Acute-on-chronic liver failure: the liver and portal haemodynamics

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Purpose of review
During acute-on-chronic liver failure (ACLF), the marked systemic inflammatory response and rapid deterioration in liver function are associated with a significant deterioration in organ perfusion and an appreciable rise in portal pressure. Indeed, the development of sepsis and multiorgan dysfunction that commonly follows presentation in these patients is intricately related to the severity of portal hypertension. It follows that understanding the drivers for rising portal pressure in ACLF will inform new therapies.

Recent findings
As this review aims to highlight, there has been a paradigm shift in understanding of the drivers of portal hypertension, from a prior focus on splanchnic vasodilatation and therapies targeting portal inflow, toward appreciation of increasing intrahepatic resistance as the trigger for further vascular derangement, especially in the context of systemic inflammatory responses.

Summary
By elaborating on those mechanisms that are especially perturbed by inflammatory responses, this article aims to show how this understanding has helped inform the identification of potential new targets for therapy in ACLF. Particular emphasis is given to agents with data supporting their progression toward clinical trials and those currently undergoing validation in clinical studies.

Keywords
angiogenesis, inflammation, intrahepatic resistance, nitric oxide

Introduction
Portal hypertension is a cardinal feature of disease progression in cirrhosis. The presence of portal hypertension, as defined by an elevated hepatic venous pressure gradient (HVPG), heralds the onset of the most fatal complications of cirrhosis which include variceal haemorrhage and ascites with risk of spontaneous bacterial peritonitis. Over the last 3 decades, our understanding of the pathophysiology of portal hypertension has increased with a shift in focus from targeting splanchnic vasodilatation with agents such as β-blockers to appreciating the role of and need for novel targets of increased intrahepatic resistance, now believed to drive the onset of portal hypertension. Furthermore, in the context of an acute decompensation of cirrhosis following an acute precipitating event such as sepsis, as is the case in acute-on-chronic liver failure (ACLF), there is a further exacerbation of haemodynamic derangements associated with a much worse prognosis.

The aim of this concise review is to highlight the key mechanisms believed to be involved in driving an increase in intrahepatic resistance, especially in the context of ACLF, and to draw from this insight into potential new targets for therapy. The controversy over the need for monitoring response to available therapies and the means by which this should be conducted will also be addressed.

Mechanisms of increased intrahepatic resistance in cirrhosis
During the progression of cirrhosis, numerous ultrastructural changes occur including fibrosis, scarring with nodule formation and vascular thrombosis which impede blood flow through the liver. However, it is increasingly accepted that about 40% of the vascular resistance in the liver results from a dynamic and modifiable component including contractile elements impacting on the sinusoids, such as changes in vascular smooth muscle cells and activation of hepatic stellate cells, in addition to the development of sinusoidal endothelial dysfunction. These perturbations are most marked in ACLF.

The role of hepatic inflammation
Liver inflammation is a further determinant of portal pressure and prognosis in cirrhosis. Our group recently showed that patients with severe biopsy proven alcoholic hepatitis have the highest portal pressure [1] and others have also shown that these patients have high incidence of organ dysfunction and mortality [2]. Conversely,
inhibition of tumour necrosis factor-α (TNFα) causes a significant reduction in portal pressure in both portal hypertensive rats [5] and in humans with cirrhosis and superadded alcoholic hepatitis [4]. Moreover, reducing the level of hepatic inflammation with agents such as leukotriene inhibitors [5] or statins [6] impacts on several mechanistic pathways (elaborated further below) including activation of hepatic stellate cells and inflammatory cascades through kupffer cells.

Infection is also common in cirrhosis [7] and a key driver of hepatic inflammation. When infection develops in patients with cirrhosis, the systemic circulation becomes even more hyperdynamic and hyporeactive to pharmacological doses of α-adrenoceptor agonists than in cirrhosis patients without this additional inflammatory stimulus [8]. It follows that modulation of gut-derived bacterial load using selective gut decontamination may favour improved haemodynamics and reduced inflammation, as has been shown with agents such as rifaximine [9] and quinolones [10,11]. Other lines of investigation have suggested that by neutralizing circulating lipopolysaccharide and thereby inflammatory stimuli, using reconstituted high-density lipoprotein administration, there is a marked reduction in portal pressure [12].

