








# Early Diagnosis and Prevention of Infections in Cirrhosis

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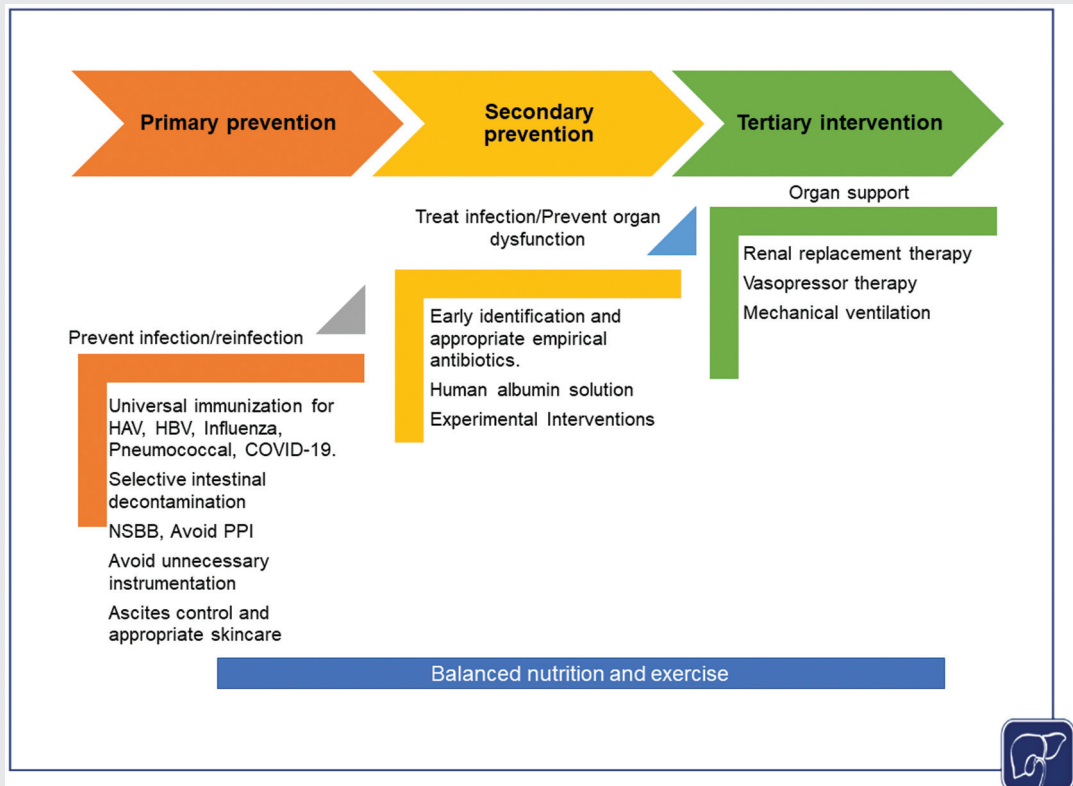
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## Graphical Abstract



Strategies to prevent infection and improve outcomes in patients with cirrhosis. HAV, hepatitis A virus; HBV, hepatitis B virus; COVID-19, novel coronavirus disease 2019; NSBB, nonselective  $\beta$ -blocker; PPI, proton pump inhibitors.

**Abstract**

Cirrhosis is a risk factor for infections. Majority of hospital admissions in patients with cirrhosis are due to infections. Sepsis is an immunological response to an infectious process that leads to end-organ dysfunction and death. Preventing infections may avoid the downstream complications, and early diagnosis of infections may improve the outcomes. In this review, we discuss the pathogenesis, diagnosis, and biomarkers of infection; the incremental preventive strategies for infections and sepsis; and the consequent organ failures in cirrhosis. Strategies for primary prevention include reducing gut translocation by selective intestinal decontamination, avoiding unnecessary proton pump inhibitors' use, appropriate use of  $\beta$ -blockers, and vaccinations for viral diseases including novel coronavirus disease 2019. Secondary prevention includes early diagnosis and a timely and judicious use of antibiotics to prevent organ dysfunction. Organ failure support constitutes tertiary intervention in cirrhosis. In conclusion, infections in cirrhosis are potentially preventable with appropriate care strategies to then enable improved outcomes.

**Keywords**

- ▶ liver failure
- ▶ infections
- ▶ antibiotics
- ▶ morbidity

Cirrhosis is a risk factor for infections.<sup>1</sup> Approximately 50% of hospital admissions in patients with cirrhosis are due to infections.<sup>2,3</sup> Furthermore, nosocomial infections occur in 15 to 30% of patients with cirrhosis compared with only 5% among the general population.<sup>2,4</sup> Sepsis is an immunological response to an infectious process that leads to end-organ dysfunction and death, highlighting the crucial role of immunity in the development of this clinical syndrome.<sup>5</sup> In patients with cirrhosis, the persistence of bacterial translocation (BT) or bacterial infections (BIs) that initially result in a proinflammatory state eventually leads to an exhaustion of the immune response. This immunoparesis further favors the development of overt sepsis.<sup>6</sup> For patients without any comorbid illness, in-hospital mortality exceeds 40% for patients with septic shock despite adequate management.<sup>5</sup> In contrast, in-hospital mortality in patients with cirrhosis and severe sepsis is as high as 75%.<sup>3,7</sup> Sepsis is also a common reason for admission of patients to the intensive care unit (ICU), and the 1-year mortality of such patients with cirrhosis is as high as 90%.<sup>3</sup> Sepsis in cirrhosis can lead to multi-organ failure and acute-on-chronic liver failure (ACLF).<sup>8,9</sup> Sepsis is an advanced stage in the natural history of cirrhosis, and the occurrence of infection with or without recovery establishes a clinically different stage, termed "critically ill cirrhotic."<sup>10</sup> Sepsis in cirrhosis leads to a worsening of liver disease and preexisting circulatory dysfunction through hypovolemia and ischemia-induced hepatocyte injury.<sup>11</sup> Therefore, preventing infections could also avoid the complications of cirrhosis that occur downstream such as further acute decompensation, recurrent infections, development of organ failures, and death. In this review, we discuss the pathogenesis, diagnosis, and biomarkers of infection, as well as incremental preventive strategies for infections and consequent organ failures in cirrhosis.

**Source of Infections in Cirrhosis**

The high incidence of BI in this population is attributed to immune dysregulation, deficiency of complement components C3 and C4, downregulation of monocyte human

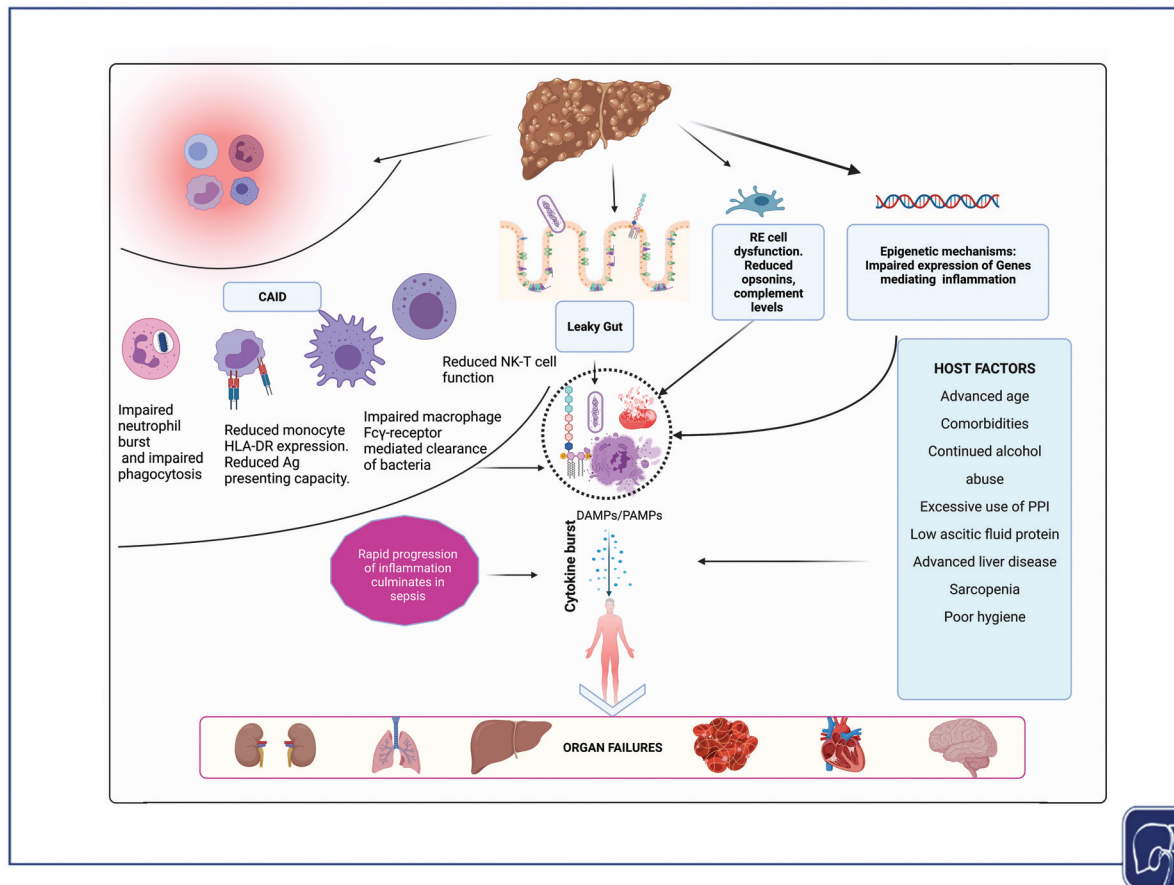
leucocyte antigen-DR expression, impaired Fc $\gamma$  receptor-mediated clearance of antibody-coated bacteria, depressed neutrophil burst and intracellular killing, and risk of BT.<sup>12</sup> In addition, the sepsis risk is worsened with the increasing severity of liver disease and is more common in decompensated cirrhosis.<sup>13</sup> The pathogenesis of sepsis in cirrhosis has been described in ▶**Fig. 1**.

