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Review Article

Bacterial Infections in Acute-on-chronic Liver Failure: Epidemiology, Diagnosis, Pathogenesis, and Management

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Abstract

Acute-on-chronic liver failure (ACLF) is a distinct condition characterized by the abrupt exacerbation of pre-existing chronic liver disease, often leading to multi-organ failures and significant short-term mortalities. Bacterial infection is one of the most frequent triggers for ACLF and a common complication following its onset. The impact of bacterial infections on the clinical course and outcome of ACLF underscores their critical role in the pathogenesis of systemic inflammation and organ failures. In addition, the evolving epidemiology and increasing prevalence of multidrug-resistant bacteria in cirrhosis and ACLF highlight the importance of appropriate empirical antibiotic use, as well as accurate and prompt microbiological diagnosis. This review provided an update on recent advances in the epidemiology, diagnosis, pathogenesis, and management of bacterial infections in ACLF.

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Introduction

Acute-on-chronic liver failure (ACLF) is a critical syndrome occurring in chronic liver diseases, often associated with heightened short-term mortality.[1] Patients with ACLF are particularly vulnerable to bacterial infections (BIs). Recently, the European Foundation for the Study of Chronic Liver Failure (EASL-CLIF) revealed that 33% of patients experiencing acute decompensation or ACLF presented with BIs, with 46% developing the complication during follow-up.[1,2] Bacterial infections rank as the primary trigger for ACLF globally, although there are geographic differences.[2,3] Notably, ACLF triggered by BIs demonstrates higher mortality rates compared to other precipitating events.[4–6] Patients without BIs as a trigger exhibit a 30-day survival rate of 71.6%, contrasting sharply with the 33.8% survival rate among those with bacterial infection-triggered ACLF.[5] Furthermore, beyond serving as a precipitant, BIs are a common complication during the clinical course of ACLF, leading to delayed hospitalization, disease progression, and increased mortality.[7–9] Of significant concern is the rising prevalence of multidrug-resistant (MDR) bacteria among cirrhosis patients globally. Given the critical role of BIs in ACLF, this review aimed to consolidate recent insights into the epidemiology, microbiology, pathogenesis, diagnosis, and treatment.

Epidemiology

Prevalence

The overall prevalence of BIs in ACLF patients is exceptionally high, ranging from 55.7% to 81.2% (as shown in Table 1).[1,6,9–11] Variations are observed across different time frames,[2,5,6,10,12,13] with the incidence of BIs upon admission and during follow-up or hospitalization ranging from 10.8% to 41% and 45.9% to 75.5%, respectively. Notably, the prevalence of BIs tends to increase with the severity of ACLF. In patients with grade 2 and 3 ACLF, the incidence of BIs escalates to 88.2% and 90%, respectively.

It's crucial to emphasize that the prevalence of BIs varies worldwide. This variation may stem from the diverse definitions of ACLF employed by different organizations. Patients with ACLF defined by varying diagnostic criteria exhibit differential disease severity, which may influence their susceptibility to bacterial infections. Furthermore, even with the same EASL-CLIF ACLF criteria, a multicenter international study reported that the incidence of BIs-triggered ACLF was 39% in Europe and 59% in Asia, with a notable 75% in the Indian subcontinent, suggesting that other factors, such as local epidemiological conditions, may also play crucial roles.

The majority of infections are nosocomial,[4,6,11,14] most likely occurring within the initial three to five days post-admission.[10,11] Approximately 21.6% to 34% of patients experience a second infection during hospitalization,[4,6,11] with 26.6% developing second infections during their hospital

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Table 1. Prevalence of bacterial infections among ACLF patients in different countries or regions

Study	Year	Region/ countries	Population	Prevalence of infection		
				Overall	On admission	During follow-up or hospitalization
Moreau[2]	2013	Europe	ACLF		32.6%	57%
Cai[11]	2017	China	HBV-ACLF	81.2%		
Fernandez[6]	2018	Europe	ACLF	66.1%	37.3%	45.9%
Mücke[5]	2018	Germany	ACLF		41%	
Shalimar[10]	2018	India	ACLF	76.7%	10.8%	73.9%
Zhang[13]	2018	China	HBV-ACLF			75.5%
Zhai[9]	2020	China	HBV-ACLF	64%		
Liu[1]	2021	China	HBV-ACLF	55.7%		
Medhat[12]	2021	Egypt	ACLF		73.1%	

