Sepsis in Patients With Cirrhosis Awaiting Liver Transplantation: New Trends and Management

Rosa Martin Mateos and Agustín Albillos

Gastroenterology and Hepatology Department, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto de Salud Carlos III, Madrid, Spain

Bacterial infections are more frequent and severe in patients with advanced liver disease and, therefore, in liver transplant candidates. The increased risk of infection in these patients parallels the severity of the immune dysfunction associated with cirrhosis, which is related to systemic inflammation and progressive immunodeficiency. Other factors contribute to this risk, such as genetic polymorphisms, proton pump inhibitor overuse, the numerous invasive procedures and hospitalizations these patients go through, or the immunosuppressive effects of malnutrition or alcohol abuse. Bacterial infections have a great impact on disease progression and significantly increase mortality rates before and after liver transplantation. Mechanisms leading to organ failure in sepsis are associated not only with the hemodynamic derangement but also with an excessive inflammatory response triggered by infection. Furthermore, prophylactic and empirical antibiotic treatment strategies in patients with cirrhosis are being modified according to the growing prevalence of multidrug-resistant bacteria in the past decade. Also, new criteria have been introduced for the diagnosis of sepsis and septic shock. These new definitions have been validated in patients with cirrhosis and show a better accuracy to predict in-hospital mortality than previous criteria based on systemic inflammatory response syndrome. Accurate prophylaxis and early identification and treatment of bacterial infections are key to reducing the burden of sepsis in patients with cirrhosis awaiting liver transplantation.

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Patients with cirrhosis present an increased risk of developing bacterial infections, which are, in addition, more severe than in the general population (estimated overall mortality of 38% and up to 70% in case of septic shock versus 10% and 40%, respectively, for a general hospital population). Notably, although overall mortality among hospitalized patients with cirrhosis is decreasing, the risk of sepsis-related death has increased over the past few years (incidence risk ratio, 4.70; 95% confidence interval, 4.61-4.79). Bacterial infections are the most identifiable triggers of acute-on-chronic liver failure (ACLF), accounting for 32% of the precipitating events. Spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTIs) are the most frequent type, followed by pneumonia and cellulitis.

Several changes in the epidemiology of bacterial infections have occurred over the past decade. The most relevant is the increasing prevalence of multidrug-resistant (MDR) bacteria both in Europe (29%) and worldwide (34%). MDR pathogens are resistant to at least 1 agent in 3 or more antimicrobial categories. When bacteria are resistant to at least 1 agent in all but 2 or fewer antimicrobial categories, they are considered extensively drug resistant, and when not susceptible to any currently available agent, they are defined as pandrug-resistant bacteria. The most common MDR pathogens are extended-spectrum β-lactamase–producing Enterobacteriaceae.

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CADIS, cirrhosis-associated immune dysfunction; DAMP, damage-associated molecular pattern; EASL, European Association for the Study of the Liver; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; MDR, multidrug-resistant; NOD2, nucleotide-binding oligomerization domain containing protein 2; PAMP, pathogen-associated molecular pattern; PMN, polymorphonuclear leukocyte; PRR, pattern recognition receptor; qSOPA, quick Sequential Organ Failure Assessment; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; TLR2, toll-like receptor 2; UTI, urinary tract infection; VATS, video-assisted thoracoscopic surgery; VRE, vancomycin-resistant enterococci; WBC, white blood cell.
(ESBLE; i.e., *Escherichia coli* and *Klebsiella pneumoniae*), AmpC β-lactamase–producing Enterobacteriaceae (i.e., *Enterobacter* and *Citrobacter spp.*), carbapenemase–producing Enterobacteriaceae (i.e., *Klebsiella spp.*, *E. Coli*, and *Enterobacter spp.*), methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci (VRE; i.e., *Enterococcus faecium*).

A higher susceptibility to infections significantly increases morbidity and mortality and, thus, deteriorates the quality of life of patients with cirrhosis awaiting liver transplantation. Strategies aimed at improving diagnosis of infection, prophylaxis, and treatment are therefore needed. This review examines the mechanisms responsible for the high rate of bacterial infections in patients with cirrhosis and provides an overview of the key clinical features and prognostic implications of sepsis in patients awaiting liver transplantation.

