transplantology

MDPI

Review

Bacterial Infections in End-Stage Liver Disease: Implications for Liver Transplantation

Alberto Ferrarese [1,*], Marco Senzolo [2], Anna Maria Cattelan [3], Lolita Sasset [3], Sara Battistella [1], Alberto Zanetto [2], Giacomo Germani [1], Francesco Paolo Russo [2], Martina Gambato [1], Filippo Pelizzaro [2], Stefania Vio [4], Domenico Bassi [5], Umberto Cillo [5] and Patrizia Burra [1,2]

[1] Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, 35128 Padua, Italy; sarabattistella93@gmail.com (S.B.); burra@unipd.it (P.B.)
[2] Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, 35128 Padua, Italy; filippo.pelizzaro@unipd.it (F.P.)
[3] Infectious Disease Unit, Padua University Hospital, 38128 Padua, Italy; annamaria.cattelan@aopd.veneto.it (A.M.C.)
[4] Radiology Unit, Padua University Hospital, 35128 Padua, Italy; stefania.vio@aopd.veneto.it
[5] Hepatobiliary Surgery and Liver Transplant Center, Padua University Hospital, 35128 Padua, Italy; cillo@unipd.it (U.C.)
* Correspondence: alberto.ferrarese@unipd.it

Abstract: Bacterial infections are a common complication in patients with decompensated liver cirrhosis. The complex landscape of cirrhosis, characterized by immune paralysis and an exhausted response to exogenous triggers, explains the higher prevalence of such infections, particularly in advanced disease stages. In clinical practice, the onset of a bacterial infection can lead to further deterioration of hepatic and extra-hepatic function, potentially resulting in acute decompensation or acute-on-chronic liver failure. This has significant clinical implications, particularly for patients awaiting a transplant. In this review, we will discuss the latest evidence on the diagnosis and therapy of bacterial infections in patients with decompensated cirrhosis. Additionally, we will analyze the impact of bacterial infections in the context of liver transplantation, discussing debated topics such as the timing of transplantation in patients with infections, potential implications for prioritization, effects on post-operative recovery, grafts, and patient survival.

Keywords: enterobacterales; sepsis; acute on chronic liver failure

Citation: Ferrarese, A.; Senzolo, M.; Cattelan, A.M.; Sasset, L.; Battistella, S.; Zanetto, A.; Germani, G.; Russo, F.P.; Gambato, M.; Pelizzaro, F.; et al. Bacterial Infections in End-Stage Liver Disease: Implications for Liver Transplantation. *Transplantology* **2024**, *5*, 129–139. https://doi.org/10.3390/transplantology5030013

Academic Editors: Alton B. Farris and Shimul A. Shah

Received: 13 March 2024
Revised: 3 June 2024
Accepted: 24 June 2024
Published: 28 June 2024

1. Introduction

The liver plays a crucial role in the inflammatory response against bacteria and is centrally involved in regulating immune defense, bacterial clearance, acute-phase protein synthesis, cytokine production, and metabolic adaptation to inflammation. The liver is exposed to food and microbial antigens from the intestine; therefore, it acts as a barrier against environmental antigens. As the primary metabolic organ, it also generates neo-antigens, and activates specialized mechanisms of immune tolerance to prevent excessive activation of both innate and adaptive immune responses [1].

The development of advanced chronic liver disease disrupts this balance, especially at advanced disease stages. Damage and peptide-associated molecular patterns trigger immune cell activation, leading to enhanced endothelial and microvascular dysfunction [2–4]. A persistent overstimulation of the innate immune system leads to a shift of immune cells toward a tolerogenic and non-responsive phenotype. This results in a form of immune paralysis, where the immune system becomes incapable of reacting effectively against exogenous injuries [5].

Understanding these aspects is crucial not only for confirming the increased susceptibility of cirrhotic patients to infections, but also for recognizing their diminished capacity to trigger counter-regulatory response to sepsis [6].

These insights help explain the detrimental prognostic role of infections in decompensated cirrhosis and end-stage liver disease (ESLD) [7]. Most of these clinically significant infections are caused by bacteria, while fungi, molds, parasites, or viruses may have a role in specific settings (e.g., sickest patients with repeated bacterial infections, huge immune dysfunction, prolonged anti-microbial therapy, and steroid treatment).

Although many aspects have been clarified in the last decades at the epidemiological, pathophysiological, and diagnostic levels, bacterial infection still represents a challenge in daily clinical practice, with many topics (prevention, early recognition, appropriate therapy, and prognosis) deserving further investigation.

These aspects are particularly important in liver transplant candidates, since bacterial infection can significantly change the natural course of the disease and therefore the likelihood of transplantation.

This brief review aims to underscore the role of bacterial infection in this setting, with a special focus on patients awaiting liver transplantation.

2. Epidemiology and Risk Factors of Bacterial Infection in Decompensated Cirrhosis

A thorough description of the epidemiology of bacterial infections in cirrhotic patients goes beyond the scope of this paper, but several novel aspects are noteworthy.

Over the past 10 years, robust data have been retrieved from international, multicenter cohort studies, shedding light on this topic and providing granular features. It has been demonstrated that bacterial infections represent the trigger factor for acute decompensation in a third of cirrhotic patients requiring hospitalization [8,9]. Additionally, they represent, along with alcohol abuse, the commonest cause of acute-on-chronic liver failure (ACLF) [10,11].

These studies further demonstrated that approximately 50% of such infections are culture-negative, particularly in cases of spontaneous bacterial peritonitis and pneumonia. The urinary tract, bloodstream, ascites, and lungs remain the most common sources of infection, therefore the initial work-up must necessarily include diagnostic procedures such as paracentesis, urinalysis, blood cultures, and Chest X-ray/CT scan.

