

# Role of endotoxemia in causing renal dysfunction in cirrhosis

Jennifer L Peng,<sup>1</sup> Witina Techasatian,<sup>1</sup> Takashi Hato,<sup>2</sup>  
Suthat Liangpunsakul <sup>1,3</sup>

<sup>1</sup>Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

<sup>2</sup>Division of Nephrology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

<sup>3</sup>Roudebush Veterans Administration Medical Center, Indianapolis, IN, USA

## Correspondence to

Dr Suthat Liangpunsakul, Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA; [sliangpu@iu.edu](mailto:sliangpu@iu.edu)

JLP and WT contributed equally.

Accepted 6 June 2019  
Published Online First 19 July 2019

## ABSTRACT

Renal failure is a challenging problem in patients with cirrhosis since mortality increases with worsening renal function, hence the inclusion of serum creatinine in calculating the Model for End-Stage Liver Disease score for liver transplant evaluation. Among the various causes, infection is the leading etiology of mortality associated with cirrhosis. Bacterial infection frequently precipitates renal failure in patients with cirrhosis with the reported prevalence around 34%. Patients with cirrhosis are at increased risk of infections due to impaired immunity and increased gut permeability leading to bacterial translocation in the setting of portal hypertension. One of the most feared complications of severely decompensated liver and renal failure is hepatorenal syndrome, of which liver transplant may be the only available treatment. Furthermore, in those with spontaneous bacterial peritonitis and urinary tract infection, progressive renal failure occurs despite resolution of infection. Thus, the effects of endotoxemia on renal function in cirrhosis have become a major focus of research. The mechanisms of the damaging effects of endotoxin on renal function are complex but, in essence, involve dysregulated inflammation, circulatory dysfunction, poor clearance of endotoxin burden, as well as vasomotor nephropathy. In this article, we will review the mechanisms of endotoxemia-induced renal dysfunction in the setting of cirrhosis through the effects on renal blood flow, renal vascular endothelium, glomerular filtration rate, and tubular function.

## INTRODUCTION

Cirrhosis, the most advanced consequence of chronic liver disease, has become a significant health concern given the increased morbidity and mortality from decompensated hepatic function.<sup>1</sup> Between 1999 and 2016, annual deaths secondary to cirrhosis in the USA increased by 65%.<sup>1</sup> Furthermore, models have projected the incidence of deaths from non-alcoholic-related cirrhosis to increase by 178% by 2030.<sup>1</sup> The mechanism by which decompensated cirrhosis creates such complications stems from disruption in systemic homeostasis that leads to widespread effects on hepatic function and other organs. Specifically, hepatic and renal functions are closely related, and, in

the setting of cirrhosis significant renal impairment can occur. Insults to both systems lead to detrimental outcomes, as seen in hepatorenal syndrome which occurs in patients with cirrhosis, refractory ascites, and compromised renal function that, at its worst, can only be resolved with liver transplant.<sup>2</sup>

Among the various causes, bacterial infection is the leading etiology of complications associated with cirrhosis and frequently precipitates renal failure with the reported prevalence around 34%.<sup>3,4</sup> The majority of infections are due to intestinal translocation of Gram-negative bacteria in the setting of spontaneous bacterial peritonitis.<sup>5</sup> Renal failure is evaluated to be caused by bacterial infection when either acute or pre-existing renal injury appears or worsens in the setting of infection.<sup>3</sup> Acute kidney injury is defined as increased serum creatinine of at least 0.3 mg/dL if it occurred within 48 hours or 1.5 times from baseline within 7 days.<sup>6</sup> Of note, serum creatinine may not accurately reflect glomerular filtration rate (GFR) in patients with cirrhosis due to muscle wasting leading to falsely low levels, increased tubular secretion of creatinine, dilution due to increased distribution volume, and elevated bilirubin which can affect accurate measurement of creatinine.<sup>7</sup>

Understanding the effects of endotoxemia at the level of renal blood flow, GFR, renal vasculature, and tubular function will be crucial to identify potential targets of intervention to mitigate the complications of acute renal failure secondary to bacteremia in patients with cirrhosis.