**Altered Immune Response in Cirrhosis and Sepsis**

**PATHOLOGICAL BACTERIAL TRANSLLOCATION**

The mucosa of the intestine is a highly organized and compartmentalized structure that controls the interactions between the gut and the liver. The intestinal surface is formed by physical defenses, including a layer of epithelial cells interconnected by tight junctions, and functional defenses, such as the mucous layer. The intestinal barrier displays a unique immune system capable of distinguishing between regular nutrient flux, self-antigens, a diverse milieu of commensal bacteria, and invading pathogens.

Cirrhosis is associated with profound alterations at different levels of the intestinal barrier. Dysbiosis (reduced abundance of protective bacteria and increased pathogenic species) and bacterial overgrowth are a result of intestinal hypomotility, changes in bile flow and composition, and impaired intestinal immunity. Disruption of the epithelial and vascular intestinal barriers enables passage of viable bacteria and pathogen-associated molecular patterns (PAMPs) through the vascular and lymphatic routes to the systemic circulation. Bacterial translocation is further aggravated in sepsis due to alterations in perfusion, vascular tone, and coagulation that lead to a hypoxic microenvironment of the intestinal tissue.

**CIRRHOSIS-ASSOCIATED IMMUNE DYSFUNCTION**

Systemic inflammation due to persistent immune system stimulation and progressive immunodeficiency characterize what is known as cirrhosis-associated immune dysfunction (CAID). Immunodeficiency affects cellular and soluble components of the immune system both at the liver and systemically. The abnormalities include the following:

1. Compromise of the immune surveillance function of the liver through damage of the reticuloendothelial system.
2. Impaired synthesis of innate immunity proteins.
3. Altered functions of circulating and intestinal populations of immune cells (specifically reduced chemotaxis and oxidative burst of neutrophils), impaired phagocytic activity of antigen-presenting cells, and exhaustion of the adaptive immune response.

On the other hand, systemic inflammation is prompted by increased intestinal permeability, bacterial overgrowth, and dysbiosis, which favors translocation of bacteria and PAMPs. Specific receptors activated by PAMPs (also called pattern recognition receptors [PRRs]) amplify proinflammatory signaling. Intracellular molecules released by injured or dead cells...
(damage-associated molecular patterns [DAMPs]) are also recognized by PRRs, and they contribute to persistent systemic inflammation in cirrhosis.

**DYSFUNCTIONAL IMMUNE RESPONSE IN SEPSIS**

The severity of CAID parallels the severity of cirrhosis, and it worsens critically with acute events. In sepsis-induced ACLF, PAMPs, such as bacterial lipopolysaccharides, bind to PRRs. Receptor engagement activates downstream signaling pathways, which leads to increased transcription and the release of inflammatory cytokines as well as the activation of innate immune cells. Sepsis triggers massive immune cell activation and overproduction of cytokines. This situation is further amplified and perpetuated by DAMPs released by cells damaged by hypoperfusion, necrosis, and apoptosis.

**Sepsis in Cirrhosis: Burden and Definitions**

**BURDEN OF SEPSIS IN CIRRHOsis AND LIVER TRANSPLANT CANDIDATES**

Patients with cirrhosis are at increased risk of sepsis and sepsis-related mortality. Septic shock is associated with higher mortality rates in intensive care units (ICUs) for these patients compared with patients without cirrhosis (71% versus 49%). Conversely, cirrhosis is an independent risk factor for sepsis and death.

**SEPSIS: A RENOVATED CONCEPT**

In an effort to improve the diagnostic accuracy of the previous definition of sepsis based on systemic inflammatory response syndrome (SIRS), new diagnostic criteria (Sepsis-3) have been proposed. Sepsis is now defined as a life-threatening situation because of organ dysfunction caused by a dysregulated response to infection. Organ dysfunction is defined as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥2 points from baseline. Septic shock can be clinically identified if vasopressors are required to maintain a mean arterial pressure ≥65 mm Hg and if serum lactate levels are ≥18 mg/dL in the absence of hypovolemia.

