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Immune Dysfunction and Infection Risk in Advanced Liver Disease

Brett McGettigan,[1] Maria Hernandez-Tejero,[1] Harmeet Malhi,[1] and Vijay Shah[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota

The risk of microbial infections is increased in cirrhosis and other forms of advanced liver disease such as alcohol-associated hepatitis. Such infections may precipitate new or further decompensation and death, especially in patients with clinical features of acute-on-chronic liver failure. The severe immune dysfunction or "immune paralysis" caused by advanced liver disease is associated with high short-term mortality. However, the pathogenic mechanisms underlying immune dysfunction and immunodeficiency are incompletely understood. Evidence to date suggests a complex, dynamic process that perturbs the physiological roles of the liver as a master regulator of systemic immunity and protector against noxious effects of exogenous molecules in the portal vein flowing from the gut. Thus, in cirrhosis and severe alcohol-associated hepatitis, the ability of hepatocytes and intrahepatic immune cells to balance normal context-dependent dichotomous responses of tolerance vs immune activation is lost. Contributing factors include loss of the gut barrier with translocation of microbial products through the portal vein, culminating in development of functional defects in innate and adaptive immune cells, and generation of immune-regulatory myeloid cells that permit microbial colonization and infection. This review addresses key evidence supporting the paradigm of immune dysfunction as a risk for microbial infections and identifies potential therapeutic targets for intervention. The primary focus is on cirrhosis-associated immune dysfunction and alcohol-associated liver disease, because the bulk of available data are from these 2 conditions.

Keywords: Cirrhosis; Alcohol-Associated Hepatitis; Acute-on-Chronic Liver Failure; Immune Paralysis; Immunity.

Immune cells are a key component of the liver, where they mediate immunity and form a front-line immune barrier in health. Diverse populations of resident and migratory immune cells are present throughout the liver. Sinusoidal tracts are lined by liver sinusoidal endothelial cells and macrophages, known as Kupffer cells (KCs). These are the most prevalent immune cell in the liver and account for ∼30% to 40% of intrahepatic leukocytes and as much as 80% of all macrophages in the human body.[1,2] Other important populations, including T cells (∼30%), natural killer cells (∼15%), B cells (∼3%), and dendritic cells, primarily reside within the portal tracts.[1,3] In contrast to the liver, nucleated cells in whole blood are predominantly neutrophils (40%–60%) and lymphoid cells (20%–40%), followed by monocytes (2%–8%). The mononuclear component is composed primarily of T cells (70%), B cells (15%), natural killer cells (10%), and monocytes (5%).[4] All immune cells in the liver have various roles, but they primarily function to support parenchymal cells, maintain homeostasis, respond to insults, and promote tissue repair.

Dysfunction of the immune system plays a significant role in acute, chronic, and malignant liver diseases. Innate and adaptive immune cells are both enriched in the liver in disease states and contribute to injury, inflammation, and fibrosis. In keeping with this, the proportions and phenotypes of immune cell subsets in the liver and peripheral blood change significantly in advanced liver disease.[5,6] These changes promote sterile inflammation, and it has been observed that the immune system's ability to perform its foundational functions, including combating infection, is diminished in chronic liver disease and particularly cirrhosis. Infection is a leading cause of death in patients with decompensated cirrhosis.[7] Moreover, there is evidence that infection may affect the clinical trajectory of liver disease. A meta-analysis reported that the presence of infection in decompensated cirrhosis increased the risk of death 4-fold compared with uninfected patients, with a 60% absolute risk of death during the 12 months after an infection.[8] Severe alcohol-associated hepatitis (AH) also carries a high risk of death (40% over 6 months),[9] and infection is the third most frequent cause of death among patients with AH.[10]

Surprisingly, the relationship between hepatic dysfunction and infection risk is not confined to patients with severe or end-stage disease. The risk of developing bacterial infections is increased in patients with metabolic-associated steatotic liver disease (MASLD), and some viral, fungal, and bacterial pathogens may promote disease progression.[11]

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; APC, antigen-presenting cell; CAID, cirrhosis-associated immune dysfunction; CD, cluster of differentiation; DAMP, damage-associated molecular pattern; G-CSF, granulocyte colony stimulating factor; IFN, interferon; IL, interleukin; KC, Kupffer cell; LPS, lipopolysaccharide; MAIT, mucosal-associated invariant T; MASLD, metabolic dysfunction-associated steatotic liver disease; MDRO, multidrug-resistant organism; MerTK, Mer proto-oncogene tyrosine kinase; mMDSC, monocytic myeloid-derived suppressor cell; NET, neutrophil extracellular trap; PAMP, pathogen-associated molecular pattern; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; Th, T helper; TIM-3, T-cell immunoglobulin and mucin domain 3; TLR, Toll-like receptor; TNF, tumor necrosis factor.**

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This review presents a paradigm of immune dysfunction and deficiency in advanced liver disease, highlights key evidence to support this paradigm, summarizes the clinical consequences of immunodeficiency due to advanced liver disease, discusses management considerations when caring for such patients, and reviews experimental therapies to combat the immune dysfunction.

The bulk of published data regarding these topics are from studies involving patients with advanced fibrotic liver disease (ie, decompensated cirrhosis and acute-on-chronic liver failure [ACLF]) caused by steatohepatitis as well as patients with AH. This review will have the same scope. However, significant gaps exist in our understanding of immune dysfunction and deficiency in other etiologies of advanced liver disease, including cholestasis, because these are severely underrepresented in the literature. Published data suggest that there are similarities in the phenotypes and mechanisms of immune dysfunction that occur in the liver diseases for which we have significant data, but there are likely notable distinctions as well. Indeed, such deficiencies in the body of published literature represent opportunities for further study.

Mechanisms of Immune Dysfunction and Deficiency in Advanced Liver Disease

Cirrhosis-Associated Immune Dysfunction

Cirrhosis-associated immune dysfunction (CAID) encompasses the wide range of immune events occurring from the onset of decompensated cirrhosis to the late stage of cirrhosis and is characterized by persistent systemic inflammation.[12] CAID is characterized by a persistent systemic inflammatory state that advances in severity as the degree of hepatic impairment progresses and pushes immune cells to the brink of exhaustion. The final consequence is a predisposition to opportunistic bacterial and fungal pathogens often described as "immune paralysis."[13] The hallmark of immune paralysis is monocyte deactivation identified by low HLA-DR expression.[14] However, this phenomenon is not exclusive to advanced chronic liver disease and is observed in other settings of profound immune cell depression, such as severe sepsis or septic shock.[15] CAID has been categorized into 2 stages based on inflammation intensity: low-grade and high-grade systemic inflammation.[12] The severity of the systemic inflammation corresponds to the progression of cirrhosis, with low-grade inflammation present in patients with compensated and decompensated cirrhosis without acute decompensation or ACLF. High-grade inflammation includes patients with decompensated cirrhosis with an acute decompensation or ACLF, or both.