## CIRRHOSIS AND ETIOLOGY OF ENDOTOXEMIA

Portal and peripheral blood endotoxin levels have been found to be higher in patients with cirrhosis when compared with healthy controls.<sup>8,9</sup> The etiology of endotoxemia in decompensated cirrhosis is multifactorial and related to impaired defense barriers within the intestinal lumen leading to systemic-wide complications. In the normal condition, the integrity of the intestinal lumen depends on a mechanical barrier consisting of tight gap junctions, an immune barrier (comprising secretory IgA, intramucosal lymphocytes, mesenteric lymph nodes) as well as systemic



© American Federation for Medical Research 2020. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Peng JL, Techasatian W, Hato T, et al. *J Investig Med* 2020;**68**:26–29.

host immunity.<sup>9-12</sup> Patients with cirrhosis have structural changes of the intestinal mucosa, such as widening of intercellular spaces, loss of tight junctions, and defects in the mucosal immune system with reduction in secretory IgA leading to the translocation of gut bacteria into the circulation.<sup>13-16</sup> In addition, endotoxemia leads to alterations in intestinal motility and a decrease in luminal bile acid, which is a suppressor of bacterial overgrowth; hence, the colonization of bacteria with high translocation capability was observed in locations with low bacterial counts such as the proximal small intestine.<sup>16,17</sup> Finally, decompensated cirrhosis can promote a predominantly immunodeficient state which, in the setting of systemic inflammation, can progress to multiorgan failure, septic shock, and death.<sup>18</sup>

Kupffer cells within the liver sinusoids express toll-like receptors, which play an important role in the phagocytosis and clearance of gut-derived bacterial endotoxins such as lipopolysaccharide (LPS).<sup>16,19</sup> Hepatocytes similarly express toll-like receptor-4 (TLR-4) receptors responsive to LPS, and, thus, are also responsible in the uptake and removal of LPS.<sup>16,20</sup> However, with large amounts of intestinal bacterial translocation, the functional capacity of the liver can become overwhelmed and endotoxin cannot be effectively removed.<sup>10</sup> Additionally, increased systemic activation of neutrophils by mediators like LPS results in inappropriate sequestration of leukocytes in hepatic microvasculature. As a result, this can lead to impaired sinusoidal perfusion and subsequent impaired Kupffer cell function.<sup>21</sup> Endotoxemia also leads to increased levels of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which binds to TNF receptor on Kupffer cells and inhibits phagocytosis.<sup>22</sup> Ultimately, in the setting of cirrhosis, dysfunctional Kupffer cells and hepatocytes lead to defective hepatic clearance of LPS, which allows LPS to enter systemic circulation.<sup>16,20,23</sup>

## MECHANISMS OF ENDOTOXEMIA-INDUCED RENAL DYSFUNCTION IN CIRRHOSIS

### Endotoxemia and renal blood flow

While nitric oxide (NO) is thought to have a vasodilatory effect to help increase renal blood flow and prevent kidney injury, an excessive production of NO can adversely affect kidney function.<sup>24</sup> In the presence of endotoxemia, increased levels of NO secondary to activated inducible nitric oxide synthase (iNOS) lead to systemic vasodilation and organ hypoperfusion.<sup>25</sup> LPS-injected rats had a fall in cortical and medullary perfusion.<sup>26</sup> Interestingly, when they were treated with NG-methyl-L-arginine, an NO synthase inhibitor, renal function improved with greater insulin clearance.<sup>26</sup> NO has been evaluated for its potential toxic effects on renal function. High levels of NO cause DNA strand damage, which triggers an energy-consuming process involving nuclear enzyme poly-ADP-ribosyltransferase that depletes cellular storage of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and ATP, leading to cell death.<sup>27</sup> Additionally, excess levels of NO can also block key enzymes in mitochondrial respiration and in the Krebs cycle, resulting in the disruption of cellular function.<sup>28</sup> Thus, these data suggest inhibition of the reactive species produced from iNOS in endotoxemia may prevent the capillary perfusion defects creating compromised renal blood flow.