Approximately 50% of infections are community acquired, and 25% each are health care-associated and nosocomial infections.<sup>4</sup> However, 70% of severe infections in cirrhosis are nosocomial and health care acquired.<sup>14</sup> Spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), skin and soft tissue infection (SSTI), and spontaneous bacteremia are frequent community-acquired infections, while UTI, lower respiratory tract infections, spontaneous bacteremia, and *Clostridium difficile* infections are frequent causes of health care and nosocomial infections.<sup>15</sup>

Cultures are positive in 45 to 60% of patients with BIs. Gram-negative bacilli (GNB), especially Enterobacteriaceae like *Escherichia coli* and *Klebsiella pneumoniae*, are more common in community-acquired infections, while gram-positive cocci (GPC), such as *Enterococcus faecalis* and *Staphylococcus aureus*, are more frequent in nosocomial infections.<sup>16</sup> Patients with advanced cirrhosis often have less-virulent strains of GNB causing sepsis.<sup>17</sup> Mixed infections (GNB and GPC) account for 5 to 10% of cases. Secondary fungal infections are noted in 10 to 15% of patients with cirrhosis.<sup>4</sup> Due to immunoparesis in advanced liver disease, even commensal strains turn pathogenic by bypassing the mucosal defenses and cause invasive sepsis by BT. Host factors, relative to bacterial factors, play a dominant role in the pathogenesis of sepsis in patients with cirrhosis.<sup>18</sup> Patients with nosocomial or hospital-acquired infections, those who have undergone invasive procedures, interventions, and/or received multiple antibiotics have higher susceptibility to gram-positive organisms.

**Consequences of Infection in Cirrhosis**

Infection in a patient with cirrhosis may lead to a shock state of sepsis and organ failures through one or more mechanisms:



**Fig. 1** Mechanism of sepsis in cirrhosis. The nonlinear bidirectional interaction of sepsis in patients with cirrhosis can be explained by a network hypothesis of cirrhosis associate immune dysfunction (CAID), gut translocation, epigenetic modulation, cytokine-mediated inflammation, and organ failures in the setting of the altered microbiome. Cirrhosis-associated immune dysfunction (CAID) and bacterial translocation through the leaky gut play a major role in predisposing cirrhosis patients for recurrent infections. The lower number of reticuloendothelial cells (Kupffer’s cells) in cirrhosis and portosystemic shunts and lower opsonin and complement levels leads to lower clearance of endotoxins and increase the systemic exposure of bacteria. Epigenetic mechanisms leading to immune cell dysfunction and impaired inflammatory response on exposure to endotoxin also lead to increased incidence of infections. Lipopolysaccharide, along with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) act through toll-like receptors (TLR) on host immune cells, leading to the production of cytokines like interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Several host factors also contribute to impaired response (to lipopolysaccharide [LPS]) in cirrhosis and lead to the development of sepsis and organ failures. HLA DR, human leucocyte antigen-DR isotype; NK, natural killer; PPI, Proton pump inhibitor; RE cell, reticuloendothelial cell. Note: This image was created with BioRender.com

worsening of the basal hyperdynamic state and low systemic vascular resistance, decreasing the response to  $\alpha$  adrenoreceptor agonists, relative adrenal insufficiency, and left ventricular diastolic dysfunction.<sup>12</sup> Acute kidney injury (AKI) occurs in about one-third of patients with cirrhosis and sepsis due to hemodynamic alterations, renal vasoconstriction, and high-circulating cytokines and is associated with poor prognosis.<sup>12,19</sup>

Patients with decompensated cirrhosis are also predisposed to pneumonia and respiratory failure as a consequence of impaired pulmonary alveolar macrophage activity, increased pulmonary permeability, basal segment collapse due to tense ascites, alteration of T-cell subset ratio, risk of aspiration or micro aspiration due to hepatic encephalopathy or endoscopic interventions, and pulmonary microangiopathy.<sup>12,20</sup> Patients with cirrhosis who require mechanical ventilation for severe pneumonia or

acute respiratory distress syndrome have mortality rates between 60 and 80%.<sup>3,20</sup>

Coagulation failure with endothelial activation is also noted in patients with sepsis and cirrhosis and is due to an increase in factor VIII, von Willebrand’s factor, and tissue factor with reduced levels of protein C, protein S, antithrombin III, and factors V, VII, and X.<sup>21</sup> These changes, along with thrombocytopenia due to hypersplenism, alter the coagulation profile from a procoagulant to anticoagulant phenotype. This increases the risk of variceal and nonvariceal gastrointestinal bleeds, interventional site bleeding, and thromboses at other sites.<sup>21</sup>

Patients with cirrhosis have vasopressin deficiency and increased levels of nitric oxide, and, further, they characteristically demonstrate preexisting arterial underfilling, reduced peripheral vascular resistance, and high cardiac output.<sup>22,23</sup> Sepsis exacerbates these hemodynamic abnormalities and worsens cardiac dysfunction and tissue hypoperfusion.<sup>24</sup> Sepsis

further augments the hyporesponsiveness to exogenous vasopressin and increases the sensitivity to nitric oxide, leading to shock.<sup>23</sup> The presence of relative adrenal insufficiency also contributes to hypotension in patients with cirrhosis.<sup>25</sup>

Cerebral failure due to systemic and neuroinflammation can result in “septic encephalopathy” in 30 to 60% of patients with cirrhosis and sepsis.<sup>26</sup> In addition, hyperammonemia, systemic inflammatory response syndrome (SIRS), and cytokine storm exacerbate cerebral edema.<sup>27</sup>

Liver dysfunction evolves within 2 hours of sepsis onset in animal models.<sup>28</sup> Liver dysfunction is noted in up to 40% of patients with sepsis and cirrhosis, but liver failure in sepsis in those without cirrhosis is under 10%.<sup>29</sup> In those without cirrhosis, the liver can withstand this injury due to its high regenerative capability as opposed to those with cirrhosis. Furthermore, endotoxin-mediated cytokine burst leads to rapid impairment in hepatic microcirculation, increased hepatic oxidative stress, and neutrophilic infiltration.<sup>30</sup> Thus, sepsis in cirrhosis can quickly lead to hepatocyte death and liver failure.

## Diagnosis of Infection and Consequent Sepsis in Cirrhosis

The diagnosis of sepsis is challenged by the currently available heterogeneous definitions in patients with cirrhosis.<sup>31</sup> Sepsis was previously defined as SIRS with proven infection.<sup>32</sup> Approximately 50 to 60% of patients with cirrhosis and infection have SIRS.<sup>33,34</sup> Hypersplenism and  $\beta$ -blocker therapy may impair the ability for a rise in white cell count (WCC) and heart rate. Furthermore, 10 to 30% of patients with decompensated cirrhosis without BI demonstrate features of SIRS due to a hyperdynamic circulation, altered mentation, and/or tense ascites that affect the pulse rate, respiratory rate, and temperature.<sup>33</sup> Although SIRS is associated with poor outcomes in cirrhosis, it is insufficient to predict or define sepsis.<sup>31,34</sup>

According to the latest SEPSIS-3 guidelines, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>5</sup> Organ dysfunction is identified by an acute change in sequential organ failure assessment (SOFA) score by 2 points or higher. This criterion is well-validated and applicable to ICU patients with cirrhosis.<sup>35</sup> However, it is known that sepsis leads to organ dysfunction, and patients present with extrahepatic organ failures.<sup>8,9</sup> Hence SOFA scores may not be appropriate for sepsis diagnosis at admission or bedside.<sup>36</sup> Conversely, the severity scores, such as chronic liver failure–SOFA (CLIF-SOFA) and consortium organ failure score (CLIF-COF) aid in predicting outcomes in patients with sepsis-related organ failure.<sup>37</sup> However, these severity scores can neither predict sepsis nor diagnose sepsis. Instead, they are aimed to predict survival and requirement for transplantation in ACLF.

Recently quick SOFA (qSOFA) has been developed to diagnose sepsis, and this is independently related to survival and is used as a bedside tool.<sup>35,36</sup> Altered mentation, systolic blood pressure 100 mm Hg or lower, and respiratory rate 22

breaths/min or higher constitute qSOFA. Thus, dynamic changes in qSOFA may predict the survival in patients with cirrhosis and infection.<sup>36</sup> Furthermore, fever is a classical sign of infection. Therefore, we consider a combination of fever and qSOFA as a valuable bedside tool to predict sepsis. A proposed approach to diagnose sepsis in patients with cirrhosis is provided in **Fig. 2**. The definition of each infection event is outlined in the footnotes of **Fig. 2**.<sup>15,38</sup>

*Key point:* fever and qSOFA are simple bedside tools to identify sepsis in patients with cirrhosis.