Because the new definition of sepsis requires a baseline calculation of the SOFA score, an easy-to-use bedside tool called the quick Sequential Organ Failure Assessment (qSOFA) has been proposed for the prompt recognition of sepsis in patients outside ICUs. This score identifies patients with suspected infection who are likely to have a poor outcome, and it is based on the presence of at least 2 of the following criteria: respiratory rate of 22 breaths per minute or greater, altered mentation, or systolic blood pressure of 100 mm Hg or lower.

Piano et al. have recently validated Sepsis-3 and qSOFA criteria in patients with cirrhosis. These new scores were significantly better at predicting in-hospital mortality than SIRS (area under the receiver operating characteristic curve = 0.78 for Sepsis-3, 0.73 for qSOFA, and 0.61 for SIRS). In addition, patients who met the Sepsis-3 criteria had a significantly higher incidence of ACLF, septic shock, and ICU admissions. Accordingly, Sepsis-3 and qSOFA are now recommended in clinical practice guidelines for the management of patients with decompensated cirrhosis.

**Mechanisms of Organ Failure in Sepsis and Clinical Approach**

Hepatic and/or extrahepatic organ failure is the hallmark of ACLF and serves to differentiate this syndrome from acute decompensation of cirrhosis. In sepsis-induced ACLF, the mechanisms underlying organ failure are related not only to the hemodynamic derangement but also to cell dysfunction and cell death mechanisms induced by the exacerbated inflammatory response. The number of organ failures is highly predictive of the risk for delisting or death in liver transplant candidates hospitalized with an infection.

**CARDIOVASCULAR DYSFUNCTION**

Portal hypertension induces a profound hemodynamic alteration characterized by peripheral vasodilation, hyperdynamic circulation, high cardiac output, and low systemic vascular resistances. In sepsis-related ACLF, cytokine-induced release of nitric oxide and reactive oxygen species contribute to arterial vasodilation, which further reduces mean arterial pressure and impairs left ventricular function and tissue perfusion.
In a recent study analyzing factors associated with survival in transplanted patients with severe ACLF, it was found that 1-year survival was associated with a significantly lower prevalence of pretransplant circulatory failure (50% versus 61%), which confirms the negative impact of the hemodynamic dysfunction on posttransplant mortality.

**Fluid Resuscitation**

Current guidelines recommend crystalloid solutions (normal 0.9% saline or pH balanced in case of hyperchloremia) as the initial fluid of choice (10–20 mL/kg).\(^{16}\) In addition, albumin has shown beneficial effects not only as a plasma expander but also as immunomodulatory therapy. Albumin may counteract systemic inflammation by binding and inactivating PAMPs, prostaglandins, and reactive oxygen and nitrogen species.\(^ {17}\) Low levels and altered function of albumin in cirrhosis is associated with a higher risk of infection and death.\(^ {18}\) Conversely, albumin infusion improves survival in patients with SBP, hepatorenal syndrome (HRS), and circulatory dysfunction after large-volume paracentesis.\(^ {19,20}\) Despite these well-known benefits, albumin failed to improve renal function or survival in infections other than SBP.\(^ {21,22}\) Until more evidence supporting the use of albumin becomes available, early initiation of volume resuscitation, independently of fluid type, will be the key factor for the hemodynamic management in patients with cirrhosis and sepsis.

**Vaspressors**

Vasopressor agents counteract arterial vasodilation, increasing mean arterial pressure, cardiac preload, and tissue perfusion. In cirrhosis, a mean arterial pressure of 60 mm Hg or higher is recommended, along with adequate hemodynamic monitoring with arterial catheters, central venous access, and initial echocardiographic assessment in patients with circulatory shock. A pulmonary artery catheter should be placed in cases of respiratory failure or hemodynamic instability.\(^ {16}\)

Norepinephrine has vasopressor as well as positive inotropic effects, and it is considered the drug of choice for septic shock in cirrhosis and in the general population.\(^ {23}\) This recommendation is based on a lower mortality and incidence of arrhythmic events associated with the use of norepinephrine as compared with dopamine.\(^ {24}\) Terlipressin, an analogue of vasopressin with a predominant vasoconstrictor effect on the splanchnic circulation, has also been tested in patients with cirrhosis and septic shock. In a small clinical trial, terlipressin was as effective as norepinephrine, and it also provided an early survival benefit (at 48 hours) and reduced the risk of variceal bleeding.\(^ {25}\) Therefore, vasopressin or terlipressin may be used as second-line treatments for persistent hypotension in patients with cirrhosis who have sepsis.