### Endotoxemia and GFR

GFR is both a function of filtration fraction as well as renal plasma flow (RPF). In mild to moderate reductions in RPF, increased renal vasoconstriction from angiotensin II on efferent arterioles and vasodilation from prostaglandins on afferent arterioles can lead to increased filtration fraction. Thus, GFR will be normal in patients with cirrhosis. However, during the course of sepsis and the aforementioned reductions in RPF, increased filtration fraction fails to compensate, leading to decreased GFR.<sup>29</sup>

Additionally, LPS causes damage to the glomerular barrier due to reduction in size selectivity and increase in glomerular pore size.<sup>30</sup> The mechanism by which this is thought to occur is secondary to inflammation given podocytes have LPS receptors, such as TLR-4 and CD14.<sup>31</sup> Thus, endotoxemia creates an inflammatory state leading to release of cytokines such as TNF $\alpha$  and oxidative stress which can impair podocytes, the specialized cells within Bowman's capsule that function in glomerular filtration.<sup>32</sup> Mice injected with LPS exhibited 70% reduction in GFR.<sup>33</sup> However, when these mice were pretreated with TNF-soluble receptor p55, GFR was reduced by only 30% and RPF was preserved, demonstrating the negative impact of LPS-induced release of TNF $\alpha$  on glomerular integrity and function.<sup>33</sup> In addition, during endotoxemia, the expression of renal extracellular superoxide dismutase, an important antioxidant, was decreased, leading to the reduction in the protective mechanism against LPS-induced reactive oxygen species. Treatment with antioxidants prevented the reduction in GFR.<sup>34</sup>

Bile cast nephropathy is an additional pathology to consider in renal dysfunction in cirrhosis. Patients with cirrhosis who develop renal dysfunction often have increased serum concentrations of bilirubin, leading to cholestasis of sepsis, which may have a direct toxic effect on renal tubules.<sup>35</sup> The exact pathogenesis remains to be elucidated, but current theory suggests that the low water solubility of bile acids leads to cast formation and a proximal bile cast tubulopathy leading to reduced GFR.<sup>36</sup>

### Endotoxemia and effects on vasculature/endothelium

The vascular endothelium is a dynamic structure that maintains a semipermeable membrane to water and other biomolecules, mediates leukocyte diapedesis through adhesion molecules, and regulates vascular tone as well as hemostasis.<sup>37</sup> Numerous molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and TNF $\alpha$ , among many others, are indicated in the pathophysiology of endotoxin-induced endothelial damage.<sup>37</sup> What exacerbates this microvascular dysfunction is the stagnation of microvascular flow.<sup>38</sup> Additionally, leukocytes have decreased velocities and increased transit time during endotoxemic states.<sup>39</sup> Rats with induced acute renal failure via LPS injection had increased levels of ICAM-1 and VCAM-1, which both promote inflammation by facilitating leukocyte adhesion to microvascular endothelium.<sup>40</sup> Given delayed microvascular flow with the aforementioned increased levels of inflammatory markers, this prolonged transit time may lead to increased exposure of renal tubular endothelial cells to an amplified inflammatory response and cause greater damage.<sup>38,41</sup>

Endotoxemia also leads to increased vascular tone due to the activation of renal endothelin receptor type A (ETA), which is involved with vasoconstriction on vascular smooth muscle.<sup>41–44</sup> LPS injection in rats led to the increase of endothelin-1 and upregulation of ETA.<sup>45</sup> The inability to block the dominating vasoconstrictive effects of endothelin during endotoxemia may cause intrarenal vasoconstriction, leading to compromised renal function in cirrhosis. Interestingly, pretreatment using an ETA antagonist blocked renal vascular hyperreactivity.<sup>45</sup>