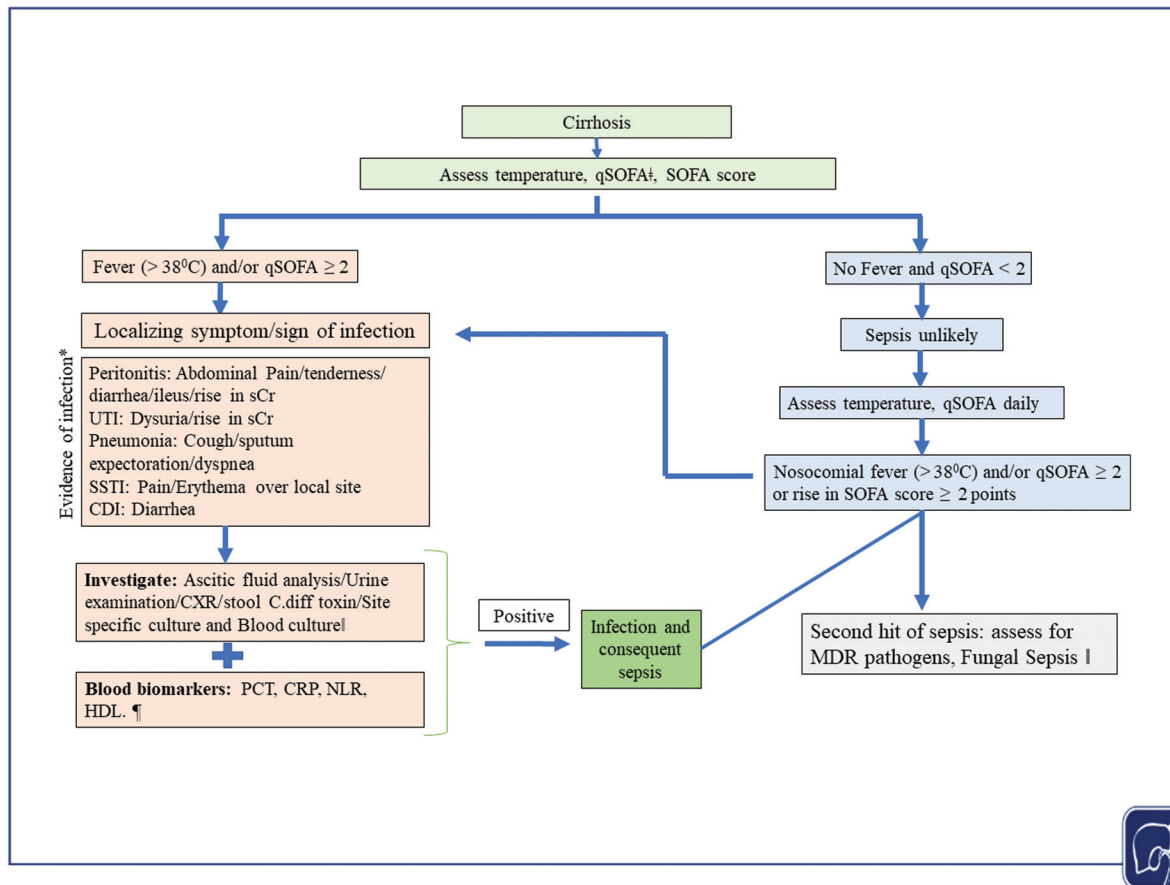
## Biomarkers of Infection and Consequent Sepsis

A promising biomarker should be economical, readily available, and sensitive enough to detect infection in cirrhosis. Several biomarkers have been evaluated in patients with cirrhosis, such as WCCs, procalcitonin (PCT), C-reactive protein (CRP), interleukin (IL)-6, neutrophil-to-lymphocyte ratio (NLR), presepsin, resistin, and high-density lipoprotein (HDL).<sup>39,40</sup> Of these, NLR is a simple biomarker that can predict infections and outcomes in patients with cirrhosis.<sup>41,42</sup> BI-induced rise in the neutrophil population and suppression of lymphocyte cells leads to high NLR.<sup>41</sup> An NLR of greater than 8.3 is suggestive of infection in cirrhosis; a higher NLR is predictive of organ failures in cirrhosis. Other leucocyte ratios, including monocyte-to-lymphocyte ratio (MLR), are also known to predict mortality in patients with cirrhosis and sepsis; however, these need further validation.<sup>41</sup>

On the contrary, CRP and IL-6 may not be suitable markers for diagnosing sepsis in cirrhosis, as the liver is either the source of production or a clearance site. In addition, organ dysfunction in sepsis may also alter the levels of these markers due to reduced clearance in the presence of renal failure (e.g., PCT). Further, the use of all sepsis biomarkers is fraught with significant overlap in the diagnostic range for SIRS and sepsis. Despite these limitations, CRP and PCT are frequently used to diagnose sepsis and have been assessed across multiple studies.<sup>43</sup> A cut-off values of greater than 25 and greater than 0.5 ng/mL for CRP and PCT, respectively, are significant for the diagnosis of sepsis.<sup>43</sup> However, utilizing these in combination with clinical evidence is crucial for the correct identification of sepsis.

HDL-related biomarkers (HDL-C and apoA-1) are significantly lower in infected patients with cirrhosis.<sup>44</sup> They negatively correlate with inflammatory markers such as CRP, WCCs, IL-6, IL-8, and tumor necrosis factor (TNF)- $\alpha$ . These biomarkers can predict infections and survival.<sup>44–47</sup> HDL and its scavenger receptor B1 can neutralize endotoxins.<sup>48</sup> A lower HDL may increase the risk of sepsis.<sup>45,48</sup>

Presepsin is the N-terminal fractional protein resulting from cleavage of CD14 receptor and endotoxin (ligand) cleaved by inflammatory serum proteases.<sup>49</sup> Resistin is a hormone produced by macrophages and adipocytes that correlates directly with inflammatory markers CRP and TNF- $\alpha$  and negatively with survival in patients with cirrhosis.<sup>50</sup> Thus, presepsin and resistin can also accurately diagnose sepsis.<sup>49</sup> BI activates the triggering receptor



**Fig. 2** Algorithm to diagnose infection and consequent sepsis in cirrhosis \*Definition of each event (modified from Bajaj et al and Kulkarni et al<sup>15,38</sup>). Spontaneous bacterial peritonitis (SBP): ascitic fluid analysis done under strict aseptic precautions showing high serum albumin ascites gradient (SAAG) with a polymorphonuclear cell count of  $\geq 250/\text{mm}^3$ . Secondary bacterial peritonitis: neutrophil count  $\geq 250/\text{mm}^3$  in ascitic fluid and evidence of an intra-abdominal source of infection with multiple organisms on culture. Urinary tract infection (UTI): urine analysis showing  $> 10$  leukocytes/field with symptoms of dysuria and/or positive urinary culture or uncountable leukocytes/field if cultures are negative. Pneumonia (lower respiratory tract infection): clinical signs of infection (fever, cough, expectoration, dyspnea) with infiltrates on chest X-ray with or without positive sputum culture. Skin and soft tissue infection (SSTI): clinical signs of infection associated with swelling, erythema, heat, and tenderness of the skin. Spontaneous bacteremia: positive blood cultures and no evident source of bacteremia. Secondary bacteremia: (1) catheter-related infection (positive blood and catheter cultures); (2) bacteremia occurring within 24 hours after an invasive procedure. *Clostridium difficile* infection: positive stool toxin in a patient with diarrhea. †Altered mentation, systolic blood pressure  $\leq 100$  mm Hg, and respiratory rate  $\geq 22$  breaths/min constitute qSOFA. ‡Fungal infections should be suspected in patients presumed to be infected, but bacterial cultures are negative, particularly in patients with diabetes mellitus, renal insufficiency, hemodialysis, prior use of antibiotics, and recent bacterial infection. ††PCT, CRP, and NLR can predict sepsis. HDL can predict the outcomes. CDI, clostridium difficile infection; CXR, chest X-ray; CRP, C-reactive protein; HDL, high-density lipoprotein; MDR, multidrug resistant; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; qSOFA, quick SOFA; SOFA, sequential organ failure assessment score; WCCs, white cell counts.

expressed on myeloid cells-1 (TREM-1) and amplifies inflammation by further increasing the production of proinflammatory cytokines. The soluble form of TREM-1 (sTREM-1) is detectable in circulation and can predict infection.<sup>51</sup> Similarly, soluble CD163 midregional proadrenomedullin (MR-proADM) and intercellular adhesion molecule 1 (ICAM1) are other markers that can aid in diagnosing sepsis.<sup>52–54</sup> However, these novel markers have not been validated and require further studies (► **Table 1**).

Additionally, a limitation of the biomarkers is that they have been assessed in heterogeneous populations and lack uniformity in cut-off values. We do, however, consider PCT, CRP, and NLR as reliable markers, as they are readily available and have fair proven diagnostic accuracy across multiple studies.<sup>41,42,55–58</sup>

## Markers of Infection Not Validated in Patients with Cirrhosis

High-mobility group box-1 (HMGB-1) is a well-known damage-associated molecular pattern (DAMP) involved in regulating gene expression.<sup>59</sup> Recent studies have demonstrated that elevation in HMGB-1 ( $> 5.9$  ng/mL) in patients with sepsis can predict mortality.<sup>60</sup> In addition, angiotensin-1 and 2 soluble receptor for advanced glycation end products (sRAGE), and soluble urokinase-type plasminogen activator receptors (suPAR) are other markers that also aid in predicting outcomes.<sup>61</sup> However, studies in patients with cirrhosis are lacking for these novel markers.

