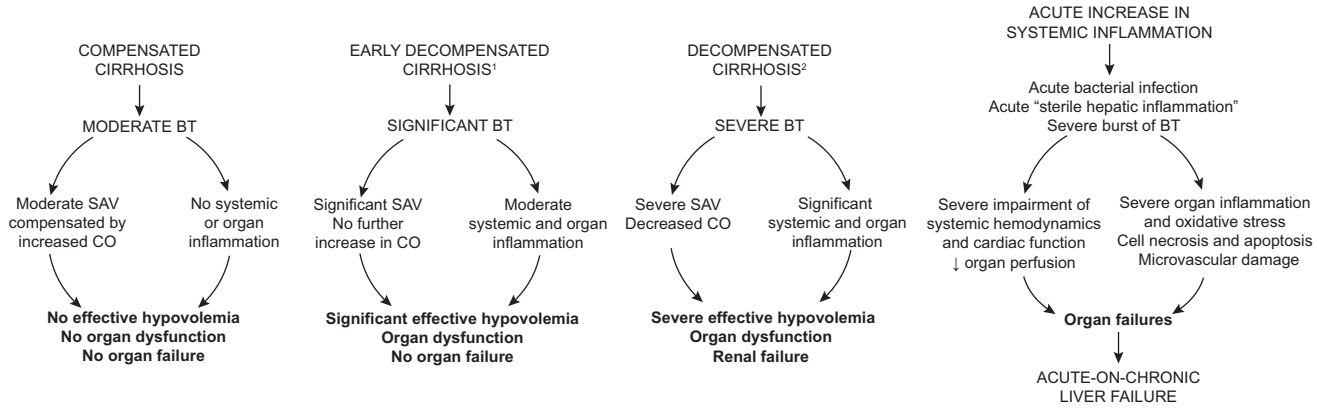

Fig. 3. The systemic inflammation hypothesis of decompensation of cirrhosis, hepatorenal syndrome and acute-on-chronic liver failure. According to the "systemic inflammation hypothesis" proposed in this article, bacterial translocation (BT) progressively impacts the natural course of cirrhosis, from the pre-ascitic compensated stage to advanced decompensation and hepatorenal syndrome. An abrupt increase in systemic inflammation represents the pathophysiological background for acute-on-chronic liver failure (ACLF). As with any hypothesis, many, but not all, concepts are demonstrated and future research on these matters is warranted. SAV, splanchnic arterial vasodilation. [1]Ascites requiring low diuretic dosage and/or minimal hepatic encephalopathy; [2]Ascites requiring high diuretic dosage and/or clinically evident hepatic encephalopathy, dilutional hyponatremia and/or type-2 HRS.

splanchnic inflammation and sustained splanchnic arterial vasodilation develop. At this stage, inflammation is restricted to the splanchnic area, cardiac function is preserved and effective hypovolemia is compensated by an increased cardiac output.

Early decompensation of cirrhosis (as defined by the first development of ascites) heralds the onset of significant systemic inflammation. Plasma C-RP concentration and cytokines start rising and arterial vasodilation intensifies. Moreover, cardiac output cannot further increase, possibly because of heart inflammation, and renal sodium retention becomes sustained. Since systemic renin-angiotensin-aldosterone and SNS activities are normal in a significant proportion of patients, subtle intrarenal mechanisms related to renal perfusion abnormalities (i.e. intrarenal activation of the renin-angiotensin system) or to local inflammation would impair renal sodium excretion. Most patients, however, present a clear increased activity of sodium-retaining systems.

In *long-standing decompensated cirrhosis*, with or without refractory ascites, or type-2 HRS, BT is severe, splanchnic, systemic and peripheral organ inflammation is significant, and SIH fully develops. Plasma levels of leukocytes, C-RP, pro-inflammatory cytokines and oxidized albumin (sensitive marker of systemic oxidative stress) are increased and systemic circulatory dysfunction progresses leading to arterial hypotension and intense compensatory overactivity of endogenous vasoconstrictor systems. Cardiac inotropic and chronotropic functions are also impaired and cardiac output declines with respect to prior levels due to myocardial inflammation. Adrenal glands respond poorly to hypotensive stress, also because of the inhibitory effect of cytokines on corticotropin-releasing factor and adrenocorticotropic hormone and adrenal inflammation, preventing a rise in cortisolemia and reducing the vascular effects of vasoconstrictors. At this stage, circulatory dysfunction is multifactorial and intimately related to splanchnic and systemic inflammation. Renal inflammation could explain an impaired renal prostaglandin synthesis leading to an imbalance between intrarenal vasoconstrictors and vasodilators. This results in intense renal sodium and water retention, hyponatremia, intrarenal vasoconstriction, and type-2 HRS. SNS hyperactivity also impairs the defenses against BT, which, along with changes in intestinal microbiome and gut mucosal function, predisposes to infections. Intra-organ inflammation also involves the brain, exacerbating the neurotoxic effect of ammonia, and predisposes to HE.