The state of immune paralysis also makes patients susceptible to uncommon infections, often occurring at unusual sites. Soft tissue infection and erysipelas represent quite uncommon sources of bacterial infection, being diagnosed, especially in patients with anasarca, ascites, and chronic lower limb edema; the rapid recognition of these infections, through differential diagnosis with other conditions such as deep vein thrombosis, appears important to prevent fasciitis or osteomyelitis [12]. Some series have shown that liver cirrhosis is present in 5–17% of patients with bacterial endocarditis, with no significant improvements in incidence and mortality over the past decades [13,14]. As expected, mortality in patients with endocarditis and liver cirrhosis is significantly higher compared to patients with endocarditis but without cirrhosis. Therefore, although endocarditis represents a rare site of infection in cirrhotic patients, it requires rapid assessment for a correct diagnosis. Spondylodiscitis represents a rare source of infection in cirrhosis, but should be considered, especially in patients with multiple comorbidities, low back pain, and positive blood cultures, without evidence of additional infectious sources (e.g., endocarditis). A case series involving 36 patients with cirrhosis and spondylodiscitis highlighted challenges in diagnosis, a high rate of local complications (such as epidural abscess), and significant in-hospital mortality (up to 15%). Finally, a recent case series described 44 cases of bacterial meningitis identified in a cohort of patients with liver cirrhosis over a broad period of time, emphasizing the difficulties in diagnosing this condition compared to the general population and the high mortality rate. Therefore, selected patients presenting with neurological manifestations inconsistent with hepatic encephalopathy deserve careful evaluation to identify such infection [15].

Regarding bacterial strains, multi-center studies showed an increasing prevalence of gram-positive strains, especially in hospital settings or high-intensity care environments [16,17]. Invasive procedures, mechanical ventilation, and placement of indwelling catheters may

explain this increased prevalence, which has been especially observed in the intensive care settings. Interesting data from France on a large cohort of patients admitted to intensive care units further highlighted that gram-positive rods were more commonly seen among cirrhotic patients than in the non-cirrhotic patients (56 vs. 47%). Notably, there was a higher prevalence of multi-drug-resistant staphylococcus aureus among cirrhotic patients, which warrant further investigation [17].

From a clinical standpoint, these studies confirm the modification of the previous paradigm in which bacterial infections in cirrhotic patients were predominantly caused by gram-negative rods, and suggest therapeutic implications.

Another emerging aspect, from an epidemiological perspective, concerns the increase in bacterial infections caused by multi-drug-resistant strains. This issue, which represents a major public health concern, is shared with many other chronic diseases and entails environmental risk factors that also require investigation. In the setting of ESLD, data from international studies and multi-center cohorts have demonstrated not only the increasing rate of infection from multi-drug-resistant organisms over time, but also the different prevalence among different regions of the world, and among different centers within the same country. Furthermore, comparative studies have highlighted how significant epidemiological changes regarding the dominant strains can occur over time within the same center. Finally, these studies confirmed the prognostically negative role of such infections in the context of ESLD, and especially in ACLF.

Taken together, this data necessitates addressing the surge of these infections with antibiotic stewardship measures for prevention, as well as continually monitoring their epidemiological trends in every hepatology center and especially in every transplant center. It is crucial for every liver transplant center to know the actual prevalence, and also to be aware of any epidemiological changes that may occur over time [18–20].

Well-recognized evidence from literature have described the main **risk factors** for bacterial infection in patients with ESLD, such as the severity of liver disease, bacterial translocation, prior bacterial infections without proper source control, frequent hospitalizations, use of vascular catheters, and/or invasive procedures. Among these, it seems appropriate to mention two additional factors, often overlooked in clinical practice. First, the role of rectal colonization by multi-drug-resistant bacteria has been demonstrated as an independent predictor of the development of invasive infection by the same strains at later disease stages. A recent European study confirmed its role in two separate cohorts of patients admitted to ICU, both in the presence of dominant gram-negative and gram-positive strains [21]. Another study from India validated these findings, in a regular ward setting [22].

Secondly, antibiotic prophylaxis has been questioned as a potential risk factor for further infections, particularly those caused by multi-drug-resistant organisms. Long-term prophylaxis with systemic antibiotics in cirrhotic patients is restricted to those having bleeding from esophageal varices, and those with prior episodes of spontaneous bacterial peritonitis. In the former group, antibiotics still have a role, especially in child-pugh classes B-C. Recent data have also confirmed the effectiveness of secondary prophylaxis also in the latter cohort, since it reduces the risk of further episodes of peritonitis, without increasing the odds of multi-drug-resistant infections [23].

3. Diagnostic Challenges

The diagnosis of bacterial infection in patients with cirrhosis can be challenging in many cases. The intrinsic characteristics of decompensated cirrhotic patients (such as low mean arterial pressure, chronic beta-blocker use, hepatic encephalopathy, and immune dysfunction) can sometimes reduce the ability to early identify the infection itself based on the clinical parameters that are usually associated with bacterial infection. Moreover, these clinical aspects can also limit the possibility of assessing the severity of the infection itself, through the reduced ability to fulfill conventional criteria of sepsis and/or septic shock. The two most accurate and reliable scores that should be used in this setting are qSOFA

and Sepsis-3: current guidelines suggest a combination of the two for the assessment of the severity of bacterial infection [24].