**Key point:** PCT, CRP, and NLR can aid in diagnosing sepsis in patients with cirrhosis.

**Table 1** Biomarkers of infection and consequent sepsis in cirrhosis

Biomarker	Cut-off	Comments	Comments
NLR	8.3 in patients with infection	Ability to predict mortality and organ failures in patients with sepsis	Advantages: easy to calculate Limitations: optimal cut-off value for predicting sepsis is unclear
PCT	0.5 ng/mL	MW: 14.5 kDa Peptide precursor of the hormone calcitonin Source: thyroid Detectable 3–4 hours after infection Half-life: 20–24 hours	Advantages: easily available Validated across multiple studies Limitations: increased in renal failure and inflammation
CRP	25 ng/mL > 10 ng/mL for infection	MW: 120 kDa Acute phase protein Source: liver Rise within 6 hours of infection Half-life: 19 hours	Advantages: easily available. Validated across multiple studies Limitations: increased in inflammation. long half-life. Remains elevated for a prolonged duration (36 hours)
IL-6	Varying cut-off IL-6 > 35 pg/mL with fever suggestive of sepsis¶	MW: 23 kDa Source: leucocytes, fibroblasts, monocytes, macrophages, T-cells and endothelial cells Rises within 2–4 hours of injury (inflammation) Half-life: < 1 hour	Needs further validation
HDL-c	< 30 mg/dL predicts infection < 17 mg/dL predicts mortality	Lipoproteins with a density ranging from 1.063 to 1.21 Pleiotropic effect: LPS neutralization, endothelial protection, and antioxidant and anti-apoptotic properties	Advantages: can be easily measured Limitations: requires further validation. levels inversely correlates with liver disease
Apo-AI	< 75 predicts infections < 50 mg/dL predicts mortality	Protein component of HDL-c Potent antioxidant and anti-inflammatory properties	Limitations: not routinely available at all centers. inversely correlates with liver disease
Presepsin	1,444 pg/mL for diagnosing sepsis	MW: 13 kDa N-terminal fractional protein resulting from cleavage of CD14 receptor and endotoxin (ligand) cleaved by inflammatory serum proteases Half-life: 4–5 hours Detectable within 2 hours of infection Plasma levels of presepsin can be considered as an indicator of activated innate immune effector cells in response to invasive pathogens	Advantages: accuracy similar to PCT and CRP Limitations: not routinely available at all centers. requires further validation
Resistin	20 ng/mL	MW: 12.5 kDa A pro-inflammatory adipokine Mainly derived from macrophage and adipocytes Half-life: 5 hours	
sTREM-1	430 pg/mL predicts infection > 600 pg/mL can predict mortality in infected cirrhosis patients	MW: 15 kDa Soluble form of TREM-1 Source: neutrophils, monocytes, and macrophages Peak levels at 2 hours after infection Short half-life: (12 minutes- in vivo)	Can predict mortality and organ Limitations: may be increased in renal dysfunction. Not widely available for routine use
sCD163	> 7,000 can predict mortality in infected cirrhosis patients 4,586 in patients with infection	MW: 130 kDa Source: activated macrophages (Kupffer's cells) and monocytes. Activation time-2 hours Half-life: 12–24 hours Correlates directly with IL-6, 8, and 10	Advantages: predicts mortality and correlated with organ failures in BI in patients with cirrhosis Limitations: not available for routine use
MR-proADM		MW: 5.1 kDa Precursor peptide of adrenomedullin, a vasoactive calcitonin peptide family member that is rapidly cleared from circulation Source: endothelial cells and vascular smooth muscle cells Half-life- hours compared with 22 minutes for ADM	Correlates with CRP, IL-6 and WCC and organ dysfunction More sensitive for SBP than other bacterial infections Limitations: cut-off values unknown. Not routinely available at all centers

Abbreviations: ADM, adrenomedullin; apoA-I, apolipoprotein A-I; CRP, C-reactive protein; HDL, high-density lipoprotein; IL, interleukin; MR-proADM, mid regional proadrenomedullin; MW, molecular weight; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; SBP, spontaneous bacterial peritonitis; sCD, soluble cluster differentiation; sTREM-1, soluble triggering receptor expressed on myeloid cell-1; WCC, white cell count. Note: References for cut-off values. Bernsmeier et al (NLR)<sup>41</sup>; Jalan et al (PCT and CRP)<sup>43</sup>; Lin et al (IL-6)<sup>40</sup>; Trieb et al (HDL and apoAI)<sup>44</sup>; Fischer et al (Presepsin and resistin)<sup>49</sup>; Tornai et al (sTREM1)<sup>51</sup>; Tornai et al (sCD163).<sup>52</sup>

**Table 2** Novel techniques for rapid diagnosis of infection

Principle	Name of the test	Turnaround time (min)	Number of organisms isolated
NAAT by real-time PCR ± microarray	Verigene	150	13 gram positive; 9 gram negative organisms including resistance testing for <i>mecA</i> , <i>vanA/B</i> , IMP, KPC, NDM, OXA, CTX-M
	Biofire Filmarray	60	8 gram positive (resistance genes: <i>mecA</i> , <i>vanA/B</i> ) 11 gram negative organisms (resistance genes: KPC) 5 candida species
	SeeGene Magicplex	360	73 gram positive (resistance genes: <i>mecA</i> , <i>vanA/B</i> ) 12 gram negative organisms and 6 candida species
	Lightcycler SeptiFast	360	6 gram positive, 10 gram negative and six fungi
	XPERT MRSA/SA	60	MRSA and MSSA
FISH	AdvanDx QuickFISH	30	2 gram positive, 3 gram negative, all <i>Enterococcus</i> and 3 candida species
	Accelerate Phenotest	90	6 gram positive, 8 gram negative, and 2 candida species
MALDI-TOF MS	Bruker's Sepsityper Vitek MS	15–20	Wide range dependent on database

Abbreviations: FISH, fluorescent in situ hybridization; MALDI-ToF, Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry; MSSA, methicillin sensitive staphylococcus aureus; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

## Novel Molecular Techniques for Diagnosis of Infection

Since the routine culture-based techniques for the infectious organism are laborious and time consuming, there is an increased risk of patients being exposed to empirical antibiotics for a longer duration which may lead to poor outcomes and increase the risk of multidrug resistant organisms (MDROs). This drawback can be overcome with newer molecular techniques that quickly identify the causative organism with a small amount of clinical specimens. Nucleic acid amplification tests with or without microarray, fluorescent in situ hybridization (FISH), and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) are novel molecular techniques for rapid detection of microorganisms from signal positive blood culture (► **Table 2**). There are also a few point-of-care (POC) tests to detect microorganisms and resistance patterns. Examples of such POC tests are Curetis Unyvero, RAPIDEC CARBA NP, and MinION. The limitation of these novel tests is that they detect the DNA of microorganisms and not the live pathogens, and the presence of background DNA in blood, lack of ideal gold standard, and contamination of the sample may compromise the interpretation of the molecular tests.<sup>62</sup> Lastly, none of these expensive tests have been validated in patients with cirrhosis. However, these novel techniques may reduce the risk of improper antibiotic exposure in patients with cirrhosis who are prone for infections with MDROs and polymicrobial organisms. Rapid diagnosis of infection and susceptibility profiles may improve the outcomes of these critically ill patients through timely deescalation/escalation of antibiotics.

## Prevention of Infection

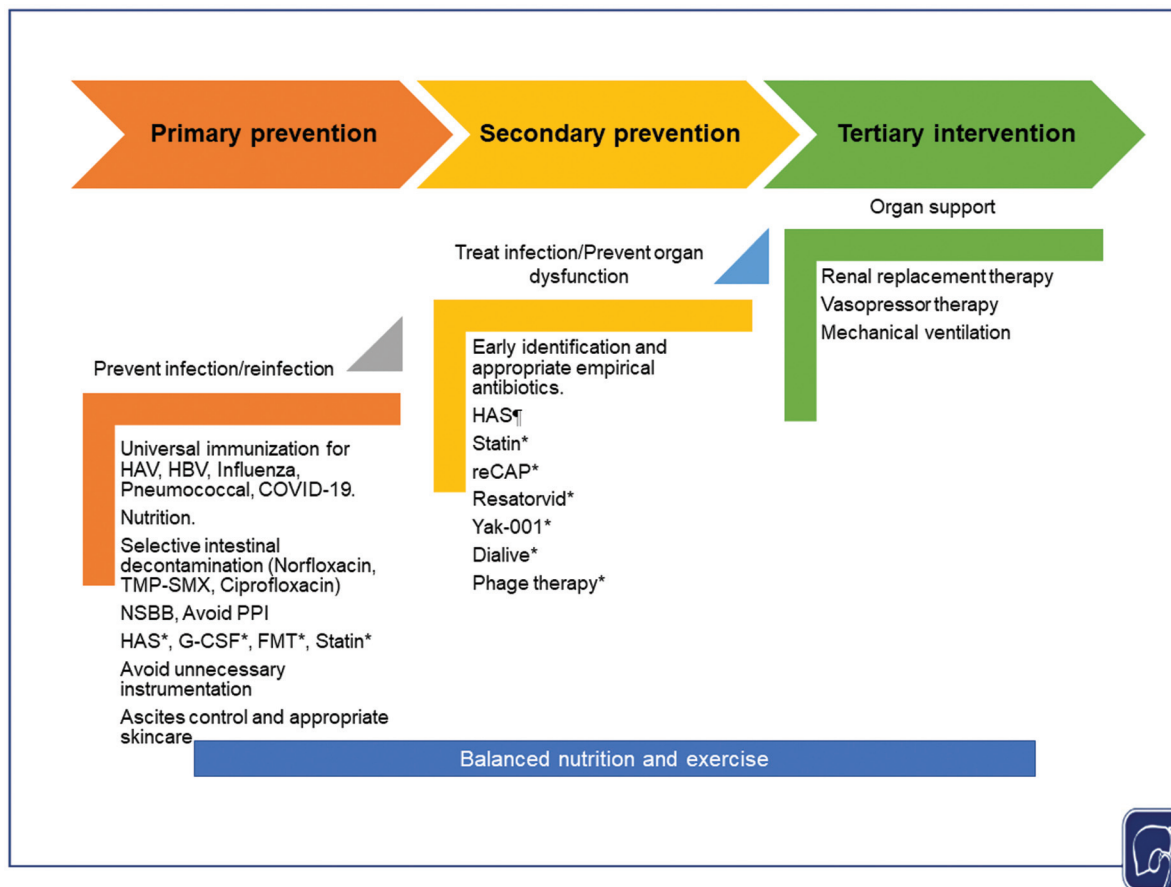
Prevention of infection may improve the quality of life, prolong survival, and reduce hospital admissions and cost

burden. Prevention of infection can be through general measures of exercise, and enhanced nutrition across the various stages of cirrhosis, primary prevention, secondary prevention, and tertiary intervention may help in managing the consequences of infection (► **Fig. 3**).

