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The Role of Endotoxemia in Causing Renal Dysfunction in Cirrhosis

Jennifer L. Peng, MD[#1], **Witina Techasatian, MD**[#1], **Takashi Hato, MD**[2], **Suthat Liangpunsakul, MD, MPH**[1,3,4]

[1]Division of Gastroenterology and Hepatology Indiana University School of Medicine, Indianapolis, IN

[2]Division of Nephrology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[3]Roudebush Veterans Administration Medical Center, Indianapolis, IN

[4]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN

[#] These authors contributed equally to this work.

Abstract

Renal failure is a challenging problem in cirrhotic patients since mortality increases with worsening renal function, hence the inclusion of serum creatinine in calculating the Model for End-Stage Liver Disease (MELD) 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%. Cirrhotic patients 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 (HRS), of which liver transplant may be the only available treatment. Furthermore, in those with spontaneous bacterial peritonitis (SBP) and urinary tract infection (UTI), 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, and glomerular filtration rate (GFR), and tubular function.

Corresponding author Suthat Liangpunsakul, MD, Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, 702 Rotary Circle, Indianapolis, IN 46202, Phone: 317-278-1630, Fax: 317-988-3180, sliangpu@iu.edu.

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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.[1] Between 1999 to 2016, annual deaths secondary to cirrhosis in the United States increased by 65%[1]. Furthermore, models have projected the incidence of deaths from nonalcoholic-related cirrhosis to increase by 178% by 2030.[1] The mechanism by which decompensated cirrhosis creates such complications stem from disruption in systemic homeostasis that leads to widespread effects not only on hepatic function but also other organs. Specifically, hepatic and renal function 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 (HRS) which occurs in patients with cirrhosis, refractory ascites, and compromised renal function that, at its worst, can only be resolved with liver transplant.[2]

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%.[3, 4] The majority of infections are due to intestinal translocation of gram-negative bacteria in the setting of SBP[5]. Renal failure is evaluated to be caused from bacterial infection when either acute or preexisting renal injury appeared or worsened in the setting of infection.[3] 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.[6] Of note, serum creatinine may not accurately reflect glomerular filtration rate in cirrhotic patients due to muscle wasting leading to falsely low levels, increased tubular secretion of creatinine, dilution due to increased distribution volume, and elevated bilirubin can affect accurate measurement of creatinine.[7]

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 to healthy controls.[8, 9] 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 of secretory IgA, intramucosal lymphocytes, mesenteric lymph nodes) as well as systemic host immunity.[9-12] 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.[13-16] 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.[16, 17] 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.[18]

Kupffer cells within the liver sinusoids express toll-like receptors (TLRs) which play an important role in the phagocytosis and clearance of gut-derived bacterial endotoxins such as lipopolysaccharide (LPS).[16, 19] Hepatocytes similarly express toll-like receptor-4 (TLR4) receptors responsive to LPS and, thus, are also responsible in the uptake and removal of LPS.[16, 20] However, with large amounts of intestinal bacterial translocation, the functional capacity of the liver can become overwhelmed and endotoxin cannot be effectively removed.[10] Additionally, increased systemic activation of neutrophils by mediators like LPS result in inappropriate sequestration of leukocytes in hepatic microvasculature. As a result, this can lead to impaired sinusoidal perfusion and subsequent impaired Kupffer cell function.[21] Endotoxemia also leads to increased tumor necrosis factor α (TNFα) levels, which bind to TNF receptor on Kupffer cells and inhibit phagocytosis.[22] 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.[16, 20, 23]

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.[24] In the presence of endotoxemia, increased levels of NO secondary to activated inducible nitric oxide synthase (iNOS) leads to systemic vasodilation and organ hypoperfusion.[25] LPS-injected rats had a fall in cortical and medullary perfusion.[26] Interestingly, when they were treated with NG-methyl-L-arginine (L-NMWA), a nitric oxide synthase inhibitor, renal function improved with greater inulin clearance.[26] 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 NAD+ and ATP leading to cell death.[27] Additionally, excess levels of NO can also block key enzymes in mitochondrial respiration and in the Kreb’s cycle resulting in the disruption of cellular function.[28] 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 Glomerular Filtration Rate

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 cirrhotic patients. However, during the course of sepsis and the aforementioned reductions in RPF, increased filtration fraction fails to compensate leading to decreased GFR.[29]