In decompensated cirrhosis, functional defects within innate immune cells are particularly prominent, and this process is driven by (1) gut-barrier dysfunction that causes deficits of microbial compartmentalization and (2) release of damage-associated molecular patterns (DAMPs) by parenchymal cells, which cause tonic activation and exhaustion of immune cells. Uncontrolled bacterial translocation into portal blood is an ideal breeding ground for the occurrence of infections, which perpetuate hepatic decompensation, systemic inflammation, and immune cell exhaustion in a vicious cycle[16,17] (Figure 1). Evidence suggests that this cycle is initiated by the development of portal hypertension and may be accelerated as the degree of portal hypertension increases.[18] Indeed, decompensated cirrhosis and AH, the 2 clinical conditions with the most data regarding immune paralysis, are both characterized by portal hypertension that is proportional to disease severity.

Gut Barrier Dysfunction

The gut-liver axis encompasses the bidirectional anatomical and functional relationship between the gut, its microbiota, and the liver. It results from the integration of signals generated by dietary, biliary, genetic, and environmental factors.[19] Cirrhosis is accompanied by a shift in the composition of the intestinal microbiome and loss of gut barrier function, which allows microbes and microbial pathogen-associated molecular patterns (PAMP), such as lipopolysaccharide (LPS), to enter the portal blood and then the systemic circulation[20] (Figure 2*A* and *B*). Gut luminal microbes are separated from portal venous blood by several barriers. These layers are the mucus layer, epithelial layer, immune layer, and vascular layer. The mucus-epithelial and gut-vascular barriers are the principal components of the gut barrier, and together, they play a critical role in immunomodulation of the gut by regulating traffic of molecules and microbes.[12]

When both barriers are disrupted simultaneously, they allow permeation of microbial products from the lumen into the portal venous circulation. The development of portal hypertension is the sentinel event that initiates breakdown of the gut-vascular barrier and may impact the mucus-epithelial barrier as well. Evidence suggests that congestion within the portal vasculature drives congestion within the intestinal mucosal microcirculation, which promotes mechanical disruption of the gut-vascular barrier.[18]

Increased portal pressure per se is not necessarily associated with higher permeation of bacterial products transmucoepithelially into the lamina propria. A second hit affecting the epithelial barrier, such as ethanol or loss of epithelial farnesoid X receptor signaling, may be required for these molecules to access the villus microcirculation.[21] Excess alcohol intake in humans and in mice also produces increased intestinal permeability secondary to the direct toxicity of alcohol on the epithelial barrier.[22,23] Likewise, current data indicate that the high-fat diet frequently consumed by patients with MASLD alters the microbiome, which in turn impairs the intestinal barrier and the gut vascular barrier.[24]

Apart from increased gut permeability, patients with cirrhosis tend to have impaired motility of their small bowel manifest as a prolonged and quiescent phase 2 of migrating motor complexes, which predisposes them to small intestinal bacterial overgrowth.[25] Other commonly associated external factors, such as the overuse of proton-pump inhibitors, frailty, multiple antibiotic courses, repeated

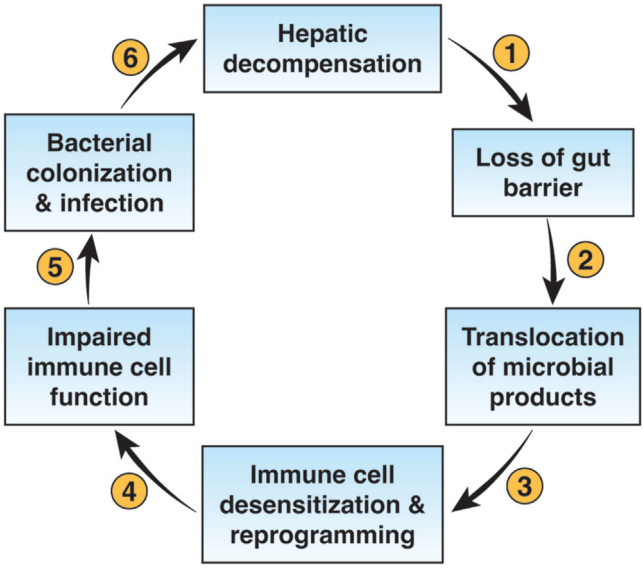

Figure 1. The cycle of CAID and infection. (*1*) Extensive hepatic parenchymal injury causes release of hepatic DAMPs and precipitates a chronic inflammatory state as the immune system and other accessory cells attempt to restore tissue homeostasis. (*2*) The intensity of systemic inflammation is further augmented as hepatic dysfunction progresses and, in concert with dysbiosis, causes a loss of gut barrier function, followed by (*3*) translocation of microbes and their products into the portal and systemic circulation. (*4* and *5*) Tonic activation of pattern recognition receptors by PAMPs and DAMPs triggers compensatory desensitization and dysfunction of immune cells via epigenetic reprogramming and other mechanisms. (*6*) Innate and adaptive immune dysfunction permit colonization by nonpathobionts and pathobionts alike, which results in an elevated risk of infection and further hepatic decompensation.

hospital admissions, and invasive procedures also confer a predisposition to the relative overgrowth of bacteria and fungi.[26–28] It is plausible that some combination of portal hypertension and the factors described above initiate impairment of the gut barrier, facilitating open traffic between the gut and liver.

Between the mucus-epithelial and gut-vascular layers lies the immune system layer consisting of gut-associated lymphoid tissue, which is distributed in collections of tertiary lymphoid tissue known as Peyer's patches and mesenteric lymph nodes. Gut-associated lymphoid tissue plays a pivotal role in host defense by serving as a niche for mucosal-associated invariant T (MAIT) cells.[29] They have a unique and conserved T-cell receptor repertoire with an unusual specificity for riboflavin metabolites of bacterial or fungal origin, which confers a key ability to respond to mucosal pathogens and preserve the gut barrier.[30] After activation, these cells rapidly release cytokines such as tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), and interleukin (IL) 17 and can lyse target cells. MAIT cells also contribute to gut barrier integrity by producing IL22, which is important for promoting antibacterial defense and maintenance of the gut barrier by controlling tight junctions and the production of antimicrobial peptides.[31] Furthermore, liver resident MAIT cells may play a key role in modulating host defense and inflammation in chronic liver disease.[29] In cirrhosis, circulating MAIT cells, a key source of gut IL22, are significantly decreased and have impaired production of TNF-α[32,33] (Figure 2*C*). Given their role in gut barrier and mucosal immunity, targeting costimulatory pathways of MAIT cells to support their expansion could be a potential immune intervention for enhancing control of infection in advanced liver disease.