## Primary Prevention

Prevention of infection (or relapse of same or similar infection) in a patient with cirrhosis constitutes primary prevention. Pneumonia (both viral and bacterial) is a frequent cause and is associated with high mortality.<sup>63,64</sup> In addition, superimposed viral hepatitis A and B is associated with increased morbidity and mortality in patients with cirrhosis.<sup>65,66</sup> Novel coronavirus disease 2019 (COVID-19) is also known to precipitate organ failures in patients with cirrhosis.<sup>67,68</sup> Therefore, all patients with cirrhosis should be vaccinated for influenza, pneumococci, hepatitis A and B, and COVID-19.<sup>66,69–71</sup>

A reduction in gut translocation by nutritional intervention, immunonutrition, selective intestinal decontamination (with prophylactic antibiotics), avoidance of unnecessary proton pump inhibitors, and timely use of  $\beta$ -blockers and experimental granulocyte-colony stimulating factor (G-CSF) therapy constitutes primary prevention. Long-term albumin infusions and norfloxacin prophylaxis to prevent infection/reinfection are part of a primary prevention strategy.<sup>72,73</sup> In addition, simvastatin may also prevent sepsis and curb the inflammatory response in patients with cirrhosis.<sup>74</sup> Finally, adequate control of ascites, pedal edema, and appropriate skincare may prevent SSTIs. Sarcopenia is known to be associated with poor outcomes in patients with cirrhosis and infections for which balanced nutrition and exercise can improve outcomes.<sup>75</sup> In addition, universal precautions, such as maintaining hand hygiene, avoiding unnecessary instrumentations, use of aseptic techniques, and careful measures



**Fig. 3** Strategies to prevent infection and improve outcomes in patients with cirrhosis. <sup>†</sup>HAS can prevent organ dysfunction in patients with SBP. \*experimental/no robust data to support the clinical use yet. COVID-19, novel coronavirus disease 2019; HAV, hepatitis A virus; HAS, human albumin solution; HBV, hepatitis B virus; FMT, fecal microbiota transplantation; G-CSF, granulocyte colony-stimulating factor; NSBB, nonselective  $\beta$ -blocker; PPI, proton pump inhibitors; reCAP, recombinant alkaline phosphatase; TMP-SMX, trimethoprim-sulfamethoxazole.

to prevent catheter-related infections, must be undertaken in all patients to prevent infections.

### Beta-Blockers

Nonselective  $\beta$ -blocker (NSBB) therapy reduces the likelihood of complications of cirrhosis (including ascites, SBP, and hepatic encephalopathy) and prolongs survival.<sup>76</sup> NSBBs have the potential to increase intestinal transit time by blocking  $\beta$ -3 receptors.<sup>77</sup> Furthermore, NSBBs counteract altered mucosal perfusion and integrity by reducing portal pressure and intestinal permeability, further reducing endotoxemia.<sup>78,79</sup>

SBP is a common cause of sepsis in cirrhosis.<sup>70</sup> NSBB, especially propranolol, has been reported to prevent SBP in patients with decompensated cirrhosis.<sup>80,81</sup> However, studies on NSBBs in decompensated cirrhosis are limited by small sample sizes and heterogeneous populations.<sup>79</sup> Furthermore, the safety of  $\beta$ -blockers in patients with advanced liver disease is still questionable, given the potential consequences of reduction in cardiac output. Several relative contraindications for the use of NSBB in decompensated cirrhosis, such as hyponatremia, refractory ascites, hypotension, infections, and AKI, have been suggested.<sup>79</sup>

In a recent randomized controlled trial, prophylactic NSBBs in patients with compensated cirrhosis noted prevention of ascites, the most common decompensation in the natural

history of cirrhosis.<sup>82</sup> However, prophylactic NSBBs could not prevent SBP or other site infections.<sup>82</sup> Nevertheless, NSBBs has the potential to reduce the risk of decompensation and infections in patients with cirrhosis by preventing BT.

*Key point:* as part of primary prevention, prophylactic NSBBs in carefully selected patients with decompensated cirrhosis may prevent BT and consequent infections.

### Proton Pump Inhibitors

Proton pump inhibitors (PPIs) reduce gastric pH and motility and promote small intestinal bacterial overgrowth.<sup>83</sup> PPIs (especially prolonged use) increase the risk of infections, such as SBP and *C. difficile* in cirrhosis, and adversely affect the outcomes.<sup>84–86</sup> Hence, it may be prudent to avoid long-term PPIs in patients with cirrhosis.

### Albumin

Elevated prostaglandin  $E_2$  ( $PGE_2$ ) and hypoalbuminemia lead to immunosuppression and infection susceptibility in acutely decompensated cirrhosis.<sup>87</sup> Albumin modulates lipopolysaccharide (LPS) presentation by modulating toll-like receptor (TLR)-4 expression, promoting bacterial killing by binding  $PGE_2$ , and preventing endothelial dysfunction due to LPS.<sup>88</sup> Patients with cirrhosis have inadequate  $PGE_2$  binding capacity and consequently have immune dysfunction. Treatment



with 20% human albumin solution (HAS) has been shown to bind more PGE<sub>2</sub> and reverse plasma-mediated immune dysfunction.<sup>87</sup> Ischemia-modified albumin, a posttranslational functional alteration in the N-terminus of albumin, is found more frequently in patients with cirrhosis, and HAS supplementation may help rebalance it.<sup>89,90</sup>

Studies on long-term HAS administration have shown variable results.<sup>72,91–94</sup> Long-term HAS administration (for outpatients) can prevent SBP- and non-SBP-related infections and reduce the incidence of kidney dysfunction.<sup>72,94,95</sup> Long-term HAS can also prevent hospital admissions, ascites recurrence, and prolong survival.<sup>72,91,92,94</sup> In addition, long-term albumin administration has an immunomodulatory effect in patients with decompensated cirrhosis.<sup>96</sup> Hence, in patients with decompensated cirrhosis, long-term HAS may reduce the incidence of sepsis-triggered ACLF by reducing infections. However, the results of the ANSWER study were contradicted by the MACTH study which concluded that HAS (and midodrine) supplementation could not prevent complications of cirrhosis.<sup>72,93</sup> It may be argued that the patients included in the MACTH trial were those with more advanced disease, a higher MELD score, and received HAS therapy for a brief duration. Studies on long-term HAS administration in sepsis are shown in ►Table 3.

**Key point:** long-term albumin therapy may prevent precipitation of sepsis-triggered ACLF in patients with decompensated cirrhosis. However, further studies are needed to ascertain the same.

### Antibiotics

Cirrhosis is associated with dysbiosis in the intestinal flora with an overgrowth of pathogenic flora and reduced autochthonous bacterial flora.<sup>97</sup> Further, the leaky gut increases the risk of BT and endotoxemia. This endotoxin-induced nitric oxide synthase (iNOS) production can exacerbate preexisting arterial vasodilation.<sup>98</sup> Selective intestinal decontamination (SID) with antibiotics (especially norfloxacin) inhibits GNB and endotoxemia. Norfloxacin has been proven to prevent SBP and also infections in patients with gastrointestinal hemorrhage.<sup>99–102</sup> Norfloxacin has favorable pharmacodynamics and pharmacokinetics.<sup>103</sup> The slow solubility, low permeability, and low systemic bioavailability of norfloxacin make it an ideal choice for SID.<sup>11</sup> Furthermore, norfloxacin can reduce the LPS translocation-induced rise in iNOS, aortic Akt activity, and proinflammatory cytokine release and control systemic vasodilation.<sup>104</sup> Primary prophylaxis is recommended for patients with decompensated cirrhosis with serum bilirubin 3.0 mg/dL or higher and low ascitic fluid protein (< 1.5 g/dL) and renal dysfunction (serum creatinine ≥ 1.2 mg/dL or blood urea nitrogen ≥ 25 mg/dL or serum sodium ≤ 130 meq/dL).<sup>70</sup>

Norfloxacin prophylaxis is reported to be associated with three major adverse outcomes as follows: (1) increased risk of infections by gram-positive organisms,<sup>16</sup> (2) increased risk of *C. difficile* infections,<sup>105</sup> and lastly, (3) increased risk of development of MDROs.<sup>16,106,107</sup> Norfloxacin prophylaxis can be associated with asymptomatic intestinal colonization with MDROs which could contribute to an increased risk of

MDRO infections and nosocomial spread of MDROs.<sup>11</sup> A recent study reported a reduction in the incidence of BIs in patients receiving prophylactic norfloxacin therapy without the added risk of infections by MDROs.<sup>38</sup> Furthermore, a multicenter intercontinental study that included more than 1,300 patients reported that norfloxacin prophylaxis is not associated with an increased risk of MDROs.<sup>4</sup> On the contrary, systemic antibiotics administered in the previous 3 months for at least 5 days, an invasive procedure during the last month and health care exposure were associated with a higher risk of MDRO development.<sup>4</sup> As such, the presence of MDROs in cirrhosis is associated with a poorer prognosis; thus, early diagnosis and treatment are crucial. Norfloxacin prophylaxis should be initiated in patients meriting prophylaxis, and a high index of suspicion for MDROs in such patients admitted for infections is necessary.<sup>11</sup>

Oral ciprofloxacin and trimethoprim-sulfamethoxazole are safer alternatives to norfloxacin in countries where norfloxacin is unavailable.<sup>108,109</sup> Administered once weekly, 750 mg of ciprofloxacin is as effective as norfloxacin in the prevention of SBP.<sup>110</sup> The efficacy of once weekly ciprofloxacin needs further extensive double-blind, randomized studies. However, a once weekly regimen may be preferred in patients deemed less compliant with medications and avoid pill burden.