Additionally, LPS cause damage to the glomerular barrier due to reduction in size-selectivity and increase in glomerular pore size.[30] The mechanism by which this is thought to occur is secondary to inflammation given podocytes have LPS receptors, such as TLR-4 and CD14.[31] Thus, endotoxemia creates an inflammatory state leading to release of cytokines such as TNFα and oxidative stress which can impair podocytes, the specialized cells within Bowman's capsule that function in glomerular filtration.[32] Mice injected with LPS exhibited 70% reduction in GFR.[33] However, when these mice were pretreated with TNF-soluble receptor p55 (TNFsRp55), GFR was reduced by only 30% and renal plasma flow was preserved demonstrating the negative impact of LPS-induced release of TNFα on glomerular integrity and function.[33] 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 (ROS). Treatment with antioxidants prevented the reduction in GFR.[34]

Bile cast nephropathy is an additional pathology to consider in renal dysfunction in cirrhosis. Cirrhotic patients 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.[35] The exact pathogenesis remains to be elucidated but current theory suggests that the low water solubility of bile acids lead to cast formation and a proximal bile cast tubulopathy leading to reduced GFR.[36]

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.[37] Numerous molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), TNFα, among many others are indicated in the pathophysiology of endotoxin-induced endothelial damage.[37] What exacerbates this microvascular dysfunction is the stagnation of microvascular flow.[38] Additionally, leukocytes have decreased velocities and increased transit time during endotoxemic states.[39] 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.[40] 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.[38, 41]

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.[41-44] LPS injection in rats led to the increase of endothelin-1 and upregulation of ETA.[45] The inability to block the dominating vasoconstrictive effects of endothelin during endotoxemia may cause intra-renal vasoconstriction leading to compromised renal function in cirrhosis. Interestingly, pretreatment using an ETA antagonist blocked renal vascular hyperreactivity.[45]

Newer research by Parikh et al has focused on the angiopoietin-Tie-2 axis in sepsis.[46] The main biomolecules implicated are angiopoietin-1 (Angpt-1) which is produced in peri-endothelial cells, angiopoietin-2 (Angpt-2) which is a competitive antagonist of Angpt-1, and Tie-2 which is a transmembrane tyrosine kinase from endothelial DNA[47]. The significance of Angpt-1 lies in that its activation leads to multimerization and cross-phosphorylation into large aggregates to maintain vascular integrity.[48] 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 (NFkB).[49, 50]

Endotoxemia and Effects on Tubular Function

Endotoxemia has been shown to upregulate TLR4 expression in proximal tubules.[51] Filtered endotoxin can interact with TLR4 on S1 segment of proximal tubules and directly cause damage in the downstream S2 and S3 tubules through the secretion of pro-inflammatory cytokines such as TNFα.[52] 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.[53] In addition, endotoxemia causes a decrease in peritubular capillary flow due to the increased production of RNS by the renal tubules.[54] Antioxidant resveratrol, which is capable of scavenging reactive nitrogen species, reversed the decline in cortical capillary perfusion and lead to restoration of renal microcirculation.[45] 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.

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Abbreviations:

Angpt-1	Angiopoietin-1
Angpt-2	Angiopoietin-2
ETA	Endothelin Receptor Type A
GFR	Glomerular Filtration Rate
HRS	Hepatorenal Syndrome
iNOS	Inducible Nitric Oxide Synthase
ICAM-1	Intercellular Adhesion Molecule-1
ICA	International Club of Ascites
IBO	Intestinal Bacterial Overgrowth
LPS	Lipopolysaccharide
MELD	Model for End-Stage Liver Disease
L-NMWA	NG-methyl-L-arginine
NO	Nitric Oxide
NFkB	Nuclear Factor Kappa-light-chain-enhancer of Activated B-Cells
ROS	Reactive Oxygen Species
RPF	Renal Plasma Flow
SBP	Spontaneous Bacterial Peritonitis
TNFsRp55	TNF-soluble Receptor p55
TLRs	Toll-Like Receptors
TLR-4	Toll-Like Receptor-4
TNFα	Tumor Necrosis Factor alpha
UTI	Urinary Tract Infection
VCAM-1	Vascular Cell Adhesion Molecule-1