The suboptimal accuracy of serum biomarkers represents an additional challenge. The presence of persistent systemic inflammation leads to elevated inflammatory markers even in the absence of infection, resulting in suboptimal diagnostic accuracy [25]. For this reason, the use of a single biomarker, such as C-reactive protein, especially in the later stages of the disease, may be an ineffective strategy due to its poor accuracy. Additionally, multi-organ dysfunction, often seen in ACLF, may limit the diagnostic accuracy of additional biomarkers, such as procalcitonin. New biomarkers, such as presepsin or neutrophil Fcγ receptor I, have been analyzed over time, but have shown suboptimal diagnostic efficacy [26,27]. A metanalysis on six studies showed that interleukin-6 seems to have a good sensitivity and specificity for the diagnosis of bacterial infection in cirrhosis, but in clinical practice, it may suffer from several perturbating events, therefore it has not been routinely used [28].

Furthermore, the diagnosis of bacterial infection in cirrhotic patients is not always associated with microbiological confirmation, as approximately 50% of cases involve culture-negative infections (such as spontaneous bacterial peritonitis and pneumonia). This aspect presents multiple implications, including the difficulty of correlating the severity of the infection, and therefore the prognosis, with a specific bacterium or class of bacteria, and not having real-time microbiological confirmation of suspected infection. In cases where there is microbiological positivity, reducing the time interval in sample processing poses an additional challenge for the future, as it influences the potential initiation of empirical antibiotic therapy or its modification into targeted therapy. Novel diagnostic tools are now being deployed to reduce the time delay associated with culture-based pathogen identification and antibiotic sensitivity testing [19].

4. Innovations in Therapy

From a **therapeutic** standpoint, the latest recommendations have reaffirmed the need for prompt diagnosis to initiate appropriate antibiotic therapy as quickly as possible. Recent algorithms also confirm the feasibility of initiating broad-spectrum empirical therapy capable of treating both gram-positive and gram-negative bacteria, taking into account the epidemiology of the center, especially in patients with sepsis and/or severe sepsis. A recent expert opinion recommends empirical therapy with meropenem and vancomycin in cases of severe bacterial infection [7]. An additional study suggests, among broad-spectrum antibiotics, the empirical combination of a beta-lactam (such as piperacillin/tazobactam) or a carbapenem with an antibiotic covering gram-positive bacteria (as vancomycin, daptomycin, and linezolid), also depending on the likely source of infection [19].

Continuous or extended infusion of antibiotics should be implemented too, especially for beta lactams, since it has been associated with improvement in infection resolution [29].

In cases where the suspicion of multi-drug-resistant infection is high, based on the patient's clinical history, and the severity of the current infection, new available drugs should be considered both as empirical therapy and as targeted therapy once the antibiogram has confirmed the presence of such an infection. Ceftazidime-avibactam (a combination of two molecules that can inactivate KPC carbapenemases and most OXA-48), meropenem-vaborbactam (active against KPC carbapenemeas but not against OXA-48- or metallo-β-lactamase-producing strains), ceftolozane–tazobactam (recommended for cases of P. aeruginosa infection), and cefiderocol (a novel siderophore cephalosporin) are novel molecules that should be kept in mind, especially against gram-negative rods. Several single-center and multi-center studies on the use of such anti-microbial agents, demonstrating the efficacy and safety of these molecules, included patients with liver disease in the study cohort, however, there are still limited studies specifically related to patients with decompensated liver cirrhosis. An Italian study documented that ceftazidime-avibactam was associated with a lower rate of treatment failure in cirrhotic patients with carbapenem-resistant Klebsiella pneumoniae infection [30]. New studies are eagerly awaited to confirm

the efficacy and safety of the new anti-microbial molecules, even in different settings, such as targeted pre-transplant prophylaxis in patients colonized by multi-drug-resistant bacteria and acute kidney injury.

A summary of the current landscape of bacterial infection in ESLD, including recent progress and unmet needs, is depicted in Table 1.

Table 1. Current concepts, novelties, and unmet needs about bacterial infection in patients with end-stage liver disease. Abbreviations. ESLD: end-stage liver disease.

	Recognized Patterns of Bacterial Infection in Cirrhosis	**Novelties**	**Unmet Needs/Areas Requiring Further Investigation**
Epidemiology	- Higher prevalence of infection in ESLD patients than in the general population - Correlation between bacterial infection and the degree of liver dysfunction - Ascites, lungs, bloodstream, and urine are the most common infection sites	- Increasing prevalence of gram-positive strains and multi-drug-resistant rods. - Rare sites of infection should be taken into account (such as erysipelas, endocarditis, meningitis, and spondylodiscitis), especially in the sickest patients	- Strategies able to predict epidemiological shifts (especially regarding predominant multi-drug resistant strains)
Pathophysiology	- Cirrhosis-associated immune dysfunction (combining persistent systemic inflammation and immune deficiency) explains the susceptibility of ESLD patients to bacterial infection	- Progress in knowledge of systemic inflammation as the key driver of disease course in ESLD patients	- Strategies able to modulate immune dysfunction at various levels are urgently awaited
Risk factors	- Indwelling catheters - Invasive procedure - Multiple hospitalizations - Absence of source control - Previous infections	- Colonization (rectal, pharyngeal swab) by multi-drug-resistant bacteria and inappropriate antibiotic prophylaxis as potential factors for subsequent invasive (multi-drug-resistant) infection	- Identification of patients deemed at the highest risk for bacterial infection, according to liver function and risk factors, that may require prophylaxis
Diagnosis	- A combination of clinical, biochemical, microbiological, and radiological features is still often needed for the diagnosis of bacterial infection in cirrhosis, given the low accuracy of serum biomarkers	- Availability of microbiological tests able to shorten turnaround times - Sepsis 3 criteria and qSOFA are the most reliable scores for the assessment of the severity of infection	- Development and validation of more accurate biomarkers
Therapy	- Severity of infection and local epidemiology to be considered at the time of empirical antibiotic therapy - De-escalating strategies and anti-microbial stewardship	- Availability of new molecules against multi-drug-resistant strains (especially Gram +ve)	- Antibiotic and non-antibiotic strategies for gut de-colonization - Development of new molecules against gram-positive strains