Rifaximin is another poorly absorbed gut-sterilizing antibiotic currently recommended to prevent recurrent episodes of hepatic encephalopathy in patients with cirrhosis.<sup>111</sup> Multiple small studies have demonstrated beneficial effects on the prevention of SBP in patients treated with prophylactic rifaximin.<sup>112,113</sup> However, the low quality of evidence does not support the role of primary prophylaxis with rifaximin for SBP prevention.<sup>114,115</sup>

**Key point:** prophylactic antibiotics, as part of primary prevention, may reduce the incidence of infections.

### Statins

Impaired immune response, increased thrombogenesis, and systemic inflammation are common to atherosclerosis and sepsis. Statins inhibit cholesterol synthesis by inhibiting hydroxy methylglutaryl coenzyme A reductase (HMG CoA). In the process, the intermediate products of cholesterol, such as mevalonate, farnesyl pyrophosphate, and geranyl pyrophosphate, which play a crucial role in several intracellular signaling pathways, are also reduced.<sup>116</sup> Hence, statins have pleiotropic effects including anti-inflammatory, anti-apoptotic, and vasoprotective properties.<sup>74</sup>

Statins function to accomplish the following: activate and increase heme oxygenase-1, an inducible and heat-shock cytoprotective protein<sup>117</sup>; decrease nitric oxide overproduction and prevent endotoxic shock<sup>118</sup>; protect hepatic microvascular circulation and prevent endotoxin-induced intrahepatic endothelial dysfunction and hepatocyte death<sup>119</sup>; decrease the effect of sepsis-induced coagulopathy through their antithrombotic properties<sup>120</sup>; and improve hepatic mitochondrial activity in sepsis.<sup>121</sup>

Through these mechanisms, statins can prevent various bacterial, viral, and fungal infections.<sup>122,123</sup> However,

**Table 3** Trials on long-term use of human albumin in patients with cirrhosis

Sl. no.	Study (year), country	Study population	Dose and duration	Outcome	Comments
1	Gentilini et al <sup>91</sup> (1999), Italy	126 cirrhosis patients with ascites Randomized to albumin plus diuretics versus diuretics alone	HAS 12.5 gm/day for 7 days Weekly albumin infusion of 25 g in the first year, followed by 25 g every 2 weeks up to 3 years	Ascites recurrence: 19, 56, 69% in HAS versus 30, 79, and 82% in SOC at 12, 24, and 36 months Hospital readmission: 5, 56, 69% in HAS versus 27, 74, and 79%, in SOC at 12, 24, and 36 months	Infection and AKI not noted on follow-up Small sample size
2	Romanelli et al <sup>92</sup> (2006), Italy	100 cirrhosis patients with first-onset ascites randomized to HAS + diuretics versus diuretics alone	HAS 25 g/week in the first year and 25 g every 2 week thereafter	Sepsis: 2 versus none HRS: 1 versus none Ascites recurrence: 51 versus 94%	Median follow-up: 84 (range: 2–120) months Limitations: small sample size
3	Caraceni et al <sup>72</sup> (2018), Italy	431 patients with cirrhosis and uncomplicated ascites. MELD: HAS: 12 (10–15) SOC: 13 (10–16)	HAS: 40 g twice weekly for 2 weeks, and then 40 g weekly for up to 18 months	HAS: reduced the incidence of SBP and non-SBP bacterial infections, renal dysfunction, HRS, hepatic encephalopathy grade 3 or 4, and potential diuretic-induced side-effects by 30 to 67.5% compared with SOC alone HAS: reduced number and duration of hospital admissions	Adherence to therapy is real-world practice is questionable
4	Solà et al <sup>93</sup> (2018), Spain	196 patients with cirrhosis and ascites awaiting liver transplant MELD: Midodrine+ HAS: 16 ± 6.2 SOC: 17 ± 6	Midodrine (15–30 mg/day) and albumin (40 g/15 days) for 1 year	Sepsis: 14 versus 15% in M + A group versus placebo ( <i>p</i> : 0.805) AKI: 14 versus 13% in M + A group versus placebo ( <i>p</i> : 0.846)	Midodrine + HAS was neither associated with a decrease in the incidence of complications of cirrhosis nor with improvement in survival Included high MELD patients. Received therapy for only 80 (30–244) days
5	Di Pascoli et al <sup>94</sup> (2019), Italy	70 patients of cirrhosis with refractory ascites MELD: HAS-15.2 ± 5.4 SOC: 14.9 ± 5	HAS 20 g twice per week (mean dose: 60.7 ± 15.2 g) for a mean duration of 408 ± 394 days	SBP: 7.9 versus 50.6% in albumin versus SOC group No SBP infection: 27.2 versus 88.6% in albumin versus SOC group HRS: 22.5 versus 57.7% in albumin versus SOC group	Nonrandomized trial Liable for bias Small sample size
6	Sharma et al <sup>95</sup> (2021), India	42 patients recovered from HRS-AKI	Midodrine 15 mg + HAS 2-g weekly versus HAS 20 g weekly for 2 months	AKI: 18% in M + HAS versus 50% in HAS M + HAS also reduced the frequency of taps. (1.9 ± 0.5 vs. 2.6 ± 0.5)	Small sample size Nonrandomized study. Prone for bias and type-II error

Abbreviations: AKI, hepatorenal syndrome; HAS, human albumin solution; HRS, hepatorenal syndrome; M + HAS, midodrine + human albumin solution; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; SOC, standard of care.

studies evaluating the role of statins in preventing sepsis in patients with cirrhosis are limited (► **Table 4**).<sup>124–128</sup> In a propensity-matched cohort (matched for age, gender, and  $\beta$ -blocker therapy) of patients with compensated cirrhosis, statin therapy reduced the risk of severe infections requiring hospitalization by 33% among 1,760 patients who received statin therapy compared with that of 1,760 patients who did not receive statins.<sup>124</sup> Simvastatin was the most commonly used drug.<sup>124</sup>

**Key point:** statin (especially simvastatin) may be useful for primary prevention of infection.

### Granulocyte–Colony Stimulating Factor

There are conflicting reports on the benefits of G-CSF in preventing sepsis in patients with cirrhosis. The mobilization of CD 34+ cells from the bone marrow to the liver, leading to regeneration and improved neutrophil function, is purported to change the hepatic microenvironment to favor regeneration and thus prevent sepsis.<sup>129,130</sup> Furthermore, with G-CSF therapy, intrahepatic and circulating dendritic cells are increased with a decrease in interferon (IFN)- $\gamma$  secreting CD8 T-cells leading to a reduction in the inflammatory response.<sup>131</sup> The addition of erythropoietin can increase Ki67+ hepatocytes and

**Table 4** Studies on statin therapy for prevention of infections in patients with cirrhosis

Sl. no.	Study (year), country	Type of study	Population	Statin and dose	Impact on progression of liver disease	Impact on infection/sepsis	Comments
1	Motzkus-Feagans et al <sup>124</sup> (2013), the United States	Retrospective	Patient with alcohol or HCV related cirrhosis without decompensation (n = 19,379) Statin user: 2,468	90.6% were on simvastatin Median duration of statin therapy-1194 (365–3103 days)	-	In the propensity-matched sample, statin users experienced lesser hospitalizations for severe infections: AHR: 0.67 (95% CI: 0.47–0.95) than nonusers.	Other cholesterol-lowering agents had no effect
2	Mohanty et al <sup>126</sup> (2016), the United States	Retrospective	685 statin users were matched with 2,062 nonusers		AHR for decompensation among statin users: 0.55 (95% CI, 0.39–0.77)	SBP: HR = 0.93 (95% CI: 0.29, 2.90)	Statins could not prevent SBP
3	Abraldes et al <sup>125</sup> (2016), Spain	Double-blind placebo-controlled randomized trial	158 cirrhosis patients with history of variceal bleed	Simvastatin 20 mg/day the first 15 days, 40 mg/day	No reduction of variceal bleed.	SBP 3.8% in placebo arm versus 0 in statin group	Simvastatin is associated with survival benefit in child A and B due to reduced risk of infections
4	Wong et al <sup>128</sup> (2017), Hong Kong	Population-based cohort study	Compensated cirrhosis (HBV predominant) 67,131 nonstatin users versus 2,053 statin users	86% simvastatin	45% reduction in composite endpoint of variceal bleed, ascites and SBP largely driven by reduction in ascites and not variceal bleed or SBP	6 (0.3%) events in statin users versus 298 (0.45%) in nonstatin users	Reduced decompensations. Improved survival. No reduction in SBP
5	Bishnu et al <sup>127</sup> (2018), India	Open-label RCT	Propranolol: 12 patient Propranolol + atorvastatin: 11	Atorvastatin 20-mg daily for 1 year		SBP in 8.33% in propranolol group versus 0 in combination group	Limitations: small sample size
6	ClinicalTrials.gov identifier: NCT03780673	Placebo-controlled double-blind randomized study	240 decompensated cirrhosis patients	Simvastatin 20 mg/day plus rifaximin 400-mg TID for 12 months	Incidence and severity of ACLF. Incidence and number of episodes of decompensation (ascites, bleed, encephalopathy)	Incidence of bacterial infection at 12 months	Underway

Abbreviations: ACLF, acute on chronic liver failure; AHR, adjusted hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis.

CD163+ M2 macrophages with a concomitant reduction in  $\alpha$ -SMA+ myofibroblasts creating an environment suitable for liver regeneration.<sup>132,133</sup> Taken together, this may improve severity scores and survival. However, there are conflicting reports on the prevention of sepsis in patients with cirrhosis<sup>132–137</sup> (–**Supplementary Table S1**; available in the online version only). A recent multicenter trial reported a lack of beneficial effects of G-CSF (with or without hematopoietic stem cell transplantation) in patients with compensated cirrhosis.<sup>137</sup> Furthermore, the effect of short-course G-CSF may not provide long-term prevention.<sup>138</sup> G-CSF may have a role in patients with early cirrhosis and low MELD score. However, despite more than a decade since the primary use of this drug, there is no concrete evidence for its role in hepatic regeneration and in preventing sepsis.

**Key point:** G-CSF can be considered in patients with low MELD scores in an effort to prevent sepsis, although the evidence for it is not robust.

## Secondary Prevention

Secondary prevention includes strategies to prevent infection-induced organ dysfunction. The early identification of sepsis and timely and judicious use of antibiotics in patients with cirrhosis can avoid the consequences of infection.