Newer research by Parikh<sup>46</sup> has focused on the angiotensin-Tie-2 axis in sepsis. The main biomolecules implicated are angiotensin-1 (Angpt-1) which is produced in periendothelial cells, angiotensin-2 which is a competitive antagonist of Angpt-1, and Tie-2 which is a transmembrane tyrosine kinase from endothelial DNA.<sup>47</sup> The significance of Angpt-1 lies in that its activation leads to multimerization and cross-phosphorylation into large aggregates to maintain vascular integrity.<sup>48</sup> As a result, Angpt-1 serves a defense function that can create a barrier to the effects of Gram-negative endotoxin. Studies have shown Angpt-1 in murine endotoxemia reduced vascular leakage as well as cellular inflammation via transcription inhibition for inflammatory molecule nuclear factor kappa-light-chain-enhancer of activated B cells.<sup>49,50</sup>

### Endotoxemia and effects on tubular function

Endotoxemia has been shown to upregulate TLR-4 expression in the proximal tubules.<sup>51</sup> Filtered endotoxin can interact with TLR-4 on the S1 segment of the proximal tubules and directly cause damage in the downstream S2 and S3 tubules through the secretion of proinflammatory cytokines such as TNF $\alpha$ .<sup>52</sup> Filtered endotoxin also reduces tubular flow rate and can cause oliguria. Thus, mice injected with LPS had significantly reduced tubular urine flow due to the accumulation of LPS in the proximal tubules.<sup>53</sup> In addition, endotoxemia causes a decrease in peritubular capillary flow due to the increased production of reactive nitrogen species (RNS) by the renal tubules.<sup>54</sup> Antioxidant resveratrol, which is capable of scavenging reactive nitrogen species, reversed the decline in cortical capillary perfusion and lead to restoration of renal microcirculation.<sup>45</sup> The schematic diagram illustrating the role of endotoxemia in causing renal dysfunction in cirrhosis is shown in figure 1.

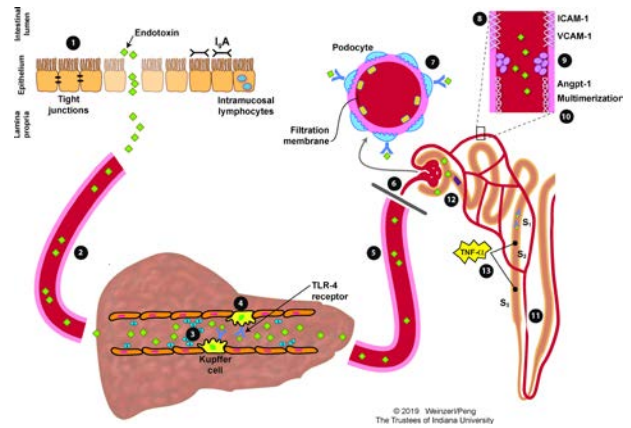
### CONCLUSION

The full extent of the effects and complications of endotoxemia on renal function in cirrhosis remains to be elucidated. At the backbone of the derangements occurring in endotoxemia is dysregulated homeostatic regulation within the body. The evidence in understanding the full pathophysiology of this issue is complex, and the treatment modality to address the full spectrum of effects will need to be equally, if not more, multifaceted.

**Contributors** JLP and WT: research references and drafted the manuscript. TH and SL: edited and finalized the manuscript.

**Funding** This study is supported in part by grants R01AA025208, R01DK107682, U01AA026917, UH2AA026903, and I01CX000361 (to SL) and K08-DK113223 (to TH).