Tonic Activation of Innate Signaling Pathways

Hepatocyte injury may occur secondary to various stressors, including toxins, lipotoxicity, gut-derived PAMPs, and cytokines (eg, TNF-α, IFN-γ). Injured and dying hepatocytes release a panoply of DAMPs, which include nuclear high mobility group box 1 protein, S100 proteins, extracellular vesicles, heat shock proteins, mitochondrial components, and nucleic acids. These constitute endogenous proinflammatory signals. Elevated portal pressure shunts portal blood containing DAMPs and PAMPs to the systemic circulation, and preclinical data suggest that they contribute to systemic and hepatic inflammatory responses by engaging damage and pathogen recognition receptors on immune cells such as the Toll-like receptors (TLR)[34–36] (Figure 2*D*).

Prolonged exposure to PAMPs and DAMPs is known to cause desensitization of immune receptors such as such as TLR-4 and epigenetic reprogramming that renders immune cells hyporesponsive[37,38] (Figure 2*E*). For example, repeated exposure of murine macrophages to LPS results in decreased production of proinflammatory cytokines, including IL1β, IL6, IL12, and TNF-α and down-regulation of activation markers and innate receptors such as HLA-DR and TLR-4.[37]

Tonic activation of the innate and adaptive immune systems in advanced cirrhosis eventually leads to features of immune cell exhaustion and impaired communication and coordination between these 2 complementary systems (discussed below). This process significantly increases the likelihood of high-grade infection and death. Indeed, the increased bacterial burden in the circulation and ascitic fluid of patients with decompensated cirrhosis, as measured by 16S ribosomal RNA, can independently predict risk of ACLF and death.[39]

As the degree of hepatic impairment progresses, the levels of circulating microbial products and injury signals, such as LPS, increase in concert with the systemic inflammatory response.[40,41] The plasma concentrations of proinflammatory (type 1) mediators such as IL1β, IL6, TNF-α, and IFN-γ, are elevated in patients with cirrhosis, regardless of etiology, and this effect is more pronounced in decompensated cirrhosis.[42,43] This is accompanied by a counter-regulatory response by immune cells and hepatocytes (eg, the acute phase response), which functions as a counterweight to unbridled type 1 inflammation. Such mediators include α_2-macroglobulin, sgp130 (IL6 signaling inhibitor), IL13, and IL10, the prototypical anti-inflammatory cytokine.[42,44,45]

If hepatic injury persists and advances, the system goes awry. Patients with ACLF exhibit a dysregulated innate immune response, characterized by a relative loss of cytokines