**RENAL FAILURE**

Bacterial infections are the most frequent triggers of renal failure in cirrhosis.\(^ {26}\) The hemodynamic dysfunction is worsened by sepsis, which further activates neurohumoral compensatory mechanisms that result in arterial renal vasoconstriction, hypoperfusion, and renal failure. On the other hand, the excessive inflammatory response contributes to the activation of cell apoptosis mechanisms and mitochondrial injury, acute tubular necrosis due to capillary leukocyte infiltration, and microthrombosis related to cytokine-mediated microvascular dysfunction.\(^ {27}\) The term acute kidney injury (AKI) is now used to define renal failure in cirrhosis, including prerenal, HRS, intrinsic (acute tubular necrosis), and postrenal injury. Differentiating HRS-AKI (previously known as type 1 HRS) from acute tubular necrosis may be challenging, and therefore, serum diagnostic biomarkers are currently under evaluation. Among them, urinary neutrophil gelatinase-associated lipocalin, a marker of tubular injury, has shown promising results.\(^ {28}\)

Prompt recognition and treatment of AKI is key to improving survival. Reduction or discontinuation of diuretics, withdrawal of all potentially nephrotoxic drugs, and plasma volume expansion if hypovolemia is suspected are the initial measures in patients presenting with AKI.\(^ {29}\) In case of progression of the AKI stage, complete withdrawal of diuretics and volume expansion with albumin (1 g/kg body weight for 2 days) are recommended to treat prerenal AKI and to perform the differential diagnosis. If HRS-AKI is diagnosed, first-line treatment consists of terlipressin (1 mg every 4–6 hours) and albumin (20–40 g/day).\(^ {30}\) Recently, terlipressin infusion has shown an earlier response and improved survival rate when compared with norepinephrine in patients with ACLF and HRS-AKI.\(^ {31}\) However, norepinephrine is an acceptable option when terlipressin is not available. Vasopressors offset the splanchnic arterial vasodilation and the activation of compensatory mechanisms that result in renal vasoconstriction. The additional benefits of albumin administration are beyond the hemodynamic effects and are related to its anti-inflammatory properties.\(^ {17}\)
Liver transplant is the definitive treatment for patients with HRS-AKI, which resolves in most cases after surgery (76% of patients at a mean of 13 ± 2 days after transplant). Treatment with vasoconstrictors and albumin is recommended because improved renal function prior to transplant increases survival. Renal replacement therapies should be considered in non-responding patients presenting with AKI and volume overload, metabolic acidosis, hyperkalemia, or hypotension, especially if they are potential candidates for liver transplantation.

OTHER ORGAN FAILURES AND RELATED COMPLICATIONS
Sepsis not only favors cardiovascular and renal failure, but it also increases the risk of acute variceal bleeding, hepatic encephalopathy, and coagulation disorders. Adrenal insufficiency is frequent in patients with cirrhosis who have sepsis and is associated with hemodynamic instability, renal dysfunction, reduced response to norepinephrine, and poor outcomes. However, it has been also described in acute decompensations due to causes other than sepsis and in nondecompensated patients. The administration of corticosteroids has shown a significant reduction in vasopressor requirements and a higher rate of shock reversal, so in cases of refractory hypotension, hydrocortisone 200-300 mg/day in divided doses has been suggested. The SCOTCH trial is currently testing the safety and efficacy of hydrocortisone in cirrhotic hypotensive patients with suspicion of sepsis (clinicaltrials.gov, NCT02602210).

Antibiotic Treatment
TRENDS IN EPIDEMIOLOGY: MDR PATHOGENS
The increasing prevalence of MDR bacterial infections is attributed to antibiotic overuse and failure to control the spread of resistant bacteria. The problem is aggravated by the scarce therapeutic options available. The global epidemiology of MDR bacterial infections in cirrhosis has been recently addressed. Estimated overall prevalence was 34%, yet values ranged widely from 73% in India to 16% in US centers. The most frequent isolated pathogens were gram-negative bacteria (57%), mainly Enterobacteriaceae, such as E. coli and K. pneumoniae. Gram-positive microorganisms accounted for 38% (S. aureus and Enterococci), and fungal infections were found in 4% of patients. The most commonly isolated MDR bacteria were ESBL, methicillin-resistant S. aureus, VRE, Pseudomonas aeruginosa, and Acinetobacter baumannii. It should be noted that the prevalence and type of MDR bacteria is highly variable among centers, and so, the local epidemiology must be considered before prophylaxis and treatment strategies are implemented.