**Competing interests** None declared.



**Figure 1** The cascade of endotoxemia leading to renal dysfunction in patients with cirrhosis starts at the intestinal lumen. (1) Translocation of gut bacterial endotoxin LPS from the intestinal lumen occurs due to impaired intestinal epithelial defense barrier, which includes tight junctions, intramucosal lymphocytes, and IgA. Subsequently, (2) endotoxin enters systemic circulation and the cirrhotic liver sinusoid. As part of the inflammatory reaction, (3) sequestration of neutrophils leads to decreased sinusoidal perfusion and endotoxin clearance. Additionally, (4) large burden of LPS overwhelms the functional capacity of TLR-4 receptors on Kupffer cells and cannot be effectively cleared. Thus, (5) endotoxin continues circulation to kidneys. At the level of the glomerulus, (6) endotoxemia activates nitric oxide and leads to vasodilation and decrease in medullary perfusion. Within the podocytes, (7) LPS binding on TLR-4 receptors damages podocyte membrane integrity and increases glomerular pore size. Within the renal vasculature, (8) inflammatory response to endotoxin activates ICAM-1 and VCAM-1 and leads to endothelial damage. (9) Leukocyte adhesion causes prolonged transit and exposure to inflammation. However, (10) Angpt-1 multimerization does create a protective effect to maintain vascular integrity. (11) ETA activation also leads to abnormal vasoconstriction. Within the tubules, (12) bile cast nephropathy also occurs and can lead to reduced GFR. (13) Endotoxin binding to TLR-4 receptors in the proximal tubules in S1 causes downstream damage on S2 and S3 with proinflammatory TNF $\alpha$ . Angpt-1, angiotensin-1; ETA, endothelin receptor type A; GFR, glomerular filtration rate; ICAM-1, intercellular adhesion molecule-1; LPS, lipopolysaccharide; TLR-4, toll-like receptor-4; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; VCAM-1, vascular cell adhesion molecule-1.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

### ORCID iD

Suthat Liangpunsakul <http://orcid.org/0000-0002-6504-8123>

### REFERENCES

- 1 Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. *BMJ* 2018;362:k2817.
- 2 Angeli P, Morando F. Optimal management of hepatorenal syndrome in patients with cirrhosis. *Hepat Med* 2010;2:87–98.
- 3 Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. *Hepatology* 2007;45:223–9.
- 4 Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495–501.