A further manifestation of hepatic inflammation seen in ACLF is a marked increase in reactive oxidant species, especially superoxide, which by reducing nitric oxide bioavailability, contributes to an increase in intrahepatic vascular resistance. A recent study showed a clear association between levels of malondialdehyde (as a measure of oxidant stress) and severity of portal pressure in cirrhosis patients, in addition to correlation with plasma endotoxin levels [13]. Numerous strategies have been successfully shown to lower portal pressure through reduction in oxidant injury and these include the use of tempol, a small membrane permeable superoxide dismutase mimetic, which lowered portal pressure in experimental cirrhosis in rats [14]. Mitochondrial superoxide dismutase levels are reduced in cirrhosis and its augmentation by adenoviral vector delivery has recently also been shown to lower portal pressure [15]. Previous studies in experimental models also suggested a potential benefit from N-acetylcycteine [16], but further studies in humans are warranted.

**Derangement in endothelial nitric oxide synthase function**

Under normal conditions, the intrahepatic vasculature responds to changes in blood flow or pressure by a compensatory increase in vasodilators, particularly nitric oxide, which has been demonstrated to be crucial in maintaining hepatic vascular tone [17]. However, in cirrhosis there is an impaired response to endothelial-dependant vasodilatation which has largely been attributed to dysfunctional endothelial nitric oxide synthase (eNOS)-derived nitric oxide generation and/or increased nitric oxide scavenging [18–21]. Moreover, cirrhosis with superadded liver inflammation is associated with increased hepatic eNOS expression, despite which there is markedly decreased hepatic eNOS activity [22].

NOS activity may be altered by the actions of inhibitors and several have been described in the context of cirrhosis including caveolin-1 [23], NOS traffic-inducing protein [22] and asymmetric dimethylarginine (ADMA) [24,25]. ADMA is ubiquitously generated from the breakdown of proteins with methylated arginine residues and is tightly regulated by its metabolism by dimethylarginine dimethylaminohydrolase (DDAH), a hydrolase enzyme particularly abundant in the liver and kidney. DDAH expression and function is reduced in cirrhosis with resultant high ADMA levels which have been shown to be directly correlated with the severity of hepatic inflammation and organ dysfunction [26,27]. Thus, attention has turned to ways of lowering ADMA through augmentation of DDAH. Experimental model studies suggest that DDAH can be promoted by activation of the farnesoid X receptor (FXR) [28] and we recently demonstrated that this strategy can lower portal pressure in cirrhotic rats [29].

Another important regulator of NOS activity is the cofactor tetrahydrobiopterin which is believed to be reduced in expression in the context of cirrhosis. Under conditions of oxidant injury and low tetrahydrobiopterin, the NOS dimer complex uncouples resulting in the promotion of superoxide generation [30]. As described above, this markedly reduces nitric oxide bioavailability. Supplementation of tetrahydrobiopterin is, hence, a potentially
attractive therapeutic option in ACLF in which there is increased oxidant injury and therefore oxidation of tetrahydrobiopterin and, indeed, a recent study deploying its supplementation over 3 days in cirrhotic rats demonstrated a significant reduction in portal pressure [31].

It is important to appreciate that vasodilatory endothelial dysfunction in cirrhosis may result not only from impaired production of nitric oxide through NOS but also by an aberrant end-effector response by the guanylate cyclase—cyclic GMP (cGMP) system (an enzymatic cascade that mediates the nitric oxide-induced vasorelaxation). For example, the vasodilatation induced by S-nitroso-N-acetylpenicillamine, a nitric oxide donor that releases nitric oxide without undergoing metabolic transformation, is impaired in cirrhotic livers [32]. This supports the argument that in addition to decreased nitric oxide generation, there is also a reduced response to nitric oxide in cirrhotic livers likely caused by dysfunction of the cGMP system [33]. It follows that phosphodiesterase-5 inhibitors, which augment the action of cGMP, may have a beneficial effect in improving hepatic haemodynamics in advanced cirrhosis. This assertion has been supported by studies using the agents sildenafil and vardenafil and demonstrating improved liver blood flow and a trend toward lower portal pressure [34,35]. However, these agents require significant further study in the ACLF scenario as has been suggested in a recent study in decompensated cirrhosis, in which the agent tadalafl had an adverse effect on renal function and systemic haemodynamics, both of which are significantly impaired in ACLF patients [36*].