HBV, hepatitis B virus; ACLF, acute-on-chronic-liver failure.

stay. Prolonged hospital stay was associated with the increased occurrence of a second infection.[4] Patients developing a second infection have a 90-day mortality rate of 67.9%, contrasting with 46.6% among those who do not experience a second infection.[11]

Regarding the types of BIs, a global study revealed that spontaneous bacterial peritonitis (SBP) was the most common in ACLF patients, followed by urinary tract infections (UTIs), pneumonia, and skin and soft tissue infections (SSTIs).[14] Moreover, types of BIs in ACLF vary across different regions, with specific characteristics observed globally: SBP and pneumonia are more prevalent in Asia, whereas UTIs are more frequent in Europe and America (as shown in Table 2).[1,2,4–6,9–11,13–15] Additionally, the sites of patient admission impact infection types, with UTIs and SSTIs more common in regular wards, while pneumonia is more prevalent in intensive care units than in general wards.[6] There exists a discrepancy regarding the predominant type of bacterial infection-triggering ACLF. Wong et al. and the CANONIC study found that SBP and pneumonia were more frequent triggers.[2,6,14] In contrast, Bajaj et al. demonstrated that infections other than SBP serve as independent predictors for developing infection-related ACLF.[4]

Microbiology

Microbiological characteristics of BIs vary significantly across different regions and time periods. Globally, gram-negative bacteria remain dominant pathogens in North Europe, South America, and Asia (26% to 47%), whereas in North America, gram-positive bacteria are more common (39%).[14] It is also noteworthy that a significant proportion of patients in this study were culture-negative, with rates ranging from 23% to 69%.[14] Enterococcus faecalis/faecium and Staphylococcus aureus were the most commonly isolated gram-positive cocci, whereas Escherichia coli and Klebsiella pneumoniae were the most commonly identified gram-negative bacilli (as shown in Table 2).[6] Notably, Klebsiella pneumoniae was much more frequently isolated from ACLF patients than those with cirrhosis and without ACLF.

With nearly a 10% increase over eight years, the incidence of extensively drug-resistant (XDR) and MDR bacteria among patients with cirrhosis and ACLF poses a serious health risk.[16] Independent predictors of MDR bacterial infection included nosocomial infection, ICU admission, and recent hospitalization.[16] Additionally, a poorer prognosis and a reduced resolution rate were linked to the isolation of MDR bacteria.[5,6,17] Frequently isolated MDR bacteria included extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae , methicillin-resistant S aureus, vancomycin-resistant enterococci, Pseudomonas aeruginosa, and Acinetobacter baumannii. Furthermore, the majority of bacteria in MDR organisms produced ESBLs. Enterobacteriaceae that produce carbapenem, P aeruginosa, and A baumannii were the most prevalent XDR bacteria.[16,18]

Substantial variations exist between different regions, with MDR rates ranging from 19% to 70% and XDR rates from 2% to 28% (as shown in Table 3).[5,6,10,11,13–16] For instance, MDR and XDR bacteria prevalence was extraordinarily high in the Indian subcontinent.[14] Notably, MDR/XDR strains exhibit significant heterogeneity across regions and even within hospitals within the same region, underscoring the importance for local hospitals to be cognizant of prevalent strains to guide antibiotic usage.[18]

Impact of BIs on ACLF outcome

Individuals with ACLF have been identified as having worse short-term outcomes when complicated with BIs (35.5–45.5% in 28-day, 50.7–56.9% in 90-day), and the mortality increased with the escalation of ACLF grades.[1,5–9,11,14,15] In ACLF-1 and ACLF-2, BIs were thought to be independent predictors of survival, either at the time of ACLF diagnosis or during follow-up, and it remained ambiguous if the bacterial infection can significantly impair the survival in patients with ACLF-3.[1,6,9] However, as reported in the CANONIC study and PREDICT study, the precipitating events were not associated with mortality, suggesting bacterial infection as a precipitating event did not increase mortality compared to other precipitating events.[2,17] As for the impact of specific types of bacterial infections on outcome, SBP and bacteremia have been demonstrated to be linked to a greater grade of ACLF and higher death rates,[19] followed by pneumonia, UTI, and SSTIs/musculoskeletal infections.[6,8,19] Bacterial ascites showed significantly lower 28-day transplant-free mortality compared with culture-positive SBP (41.3% vs 65.5%).[20] Patients with ACLF and nosocomial bloodstream infections tended to be complicated by other types of infection.[21] Multiple site infection was also common in ACLF patients (9.4% to 37.8%) and patients with multiple site infections had an increased incidence of sepsis, septic shock, ACLF-3, and 28-day mortality.[1,9–11,13]