5. Prognostic Implications: Looking at Liver Transplantation

The prognosis of bacterial infection in ESLD patients varies and depends on several factors, including the severity of the infection, the severity of liver disease, the promptness of diagnosis, and the timely initiation of appropriate therapy. Cirrhosis itself is associated with mortality in patients with sepsis. The development of sepsis, in turn, significantly increases short- and long-term mortality in cirrhosis, thus linking these two conditions in a prognostically negative manner. Despite advancements in outcomes for patients with cirrhosis and septic shock in recent decades, mortality rates, especially in the ICU and in-hospital settings, remain high [31,32].

The role of bacterial infections in ESLD has significant prognostic implications in the liver transplant setting (Figure 1).

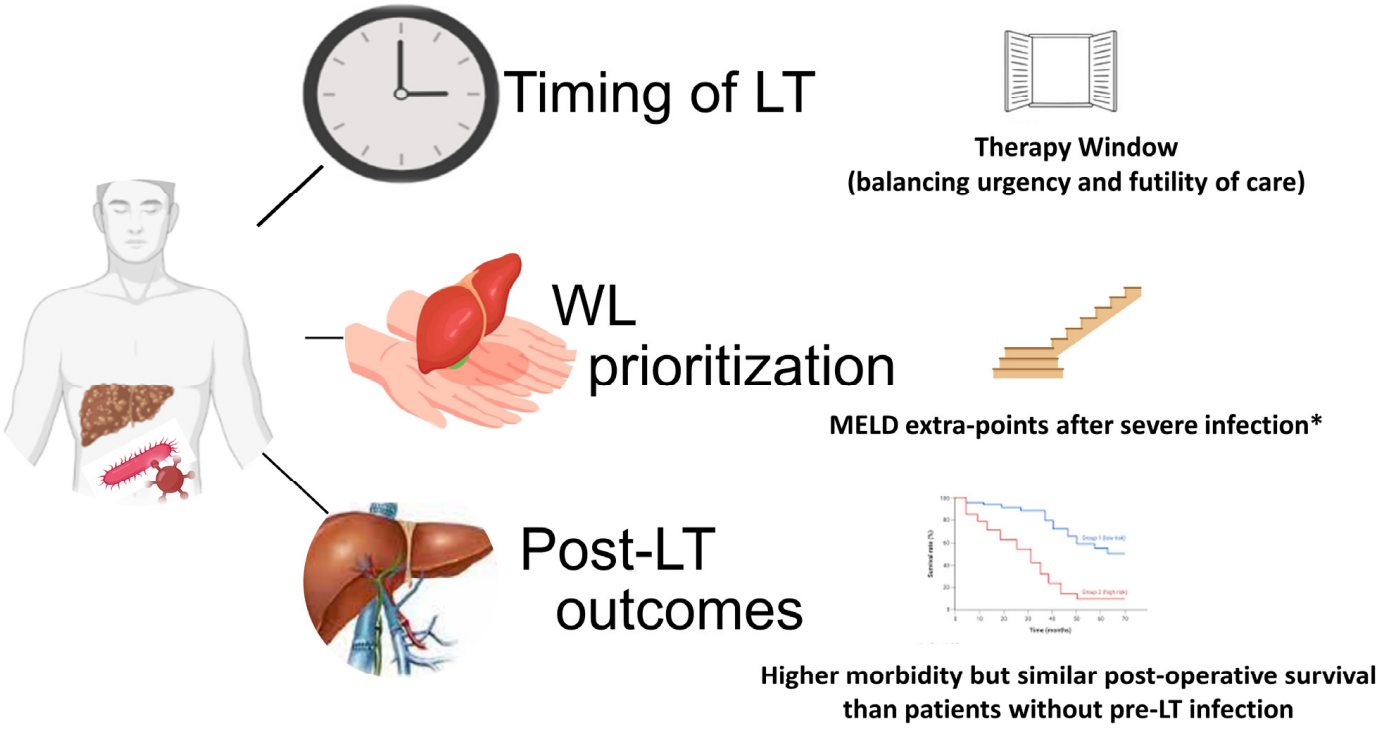

Figure 1. Severe bacterial infection in cirrhosis: implications for liver transplantation. Abbreviations: LT: liver transplantation; PSC: primary sclerosing cholangitis; WL: waiting list. * The possibility of granting MELD extra points in order to increase prioritization for liver transplantation after a severe infection is still debated.

The first issue concerns the possibility of proceeding with a transplant in cases of recent or ongoing infection. In fact, infections may increase intraoperative complications, persist post-operatively, and worsen due to immunosuppressive therapy, with a negative impact on patient and graft survival. Several studies have attempted to address these concerns, however data should be interpreted with caution, since many of these considered only patients who were transplanted, without an intention-to-treat design. Infection control and the patient's stabilization could be optimal endpoints to pursue prior to transplant. For instance, we demonstrated that those patients who survived infection while on the waiting list had a similar probability of death and of undergoing liver transplantation to that of matched controls without any episode of infection [33]. In another study on patients with ACLF, mainly caused by bacterial infection, clinical improvement of the patients in the pre-transplant period (defined by recovery of at least one previously failed organ system) resulted in significantly better post-operative survival [34].