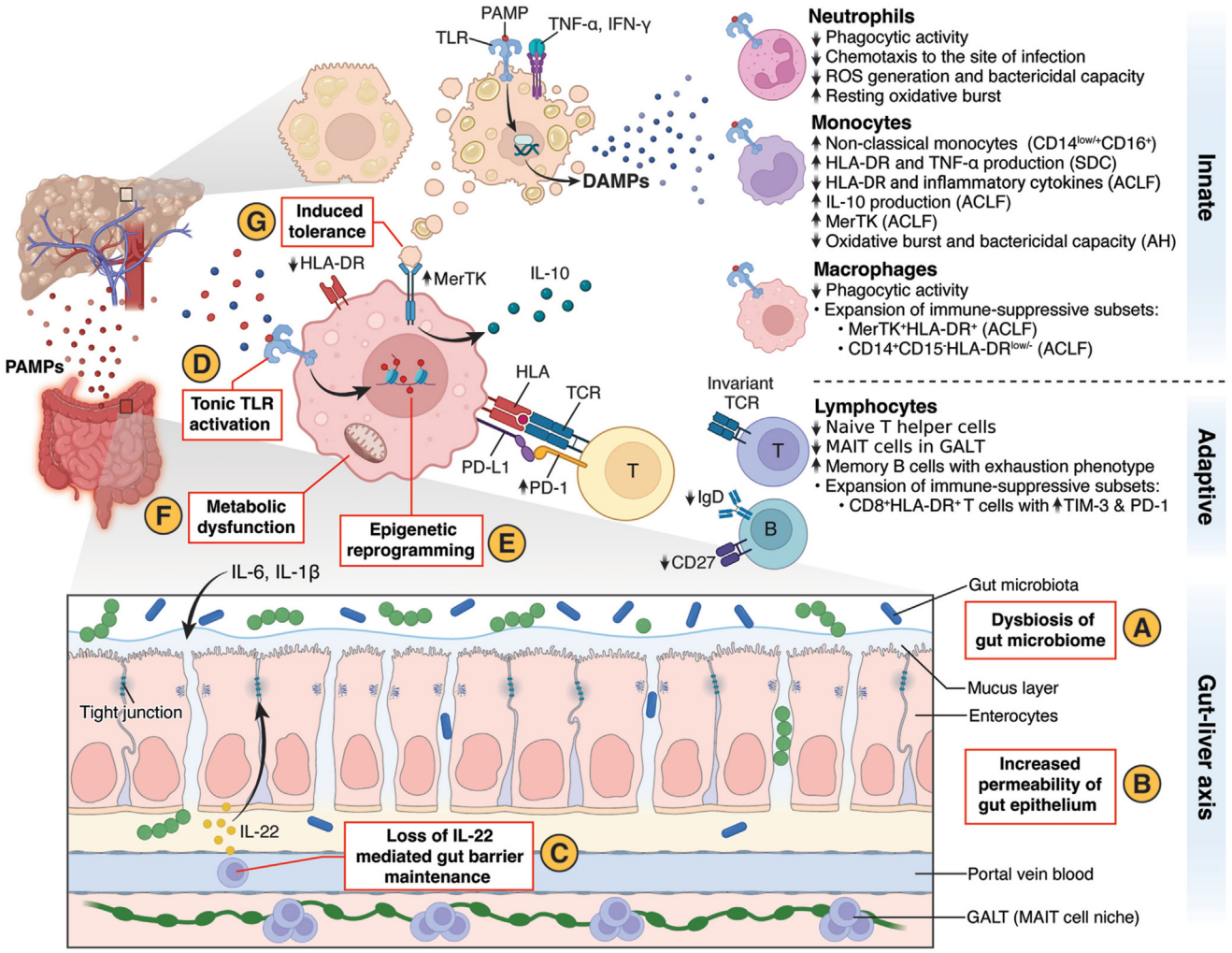

Figure 2. Mechanisms of immune cell dysfunction in advanced liver disease. (*A* and *B*) Portal hypertension, chronic systemic inflammation (eg, IL6 and IL1β), and dysbiosis of the gut microbiome lead to loss of intestinal barrier function due to altered mucus function and loss of epithelial tight junctions. (*C*) Loss of MAIT cells and their production of IL22, which maintains enterocyte tight junctions, further contributes to this process. Hepatocyte injury occurs due to various stressors, including lipotoxicity, gut-derived PAMPs, and cytokines (eg, TNF-α, IFN-γ). (*D*) Injured hepatocytes release DAMPs that activate innate immune cells. Microbes and their byproducts are translocated to the systemic circulation via portal blood, which further activates tissue-resident and circulating immune cells. Tonic activation of immune cells via pathogen recognition receptors, such as TLRs, results in a phenotype of immune cell exhaustion and functional defects in neutrophils, monocytes, and macrophages. (*E* and *F*) This phenotype may arise due to epigenetic reprogramming and metabolic dysfunction, including hyperammonemia, impaired mitochondrial function, and altered amino acid metabolism. (*G*) Immune-regulatory subsets of myeloid cells that are MerTK$^+$ or HLA-Dr^{low} contribute to acquired immune deficiency by suppressing T-cell activation via PD-1 agonism and production of IL10. This induced tolerance is controlled by the MerTK signaling pathway. CD8$^+$HLA-DR$^+$ lymphocytes may also suppress T-cell activation in advanced liver disease. GALT, gut-associated lymphoid tissue; SDC, stable decompensated cirrhosis.

involved in activating and shaping the adaptative immune system (IFN, IL17a, and IL7) compared with patients with decompensated cirrhosis without ACLF. This suggests a shift in systemic immunity toward an overactive innate response and an exhausted adaptative state as the disease progresses from acute decompensation to ACLF.[15,42]

Functional Defects in Innate Immune Cells

Neutrophils. Neutrophils play an essential role as first responders to infection and destroy microbes by using phagocytosis, release of reactive oxygen species (ROS) via oxidative burst, expulsion of neutrophil extracellular traps (NETs), and other tools.[46] Cirrhotic neutrophils acquire defects in several of these key physiological processes, which permits bacterial colonization and infection. Ex vivo and in vivo studies of human neutrophils in the setting of cirrhosis have revealed impaired migration, phagocytic capacity, production of ROS, and intracellular killing of bacteria, and increased resting oxidative burst relative to controls.[47–49] Impaired phagocytic capacity and elevated resting oxidative burst have been used to predict 90-day mortality of patients with stable cirrhosis.[50] Studies

investigating the mechanisms responsible for neutrophil defects in advanced liver disease are lacking, although some data suggest that endotoxin or ammonia drive this process via mitogen-activated protein kinase signaling.[51,52]

Under stress, a neutrophil may extrude NETs, which are filamentous structures composed of chromatin and other proteins. They may play a key role in host immunity and the pathogenesis of inflammatory diseases, including the development of portal hypertension via formation of microthrombi.[53,54] Alcohol-exposed neutrophils have impaired NET formation,[55] and the presence of circulating NET-like structures (myeloperoxidase-DNA complexes) has been associated with poor outcomes in acute liver failure.[56] However, data regarding the role of NETosis in CAID or infection risk in advanced liver disease is lacking.

Neutrophils from patients with AH show evidence of impaired phagocytosis, but they maintain a robust oxidative burst and, consequently, their capacity to kill ingested bacteria.[49] In patients with AH superimposed on cirrhosis, ex vivo neutrophils were found to have impaired phagocytosis and produced ROS at rest, consistent with baseline activation of the oxidative burst response.[51] This phenotype was associated with increased infection risk, organ failure, and death. Surprisingly, the dysfunction could be overcome by exposing the cells to healthy plasma or removing endotoxin from diseased plasma, suggesting that neutrophil dysfunction in advanced liver disease is driven by persistent and reversible activation of PAMP and DAMP pathways.

Monocytes. Monocytes may present antigens or initiate inflammatory cascades via cytokine secretion, and their primary role is to replenish the pool of tissue antigen-presenting cells (APCs). They are precursors to mature macrophages and dendritic cells and are recruited to injured tissues. In patients with decompensated cirrhosis, the peripheral monocyte compartment expands in proportion to the degree of hepatic impairment. Cirrhotic monocytes express cluster of differentiation (CD) 16 (nonclassical marker), HLA-DR, a marker of myeloid cell activation, and spontaneously produce TNF-α.[57] This phenotype has been associated with several chronic inflammatory diseases. In contrast, peripheral monocytes isolated from patients with end-stage hepatic failure (eg, ACLF) have low (or negative) surface expression of HLA-DR, suggesting a burned-out phenotype.[38,57] Monocytes from patients with stable cirrhosis maintain their capacity to secrete proinflammatory cytokines in response to TLR-4 activation, whereas monocytes from patients with ACLF have an impaired response to TLR-4 stimulation and secrete increased IL10 compared with controls.[58]

Apart from innate immune signaling, there is evidence that metabolic factors influence monocyte function in advanced liver disease. Metabolomic analysis of peripheral blood of patients with ACLF identified signs of severe mitochondrial dysfunction and increased production of toxic amino acid metabolites compared with controls. This may lead to build up of toxic metabolites within immune cells and impaired antibacterial function. In a 2019 study published in *Gut*, Korf et al[59] showed that monocytes conditioned with plasma from ACLF patients had increased production of IL10, loss of HLA-DR, and impaired phagocytosis. This phenotype was reduced with administration of a glutamine synthetase inhibitor. Thus, modulating immunometabolism within innate immune cells may prove to be a viable therapeutic target.

Ex vivo monocytes isolated from patients with severe AH had impaired intracellular killing of bacteria as well as oxidative burst. These observations negatively correlated with the expression of the major subunit of reduced nicotinamide adenine dinucleotide phosphate oxidase (gp-91^{phox}) and positively correlated with death at 28 and 90 days.[60] Importantly, the authors were also able to predict infection risk within 2 weeks of peripheral blood mononuclear cell collection based on the degree of oxidative burst impairment with high sensitivity and specificity. These data further support that impairment of phagocytosis and intracellular killing by innate immune cells play a key role in the relative immunodeficiency present in patients with severe AH.

Macrophages. KCs are a self-renewing population of tissue-resident macrophages that are embryonically derived from fetal liver and yolk sac progenitors.[61] They are APCs that constantly sense the sinusoidal microenvironment. Thus, they are positioned to be sentinel cells and either promote immune tolerance or rapid response to an insult or infection.[62] KCs are depleted in disease states, and the intrahepatic monocyte-derived macrophage pool expands to repopulate the KC niche.[61] A fraction of these cells acquire a KC-like phenotype, including the capacity for self-renewal.[63]

Although few studies have characterized the antimicrobial function of human hepatic macrophages in the setting of advanced liver disease, it is plausible that the functional aberrations observed in circulating human monocytes persist in monocyte-derived KC. Two studies have demonstrated evidence that the phagocytic capacity of the reticuloendothelial system is impaired in patients with cirrhosis.[64,65] Furthermore, this defect positively correlated with the risks of bacterial infection and death.