**Activation of the sympathetic and neuro-humoral systems**

Splanchnic vasodilation with reduction of effective arterial blood volume has as a consequence renal vasoconstriction, sympathetic stimulation, stimulation of the renin–angiotensin–aldosterone system and vasopressin secretion [37]. These pathophysiological responses are the key to the development of progressive ascites and subsequent renal vasoconstriction and dysfunction as portal hypertension evolves, most marked in ACLF [38]. Indeed, patients with ACLF have been shown to have a marked increase in norepinephrine levels and these correlate with the severity of inflammation and portal pressure [39]. Moreover, an increasing interest has developed in the possible relationship between inflammation and angiotensin II in promoting endothelial dysfunction as angiotensin II, through activation of the angiotensin II type 1 receptor and NAD(P)H oxidases, induces generation of inflammatory mediators in the blood vessel wall, including generation of ADMA [40]. There are also increasing data to support the role of the renin–angiotensin system in promoting progression of fibrosis (as recently reviewed by Abbas *et al.* [41]) through mechanisms including stellate cell activation. These developments in knowledge resulted in numerous studies that explored the role of angiotensin II inhibitors or its receptor blockers in patients with portal hypertension, many of which suggested haemodynamic benefits [42–44]. However, a recent meta-analysis has cautioned on the application of these agents in severely decompensated patients, such as those with ACLF, who risk hypotension and renal insufficiency [45*].

A further novel vaso-modulating agent, urotensin II, has generated interest by the fact that it promotes mesenteric vasodilatation, while also promoting reduction in renal blood flow and increased portal pressure, and its levels are markedly increased in patients with cirrhosis. Furthermore, urotensin II concentrations correlate with the severity of disease and with portal pressure gradient suggesting that it is likely to be of relevance to the pathology of ACLF [46]. Studies in animal models have shown that infusion of urotensin II into normal rats can promote fibrogenesis, while also increasing portal pressure [47], whereas inhibition of the urotensin II receptor in cirrhotic rats lowered portal pressure, while also increasing splanchnic vascular resistance [48]. Thus, inhibition of urotensin II shows promise as a novel target for therapy of portal haemodynamic derangements in advanced cirrhosis, but clinical studies are awaited.

**The role of proangiogenic factors**

Angiogenesis refers to the process of new vessel formation from preexisting blood vessels or from endothelial progenitor cells derived from the bone marrow, often triggered by tissue hypoxia. This occurs in conjunction with sinusoidal vascular remodelling, in which an increased density of contractile hepatic stellate cells wrap around sinusoidal endothelial cells that have undergone capillarization through loss of fenestrae [49,50**]. These processes have been shown to contribute to increased intrahepatic resistance beyond the established association between angiogenesis and degree of hepatic fibrosis [51].

Numerous factors including vascular endothelial growth factor and its receptors, angiopoietin-1 and platelet-derived growth factor, have been shown to be important for angiogenesis, especially on the background of inflammatory chronic liver disease as encountered in ACLF [49,52]. In turn, studies targeting these pathways in animal models of cirrhosis have all confirmed a decrease in portal pressure [53*], with some multitarget receptor tyrosine kinase inhibitors such as sorafenib [54] and sunitinib [55] also demonstrating a reduction in hepatic inflammation. However, use of such agents for targeting intrahepatic resistance in ACLF should be tempered with a degree of caution, as there is a thought that angiogenesis may also be important for tissue regeneration and repair. Furthermore, angiogenesis promoting
intrahepatic collaterals in theory may facilitate decompressing shunts which offset further rise in intrahepatic resistance. Thus, blocking such mechanisms may prove detrimental, and some evidence for this comes from a study using the agent cilengitide to inhibit angiogenesis, which showed an aggravation of hepatic inflammation and fibrosis [56*]. Clearly, further mechanistic and dose-ranging studies are needed before application to severe decompensated cirrhosis in patients with ACLF.