Fungal isolation in patients with cirrhosis is an infrequent event, but it entails a very poor prognosis: mortality rates associated with invasive fungal infection and colonization are 71% and 67%, respectively, at 90 days of ACLF diagnosis. The incidence of fungal infections increases in second infections and during the follow-up period after ACLF diagnosis, which reflects the progressive impairment and exhaustion of the immune system.

EMPIRICAL ANTIBIOTIC TREATMENT
Timely initiation of an adequate empirical antibiotic treatment is key to improving survival in patients with sepsis. The growing incidence of MDR pathogens has progressively compromised treatment success with the standard strategies and thus, empirical broad-spectrum antibiotics, particularly in health care–related infections, are associated with higher survival rates than standard therapies. To counteract the risk of possible antibiotic resistances, once the pathogen is identified, treatment should be tailored according to microbial sensitivity. In patients who fail to respond to a broad–spectrum antibiotic course, a fungal infection should be suspected and investigated. The empirical antibiotic treatment recommended according to the European Association for the Study of the Liver (EASL) guidelines is shown in Table 1.

Known risk factors for MDR infections are the use of systemic antibiotics, invasive procedures or exposure to the health care environment in the previous months, presence of certain genetic polymorphisms of proteins involved in antigen recognition, overuse of proton pump inhibitors, malnutrition, and alcohol abuse (Fig. 1). For antibiotic selection, besides the type of infection and context (community or hospital acquired), other factors to consider are local resistance rates, previous prophylactic antibiotic treatments, and prior colonization or episodes of MDR bacterial infections.
TABLE 1. Recommended Empirical Antibiotic Treatment According to EASL Guidelines

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Community-Acquired Infection</th>
<th>Hospital-Acquired Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP or spontaneous bacterial empyema</td>
<td>Third-generation cephalosporin piperacillin-tazobactam, or carbapenems*</td>
<td>Carbapenem alone or combined with daptomycin, vancomycin, or linezolid**</td>
</tr>
<tr>
<td>UTI</td>
<td>Uncomplicated: ciprofloxacin or cotrimoxazole</td>
<td>Uncomplicated: nitrofurantoin or fosfomycin</td>
</tr>
<tr>
<td></td>
<td>If sepsis: third-generation cephalosporin or piperacillin-tazobactam</td>
<td>If sepsis: meropenem plus teicoplanin or vancomycin</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Piperacillin-tazobactam or ceftriaxone plus m carbapenems*</td>
<td>Ceftazidime or meropenem plus levofloxacin with or without glycopeptides or linezolid**</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Piperacillin-tazobactam or third-generation cephalosporin plus oxacillin</td>
<td>Third-generation cephalosporin or meropenem plus oxacillin or glycopeptides or daptomycin or linezolid</td>
</tr>
</tbody>
</table>

NOTE: See Angeli et al. (13) (2018).
*In countries with high rates of bacterial resistance.
**If high prevalence of MDR gram positive bacteria or sepsis.

**CURRENT STRATEGIES FOR INFECTION PROPHYLAXIS**

**Screening**

In liver transplant candidates, a previous episode of SBP or ESBLE infection and/or recent exposure to β-lactam agents have been found to increase the risk of preoperative ESBLE colonization. On the other hand, pretransplant methicillin-resistant, vancomycin-resistant, or carbapenemase-producing bacteria colonization is a strong risk factor for MDR infections during the postoperative period. Rectal and nasal surveillance cultures have detected methicillin-resistant and vancomycin-resistant bacteria in 7% and 15%, respectively, of liver transplant candidates. Rectal swabs may serve as noninvasive screening tools to identify patients colonized by MDR pathogens who are, therefore, at a higher risk of presenting MDR infections in the postoperative period.