- 5 Fukui H, Matsumoto M, Bode C, *et al.* Endotoxaemia in patients with liver cirrhosis and upper gastrointestinal bleeding: detection by the chromogenic assay with plasma Tween 80 pretreatment. *J Gastroenterol Hepatol* 1993;8:577–81.
- 6 Wong F. Acute kidney injury in liver cirrhosis: new definition and application. *Clin Mol Hepatol* 2016;22:415–22.
- 7 Mindikoglu AL, Pappas SC. New Developments in Hepatorenal Syndrome. *Clin Gastroenterol Hepatol* 2018;16:162–77.
- 8 Tachiyama G, Sakon M, Kambayashi J, *et al.* Endogenous endotoxemia in patients with liver cirrhosis—a quantitative analysis of endotoxin in portal and peripheral blood. *Jpn J Surg* 1988;18:403–8.
- 9 Bode C, Kugler V, Bode JC. Endotoxemia in patients with alcoholic and non-alcoholic cirrhosis and in subjects with no evidence of chronic liver disease following acute alcohol excess. *J Hepatol* 1987;4:8–14.
- 10 Fukui H. Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. *World J Hepatol* 2015;7:425–42.
- 11 Tsiaoussis GI, Assimakopoulos SF, Tsamandas AC, *et al.* Intestinal barrier dysfunction in cirrhosis: Current concepts in pathophysiology and clinical implications. *World J Hepatol* 2015;7:2058–68.
- 12 Aguirre Valadez JM, Rivera-Espinosa L, Méndez-Guerrero O, *et al.* Intestinal permeability in a patient with liver cirrhosis. *Ther Clin Risk Manag* 2016;12:1729–48.
- 13 Pérez-Paramo M, Muñoz J, Albillos A, *et al.* Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. *Hepatology* 2000;31:43–8.
- 14 Nakatani Y, Fukui H, Kitano H, *et al.* Endotoxin clearance and its relation to hepatic and renal disturbances in rats with liver cirrhosis. *Liver* 2001;21:64–70.
- 15 Ponziani FR, Zocco MA, Cerrito L, *et al.* Bacterial translocation in patients with liver cirrhosis: physiology, clinical consequences, and practical implications. *Expert Rev Gastroenterol Hepatol* 2018;12:641–56.
- 16 Mencin A, Kluge J, Schwabe RF. Toll-like receptors as targets in chronic liver diseases. *Gut* 2009;58:704–20.
- 17 Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005;41:422–33.
- 18 Noor MT, Manoria P. Immune Dysfunction in Cirrhosis. *J Clin Transl Hepatol* 2017;5:1–9.
- 19 Fox ES, Thomas P, Broitman SA. Clearance of gut-derived endotoxins by the liver. Release and modification of 3H, 14C-lipopolysaccharide by isolated rat Kupffer cells. *Gastroenterology* 1989;96:456–61.
- 20 Jirillo E, Caccavo D, Magrone T, *et al.* The role of the liver in the response to LPS: experimental and clinical findings. *J Endotoxin Res* 2002;8:319–27.
- 21 Brown KA, Brain SD, Pearson JD, *et al.* Neutrophils in development of multiple organ failure in sepsis. *Lancet* 2006;368:157–69.
- 22 Isayama F, Hines IN, Kremer M, *et al.* LPS signaling enhances hepatic fibrogenesis caused by experimental cholestasis in mice. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G1318–28.
- 23 Deng M, Scott MJ, Loughran P, *et al.* Lipopolysaccharide clearance, bacterial clearance, and systemic inflammatory responses are regulated by cell type-specific functions of TLR4 during sepsis. *J Immunol* 2013;190:5152–60.
- 24 Fremstad D, Jacobsen S, Lunde KM. Influence of serum protein binding on the pharmacokinetics of quinidine in normal and anuric rats. *Acta Pharmacol Toxicol* 1977;41:161–76.
- 25 Weigert AL, Higa EM, Niederberger M, *et al.* Expression and preferential inhibition of inducible nitric oxide synthase in aortas of endotoxemic rats. *J Am Soc Nephrol* 1995;5:2067–72.
- 26 Millar CG, Thiemeermann C. Intrarenal haemodynamics and renal dysfunction in endotoxaemia: effects of nitric oxide synthase inhibition. *Br J Pharmacol* 1997;121:1824–30.
- 27 Zingarelli B, O'Connor M, Wong H, *et al.* Peroxynitrite-mediated DNA strand breakage activates poly-adenosine diphosphate ribosyl synthetase and causes cellular energy depletion in macrophages stimulated with bacterial lipopolysaccharide. *J Immunol* 1996;156:350–8.
- 28 Thiemeermann C, Ruetten H, Wu CC, *et al.* The multiple organ dysfunction syndrome caused by endotoxin in the rat: attenuation of liver dysfunction by inhibitors of nitric oxide synthase. *Br J Pharmacol* 1995;116:2845–51.