Interestingly, a study by Bernsmeier et al[66] discovered a subset of Mer proto-oncogene tyrosine kinase ($MerTK^+$) monocytes and macrophages that was expanded in the peripheral blood and tissues (liver, lymph node, and ascitic fluid) of patients with ACLF. Ex vivo analysis of this $MerTK^+$ population revealed impaired production of type 1 cytokines (IL6 and TNF) after LPS stimulation and increased capacity for transendothelial migration compared with healthy controls.[66]

Immune-Suppressive Myeloid Cells

In advanced liver disease, innate immune cells, such as macrophages, have a decreased ability to initiate an adaptive immune response, and in some cases, they are actively immune suppressive. Ex vivo studies in patients with ACLF have identified distinct immune-regulatory myeloid populations. One study discovered circulating $CD14^+CD15^-HLA\text{-}DR^{low/-}$ myeloid cells that suppressed T-cell proliferation (likely via programmed cell death-ligand 1 [PD-L1]) responded poorly to innate immune stimuli and

had increased production of the prototypical anti-inflammatory cytokine IL10.[38]

A second study discovered that MerTK expression was elevated on monocytes and macrophages in the peripheral blood and tissues of patients with decompensated cirrhosis.[66] The degree of MerTK expression positively correlated with the degree of hepatic impairment, and MerTK$^+$ cells had impaired production of proinflammatory mediators such as TNF-α and IL6. MerTK is a receptor tyrosine kinase that is expressed on macrophages and is activated by Gas6 and other ligands typically found on apoptotic cells. It is primarily expressed by M2 and pro-resolution macrophages and may play a key role in macrophage polarization.[67,68] Stimulation of this receptor is known to suppress production of type 1 cytokines, TNF-α and IL6, and induces production of IL10. It is plausible that immune-suppressive myeloid cells arise in advanced liver disease as a compensatory response to control unchecked inflammation.

Loss of Adaptive Immunity

There is a relative paucity of published studies evaluating the effects of cirrhosis on adaptive immune cells. However, patients with cirrhosis tend to have lymphopenia regardless of etiology, and this is primarily due to impaired maturation and increased apoptosis of CD4$^+$ T-helper (Th) cells—particularly the naïve T-cell repetoire[69–71]—whereas memory T cells tend to be preserved. Interestingly, patients with cirrhosis have higher levels of CD8$^+$HLA-DR$^+$ T cells, which have higher expression of the inhibitory molecules T-cell immunoglobulin and mucin domain 3 and programmed cell death 1 (PD-1) and represent an immunosuppressive subset that may induce impaired phagocytosis and cytokine production in innate immune cells such as neutrophils and monocytes.[72,73] These data suggest that T-cell function is also deranged in cirrhosis.

Similar features have been observed in patients without cirrhosis with alcohol misuse. Chronic alcohol toxicity results in an overall decrease in the circulating abundance of T and B lymphocytes. Additionally, the remaining lymphocytes exhibit dysfunctional behavior. T cells show increased expression of surface activation markers and an impaired response to infectious insults—particularly in their recruitment to infection sites.[70] In contrast, patients with hepatitis B virus cirrhosis tend to maintain normal lymphocyte counts and relatively well-preserved T-cell function. However, these patients exhibit a loss of memory B cells despite a constant total B-cell frequency.[74] The mechanisms underlying lymphocyte dysfunction caused by cirrhosis, regardless of etiology, remain poorly understood.

The Clinical Consequences of Liver-Mediated Immune Dysfunction

Liver Disease as a Driver of Infection

The liver is a complex network of nonhematopoietic cell populations and a wide repertoire of immune cells that constantly sense a milieu of exogenous molecules and microbes and modulate the immune response accordingly.[75] Thus, injury to this system may impact host immunity. Indeed, the degree of immunodeficiency in cirrhosis positively correlates with the progression of hepatic impairment and is particularly prominent in the most severe forms of disease such as ACLF.[13] This clinical entity is characterized by acute decompensation of cirrhosis, relative immunodeficiency, multiorgan failure, and high short-term mortality (15% at 28 days).[76]

That infection is the primary complication of CAID is therefore not surprising. Bacterial and fungal infections both have a higher prevalence in patients with cirrhosis compared with the general population. Bacterial infections are 5- to 6-times more prevalent even in the earlier phases of decompensated cirrhosis with a high-related mortality rate.[71] Fungal infections are more prevalent in patients with cirrhosis with Child-Turcotte-Pugh scores of 7 to 15 and those with organ dysfunction consistent with ACLF, although not as frequent as bacterial infections, representing 3% to 7% of culture-positive infections in cirrhosis.[71] Of note, fungal infections occur primarily in a nosocomial setting in the end-stages of liver disease (eg, ACLF) and have been associated with poorer outcomes.[27]

The impact of CAID on infection risk and outcomes also extends to viral infection. A stepwise increase in mortality has been observed in patients admitted to the hospital with severe acute respiratory distress syndrome due to coronavirus disease 2019 infection with precirrhotic liver disease (8%), Child-Turcotte Pugh class A (22%), Child-Turcotte-Pugh class B (39%), and Child-Turcotte-Pugh class C (54%) cirrhosis.[77,78]

A global study describing infections in patients with cirrhosis found 48% of infections were community acquired, 26% were health care-associated (ie, diagnosed $<$48 hours after admission), and 26% were nosocomial (ie, diagnosed $>$48 hours after admission). Positive bacterial cultures were obtained in 59% of patients, and the most common infections were spontaneous bacterial peritonitis (27%), followed by urinary tract infections and pneumonia.[79] Another North American study found that nosocomial infections developed in 15% of hospitalized patients with cirrhosis (1.5- to 2-fold times higher than in the general population) and were associated with an increased risk of death. In approximately half of these patients, the nosocomial infection developed after treatment of another infection,[28,80] which is notable because the presence of a second infection during hospitalization is a predictor of death independent of liver disease severity.[81] In summary, the predisposition to infections induced by CAID and other forms of advanced liver disease has a major clinical impact and is a leading cause of morbidity and mortality.[82,83]

Infection as a Driver of Cirrhotic Decompensation

The correlation between bacterial infections and episodes of decompensation, such as hepatic encephalopathy, gastrointestinal bleeding, and ascites, has been well-established.[84–86] However, whether bacterial infections happen because of decompensation or, if contrarily, bacterial infections are the trigger of decompensation has been

widely debated.[87] There are data to support the position that bacterial infections occur before decompensation in >80% of cases, and patients who present with bacterial infections are at a higher risk of developing further decompensations (45% in patients with vs 15% without infections).[88] Bacterial infections are not only reported as the most common precipitating event for developing liver related complications but are also a frequent cause of dysfunction and failure of organs other than the liver. Bacterial infections are recognized as the most common precipitating event of acute kidney injury, and when triggered by bacterial infection, ACLF, show a further increase in short-term mortality.[83,85] After bacterial infections, patients with cirrhosis have a substantial risk of early hospital readmissions.[89,90] Therefore, bacterial infections adversely influence the risk of decompensation and survival in compensated and decompensated cirrhosis, underpinning that the occurrence of bacterial infections should be considered a specific prognostic stage of the disease.[8,91]