The most challenging decision concerns the sickest patients, such as those who simultaneously present severe bacterial infection (e.g., septic shock) and severe ACLF. In such

patients, the therapeutic window that includes transplantation is often narrow, without enough time to achieve a significant clinical improvement. Here, the challenge lies in identifying the correct window that balances infection control with the benefit of transplantation, without falling into the futility of the procedure [35,36].

Data from a multi-center French study, which examined patients transplanted for ACLF grade 3 (i.e., development of three or more organ failures), showed that half of the patients admitted to the ICU with ACLF-3 had septic shock, while 30% developed septic shock during their stay in intensive care. Infection control from a clinical perspective for at least 24 h was found to be a prerequisite for liver transplant procedures [37]. In another study from France on 200 patients being admitted to the ICU for ACLF, the presence of uncontrolled infection was the main reason for transplant ineligibility in 12% of cases, whereas sepsis was the most common cause of death before transplant. Sepsis was not an independent predictor of ineligibility for transplantation, however. Therefore, the authors concluded that sepsis by itself should not be considered as an absolute contraindication to transplantation in such a cohort of patients [38].

The dynamic course of the disease and the coexistence of other conditions, such as severe leukopenia (<500 white blood cells per μL) multi-drug/pandrug resistant bacteria or fungi, may also be other factors that can suggest a delay in transplantation [39].

The second issue is associated with prioritizing patients with bacterial infections. The rationale is the higher risk of patients who recovered from an infection developing a further bacterial infection, especially when source control is not easy to obtain or in sickest, and frailest patients. Notably, according to a study from the US, second infections independently increase mortality in hospitalized patients with cirrhosis [40]. In an organ allocation model based on the sickest-first policy, worsening clinical conditions (including hepatic and extrahepatic function) could theoretically prioritize patients for liver transplantation. However, this is not a rule that applies universally; for instance, in a MELD-based setting, some patients who are underserved by the MELD score (such as ACLF patients) may continue to be under-prioritized even after a bacterial infection [41]. Additionally, there are further issues to be addressed. Among these, the heterogeneity in prioritization rules (e.g., MELD extra-points) among various transplant programs worldwide; the difficulty in defining the severity of the infection in cirrhosis, due to the aforementioned reasons; the identification of infections that may actually alter the clinical course of the patient (sepsis, septic shock?) and thus warrant prioritization on the waiting list. Therefore, improvements to allocation rules are eagerly awaited in order to grant more equity [42]. A specific group of patients with recurrent infections requiring appropriate prioritization involves those with primary sclerosing cholangitis. The recent US Transplant Network recommendations emphasize the possibility of ensuring prioritization based on specific clinical criteria [43]. This aspect had already been acknowledged by other organ allocation guidelines outside the US [44]. Patients with polycystic liver disease who experience recurrent infections are currently being considered eligible for exception points in some transplant programs, too [45].

The third issue is the possible role of pre-transplant infection on post-operative outcome, including recurrence of the same infection. In our cohort, previous bacterial infection while on the waiting list was not a predictor of death after transplantation [33]. Nevertheless, this infection occurred during the waiting list period, and was not only close to surgery. Another study from Italy investigated the prognostic impact of bacterial infection occurring within 28 days before liver transplantation in n = 84 patients; notably, one third of patients developed severe sepsis or septic shock. When compared with patients without pre-transplant infection, the former group experienced a higher rate of post-transplant infection (48% vs. 30%), but only one patient had the same causative pathogen. The overall 90-day mortality rate was not significantly different between the groups [46]. In another study from Italy on more than 100 patients that underwent transplant after an episode of infection (21% within 7 days from infection improvement/resolution), the authors demonstrated that infected patients had a higher prevalence of post-transplant overall infection

and bacterial infection than those who did not experience pre-transplant infections. Again, post-operative survival was not different between cohorts [47]. These data have been confirmed in a smaller single center, both in a small study from Korea [48], and in a further study from the US, where pre-transplant infection seemed to be associated with increased early morbidity but not mortality after transplant [49]. A small cohort from Egypt on living donor liver transplantation showed slightly different data, since pre-transplant candidates with infection experienced higher mortality than those without, although post--operative hospital and ICU stays were similar. Notably, the study also included possible colonization and fungal infections, which could introduce bias into the data [50]. A recent report from Taiwan, including more than 1200 liver transplant candidates, focused specifically on bloodstream infection, occurring within 1 month before transplant in 7.1% of patients. The authors showed that ICU and in-hospital stays were significantly longer (26.7 $\pm$ 21.5 vs. 20.8 $\pm$ 19.5 and 62.8 $\pm$ 36. vs. 53.8 $\pm$ 36.9, respectively) in patients with bloodstream infection before transplant. Notably, in-hospital mortality, but not 90-d mortality, was significantly higher in the former group (7.6% vs. 2.9% and 4.4 vs. 2.1%, respectively). Moreover, causes of death were not reported, and the rate of post-transplant bacteria was low and not different between cohorts [51].

Taken together, these data suggest that pre-liver transplant bacterial infection may have implications for post-transplant morbidity, as evidenced by increased intensive care and in-hospital stays, but not for mortality. The worse pre-transplant condition, which is expected in infected patients, may contribute to a prolonged post-operative course. Interestingly, post-transplant mortality does not appear to be significantly influenced by the pre-transplant infection. This finding underscores the complexity of post-transplant outcomes, which are not solely determined by the severity of the pre-transplant condition but are influenced by various factors related to both the donor and recipient, as well as the post-operative course. It is important to note that most studies do not consider mortality specifically related to post-transplant bacterial infections: this aspect will need further investigation in the future.