Recipient colonization by MDR bacteria is not a contraindication for transplantation; however, contact isolation precautions, hand hygiene compliance, and antibiotic control policies are recommended. Intestinal
decontamination significantly reduces rectal colonization by gram-negative bacteria; however, the long-term benefit is uncertain, and in addition, concerns over the potential risk of selecting highly resistant strains have been raised.\(^{(52)}\) Currently, a randomized multicenter clinical trial aims to analyze the impact of intestinal MDR bacterial colonization in liver and kidney transplant recipients, and the effect of decontamination strategies with colistin and neomycin on reducing posttransplant infections (ENTHERE Study, EudraCT: 2013-004838-15).

**Antibiotic Prophylaxis**

Translocation of bacteria increases the risk of infections, and thus, the use of prophylactic antibiotics may be effective at decreasing bacterial concentrations in the gut. However, due to the potential risk of selecting highly resistant pathogens, prophylaxis should be strictly restricted to patients with a high risk of infection, such as those patients with gastrointestinal bleeding, advanced cirrhosis, or a previous episode of SBP.

**Acute Gastrointestinal Bleeding**

The risk of bacterial infections is greater in patients with cirrhosis presenting with acute gastrointestinal bleeding than in those hospitalized for other reasons (44%-66% versus 32%-34%).\(^{(53)}\) Antibiotic prophylaxis decreases the risk of infection, rebleeding, and all-cause mortality.\(^{(53)}\) Ceftriaxone (1 g/24 hours) is recommended in patients with at least 2 of the following conditions: ascites, hepatic encephalopathy, jaundice, or severe malnutrition.\(^{(54)}\) Ceftriaxone is also recommended in patients with active bleeding, on quinolone prophylaxis on admission, with previous quinolone-resistant infections, or in areas of high prevalence of quinolone-resistant bacteria (≥20%). Oral quinolones (norfloxacin 400 mg/12 hours) are appropriate for all remaining cases. Guidelines suggest 7 days of antibiotic therapy; however, a shorter course may be acceptable in Child A patients or as guided by bacterial cultures collected just before starting prophylaxis.\(^{(55)}\)

**Spontaneous Bacterial Peritonitis**

Patients with advanced cirrhosis—defined as Child score ≥9 and serum bilirubin ≥3 mg/dL, low ascitic fluid protein concentrations (<15 g/L), and either impaired renal function or hyponatremia—have an increased risk of developing a first episode of SBP (1-year probability of 61%). In these patients, current guidelines recommend longterm primary prophylaxis with norfloxacin (400 mg/day), which has shown to reduce the incidence of SBP, to delay the development of HRS-AKI, and to increase 3-month survival rates.\(^{(56)}\) Patients recovering from a first episode of SBP should be considered for liver transplantation because survival drops to 30%-50% in the first year and to 25%-30% in the second year. In these cases, secondary prophylaxis with norfloxacin 400 mg/day is recommended to reduce the risk of recurrence.\(^{(57)}\) Despite promising results, rifaximin cannot be yet considered an alternative to norfloxacin for secondary prophylaxis.\(^{(13)}\)

**General Prophylaxis**

In a randomized placebo-controlled trial by Moreau et al.,\(^{(58)}\) norfloxacin (400 mg/day) failed to reduce 6-month overall mortality in patients with advanced cirrhosis (Child C). However, a survival benefit was found in those with an ascitic fluid protein concentration of <1.5 g/dL. In addition, norfloxacin significantly decreased the incidence of bacterial infections without increasing the risk of *Clostridium difficile* or MDR infections (NORFLOCIR trial, NCT01037959).

**Nonantibiotic Prophylaxis**

Long-term administration of albumin (40 g twice weekly for 2 weeks, and then 40 g weekly for up to 18 months) has been recently shown to increase overall survival in patients with cirrhosis and uncomplicated ascites.\(^{(59)}\) However, other authors recently showed that treatment with albumin and midodrine in patients awaiting liver transplantation failed to prevent complications (including infections, renal failure, hyponatremia, hepatic encephalopathy, or gastrointestinal bleeding) or improve survival.\(^{(60)}\) Thus, feasibility, timing, and exact doses of albumin for preventing infections and improving survival in cirrhosis need to be further addressed.