The Effects of Alcohol on Infection Risk and Outcomes

Apart from cirrhosis, factors related to other etiologies of advanced liver disease, such as chronic alcohol use, can impact host immunity. In rat models of chronic alcohol use, alcohol induces changes in the gut microbiota composition and a loss of tight junctions in the gut epithelial layer, which may contribute to increased intestinal permeability.[92] Although further studies are necessary to establish cause and mechanism, these factors may predispose patients with ALD to a higher risk of infection. Several studies have reported a higher frequency of bacterial infections in patients with ALD compared with those with non-ALD.[93,94] Differences were significant for ALD patients vs non-ALD in earlier phases of the disease (ie, Child-Pugh A/B),[94] supporting active alcohol consumption as an independent risk factor for infection.[93] Additionally, a recent European study reporting triggers of cirrhosis decompensation showed that bacterial infections and severe alcoholic-related hepatitis, alone or in combination, accounted for 96% to 97% of cases of acute decompensation in both stable and unstable decompensated phenotypes.[95]

Strategies for Managing Immune Deficiency Caused by Advanced Liver Disease

Future therapies for advanced liver disease would ideally prevent colonization by pathobionts, potentially by reversing immune cell dysfunction, reducing bacterial burden, or shifting microbiome composition. In the absence of such preventive therapies, early diagnosis and prompt source control and antimicrobial therapy are paramount. Identification and risk stratification of patients who are at risk of sepsis based on clinical, biochemical, immunological, and microbiological data is an area of urgent unmet need.[16]

Prophylactic Strategies

In view of the concerns regarding the emergence and spread of antimicrobial resistance in cirrhosis, antibiotic prophylaxis is indicated in, but restricted to, evidence-based indications of acute gastrointestinal bleeding, low protein ascites, and previous spontaneous bacterial peritonitis.[96,97] Also, screening for multidrug-resistant organisms (MDRO) carriage is important because it is significantly associated with MDRO infection and treatment failures with empirical antibiotic regimens in critically ill patients with cirrhosis and in patients after liver transplant.[98,99] Ruling out MDRO colonization in noncritically ill patients with decompensated cirrhosis may be a useful strategy to prevent infections, but further studies to demonstrate the benefit of this approach are required. The influence of outpatient medication on infection risk (eg, previous use of antibiotics) and the presence of previous infections (by sensitive or MDRO organisms) should be kept in mind as well.

Patients with cirrhosis require influenza, pneumococcal, herpes zoster, hepatitis A and B, tetanus-diphtheria-acellular pertussis, measles-mumps-rubella, and varicella vaccines. However, the immune response to vaccinations correlates inversely with the degree of hepatic decompensation, with a nonprotective response to vaccination in late stages of the disease.[28] Although the clinical trials of coronavirus disease 2019 vaccines have not included patients with cirrhosis,[100] it is reasonable to consider vaccinating patients with cirrhosis given the high risk of this population.[101]

Early Diagnosis and Treatment

Early diagnosis and adequate empiric treatment (as guided by local antibiogram data) when systemic inflammatory response syndrome criteria are met and an infectious source is suspected is of paramount clinical importance. Unfortunately, the emergence of multidrug resistance has complicated treatment, and a more complex approach, including the use of broad-spectrum antibiotics, new administration strategies, and de-escalation policies is required.[102]

Another challenge in the setting of immune paralysis is the difficulty of diagnosis because patients are frequently unable to mount an adequate systemic inflammatory response (eg, fever, leukocytosis) and are commonly colonized by bacteria including MDROs. There is a high prevalence of rectal colonization by MDR bacteria in specific subsets of patients with cirrhosis, and circulating 16S (bacterial) DNA is elevated in subsets of uninfected patients with AH.[98,103] Furthermore, culture-negative infection, such as neutrocytic ascites, has long been a known issue in advanced liver disease, and clinical guidelines recommend empiric treatment despite lack of culture data.

Taken together, these data suggest that in cirrhosis and other forms of advanced liver disease, the line between infection and colonization becomes increasingly blurred. If excessive microbial burden in advanced liver disease is indeed driving immune system exhaustion, then there may be a need for clinical criteria to clarify and expand the

indications for empiric antibiotic use in such patients. These criteria may incorporate clinical data and more advanced molecular diagnostic assays.

The issue of the false-negative cultures in cirrhotic patients has long been a challenge. As an example, because classical culture techniques failed to grow bacteria in up to 65% of neutrocytic ascitic fluid samples, an optimized bedside inoculation of blood culture bottles with ascitic fluid was implemented to increase the sensitivity to >80%.[104,105] However, the identification of bacterial DNA by polymerase chain reaction may be a more appropriate alternative to bacterial culture for pathogen identification given the unique challenges of identifying infection vs colonization, as described above.[106,107] This approach may be considered even in culture-negative patients who exhibit a high risk for bacterial infection, but the prognostic relevance of ascitic bacterial DNA or the gut microbiome, or both, as markers of bacterial translocation for certain risk groups must be further evaluated.

Rapid multiplex polymerase chain reaction "syndromic panels" that can simultaneously detect and identify multiple pathogens associated with typical clinical syndromes, such as bloodstream, respiratory, gastrointestinal, or central nervous system infections,[108] may be of value in patients with cirrhosis. Also, newer technologies, including metagenomic next-generation sequencing, with a much higher yield than traditional culture-based methods, could play a role in some specific diagnostic scenarios such as polymicrobial or fungal infections, or both. [109,110]

Specific metagenomic techniques can also be used to detect MDRO and extensively drug-resistant genes in the identified organisms.[108] The drawbacks to metagenomics (ie, cost and technical challenges) have diminished over time, and clinical application for this approach may be explored to detect organisms in fluids if infections are suspected but cannot be cultured.[28]

Experimental Therapies and Potential Therapeutic Targets

The Direction of Future Therapies

The mechanisms that drive immunodeficiency in patients with advanced liver disease are complex and poorly understood. Infection will continue to be a significant source of morbidity and mortality in such patients until therapeutic approaches are developed to counteract immune dysfunction. This will require better understanding of the cellular networks and signaling pathways that control inflammation as well as the molecular triggers of these networks and pathways (Figure 2). Future therapies may target 1 or many of these processes and take advantage of novel strategies such as cellular therapies, phage approaches, or fecal microbiota transplantation. Indeed, there has been extensive study of experimental therapeutics in humans (Table 1)[111–120] and preclinical models (Table 2)[38,59,66,121–126] to reverse immune dysfunction in advanced liver disease. However, few studies have examined whether these therapeutics effectively counteract immune deficiency, and those that do, have been primarily focused on patient populations with ACLF and severe AH. Thus, further study into therapeutic approaches to reverse immune dysfunction and prevent against serious infection is needed. Several promising therapeutic targets are discussed in this section.