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. [PubMed: 30021785]
2. Angeli P, Morando F. Optimal management of hepatorenal syndrome in patients with cirrhosis. Hepat Med 2010;2:87–98. [PubMed: 24367209]
3. Fasolato S, Angeli P, Dallagnese L,et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 2007;45:223–229. [PubMed: 17187409]

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;20:1495–1501. [PubMed: 7982650]
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;8:577–581. [PubMed: 8280847]
6. Wong F Acute kidney injury in liver cirrhosis: new definition and application. Clin Mol Hepatol 2016;22:415–422. [PubMed: 27987536]
7. Mindikoglu AL, Pappas SC. New Developments in Hepatorenal Syndrome. Clin Gastroenterol Hepatol 2018;16:162–177 e161. [PubMed: 28602971]
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;18:403–408. [PubMed: 3172582]
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. [PubMed: 3571935]
10. Fukui H Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. World J Hepatol 2015;7:425–442. [PubMed: 25848468]
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;7:2058–2068. [PubMed: 26301048]
12. Aguirre Valadez JM, Rivera-Espinosa L, Mendez-Guerrero O, et al. Intestinal permeability in a patient with liver cirrhosis. Ther Clin Risk Manag 2016;12:1729–1748. [PubMed: 27920543]
13. Perez-Paramo M, Munoz J, Albillos A, et al. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. Hepatology 2000;31:43–48. [PubMed: 10613726]
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. [PubMed: 11169075]
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;12:641–656. [PubMed: 29806487]
16. Mencin A, Kluwe J, Schwabe RF. Toll-like receptors as targets in chronic liver diseases. Gut 2009;58:704–720. [PubMed: 19359436]
17. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology 2005;41:422–433. [PubMed: 15723320]
18. Noor MT, Manoria P. Immune Dysfunction in Cirrhosis. J Clin Transl Hepatol 2017;5:50–58. [PubMed: 28507927]
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;96:456–461. [PubMed: 2642878]
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;8:319–327. [PubMed: 12537690]
21. Brown KA, Brain SD, Pearson JD, et al. Neutrophils in development of multiple organ failure in sepsis. Lancet 2006;368:157–169. [PubMed: 16829300]
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:G1318–1328. [PubMed: 16439470]
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;190:5152–5160. [PubMed: 23562812]
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 (Copenh) 1977;41:161–176. [PubMed: 579055]

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;5:2067–2072. [PubMed: 7579055]
26. Millar CG, Thiemermann C. Intrarenal haemodynamics and renal dysfunction in endotoxaemia: effects of nitric oxide synthase inhibition. Br J Pharmacol 1997;121:1824–1830. [PubMed: 9283724]
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;156:350–358. [PubMed: 8598485]
28. Thiemermann 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;116:2845–2851. [PubMed: 8680715]
29. Mindikoglu AL, Weir MR. Current concepts in the diagnosis and classification of renal dysfunction in cirrhosis. Am J Nephrol 2013;38:345–354. [PubMed: 24107793]
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:F242–248. [PubMed: 19004933]
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;19:704–713. [PubMed: 18256364]
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;59:2243–2249. [PubMed: 11380827]
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:F532–537. [PubMed: 12556364]
35. Moseley RH. Sepsis and cholestasis. Clin Liver Dis 2004;8:83–94. [PubMed: 15062195]
36. Bairaktari E, Liamis G, Tsolas O, et al. Partially reversible renal tubular damage in patients with obstructive jaundice. Hepatology 2001;33:1365–1369. [PubMed: 11391524]
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:F1140–1149. [PubMed: 11997331]
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:F261–268. [PubMed: 16926442]
39. Fry DE. Sepsis, systemic inflammatory response, and multiple organ dysfunction: the mystery continues. Am Surg 2012;78:1–8. [PubMed: 22273282]
40. Cunningham PN, Wang Y, Guo R, et al. Role of Toll-like receptor 4 in endotoxin-induced acute renal failure. J Immunol 2004;172:2629–2635. [PubMed: 14764737]
41. Goddard CM, Allard MF, Hogg JC, et al. Prolonged leukocyte transit time in coronary microcirculation of endotoxemic pigs. Am J Physiol 1995;269:H1389–1397. [PubMed: 7485572]
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. [PubMed: 21503257]
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. [PubMed: 30095297]
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. [PubMed: 24989426]
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;81:370–378. [PubMed: 21975863]

46. Parikh SM. Dysregulation of the angiopoietin-Tie-2 axis in sepsis and ARDS. Virulence 2013;4:517–524. [PubMed: 23652985]