### Antibiotics

Appropriate empirical antibiotics have a significant role in patients with cirrhosis and sepsis. Early appropriate antibiotic initiation may prevent organ failures. A delay in 1 hour in initiating antibiotic therapy may increase the risk of mortality by nearly 7%.<sup>139</sup>

A broad-spectrum empirical antibiotic use with imipenem/cilastatin with or without vancomycin has been associated with significant improvement in survival in patients with cirrhosis and severe sepsis.<sup>140</sup> Furthermore, a broad-spectrum empirical antibiotic has been associated with a shorter duration of hospital stay and was more economical than the standard treatment.<sup>140</sup> The proper use of empirical antibiotics may also prevent the development of BI-induced ACLF.<sup>141</sup> Appropriate antibiotic therapy has led to a lower progression rate of ACLF grade (fewer patients with appropriate antibiotic therapy progressed to grade 2–3) and improved survival.<sup>142</sup> On the contrary, inappropriate empirical use of glycopeptides increases the risk of mortality in patients with BI-induced ACLF.<sup>143</sup> Therefore, empirical antibiotic administration and timely antibiotic de-escalation are of paramount importance in patients with cirrhosis.<sup>144</sup> However, there is a lack of studies on antibiotic stewardship in patients with cirrhosis.

**Key point:** appropriate empirical antibiotics, as part of secondary prevention, are associated with improved survival and outcomes in patients with cirrhosis and severe sepsis.

### Albumin

Prophylactic HAS is recommended for patients with SBP to prevent AKI.<sup>115</sup> However, the role of albumin in improving

outcomes in hospitalized patients with non-SBP sepsis is contentious. A recent study reported no beneficial effects with supplementation of HAS in hospitalized patients with decompensated cirrhosis. The patients included were sick and received albumin only for a median duration of 8 days.<sup>145</sup> The high dosing used in the study led to a significant number of patients developing fluid overload. However, it is known that low baseline serum albumin is associated with a higher incidence of sepsis and mortality.<sup>8,15,45</sup> In addition, patients who develop a second infection have lower baseline serum albumin than those who do not develop them.<sup>15</sup> Furthermore, albumin administration can prevent kidney injury, nosocomial infections, and lead to a better progression of ACLF grade.<sup>146</sup>

**Key point:** albumin administration in patients with SBP prevents renal injury. Further studies are required to assess the role of albumin, administered both in inpatients and outpatients, in preventing infections and infection-triggered multiorgan failure.

### Statins

In preclinical models of infection-induced ACLF, simvastatin prevented organ dysfunction and prolonged survival.<sup>30</sup> A recent retrospective study demonstrated that statin therapy was associated with a lower rate of infections and a reduction in the risk of hospitalizations for ACLF events in patients with cirrhosis.<sup>147</sup> A trial of simvastatin (20 mg/day) and rifaximin (400-mg TID) for 12 months in decompensated cirrhosis to prevent ACLF is underway (ClinicalTrials.gov identifier: NCT03780673). Further research is required to confirm whether simvastatin can be used for the secondary prevention of complications of sepsis-induced ACLF, especially in patients with decompensated cirrhosis who have a high risk of rhabdomyolysis.<sup>125</sup>

**Key point:** as part of the secondary preventive strategy, further studies are required to confirm the role of simvastatin in preventing the consequences of sepsis-induced ACLF.

## Tertiary Intervention

Tertiary intervention comprises organ failure support, such as renal replacement therapy, vasopressor therapy, and mechanical ventilation, in patients with cirrhosis and sepsis.

### Nutrition in Cirrhosis to Prevent Infection

Protein-energy malnutrition is common in patients with cirrhosis due to altered nutrient utilization, that is, increased fat and protein utilization and decreased carbohydrate utilization. Further, cirrhosis (especially decompensated cirrhosis) is a catabolic state associated with rapid muscle loss that may impact the outcome.<sup>148</sup> Protein-energy malnutrition leads to impairment in T-cell response, hypocomplementemia, and reduced immunoglobulin levels, lowering the defense immune response and increased susceptibility to infections.<sup>149</sup> Energy is also required to mount an appropriate immune response to infection.<sup>150</sup> Furthermore, low muscle mass is an independent predictor of mortality in patients with cirrhosis and infections.<sup>150</sup> Therefore, sarcopenia and

malnutrition predispose cirrhosis patients to infections and negatively impact the outcomes.<sup>150,151</sup> Furthermore, sepsis may aggravate energy expenditure in patients with cirrhosis and further accelerate protein degradation.<sup>151,152</sup> Therefore, a daily energy intake of 35 to 40 kcal/kg body weight and 1.2 to 1.5 g/kg protein is recommended. In addition, carbohydrate-containing late evening snacks may improve the nutritional status of patients with cirrhosis. It is also recommended to evaluate and supplement micronutrient deficiencies in cirrhosis patients.<sup>153</sup> Further studies are required to assess the role of calorie intake in preventing infection.

*Key point:* sarcopenia and malnutrition can adversely affect outcomes of sepsis in patients with cirrhosis. A multidisciplinary approach is essential to prevent malnutrition and sarcopenia in this population.

## The Challenges of Bacterial Resistance

The epidemiology of infections has changed in recent years. The burden of MDROs and XDR (extensively drug resistant) organisms is rapidly increasing and is a serious global threat.<sup>154</sup> The incidence of MDROs has increased from 20% in 2012 to more than 30% in recent years among patients with cirrhosis.<sup>4,14,106</sup> MDROs are associated with an increased risk of organ failures, septic shock, and mortality.<sup>106,155</sup> MDR infections are also associated with an increased health care and cost burden. Nosocomial and health care-associated infections are frequently caused by MDROs.<sup>106</sup> Susceptible bacteria develop resistance to antibiotics by accumulating mutations or acquiring resistance genes that protect the cell against antibiotics.<sup>156</sup> Antibiotic resistance genes (ARGs) can cause phenotypic resistance through enzymatic inactivation, target modification of the antibiotic, or by preventing intracellular accumulation through efflux pumps.<sup>154,156</sup> The densely populated intestinal microbial ecosystem provides an opportunity for the horizontal transfer of resistance genes among microbes through conjugation and transduction.<sup>156</sup> Enterococci, the widely prevalent commensal in patients with cirrhosis, can acquire, conserve, and disseminate resistance traits and thus increasing the risk of MDROs.<sup>157,158</sup> Shotgun metagenomic sequencing (MGS) and functional metagenomics are excellent culture-independent methods to characterize the “human resistome (ARGs).” Antimicrobial resistance bioinformatic databases, such as the ResFinder, ARG-ANNOT, Resistance Determinants Database (RED-DB), National Center for Biotechnology Information (NCBI) Pathogen Detection Reference Gene catalog, and Comprehensive Antibiotic Resistance Database (CARD), curate information from the published literature into their database to support genotype sequence analysis.<sup>158,159</sup> The knowledge and understanding of the resistome aids in assessing the burden and impact of antimicrobial resistance genes on outcomes in patients with cirrhosis.

*Key point:* antimicrobial resistance is a global threat. Novel techniques aid in the rapid diagnosis of infection and susceptibility patterns and may improve outcomes in patients with cirrhosis.

## Prevention of Multidrug Resistant Infections

The risk factors for MDROs include recurrent health care exposure, prolonged use of indwelling medical devices including vascular lines, urinary catheters, feeding tubes, endotracheal tubes, after prolonged hospitalization, colonization of MDROs in immunosuppressed patients, and lastly, the injudicious use of antibiotics.<sup>160</sup> Patients with cirrhosis are immunosuppressed and are frequently exposed to health care settings due to the need for paracentesis, variceal ligation, hepatocellular carcinoma management, and optimization for liver transplantation. Moreover, patients with cirrhosis frequently require hospitalization.<sup>161</sup> Antimicrobial stewardship is the need of the hour to prevent the exponential rise in incidence of MDRO infections. Antimicrobial stewardship not only includes judicious use of empirical antibiotics but also useful in timely deescalation and withdrawal.<sup>158</sup> Restricting prolonged antibiotic use is also a part of antimicrobial stewardship; however, data on the optimum duration of therapy for infections other than SBP in cirrhosis is lacking.<sup>115</sup> Cirrhosis patients, especially those planned for transplantation, should undergo nasal and rectal swab assessment for MDR organisms. Health care personnel involved in care of cirrhosis patients should also be evaluated for colonization of MDROs. Incorporating rapid detection methods (as discussed earlier) for the early identification of MDROs and isolating those who develop MDR infections is ideal. Education and training of health care personnel on universal precautions, including hand hygiene, avoiding unnecessary instrumentation, antimicrobial stewardship, and aseptic precautions, while performing paracentesis and variceal ligation, should be a part of hospital policy. Hospital-based policies aimed to monitor the incidence and local-susceptibility patterns and incorporating the changes in antibiotic policies are essential. National surveillance programs to understand the cause and prevalence of AMRs are needed. Novel nonantibiotic strategies, as discussed in this review, may also reduce the incidence of MDROs. Education, judicious use of antimicrobials, infection control precautions, frequent surveillance programs, and robust administrative support can contain MDR infections.