AXL/Mer Proto-Oncogene Tyrosine Kinase

MerTK (Mer) is part of a class of receptor tyrosine kinases that are expressed by macrophages that have an M2-like and tissue-repair phenotype as well as tumor-associated macrophages. MerTK plays a key role in suppression of proinflammatory mediators and promotes production of proresolution mediators (eg, IL10, resolvins), matrix remodeling, and clearance of apoptotic cells. Its canonical agonist, Gas6, complexes with phosphatidylserine, which is present on the surface membrane of apoptotic cells and stimulates these functions in a positive feedback and autocrine fashion.[127–129] As stated previously, populations of MerTK^{+} monocytes and tissue macrophages may arise in patients with ACLF, and these cells seem to have impaired production of proinflammatory cytokines (TNF-α and IL6).[66] Intriguingly, the small-molecule inhibitor of MerTK, UNC569, rescued production of these cytokines in primary human monocytes that had been conditioned by plasma from patients with ACLF.[66] It is worth noting that UNC569 treatment did not affect monocyte oxidative burst or intracellular killing of bacteria. MerTK may represent a novel therapeutic target to counteract the loss of proinflammatory cytokines seen in patients with ACLF that likely contributes to immune paralysis.

However, patient selection would be paramount from a safety perspective because inhibition of MerTK in patients with residual immune function, such as compensated cirrhosis, might induce a sepsis-like state. For example, anti-CD19 chimeric antigen receptor–T-cell therapy used to treat acute B cell leukemia has similar risks. Chimeric antigen receptor–T cells can induce cytokine release syndrome, a deadly syndrome characterized by elevated levels of IL6 and IFN-γ.[130]

Programmed Cell Death 1/Programmed Cell Death-Ligand 1

T cells play a key role in the adaptive immune response, and activation of Th cells requires a complex coordination of receptor-ligand engagement with an appropriate downstream signaling cascade. APCs, such as macrophages, present antigens on HLA molecules to Th cells, which engage these complexes via antigen-HLA–specific T-cell receptors. This serves as "signal 1″ and precipitates an intracellular signaling cascade that results in T-cell activation, provided there is an accompanying activating "signal 2″ such as CD86-CD28 (on APC and Th cells respectively) costimulation. If signal 2 is negative, such as PD-L1 on APCs engaging PD-1 receptors on Th cells, then T-cell activation will be suppressed.[131] In health, T-cell activation may be controlled to prevent inappropriate adaptive immune responses. In disease states such as cancer, PD-1 signaling is a

Table 1. Human Trials of Experimental Therapies for the Treatment of Immune Dysfunction and Dysbiosis in Advanced Liver Disease

Site of action	Type of intervention	Target	Molecule	Mechanism of action/effect	Population	Study Design	Ref.
Intestinal microbiome	Carbon nanoparticles	Bacteria-derived products	Yaq-001	Adsorbs bacterial toxins	Patients with cirrhosis with diuretic-responsive ascites and Child-Pugh score of 7–8 (n = 28)	Safety clinical trial	111
	Antimicrobial therapy	Pathobionts	Norfloxacin	Intestinal decontamination and reduction of bacterial translocation	Uninfected patients with cirrhosis	Clinical trial	112
	Prebiotics and probiotics	Commensal bacteria and pathobionts		Microbiome immunomodulation	Patients with cirrhosis on the waiting list for liver transplantation	Meta-analysis	113
	Fecal microbiota transplant	Pathobionts		Microbiome immunomodulation; Amelioration of CAID and ↑of antibacterial cytokine responses.	Patients with cirrhosis with recurrent hepatic encephalopathy	Clinical trial	114
Epithelial barrier	Nonselective β-blocker	β1 and β2 receptors	Propranolol, nadolol, timolol	↓HVPG, ↓leaky gut, ↓systemic inflammation	All causes of decompensated cirrhosis	Meta-analysis	115
	Albumin	PGE2, antioxidant effects		Improve circulatory dysfunction, ↓leaky gut, ↓systemic inflammation	All causes of decompensated cirrhosis with ACLF		116
Extracellular mediators	Cytokine therapy	KCs	IL-22 Fc	Antioxidant, antiapoptotic, antisteatotic, antimicrobial, and pro-proliferative effects	Patients with AH	Safety clinical trial	117
Cell-based therapies	Hematopoietic grown factor	$CD34^+$ stem cells	G-CSF	Mobilize bone marrow $CD34^+$ hematopoietic stem cells through G-CSF receptor	Patients with cirrhosis with ACLF	Clinical trial	118
Metabolite therapies	BCAA granules	Neutrophils		Restore neutrophil phagocytic activity	All causes of compensated and decompensated cirrhosis	Pre-post study clinical trial	119,120

BCAA, branched-chain amino acid; HVPG, hepatic venous pressure gradient; Ref., reference.

Table 2. Preclinical Studies of Therapeutic Targets to Reverse Immune Dysfunction in Advanced Liver Disease

Site of action	Type of intervention	Target	Molecule	Mechanism of action/effect	Disease model	Ref.
Cell surface mediators	TLR inhibitors	Neutrophils	TLR-7/8 inhibitors (CL097, R848)	Restored oxidative burst; Improved bacterial killing	Neutrophils from patients with AH-related cirrhosis	121
	TLR agonists	Neutrophils, monocytes	TLR-3 agonists (RGC100, ARNAX, poly-IC)	↓mMDSCs, improved phagocytic capacity	In vitro functional studies with PBMCs from patients with advanced chronic liver diseases	38
	RTK inhibitors (small molecule)	Myeloid cells	UNC569 (MerTK)	Improved LPS-induced cytokine production; up-regulated HLA-DR	Blood and liver cells from acute decompensation and patients with ACLF	66
			Bemcentinib (AXL)	Improved LPS-induced cytokine production	Murine model of sepsis	122
	PD-L1/PD-1/TIM-3 inhibitors (targeted antibodies)	Myeloid cells		Restored monocyte innate immune responses; restored KC and monocyte antimicrobial responses	Liver macrophages from patients with all causes of cirrhosis.[123] Murine model of APAP-induced liver injury.[124]	123, 134
		Neutrophils		Improved neutrophil phagocytosis and oxidative burst capacity	PBMCs from AH, AH-related cirrhosis, and healthy donors	125
Intracellular mediators	Glutamine synthetase inhibitor	Glutamine synthetase	Methionine sulfoximine	Improved monocyte phagocytic capacity and proinflammatory cytokine production; reduced IL10 production	Monocytes from patients with ACLF	59
Cell-based therapies	Engineered cell transfer	Macrophage	CAR-M cells	Reconstitution of peripheral and tissue niches with immune-competent and/or restorative hematopoietic cells	Liver injury CCl_4-induced murine model treated with human iPSC-macrophages	126