Infections caused by MDR bacteria are more likely to contribute to the development of ACLF compared to infections caused by susceptible strains.[22] Although colonization by

Table 2. Site of infections and pathogens in patients with ACLF and bacterial/fungal infections

Study	Year	Region	popu-lation	Site of infections	Pathogens
Moreau*[2]	2013	Europe	ACLF	SBP 10.6%; Pneumonia 6.1%; UTI 6.1%; Skin infections 2.4%; Unproved 6.1%; Other 5.2%	
Bajaj[4]	2014	North America	ACLF	UTI 28.5%; SBP 22.5%; Spontaneous bacteremia 13.2%; SSTI 12.2%; Respiratory 9.9%; Other 9.6%; Clostridium difficile 4.1%	Gram-positive 32.9%; Gram-negative 26.8%; No organism 22.7%; Fungi 17.6%
Cai[11]	2017	China	HBV-ACLF	Respiratory tract infection 49.4%; SBP 37.3%; UTI 13.3%; Infectious diarrhea 11.7%	Gram-positive 59.8%; Staphylococcus; Enterococcus; Streptococcus; Cryptococcus; Gram-negative 55.3%; E. coli; Klebsiella; Acinetobacter baumannii; Pseudomonas aeruginosa; Fungi 15.9%; Candida-related; Trichosporon pullulans
Fernandez*[6]	2018	Europe	ACLF	SBP 9.8%; Pneumonia 7.7%; Urinary infections 6.0%; Unproven infections 3.8%; SSTI 2.9%; Secondary peritonitis 2.6%; Bacteriaemia 2.2%; Other 1.4%	Gram-positive; Staphylococcus aureus; Enterococcus faecalis; Enterococcus faecium; Gram-negative; E. coli; Klebsiella pneumoniae; Enterobacter spp.
Mücke[5]	2018	Germany	ACLF	SBP 32.4%; Pneumonia 25.4%	Gram-positive 52.1%; Enterococcus spp. 24.2%; Staphylococcus aureus 15.2%; Coagulase negative staphylococci 10.9%; Gram-negative 47.9%; E. coli 26.7%; Other Enterobacteriaceae 9.1%; Pseudomonas spp. 4.2%; Klebsiella spp. 3.6%
Shalimar[10]	2018	India	ACLF	Respiratory tract infections 45%; SBP 21.1%; UTI 15.2%; Cellulitis 5.2%; Spontaneous bacteremia 3.9%	Gram-negative 91.6%
Zhang[15]	2018	China	AILD-ACLF	Respiratory tract 42.5%; Peritoneum 22.5%; Bloodstream 7.5%; Biliary tract 7.5%; Urinary tract 5.0%; Intestinal tract 5.0%; SSTI 2.5%; Undetermined 7.5%	Gram-positive; Enterococcus faecalis; Staphylococcus aureus; Gram-negative; E. coli; Klebsiella pneumoniae
Zhai[9]	2020	China	HBV-ACLF	Pneumonia 55.7%; SBP 47.6%; Bacteremia 20.0%; UTI 11.4%; Spontaneous bacterial empyema 7.0%	Gram-positive 25.2%; Enterococcus faecium 9.0%; Staphylococcus aureus 3.3%; Staphylococcus epidermidis 2.9%; Gram-negative 49.5%; E. coli 18.6%; Klebsiella pneumoniae 11.4%; Acinetobacter baumannii 5.7%; Fungi 25.2%; Aspergillus fumigatus 11%; Candida albicans 8.6%
Liu[1]	2021	China	HBV-ACLF	Bacterial peritonitis 36.1%; Pneumonia 23.7%; Unproven 10.3%; Bloodstream infection 3.1%; Biliary tract infection 3.1%; Other infection 1.0%	Gram-positive 31.6%; Gram-negative 68.4%
Wong[14]	2021	South Europe	ACLF	UTI 22%; SBP 19%; Pneumonia 14%; Bacteriaemia 11%; SSTI 11%	
		North Europe	ACLF	SBP 49%; UTI 23%; Pneumonia 17%; Bacteriaemia 2%; SSTI 4%	
		South America	ACLF	SBP 33%; UTI 28%; Pneumonia 12%; SSTI 12%; Bacteriaemia 7%	
		North America	ACLF	UTI 32%; SBP 14%; Pneumonia 14%; Bacteriaemia 11%; SSTI 4%	
		Indian subcontinent	ACLF	SBP 43%; Pneumonia 30%; UTI 11%; Bacteriaemia 2%; SSTI 6%	
		Other Asian areas	ACLF	SBP 35%; Pneumonia 26%; UTI 17%; Bacteriaemia 7%; SSTI 5%	
Zhang[13]	2022	China	HBV-ACLF	SBP 31.54%; UTI 26.53%; Pulmonary infection 12.99%; Cholecystitis 6.49%; Other infections 1.30%	Gram-positive 23.76%; Enterococcus faecium 12.37%; Enterococcus faecalis 8.91%; Gram-negative 62.87%; E. coli 36.14%; Klebsiella pneumoniae 12.87%; Acinetobacter baumannii 4.95%; Fungi 13.37%