Finally, ACLF likely results from an acute and severe systemic inflammatory response to bacterial infections (PAMPs), acute liver injury such as acute alcoholic hepatitis (DAMPs), or, hypothetically, to a burst of PAMPs translocation leading to rapid and severe impairment of cardiovascular function, organ hypoperfusion, severe organ inflammation, microvascular coagulation, cell necrosis/apoptosis and multiorgan dysfunction/failure. Such an intense inflammatory storm can be followed by a state of relative immune paralysis, a recognized cause of delayed mortality in septic patients [14], caused by apoptosis of immune cells and high levels of anti-inflammatory cytokines. Indeed, evidence of this process has already been provided in patients with ACLF [129].

The impact of SIH on future research and treatments

We proposed that BT and systemic inflammation are the initial events leading to decompensation and organ failure in cirrhosis. However, alternative hypotheses, i.e. splanchnic arterial vasodilation due to portal hypertension comes first, followed by BT and systemic inflammation or that both pathways contribute in parallel, are also possible. Thus, studies assessing the chronological relationship between BT, systemic inflammation, cardiovascular dysfunction, decompensation and extrahepatic organ failure are needed.

These studies would require better experimental models of cirrhosis reproducing not only decompensation (i.e. ascites development) but also the development of extrahepatic organ failure. Clinical studies would also require sensitive markers of systemic and intestinal inflammation. At present, there are several plasma biomarkers for the diagnosis, assessment of severity and treatment response of systemic inflammation associated with sepsis and autoimmune, metabolic, cardiovascular, respiratory, neurological, renal, skin and bowel diseases [130–132]. Sensitive fecal biomarkers of intestinal inflammation in

inflammatory bowel or graft-versus-host diseases also exist [133–135]. However, few data on these biomarkers in cirrhosis are available.

Cirrhosis is characterized by exaggerated inflammatory responses, with marked individual variability, irrespective of the grade of liver failure. For example, prior decompensation is lacking in 20% of patients with ACLF [11], which, therefore, represents the debut of symptomatic disease. These patients are younger and develop more organ failures than those with a history of decompensation. Whether this is due to exaggerated inflammatory response, impaired immune-tolerance or both warrants investigation. The paradoxical coexistence of exaggerated inflammatory response and immune paralysis predisposing to sepsis is also an intriguing feature of decompensated cirrhosis [20]. Finally, the burden of viable bacteria or PAMPs released into the systemic circulation from a localized infection or BT could also determine the grade of inflammatory response. Therefore, sensitive BT markers would be also important.

The mechanism(s) of organ failure also require investigation. AKI in sepsis and cirrhosis have been traditionally attributed to impaired macrovascular renal perfusion secondary to cardiovascular dysfunction [136,137]. Now, there is evidence that AKI in sepsis [87,138], and, possibly, in cirrhosis, occurs with preserved total renal perfusion. Disturbances in renal cortical microcirculation and microvascular coagulation due to intrarenal inflammation, significantly reduce capillary perfusion. Impaired tubular cell function is also important since it reduces proximal sodium reabsorption, activates glomerular-tubular feedback, increases intrarenal renin release, and produces intense vasoconstriction of the afferent glomerular arteriole in cortical nephrons. The net effect is the renal blood flow redistribution to the medulla and severely impaired glomerular filtration rate. Microvascular coagulation and cell function impairment are potential mechanisms of other organ failures.

Finally, current strategies for prophylaxis and treatment of decompensation and organ failure in cirrhosis relying on measures aimed to prevent or improve specific problems related to each complication (i.e. ammonia production or excretion in HE, circulatory dysfunction in ascites and HRS and intestinal bacterial overgrowth in patients predisposed to develop infections) could be expanded. The SIH implies that patients may also benefit from the prevention and treatment of systemic inflammation, as suggested by existing evidence. As an example, long-term selective intestinal decontamination, by decreasing BT and systemic inflammation, reduces the prevalence of SBP, HRS-AKI, encephalopathy and mortality in advanced cirrhosis [139]. BT and systemic inflammation are, therefore, new potential therapeutic targets for the prevention and treatment of decompensated cirrhosis and ACLF.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

All authors contributed equally to the conception, writing and revision of this review article.

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