APAP, *N*-acetyl-*p*-aminophenol (acetaminophen); iPSC, induced pluripotent stem cell; mMDSCs, monocytic myeloid-derived suppressor cells; PBMCs, peripheral blood mononuclear cells; TIM-3, T-cell immunoglobulin and mucin domain 3.

mechanism by which a tumor may subvert immune surveillance.[132]

As stated previously, ex vivo studies in ACLF and severe AH suggest that immune regulatory $CD8^+$ and myeloid cells suppress T-cell function via this same mechanism.[38,73,133] Furthermore, inhibiting PD-1 signaling in vitro alleviated T-cell suppression, suggesting that targeting this pathway may abrogate the relative immunodeficiency that occurs in advanced liver disease (Table 2). Another advantage of such a strategy is that immune checkpoint inhibitors are readily available therapeutics. However, clinical studies, including randomized controlled trials, would be necessary to evaluate the benefits and risks (eg, checkpoint inhibitor hepatitis) of using PD1/PD-L1 inhibitors to treat immune paralysis.

Toll-Like Receptor

Modulation of TLR signaling has a profound impact on innate immune cell function, and agonizing these pathways (eg, TLR-3) may prove to be a key therapeutic target for counteracting innate immune cell dysfunction caused by desensitization to bacterial products.[38] Alternatively, it is also plausible that targeted inhibition of TLR pathways (eg, TLR-4) could abrogate innate immune paralysis by reducing long-term tonic activation of these receptors and the epigenetic-mediated immune tolerance that it confers.[12,134] In 2018, Bernsmeier et al[38] discovered that peripheral blood mononuclear cells isolated from patients who met European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) criteria for ACLF were low in expression of HLA-DR and had a phenotype and function consistent with monocytic myeloid-derived suppressor cells, which are an immune-repressive subset of monocytes known to promote progression of various malignancies, including hepatocellular carcinoma.[135] Intriguingly, the authors also found that ex vivo antagonism of TLR-4 promoted expansion of the monocytic myeloid-derived suppressor cell subset whereas TLR-3 agonism rescued their capacity to phagocytize *Escherichia coli* and resulted in up-regulation of HLA-DR, a marker of monocyte activation.[38]

In line with these data, a randomized placebo-controlled trial found that administration of a TLR-4 antagonist (TAK-242) to patients with severe sepsis tended to reduce mortality, although it did not affect serum IL6 levels. Patients with severe sepsis have features of immune paralysis like ACLF patients[136]; therefore, this agent may have better success in those with sepsis and profound hepatic dysfunction. Of note, TLR-3 and TLR-4 signaling pathways have been implicated in hepatic fibrosis in preclinical models.[137,138] Therefore, the use of TLR agonists as long-term therapy is likely not a safe option.

Granulocyte Colony Stimulating Factor

Granulocyte colony stimulating factor (G-CSF) is a peptide that is secreted by macrophages and endothelial cells and facilitates maturation and mobilization of bone marrow granulocyte precursors—particularly neutrophils—in the steady state and emergent situations such as infection.[139] It exerts its function by binding to its cognate receptor encoded by the colony stimulating factor 3 receptor (*CSF3R*) gene in humans. Recombinant G-CSF peptides, such as filgrastim, are approved for the treatment of neutropenic fever. Small, single-center randomized clinical trials in China and India have reported increased survival and reduced rates of bacterial infection in patients with ACLF that are treated with G-CSF agents.[118] However, a large multicenter randomized trial in Germany failed to identify any clinical benefit (eg, survival or infection rate) when patients with ACLF were treated with ratiograstim compared with controls (standard medical therapy).[118] Of note, this study was not blinded or placebo controlled for logistical reasons. There are no clinical trials that have evaluated infection rate or outcomes in patients with AH treated with G-CSF analogues.

Given that peripheral neutrophils also have neutrophil dysfunction, such as impaired phagocytosis and migration, G-CSF administration may counteract this defect by refreshing the neutrophil pool with endogenous neutrophils. On the other hand, if the neutrophil defects in advanced liver disease are inducible by systemic and microenvironment factors, then endogenous cell therapies or nongenetically modified exogenous cell therapies may not adequately overcome these factors because they would theoretically be influenced by said factors.

Interleukin 22

IL22 is a cytokine in the IL10 family and putatively has anti-inflammatory and regenerative function that exerts its effects by binding IL22R, which is primarily expressed by endothelial cells and fibroblasts.[140] A pilot study that treated patients with severe AH with a recombinant fusion protein of human IL22, showed favorable outcomes as determined by Lille Model for Alcoholic Hepatitis and Model for End-Stage Liver Disease scores, a reduction in markers of inflammation, and increased expression of markers of hepatic regeneration.[117] In a mouse model of ACLF, IL22 therapy restored the ability of KCs to produce IL6 in response to bacterial infection and resulted in increased expression of genes with antimicrobial functions.[141] These preclinical data suggest that IL22 may counteract the immunodeficiency of CAID. Further studies are necessary to clarify its role.

Albumin

Albumin, a pleiotropic molecule synthesized exclusively in the liver, has multiple potential benefits in cirrhosis beyond volume expansion.[142] There are several types of albumin, including ovalbumin, human serum albumin, and bovine serum albumin. Human serum albumin is currently used to treat patients with decompensated cirrhosis, available in a 5% concentration (near iso-oncotic solution) for intravascular volume expansion, or a 20% concentration (hyperoncotic solution) for restoring colloid osmotic pressure and preserving fluid balance among compartments.[143] Albumin has multiple potential benefits in cirrhosis beyond

volume expansion. Among its nononcotic immunomodulatory properties, albumin has been shown to attenuate prostaglandin E_2-mediated immune dysfunction in patients with decompensated cirrhosis.[144] Additionally, it exerts antioxidant effects by scavenging ROS in preclinical models of chronic liver failure.[145]

A recent study that aimed to prevent infections and death through intravenous albumin in hospitalized patients with cirrhosis failed to show a beneficial effect.[146] However, another recent study provided evidence supporting the potential benefit from albumin administration in hospitalized patients with ACLF, using a novel liver dialysis device (DIALIVE; ALIVER) designed to exchange dysfunctional albumin and remove DAMPs and PAMPs.[116] Conducting randomized controlled trials in patients with advanced cirrhosis is challenging, and the immunomodulatory role of albumin is still debated.

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Author names in bold designate shared co-first authorship.

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Correspondence
Address correspondence to: Vijay Shah, MD, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. e-mail: shah.vijay@mayo.edu.

Conflicts of interest
The authors disclose no conflicts.