Author Contributions: A.F., P.B. and M.S. participated in research design, performance of the research and writing of the manuscript. A.M.C., L.S., G.G., S.B., A.Z., F.P.R., M.G., U.C., D.B., S.V. and F.P. participated in performance of the research and reviewing the final draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ACLF	acute-on-chronic liver failure
ESLD	end-stage liver disease
ICU	intensive care unit
LT	liver transplantation

References

1. Ahmed, O.; Robinson, M.W.; O'Farrelly, C. Inflammatory processes in the liver: Divergent roles in homeostasis and pathology. *Cell. Mol. Immunol.* **2021**, *18*, 1375–1386. [CrossRef] [PubMed]
2. Albillos, A.; Martin-Mateos, R.; Van der Merwe, S.; Wiest, R.; Jalan, R.; Alvarez-Mon, M. Cirrhosis-associated immune dysfunction. *Nat. Rev. Gastroenterol. Hepatol.* **2022**, *19*, 112–134. [CrossRef] [PubMed]
3. Van der Merwe, S.; Chokshi, S.; Bernsmeier, C.; Albillos, A. The multifactorial mechanisms of bacterial infection in decompensated cirrhosis. *J. Hepatol.* **2021**, *75* (Suppl. 1), S82–S100. [CrossRef] [PubMed]

4. Arroyo, V.; Angeli, P.; Moreau, R.; Jalan, R.; Clària, J.; Trebicka, J.; Fernández, J.; Gustot, T.; Caraceni, P.; Bernardi, M. The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. *J. Hepatol.* **2021**, *74*, 670–685. [CrossRef] [PubMed]
5. Engelmann, C.; Clària, J.; Szabo, G.; Bosh, J.; Bernardi, M. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. *J. Hepatol.* **2021**, *75* (Suppl. 1), S49–S66. [CrossRef] [PubMed]
6. Simonetto, D.A.; Piccolo Serafim, L.; Gallo de Moraes, A.; Gajic, O.; Kamath, P.S. Management of Sepsis in Patients with Cirrhosis: Current Evidence and Practical Approach. *Hepatology* **2019**, *70*, 418–428. [CrossRef] [PubMed]
7. Bajaj, J.S.; Kamath, P.S.; Reddy, K.R. The Evolving Challenge of Infections in Cirrhosis. *N. Engl. J. Med.* **2021**, *384*, 2317–2330. [CrossRef] [PubMed]
8. Piano, S.; Singh, V.; Caraceni, P.; Maiwall, R.; Alessandria, C.; Fernandez, J.; Soares, E.C.; Kim, D.J.; Kim, S.E.; Marino, M.; et al. Epidemiology and Effects of Bacterial Infections in Patients with Cirrhosis Worldwide. *Gastroenterology* **2019**, *156*, 1368–1380.e10. [CrossRef] [PubMed]
9. Bajaj, J.S.; O'Leary, J.G.; Tandon, P.; Wong, F.; Garcia-Tsao, G.; Kamath, P.S.; Biggins, S.W.; Lai, J.C.; Vargas, H.E.; Maliakkal, B.; et al. Nosocomial Infections Are Frequent and Negatively Impact Outcomes in Hospitalized Patients with Cirrhosis. *Am. J. Gastroenterol.* **2019**, *114*, 1091–1100. [CrossRef]
10. Moreau, R.; Jalan, R.; Gines, P.; Pavesi, M.; Angeli, P.; Cordoba, J.; Durand, F.; Gustot, T.; Saliba, F.; Domenicali, M.; et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* **2013**, *144*, 1426–1437.e9. [CrossRef]
11. Fernández, J.; Acevedo, J.; Wiest, R.; Gustot, T.; Amoros, A.; Deulofeu, C.; Reverter, E.; Martinez, J.; Saliba, F.; Jalan, R.; et al. Bacterial and fungal infections in acute-on-chronic liver failure: Prevalence, characteristics and impact on prognosis. *Gut* **2018**, *67*, 1870–1880. [CrossRef]
12. Wang, H.S.; Hsiao, C.T.; Fann, W.C.; Chang, C.P. Predictor of gram-negative bacteremia in cirrhotic patients with skin and soft-tissue infections. *Medicine* **2023**, *102*, e34075. [CrossRef]
13. Allaire, M.; Ollivier-Hourmand, I.; Garioud, A.; Heng, R.; Dao, T.; Cadranel, J.F.D. Infectious endocarditis in the case of cirrhosis: Where do we stand? *Eur. J. Gastroenterol. Hepatol.* **2018**, *30*, 1406–1410. [CrossRef]
14. Garg, R.; Aggrawal, M.; Ahuja, K.R.; Signh, A.; Sanaka, M.R.; McCullough, A. Trends and outcomes of infective endocarditis in cirrhosis: A propensity-matched national study. *Eur. J. Gastroenterol. Hepatol.* **2021**, *33* (Suppl. S1), e580–e586. [CrossRef]
15. Pagliano, P.; Boccia, G.; De Caro, F.; Esposito, S. Bacterial meningitis complicating the course of liver cirrhosis. *Infection* **2017**, *45*, 795–800. [CrossRef]
16. Gustot, T.; Felleiter, P.; Pickkers, P.; Sakr, Y.; Rello, J.; Velissaris, D.; Pierrakos, C.; Taccone, F.S.; Sevcik, P.; Moreno, C.; et al. Impact of infection on the prognosis of critically ill cirrhotic patients: Results from a large worldwide study. *Liver Int.* **2014**, *34*, 1496–1503. [CrossRef]
17. Karvellas, C.J.; Gustot, T.; Fernandez, J. Management of the acute on chronic liver failure in the intensive care unit. *Liver Int.* **2023**. [CrossRef]
18. Fernández, J.; Prado, V.; Trebicka, J.; Amoros, A.; Gustot, T.; Wiest, R.; Deulofeu, C.; Garcia, E.; Acevedo, J.; Fuhrmann, V.; et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. *J. Hepatol.* **2019**, *70*, 398–411. [CrossRef]
19. Fernández, J.; Piano, S.; Bartoletti, M.; Wei, E.Q. Management of bacterial and fungal infections in cirrhosis: The MDRO challenge. *J. Hepatol.* **2021**, *75* (Suppl. S1), S101–S117. [CrossRef]
20. Ferrarese, A.; Feltracco, P.; Barbieri, S.; Cillo, U.; Burra, P.; Senzolo, M. Outcome of critically ill cirrhotic patients admitted to the ICU: The role of ACLF. *J. Hepatol.* **2019**, *70*, 801–803. [CrossRef]
21. Prado, V.; Hernández-Tejero, M.; Mücke, M.M.; Marco, F.; Gu, W.; Amoros, A.; Toapanta, D.; Reverter, E.; Peña-Ramirez, C.; Altenpeter, L.; et al. Rectal colonization by resistant bacteria increases the risk of infection by the colonizing strain in critically ill patients with cirrhosis. *J. Hepatol.* **2022**, *76*, 1079–1089. [CrossRef] [PubMed]
22. Verma, N.; Divakar Reddy, P.V.; Vig, S.; Angrup, A.; Biswal, M.; Valsan, A.; Garg, P.; Kaur, P.; Rathi, S.; De, A.; et al. Burden, risk factors, and outcomes of multidrug-resistant bacterial colonisation at multiple sites in patients with cirrhosis. *JHEP Rep.* **2023**, *5*, 100788. [CrossRef] [PubMed]
23. Crocombe, D.; O'Brien, A. Antimicrobial prophylaxis in decompensated cirrhosis: Friend or foe? *Hepatol. Commun.* **2023**, *7*, e022. [CrossRef] [PubMed]
24. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J. Hepatol.* **2018**, *69*, 406–460. [CrossRef] [PubMed]
25. Pieri, G.; Agarwal, B.; Burroughs, A.K. C-reactive protein and bacterial infection in cirrhosis. *Ann. Gastroenterol.* **2014**, *27*, 113–120. [PubMed]
26. Ferrarese, A.; Frigo, A.C.; Mion, M.M.; Plebani, M.; Russo, F.P.; Germani, G.; Gambato, M.; Cillo, U.; Cattelan, A.; Burra, P.; et al. Diagnostic and prognostic role of presepsin in patients with cirrhosis and bacterial infection. *Clin. Chem. Lab. Med.* **2021**, *59*, 775–782. [CrossRef] [PubMed]