## Future Strategies and Novel Interventions

Immunonutrition is defined as the use of specific nutrients to modulate immune system activity.<sup>162</sup> Omega-3 fatty acids (FAs) modulate prostaglandin (PG) metabolism and decrease triglycerides; furthermore, they can lower cholesterol levels at high doses and hence have antithrombotic and anti-inflammatory properties.<sup>163</sup> Omega-3 FAs inhibit the formation of omega-6 FA-derived proinflammatory eicosanoids such as PGE<sub>2</sub> and leukotriene B<sub>4</sub> (LTB<sub>4</sub>). Conversely, these omega-3 FAs can form potent anti-inflammatory lipid mediators such as resolvins and protectins.<sup>164</sup> Altogether, omega-3 FAs suppress the activity of nuclear factor kappa B and reduce the production of proinflammatory enzymes and cytokines, including cyclooxygenase-2, TNF- $\alpha$ , and IL-1 $\beta$ .<sup>165</sup> Recently, intravenous lipid emulsions were evaluated for the prevention of sepsis in patients with ACLF.<sup>45</sup> Fish oil-based lipid emulsions suppressed endotoxin levels, IL-1 $\beta$ , CRP, and prevented the rise

**Table 5** Mechanisms and role of drugs in prevention of infections in patients with cirrhosis

Sl. no.	Modality	Role	Dose	Beneficial effect	Comments
1	NSBBs	Preprimary and primary prevention	Propranolol 20–80 per day or carvedilol at 3.125–25.0 mg based on tolerance	Reduces portal pressure Reduces intestinal permeability Reduces endotoxemia	Can reduce infections and improve survival Disadvantages: risk of renal dysfunction and cardiac suppression in advanced cirrhosis patients
2	Albumin	Preprimary and primary prevention	40 g twice weekly for 2 weeks followed by 40 g weekly	Modulate Toll-like receptor (TLR) 4 expression PGE2 mediated bacterial killing Reverses plasma-mediated immune dysfunction	Definitive role in SBP treatment to prevent kidney injury and prolong mortality. Long-term therapy may prevent ACLF in decompensated cirrhosis patients Limitations: doubtful role of albumin for prevention of non-SBP sepsis induced organ failures
3	Antibiotics	Primary and secondary prevention	Norfloxacin 400 mg/day Trimethoprim-sulfamethoxazole Ciprofloxacin 750 mg once weekly Broad-spectrum antibiotics in severe sepsis (secondary prevention)	Rebalances gut dysbiosis Inhibits gram-negative bacteria and endotoxemia	Prevent infection/SBP/renal injury in patients with gastrointestinal hemorrhage and in patients with low ascitic fluid protein Limitations: prophylactic antibiotics may increase the risk of MDROs
4	Statins	Preprimary, primary, and secondary prevention	Simvastatin (20–40 mg/day) ± rifaximin (400 mg TID)	Anti-inflammatory, antiapoptotic, vasoprotective Decrease the effect of sepsis-induced coagulopathy Prevent endotoxin-induced intrahepatic endothelial dysfunction and hepatocyte death	Existing evidence support preprimary prophylaxis role. Further clinical studies required to confirm the role of simvastatin in preventing sepsis and the consequences of sepsis induced ACLF Limitations: risk of rhabdomyolysis is high in decompensated cirrhosis patients
5	G-CSF	Primary prevention	G-CSF (5 mg/kg/d) for 5 days and then every third day (12 total doses), along with subcutaneous darbepoetin (40 µg/week) for 4 weeks or EPO	Regeneration and improvement in neutrophil function by mobilization of CD 34+ cells from the bone marrow to the liver Increased intrahepatic and circulating dendritic cells and decreased interferon (IFN)-γ secreting CD8 T cells	May be used as an experimental drug in early cirrhosis patients with low MELD score

Abbreviations: ACLF, acute-on-chronic liver failure; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; MDROs, multidrug resistance organisms; MELD, model for end-stage liver disease; NSBBs, nonselective β-blockers; SBP, spontaneous bacterial peritonitis.

in TNF-α. Additionally, there was an increase in TLR expression with omega-3 FA lipid emulsions. Omega-6 FAs had a similar change but to a lesser extent. Compared with the control arm, omega-6 FAs and omega-3 FAs reduced sepsis by 53 and 86%, respectively.<sup>45</sup> However, further studies are required to validate the role of these lipid emulsions as nutritional supplements and immunomodulators in patients with cirrhosis.

Fecal (or intestinal) microbiota transplantation (FMT) is a therapeutic modality for recurrent *C. difficile* infections. MDROs are common in patients with advanced cirrhosis due to frequent use of antibiotics and recurrent hospitalizations.<sup>14</sup> Gut ARGs proportionately increases with the

severity of liver disease and correlate with hospitalizations and mortality in patients with cirrhosis.<sup>166</sup> Recently the effect of FMT on ARGs in cirrhosis was evaluated.<sup>167</sup> Twenty patients treated with FMT were compared with 20 controls.<sup>167</sup> Ten patients received 15 capsules (orally) of 4.125-g stool, and 10 received 5 days of broad-spectrum antibiotics followed by 90 mL of 27-g stool enema. There was a significant decrease in ARGs with FMT (more so with the oral route) compared with placebo.<sup>167</sup> Further extensive, randomized controlled studies are required to evaluate the role of FMT in reducing the burden of MDROs and thus preventing sepsis.

Recent studies show encouraging results in preventing alcohol-related liver disease through bacteriophage-mediated inhibition of cytolytic *E. faecalis*.<sup>168</sup> Phage therapy has been utilized in the prevention and treatment of HBV infection.<sup>169</sup> Furthermore, bacteriophages have strong anti-inflammatory properties independent of antibacterial properties.<sup>170</sup> Bacteriophages have been used in sepsis treatment.<sup>170</sup> However, bacteriophages are strain specific and are limited by studies in preclinical models. Future studies should evaluate the role of phage therapy in preventing chronic liver disease (preprimary prevention) and treating sepsis in patients with cirrhosis (secondary prevention).

Sepsis is a common precipitant of ACLF through the LPS-TLR4 pathway.<sup>171</sup> Recombinant alkaline phosphatase (recAP), developed from intestinal and placental alkaline phosphatase, dephosphorylates the LPS, reduces its activity, and reduces hepatic TLR4 expression.<sup>171,172</sup> Thus, recAP may reduce the risk of organ dysfunction in sepsis-induced ACLF as part of secondary prevention.<sup>171</sup> Resatorvid (TAK-242) is a small-molecule inhibitor of TLR4.<sup>173</sup> Intravenous resatorvid may prevent organ dysfunction. Phase-II trials of this drug are underway (identifier: NCT04620148). Yak-001, an orally administered, nonabsorbable, synthetic microporous carbon has a high adsorptive capacity for bacterial products, LPS, and proinflammatory cytokines. Yak-001 was found to be safe and effective in reducing endotoxemia and inflammatory mediators in patients with decompensated cirrhosis in phase-II trials.<sup>174</sup> Recently, obeticholic acid was shown to prevent BT in preclinical studies.<sup>175</sup> While the preliminary data are very encouraging, the clinical utility of these drugs for the prevention of sepsis and consequent organ dysfunction requires further validation.

There is elevated COX-derived PGE<sub>2</sub> in patients with acute hepatic decompensation; the COX inhibitor indomethacin helps restore macrophage immune function and improve survival in the mouse model of liver injury and thus may prevent infection.<sup>176</sup> However, preexisting platelet dysfunction and risk of renal failure prohibit us from exploring these drugs in patients with cirrhosis. Lastly, DIALIVE, a novel liver dialysis device that replaces dysfunctional albumin and removes pathogen and damage-associated molecular patterns (DAMPs), has been shown to improve outcomes in patients with ACLF.<sup>177,178</sup> Further studies should evaluate the role of such novel devices in the prevention of organ failures in sepsis-induced ACLF.

**Key point:** many therapeutic and preventive strategies are evolving. Further multicenter research involving novel interventions may improve the outcomes of critically ill cirrhosis patients and reduce the global mortality attributed to liver diseases.

## Conclusion

Infections and consequent sepsis remain a challenging clinical conundrum in the management of patients with cirrhosis. Due to ill-defined diagnostic criteria, lack of absolute biomarker cut-offs, and overlap with secondary organ failures, prevention, early diagnosis, and timely therapy remain a challenge. Yet, there have been major advances in under-

standing the frequency, consequences, and therapy of infections and sepsis in cirrhosis. It is crucial to prevent sepsis in patients with cirrhosis at primary and secondary levels with several advanced measures (► **Table 5**). The progression of sepsis-induced liver failure may be mitigated with early identification and appropriate management. In addition, universal precautions are required at all stages to avoid infections, secondary sepsis, and organ failures in patients with cirrhosis. Despite the availability of multiple interventions, successful management of patients with cirrhosis and sepsis remains a challenge in 2022 in view of the need for advanced organ support, scarcity of donors for transplantation, and COVID-19-related interruptions in therapy.

## Lay Summary

Infections in patients with cirrhosis significantly contribute to morbidity and mortality. Infections in cirrhosis frequently lead to organ failures. Therefore, preventing infections may improve the outcomes of patients with cirrhosis by preventing downstream complications. In this article, we discussed several measures, including antibiotic and nonantibiotic-based interventions, to prevent infections in cirrhosis and improve outcomes.

## Abbreviations

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ARG, antibiotic resistance gene; BI, bacterial infection; BT, bacterial translocation; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; CLP, cecal ligation and puncture; COVID-19, novel coronavirus disease 2019; CRP, C-reactive protein; FA, fatty acid; FMT, fecal microbiota transplantation; G-CSF, granulocyte-colony stimulating factor; GNB, gram-negative bacilli; GPC, gram-positive cocci; HAS, human albumin solution; HO-1, heme oxygenase-1; ICU, intensive care unit; IFN, interferon; iNOS, endotoxin-induced nitric oxide synthase; LPS, lipopolysaccharide; LTb4, leukotriene B4; MDRO, multi-drug resistant organism; MR-proADM, mid-regional pro-adrenomedullin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NLR, neutrophil-to-lymphocyte ratio; NSBB, Non-selective  $\beta$ -blocker; PCT, procalcitonin; PG, prostaglandin; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; PPI, proton pump inhibitor; qSOFA, quick sequential organ failure assessment; recAP, recombinant alkaline phosphatase; SBP, spontaneous bacterial peritonitis; SID, selective intestinal decontamination; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; SSTI, skin and soft tissue infection; UTI, urinary tract infection; TLR, toll-like receptor; TNF, tumor necrosis factor; TREM-1, triggering receptor expressed on myeloid cells-1; WCC, white cell count.

## Authors' Contributions

K.R.R. and N.R.P. developed the study concept; A.V.K., K.K., and M.P. wrote the initial draft; A.V.K. and M.P. prepared the figures; J.P.A., M.S., and K.K. prepared the tables; J.P.A., D.N.R., N.R.P., and K.R.R. critically assessed the draft. K.R.R. and A.V.K. are the guarantors of the article. All members approved the final manuscript.

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**Conflict of Interest**

None declared.

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