47. Barton WA, Tzvetkova D, Nikolov DB. Structure of the angiopoietin-2 receptor binding domain and identification of surfaces involved in Tie2 recognition. Structure 2005;13:825–832. [PubMed: 15893672]

48. Kim KT, Choi HH, Steinmetz MO, et al. Oligomerization and multimerization are critical for angiopoietin-1 to bind and phosphorylate Tie2. J Biol Chem 2005;280:20126–20131. [PubMed: 15769741]

49. Witzenbichler B, Westermann D, Knueppel S, et al. Protective role of angiopoietin-1 in endotoxic shock. Circulation 2005;111:97–105. [PubMed: 15611372]

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 angiopoietin-1. Blood 2003;102:4407–4409. [PubMed: 12933576]

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;168:5817–5823. [PubMed: 12023385]

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:F1034–1043. [PubMed: 16332927]

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;26:3035–3044. [PubMed: 25855781]

54. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? Lancet 1991;337:776–778. [PubMed: 1706450]

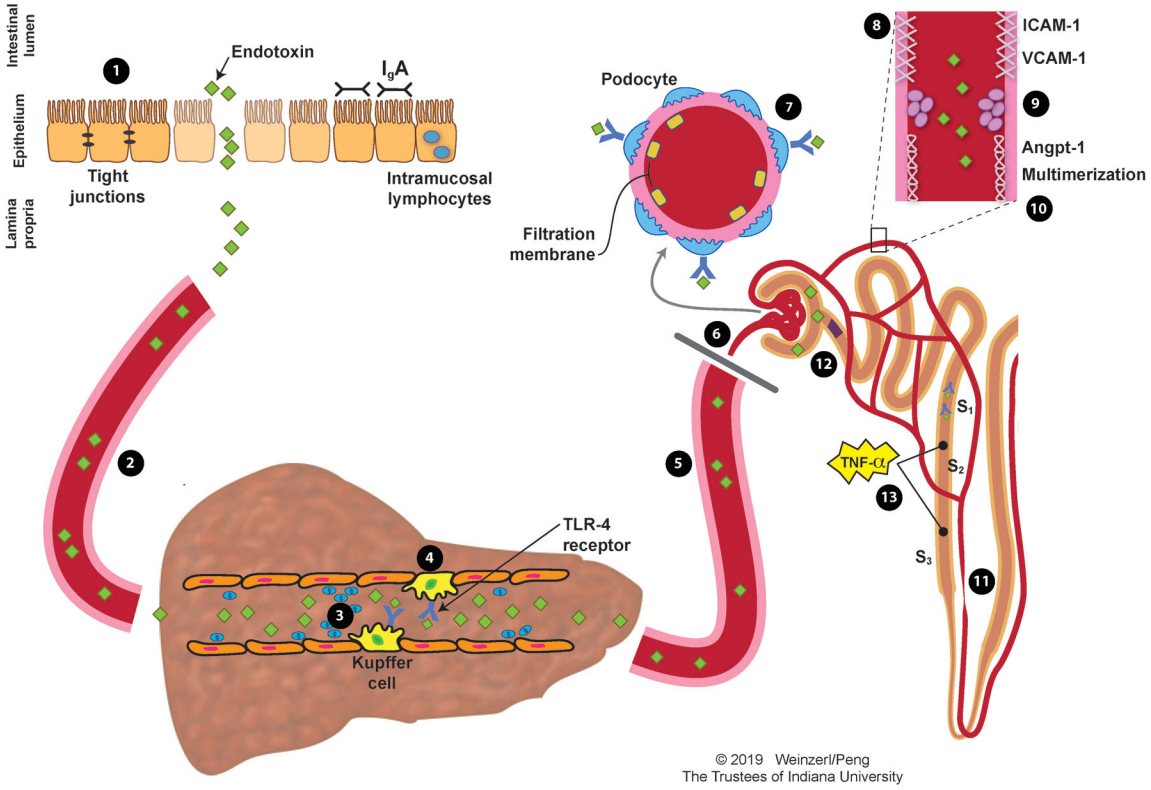

Figure 1:

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 a 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 damage podocyte membrane integrity and increase glomerular pore size. Within 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 proximal tubules in S1 cause downstream damage on S2 and S3 with pro-inflammatory TNFα.