**Specific Considerations for Liver Transplant Candidates With Sepsis**

Septic shock within 1 month before liver transplantation is associated with a 2.4-fold increase in transplant futility.\(^{(61)}\) Furthermore, several studies have shown that peritransplant infections and sepsis significantly increase 90-day mortality.\(^{(61,62)}\) However, other authors did not find differences in mortality if pretransplant infections...
TABLE 2. Considerations for Management and Relisting Patients for Liver Transplantation After Common Bacterial and Fungal Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bacteriuria or candiduria</td>
<td>Not a contraindication</td>
</tr>
<tr>
<td>UTI with negative blood cultures</td>
<td>Not a contraindication; peritransplant antibiotic treatment</td>
</tr>
<tr>
<td>Bacterial SBP</td>
<td>Reactivate if repeated paracentesis shows a &gt;25% decrease in PMN count ≥48 hours after treatment initiation</td>
</tr>
<tr>
<td>Fungal SBP</td>
<td>Requires a full course of therapy and a PMN count &lt;250 cells/mm³ off treatment; always rule out secondary causes</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Reactivate patients after ≥7 days of therapy when clinical improvement is documented</td>
</tr>
<tr>
<td>ICU patients: clinical improvement is required to achieve oxygen levels above local standards</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion requires a thoracentesis. Parapneumonic effusion requires no additional intervention</td>
<td></td>
</tr>
<tr>
<td>Empyema requires drainage; complete course of antibiotics and VATS is sometimes required</td>
<td></td>
</tr>
<tr>
<td>Central line spontaneous bacteremia</td>
<td>Antibiotics for 7-14 days</td>
</tr>
<tr>
<td>Reactivation can be considered before completion of antibiotics if patient has documented rapid clinical improvement with negative repeat blood cultures for ≥48 hours</td>
<td></td>
</tr>
<tr>
<td>Fungemia</td>
<td>Completion of a course of treatment with repeat negative blood cultures off therapy is required in addition to exclusion of a secondary source</td>
</tr>
<tr>
<td>C. difficile diarrhea</td>
<td>Therapy for at least 7 days is required in addition to clinical improvement and normalization of WBCs prior to reactivation. A sigmoidoscopy can be performed to assess mucosal healing. Consider fidaxomicin or fecal microbiota transplantation to decrease relapse rate and VRE colonization</td>
</tr>
<tr>
<td>Cholecystitis Nonoperative candidates</td>
<td>Surgical intervention</td>
</tr>
<tr>
<td>IV antibiotics are first-line therapy</td>
<td></td>
</tr>
<tr>
<td>C-tube placement should be considered in those without a clinical response</td>
<td></td>
</tr>
<tr>
<td>Endoscopic gallbladder stenting or aspiration should only be considered when C-tube placement is contraindicated and IV antibiotics are failing</td>
<td></td>
</tr>
<tr>
<td>Transplant reactivation should occur after an adequate clinical response</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Adapted from Nadim et al. (2016). (16)

were adequately treated. Therefore, careful individual assessment and a multidisciplinary approach are recommended to decide when a patient should be provisionally or definitively removed from the waiting list or reactivated for liver transplantation. So far, only uncontrolled sepsis is considered a formal contraindication and successfully treated prior sepsis or septic shock should not preclude the intervention.

Table 2 shows current recommendations for the management of patients on the waiting list presenting bacterial or fungal infections. UTIs do not generally contraindicate transplantation. However, pneumonia, bacteremia, and C. difficile diarrhea require at least 7 days of antibiotic treatment and signs of clinical improvement before relisting the candidate for transplantation. In the case of bacterial SBP, it is suggested to reactivate the patient on the waiting list 48 hours after treatment initiation if there is also a decrease in polymorphonuclear leukocyte (PMN) count >25% in the ascitic fluid.

Conclusions

Patients with advanced liver disease are at significant risk of bacterial infections, which has a profound clinical impact and worsens prognosis. The growing incidence of MDR bacterial infections has become a major concern. Organ failure in sepsis is related not only to the hemodynamic derangement but also to an excessive inflammatory response against pathogens. A key component of the management of patients with cirrhosis who have sepsis while awaiting liver transplantation should be to prioritize early empiric antibiotic therapy and hemodynamic resuscitation.

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