Emerging therapies for clinical application in lowering portal pressure

For three decades, nonselective β-adrenoceptor antagonists have been considered as a prophylactic therapy against variceal bleeding in patients with cirrhosis and portal hypertension [57]. Newer generation of agents such as carvedilol have promising data to show that they may be effective in preventing the first episode of variceal bleeding in cirrhosis [58]. However, specific controlled studies addressing use of β-blockers in patients with severe decompensation of cirrhosis with high risk of sepsis and renal dysfunction are lacking. A recent study performed in France alludes to an increased risk of mortality in patients with decompensated cirrhosis and refractory ascites, especially from sepsis [59**]. Notwithstanding some potential weaknesses in the study in that it was not randomized and the patients not assigned to β-blockers did not have varices (an independent prognostic risk), this study does suggest that patients with ACLF and incipient organ failure may be compromised from β-blocker therapy. Indeed, the increased incidence of renal dysfunction and reduced organ perfusion in advanced cirrhosis might be anticipated to be further adversely affected by decreases in arterial pressure as a consequence of β-blocker therapy. Thus, there is still clearly a need to explore other therapeutic options to lower portal pressure in current clinical studies.

Among several emerging therapeutic candidates, 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors (‘statins’) appear attractive in that they target several aspects of the pathophysiology of portal hypertension and are widely available. Statins promote endothelial nitric oxide generation, while also inhibiting the RhoA/Rho kinase system, which ordinarily decreases availability of phosphorylated active eNOS [60,61]. An early study in patients with cirrhosis showed that simvastatin decreased hepatic sinusoidal resistance within 1 h of therapy and improved liver blood flow [62]. A more recent randomized controlled study by the same group treating cirrhotic patients with simvastatin for 1 month demonstrated a modest reduction (8%) in portal pressure, but also an improvement in indocyanine green clearance implying improved hepatic perfusion without impaired systemic haemodynamics [63*]. Although encouraging, further long-term safety of statins in cirrhosis needs to be assessed, especially in ACLF, in which increased catabolism is likely to be associated with preexistent low cholesterol levels, which may have implications on immune function [64].

Given the importance of nitric oxide in maintaining intrahepatic vascular tone, as described above, and the numerous factors contributing to low nitric oxide generation in advanced cirrhosis, a strategy to deliver nitric oxide to the liver would appear intuitive. Early work describing an agent NCX-1000 (an urso-deoxycholic acid derivative believed to have the properties to liberate nitric oxide within the liver) appeared promising with cirrhotic models showing a significant decrease in portal pressure [65]. However, a more recent clinical study has demonstrated no significant portal pressure lowering effect in patients with cirrhosis and, most importantly, a lowering of mean arterial pressure, suggesting that the release of nitric oxide may indeed not be confined to the liver [66]. In search of alternative strategies to increase hepatic nitric oxide, studies in a bile duct-ligated model of portal hypertension have suggested that increasing DDAH levels with an FXR agonist to lower levels of the eNOS inhibitor, ADMA, results in a significant reduction in portal pressure and reduces hepatic inflammation [29*]. These agents are already in clinical trials for primary biliary cirrhosis and fatty liver disease and clinical trials in decompensated cirrhosis and ACLF are awaited.

Monitoring response to therapy

It is now well accepted that a reduction in portal pressure to below 12 mmHg or a greater than 20% reduction in pressure from baseline measure determines a significantly reduced risk of bleeding on long-term follow-up [67,68]. However, it has also become apparent that a significantly elevated portal pressure also has prognostic value in determining risk of complications from portal hypertension and survival and this is especially the case in ACLF. For example, in patients presenting with acute severe alcoholic hepatitis, a significantly elevated HVPG has been shown to be associated with increased mortality, especially from sepsis and renal dysfunction and to correlate with the severity of hepatic inflammation [1,69]. Measurement of HVPG has also shown benefit in reflecting good response to antiviral therapy and risk of disease progression [70].