27. Dang, Y.; Lou, J.; Yan, Y.; Yu, Y.; Chen, M.; Sun, G.; Li, N. The role of the neutrophil Fcγ receptor I (CD64) index in diagnosing spontaneous bacterial peritonitis in cirrhotic patients. *Int. J. Infect. Dis.* **2016**, *49*, 154–160. [CrossRef]
28. Wu, Y.; Wang, M.; Zhu, Y.; Lin, S. Serum interleukin-6 in the diagnosis of bacterial infection in cirrhotic patients: A meta-analysis. *Medicine* **2016**, *95*, e5127. [CrossRef]
29. Bartoletti, M.; Giannella, M.; Lewis, R.E.; Caraceni, P.; Tedeschi, S.; Paul, M.; Schramm, C.; Bruns, T.; Merli, M.; Cobos-Trigueros, N.; et al. Extended Infusion of β-Lactams for Bloodstream Infection in Patients with Liver Cirrhosis: An Observational Multicenter Study. *Clin. Infect. Dis.* **2019**, *69*, 1731–1739. [CrossRef]
30. Feldman, S.; Russo, A.; Ceccarelli, G.; Borrazzo, C.; Madge, C.; Venditti, M.; Merli, M. Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections in Patients with Liver Cirrhosis. *J. Clin. Exp. Hepatol.* **2022**, *12*, 1293–1300. [CrossRef]
31. Arvaniti, V.; D'Amico, G.; Fede, G.; Manousou, P.; Tsochatzis, E.; Pleguezuelo, M.; Burroughs, A.K. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* **2010**, *139*, 1246–1256.e5. [CrossRef] [PubMed]
32. Dionigi, E.; Garcovich, M.; Borzio, M.; Leandro, G.; Majumdar, A.; Tsami, A.; Arvaniti, V.; Roccarina, D.; Pinzani, M.; Burroughs, A.K.; et al. Bacterial Infections Change Natural History of Cirrhosis Irrespective of Liver Disease Severity. *Am. J. Gastroenterol.* **2017**, *112*, 588–596. [CrossRef] [PubMed]
33. Ferrarese, A.; Vitale, A.; Sgarabotto, D.; Russo, F.P.; Germani, G.; Gambato, M.; Cattelan, A.M.; Angeli, P.; Cillo, U.; Burra, P.; et al. Outcome of a First Episode of Bacterial Infection in Candidates for Liver Transplantation. *Liver Transpl.* **2019**, *25*, 1187–1197. [CrossRef] [PubMed]
34. Huebener, P.; Sterneck, M.R.; Bangert, K.; Drolz, A.; Lohse, A.W.; Kluge, S.; Fischer, L.; Fuhrmann, V. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. *Aliment. Pharmacol. Ther.* **2018**, *47*, 1502–1510. [CrossRef] [PubMed]
35. Artru, F.; Trovato, F.; Morrison, M.; Bernal, W.; McPhail, M. Liver transplantation for acute-on-chronic liver failure. *Lancet Gastroenterol. Hepatol.* **2024**, *9*, 564–576. [CrossRef] [PubMed]
36. Linecker, M.; Krones, T.; Berg, T.; Niemann, C.U.; Steadman, R.H.; Dutkowski, P.; Clavien, P.A.; Busuttil, R.W.; Truog, R.D.; Pertrowsky, H. Potentially inappropriate liver transplantation in the era of the "sickest first" policy—A search for the upper limits. *J. Hepatol.* **2017**, *68*, 798–813. [CrossRef]
37. Artru, F.; Louvet, A.; Ruiz, I.; Levesque, E.; Labreuche, J.; Ursic-Bedoya, J.; Lassailly, G.; Dharancy, S.; Boleslawski, E.; Lebuffe, G. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. *J. Hepatol.* **2017**, *67*, 708–715. [CrossRef] [PubMed]
38. Sacleux, S.C.; Ichaï, P.; Coilly, A.; Boudon, M.; Lemaitre, E.; Sobesky, R.; De Martin, E.; Cailliez, V.; Kounis, I.; Poli, E.; et al. Liver transplant selection criteria and outcomes in critically ill patients with ACLF. *JHEP Rep.* **2023**, *6*, 100929. [CrossRef]
39. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. *J. Hepatol.* **2023**, *79*, 461–491. [CrossRef]