- 29 Mindikoglu AL, Weir MR. Current concepts in the diagnosis and classification of renal dysfunction in cirrhosis. *Am J Nephrol* 2013;38:345–54.
- 30 Axelsson J, Rippe A, Venturoli D, *et al.* Effects of early endotoxemia and dextran-induced anaphylaxis on the size selectivity of the glomerular filtration barrier in rats. *Am J Physiol Renal Physiol* 2009;296:F242–8.
- 31 Banas MC, Banas B, Hudkins KL, *et al.* TLR4 links podocytes with the innate immune system to mediate glomerular injury. *J Am Soc Nephrol* 2008;19:704–13.
- 32 Reiser J, Altintas MM. Podocytes. *F1000Res* 2016;5.
- 33 Knotek M, Rogachev B, Wang W, *et al.* Endotoxemic renal failure in mice: Role of tumor necrosis factor independent of inducible nitric oxide synthase. *Kidney Int* 2001;59:2243–9.
- 34 Wang W, Jittikanont S, Falk SA, *et al.* Interaction among nitric oxide, reactive oxygen species, and antioxidants during endotoxemia-related acute renal failure. *Am J Physiol Renal Physiol* 2003;284:F532–F537.
- 35 Moseley RH. Sepsis and cholestasis. *Clin Liver Dis* 2004;8:83–94.
- 36 Bairaktari E, Liams G, Tsolas O, *et al.* Partially reversible renal tubular damage in patients with obstructive jaundice. *Hepatology* 2001;33:1365–9.
- 37 Brodsky SV, Yamamoto T, Tada T, *et al.* Endothelial dysfunction in ischemic acute renal failure: rescue by transplanted endothelial cells. *Am J Physiol Renal Physiol* 2002;282:F1140–9.
- 38 Wu L, Tiwari MM, Messer KJ, *et al.* Peritubular capillary dysfunction and renal tubular epithelial cell stress following lipopolysaccharide administration in mice. *Am J Physiol Renal Physiol* 2007;292:F261–8.
- 39 Fry DE. Sepsis, systemic inflammatory response, and multiple organ dysfunction: the mystery continues. *Am Surg* 2012;78:1–8.
- 40 Cunningham PN, Wang Y, Guo R, *et al.* Role of Toll-like receptor 4 in endotoxin-induced acute renal failure. *J Immunol* 2004;172:2629–35.
- 41 Goddard CM, Allard MF, Hogg JC, *et al.* Prolonged leukocyte transit time in coronary microcirculation of endotoxemic pigs. *Am J Physiol* 1995;269:H1389–97.
- 42 Adawi D, Kasravi FB, Molin G. Manipulation of nitric oxide in an animal model of acute liver injury. The impact on liver and intestinal function. *Libyan J Med* 2007;2:73–81.
- 43 Chuang CL, Chang CC, Hsu SJ, *et al.* Endotoxemia-enhanced renal vascular reactivity to endothelin-1 in cirrhotic rats. *Am J Physiol Gastrointest Liver Physiol* 2018;315:G752–G761.
- 44 Chuang CL, Huang HC, Chang CC, *et al.* Lipopolysaccharide enhanced renal vascular response to endothelin-1 through ETA overexpression in portal hypertensive rats. *J Gastroenterol Hepatol* 2015;30:199–207.
- 45 Holthoff JH, Wang Z, Seely KA, *et al.* Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury. *Kidney Int* 2012;81:370–8.
- 46 Parikh SM. Dysregulation of the angiotensin-Tie-2 axis in sepsis and ARDS. *Virulence* 2013;4:517–24.
- 47 Barton WA, Tzvetkova D, Nikolov DB. Structure of the angiotensin-2 receptor binding domain and identification of surfaces involved in Tie2 recognition. *Structure* 2005;13:825–32.
- 48 Kim KT, Choi HH, Steinmetz MO, *et al.* Oligomerization and multimerization are critical for angiotensin-1 to bind and phosphorylate Tie2. *J Biol Chem* 2005;280:20126–31.
- 49 Witzensbichler B, Westermann D, Knueppel S, *et al.* Protective role of angiotensin-1 in endotoxic shock. *Circulation* 2005;111:97–105.
- 50 Tadros A, Hughes DP, Dunmore BJ, *et al.* ABIN-2 protects endothelial cells from death and has a role in the antiapoptotic effect of angiotensin-1. *Blood* 2003;102:4407–9.
- 51 Cunningham PN, Dyanov HM, Park P, *et al.* Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. *J Immunol* 2002;168:5817–23.
- 52 El-Achkar TM, Huang X, Plotkin Z, *et al.* Sepsis induces changes in the expression and distribution of Toll-like receptor 4 in the rat kidney. *Am J Physiol Renal Physiol* 2006;290:F1034–43.
- 53 Nakano D, Doi K, Kitamura H, *et al.* Reduction of Tubular Flow Rate as a Mechanism of Oliguria in the Early Phase of Endotoxemia Revealed by Intravital Imaging. *J Am Soc Nephrol* 2015;26:3035–44.
- 54 Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991;337:776–8.