Despite all these valuable reasons for adopting routine HVPG measurement, this has failed to occur outside of specialist centres and clinical trials, in part, due to the lack of consistency in method of measurement and recording, as reviewed by Groszmann and Wongcharatraewee [71]. The technique, although safe and relatively simple, does have technical requirements and a need for quality control of the data output, especially with
reference to standardization of, for example, inferior vena cava pressure to calculate HVPG, rather than an arbitrary free hepatic vein or right atrial pressure measurement. Furthermore, debate continues on the timing of a second measurement following an intervention (1–6 months) and this is especially relevant in ACLF and acute variceal bleeding, as such time frames lose the benefit on the potential to be informed on risk of progression to further organ dysfunction and rebleeding. In this respect, the acute haemodynamic effect of agents such as propranolol given intravenously may well prove valuable in prognostication during acute decompensation of cirrhosis [72]. However, further validation studies are required before such protocols are adopted into clinical practice. At present, more energy is required in clinical studies to validate the benefit of portal pressure reduction and hepatic blood flow measurement following interventions in decompensated cirrhosis and to provide a standard against which new noninvasive technologies to determine intrahepatic resistance can be compared.

Conclusion
With an increasing understanding of the pathophysiology of ACLF and the important effects that hepatic inflammation and oxidative injury convey on intrahepatic resistance, a number of potential new targets for therapy have emerged, as highlighted in this review. However, most of these potential agents have been assessed in rodent models or ex-vivo perfusion systems and thus their clinical applicability needs to be interpreted with some caution, as has been demonstrated with agents such as NCX-1000. This said, one remains optimistic given the data emerging on agents such as the statins, and that a new treatment with relevance to the inflammatory environment of ACLF will be unveiled and validated over the coming years. There is also clearly a need to have a measure of treatment response and further studies are required to establish the value and long-term significance of demonstrating acute HVPG reduction, while awaiting validation of newer noninvasive technologies.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest ** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 209).


15. Generation of superoxide, as a manifestation of inflammatory responses and increased eNOS uncoupling is highlighted in this manuscript, and the importance of targeting this to lower intrahepatic resistance.


17. As with [14] importance of increased oxidative stress to improve NOS function but here highlighting that gene therapy may also be a future strategy.


26 Mookerjee RP, Dalton RN, Davies NA, et al. Inflammation is an important determinant of levels of the endogenous nitric oxide synthase inhibitor asymmetric dimethylarginine (ADMA) in acute liver failure. Liver Transpl 2007; 13:400–408.


30 Novel target for therapy in portal hypertension, especially relevant to ALCF, in which cepharaxin drives a reduction in FXR signaling.


37 This article highlights the need for caution in interpreting and translating model data to the portal system. Here, organ perfusion appears impaired with phosphodiesterase-5 inhibition and cautions the need for further study.


42 Abbas G, Silveira MG, Linder KD. Hepatic fibrosis and the renin-angiotensin system. Am J Ther 2010 (Epub ahead of print)


47 This article shows caution in interpretation of data supporting a role for angiotensin blockade in advanced cirrhosis and suggests that such treatments may be even deleterious in ALCF.


53 An excellent overview of new targets for lowering intra-hepatic resistance.


57 A useful review to summarize the many factors that impact on increased intrahepatic resistance and thereby serve as potential targets for therapy.


61 This article provides with the observation that blocking angiogenic pathways may actually promote inflammation and/or fibrosis. Once again a reminder of the need for further studies in human and caution in interpretation of preliminary animal model data.


65 An important article when considering therapy for portal hypertension in ALCF. This manuscript suggest that in this high-risk population with refractory ascites and likely underlying risk of sepsis, beta-blockade may have deleterious consequences and needs systematic evaluation in this cohort.


70 Promising data to support the use of this relatively cheap and available therapy to target portal hypertension, with mechanistic data to support its use provided in [61,62].