40. Bajaj, J.S.; O'Leary, J.G.; Reddy, K.R.; Wong, F.; Olson, J.C.; Subramaniam, R.M.; Brown, G.; Noble, N.A.; Thacker, L.R.; Kamath, P.S. Second infections independently increase mortality in hospitalized patients with cirrhosis: The North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology* **2012**, *56*, 2328–2335. [CrossRef]
41. Sundaram, V.; Shah, P.; Mahmud, N.; Lindenmeyer, C.C.; Klein, A.S.; Wong, R.J.; Karvellas, C.J.; Asrani, S.K.; Jalan, R. Patients with severe acute-on-chronic liver failure are disadvantaged by model for end-stage liver disease-based organ allocation policy. *Aliment. Pharmacol. Ther.* **2020**, *52*, 1204–1213. [CrossRef] [PubMed]
42. Jalan, R.; Gustot, T.; Fernandez, J.; Bernal, W. 'Equity' and 'Justice' for patients with acute-on chronic liver failure: A call to action. *J. Hepatol.* **2021**, *75*, 1228–1235. [CrossRef] [PubMed]
43. Mehta, S.; Rosenstengle, C.A. Policy Corner: Cholangitis exception update. *Liver Transpl.* **2024**, *30*, 321–322. [CrossRef] [PubMed]
44. Cillo, U.; Burra, P.; Mazzaferro, V.; Belli, L.; Pinna, A.D.; Spada, M.; Nanni Costa, A.; Toniutto, P. A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model". *Am. J. Transplant.* **2015**, *15*, 2552–2561. [CrossRef]
45. Congly, S.E.; Marquez, V.; Bhanji, R.A.; Bhat, M.; Wong, P.; Huard, G.; Zhu, J.H.; Brahmania, M. Exception points for liver transplantation: A Canadian review. *Can. Liver J.* **2023**, *6*, 201–214. [CrossRef] [PubMed]
46. Bertuzzo, V.R.; Giannella, M.; Cucchetti, A.; Pinna, A.D.; Grossi, A.; Ravaioli, M.; Del Gaudio, M.; Cristini, F.; Viale, P.; Cescon, M. Impact of preoperative infection on outcome after liver transplantation. *Br. J. Surg.* **2017**, *104*, e172–e181. [CrossRef] [PubMed]
47. Incicco, S.; Tonon, M.; Zeni, N.; Gambino, C.; Gagliardi, R.; Calvino, V.; Barone, A.; Zilio, G.; Feltracco, P.; Burra, P.; et al. Impact of bacterial infections prior to liver transplantation on post-transplant outcomes in patients with cirrhosis. *JHEP Rep.* **2023**, *5*, 100808. [CrossRef] [PubMed]
48. Kim, I.K.; Park, J.S.; Ju, M.K. Impact of Pre-Transplant Bacterial Infections on Post-Operative Outcomes in Patients after Liver Transplantation. *Surg. Infect.* **2017**, *18*, 170–175. [CrossRef] [PubMed]
49. Heldman, M.R.; Ngo, S.; Dorschner, P.B.; Helfrich, M.; Ison, M.G. Pre- and post-transplant bacterial infections in liver transplant recipients. *Transpl. Infect. Dis.* **2019**, *21*, e13152. [CrossRef]

50. Saleh, A.M.; Hassan, E.A.; Gomaa, A.A.; El Baz, T.M.; El-Abgeegy, M.; Seleem, M.I.; Abo-Amer, Y.E.; Elsergany, H.F.; Mahmoud, E.I.E.; Abd-Elsalam, S. Impact of pre-transplant infection management on the outcome of living-donor liver transplantation in Egypt. *Infect. Drug Resist.* **2019**, *12*, 2277–2282. [CrossRef]
51. Lee, I.K.; Chang, P.H.; Li, W.F.; Yeh, C.H.; Yin, S.H.; Lin, Y.C.; Tzeng, W.J.; Liu, Y.L.; Wang, C.C.; Chen, C.L.; et al. Risk factors for pre-transplantation bacteremia in adults with end-stage liver disease: Effects on outcomes of liver transplantation. *Clin. Transplant.* **2024**, *38*, e15163. [CrossRef] [PubMed]