In studies marked with *, the prevalence of a certain type of infection was calculated in all included patients whether they were infected or not, and in other studies, the prevalence was calculated solely in patients with infections. SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; *E. coli*, Escherichia coli; HBV, hepatitis B virus; ACLF, acute-on-chronic-liver failure.

Table 3. Prevalence and strain of MDROs

Study	Year	Region	Prevalence of MDR	MDR/XDR
Cai[11]	2017	China	46.8%	ESBL resistant strain; MRSA; VRE
Fernandez[6]	2018	Europe	15.8% at diagnosis of ACLF; 18.8% during follow-up	
Mücke[5]	2018	Germany	23.8%	MRGN 7.5%; VRE 12.5%; MRSA 5%
Shalimar[10]	2018	India	29.2%	
Zhang[15]	2018	China	3/7 in culture-positive samples	ESBL E. coli; MRSA
Fernandez[16]	2019	Europe (in decompensated cirrhosis and ACLF)	29.2% in CANONIC series; 38% in second series	ESBL-producing Enterobacteriaceae; VSE; MRSA
Wong[14]	2021	Global	MDR 39%; XDR 13%	
		South Europe	MDR 28%; XDR 5%	
		North Europe	MDR 29%; XDR 5%	
		South America	MDR 27%; XDR 4%	
		North America	MDR 19%; XDR 2%	
		Indian subcontinent	MDR 70%; XDR 28%	
		Other Asian areas	MDR 31%; XDR 4%	
Zhang[13]	2022	China	MDR 52.97%; XDR 4.95%	

ESBL, extended spectrum beta-lactamase; MRSA, methicillin resistant staphylococcus aureus; VRE, vancomycin-resistant enterococcus; VSE, vancomycin-susceptible enterococcus faecium; MRGN, multidrug-resistant gram-negative bacteria; MDR, multidrug-resistant; XDR, extensively drug-resistant; CANONIC, EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis.

MDR bacteria does not correlate with increased mortality, infections from these bacteria result in a lower resolution rate and a higher incidence of septic shock. Consequently, this leads to increased short-term mortality due to the failure of empirical antimicrobial treatment.[5,6,16,22]

Diagnosis

Diagnostic criteria

Table 4 outlines the diagnostic criteria for different types of BIs in patients with cirrhosis and ACLF. Though there is high-

Table 4. Diagnostic criteria for bacterial infections according to the infection sites

Infections sites	Diagnostic criteria
SBP	Polymorphonuclear cell count in ascitic fluid >250/mm3 with/without a positive fluid culture
UTI	abnormal urinary sediment (>10 leukocytes/high power field) and positive urinary culture or uncountable leukocytes per field if negative cultures
Spontaneous bacteremia	positive blood cultures and no cause of bacteremia
Secondary bacteremia	(1) catheter-related infection (positive blood and catheter cultures); (2) bacteremia occurring within 24 h after an invasive procedure
Pneumonia	radiologic evidence of a new pulmonary infiltrate, or progression of a previous one, consolidation or cavitation, plus at least one of the following criteria (fever ≥38°C, leucocyte count of >12,000/mm^3 or 20 breaths per minute, rales or bronchial breath sounds or worsening of gas exchange) and/or organisms cultured from blood, pleural fluid or a specimen obtained by transtracheal, aspirate, bronchoalveolar lavage, or biopsy
Bronchitis	clinical features of infection, no radiographic infiltrates and positive sputum culture
SSTI	clinical signs of infection associated with swelling, erythema, heat and tenderness in the skin
Cholangitis	cholestasis, right upper quadrant pain and/or jaundice and radiological data of biliary obstruction
Spontaneous bacterial empyema	PMN count in pleural fluid ≥250/mm^3
Secondary peritonitis	PMN count in ascitic fluid ≥250/mm^3 and evidence (abdominal CT/ surgery) of an intra-abdominal source of infection
CDI	Diarrhea with a positive C. difficile assay
Bacterial enterocolitis	Diarrhea or dysentery with a positive stool culture for Salmonella, Shigella, Yersinia, Campylobacter, or pathogenic E. coli
Unproven	Presence of fever and leukocytosis requiring antibiotic therapy without any identifiable source

SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection; SSTI, skin and soft tissue infections; CDI, Clostridium difficile infection.

Table 5. New biomarkers and scores for the diagnosis of bacterial infections or sepsis

Biomarkers/Model	Cut-off value	Sensitivity	Specificity	AUROC
AFLAC	242 ng/mL (SBP)[24]	95.5%	97%	0.98
	51.4 ng/mL (SBP)[25]	95.8%	74.4%	0.898
	[26]	95.4%	89.0%	0.958
Ascitic fluid calprotectin	[26]	94.2%	86.7%	0.91
In situ hybridization	[28]	91%	100%	
droplet digital polymerase chain reaction	[28]	80.5%	95.3%	
leukocyte esterase reagent strips (ascites)	"trace"[27]	100%	91.1%	
PCT	1.01ng/ml (BI)[33]	42.68%	78.85%	0.633
PCT	1.01ng/ml (BI)[31]	42.6%	78.8%	0.637
PCT	0.765ng/ml (sepsis)[29]	55.3%	81.6%	0.690
PCT	0.9ng/ml (BI)[30]	80.3%	86.6%	0.909
CRP	17.5mg/L (BI)[33]	64.02%	66.35%	0.685
CRP	17.5mg/L (BI)[31]	63.91%	67.28%	0.692
CRP	5.3mg/dl (BI)[30]	54.9%	69.6%	0.648
CRP	13.5mg/L (sepsis)[29]	68.5%	57.7%	0.654
Presepsin	404.5pg/ml (sepsis)[29]	96.8%	59.2%	0.790
Presepsin	2,300 pg/ml (BI)[30]	81.7%	92.7%	0.959
Presepsin+CLIF-SOFA score	[29]			0.913
sTREM-1	607.94pg/ml (sepsis)[29]	62.8%	81.6%	0.752
sTREM-1+CLIF-SOFA score	[29]			0.876
Novel score	4 points (BI)[31]	78.05%	55.29%	0.740
Serum PGE2	141pg/ml (BI)[32]	78.4%	81.5%	0.83

BI, bacterial infection; AFLAC, ascitic fluid lactoferrin; SBP, spontaneous bacterial peritonitis; PCT, procalcitonin; CRP, C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cell-1; CLIF-SOFA, Chronic liver failure sequential organ failure assessment; PGE2, prostaglandin E2.

er diagnostic agreement in patients with ACLF than in those without ACLF, challenges persist in assessing the presence of bacterial infections. Firstly, specific types of BIs, such as SBP, exhibit unsatisfactory interobserver agreement. Secondly, distinguishing between colonization and infection remains problematic, particularly in assessing respiratory infections. Thirdly, a significant proportion of patients with suspected BIs cannot be definitively classified as a particular type and are thus labeled as having unproven infections.[23] Consequently, there is a pressing need for new biomarkers and technologies to enhance the diagnosis of bacterial infections in patients with cirrhosis and ACLF.

The emerging technologies and biomarkers

There is a growing interest in exploring new diagnostic biomarkers or technologies (as shown in Table 5).[24–33] For the diagnosis of SBP, manual measurement of polymorphonuclear neutrophils (PMN) count may yield false negatives due to PMN lysis, potentially causing delays in diagnosis and empirical antibiotic use.[24] Ascitic fluid lactoferrin has emerged as a promising alternative for diagnosing SBP, as it remains stable at room temperature, eliminating the need for manual measurement.[24–26] Nonetheless, the absence of a standardized cutoff value poses a limitation, attributed to discrepancies in processing techniques among enzyme-linked immunosorbent assay kit manufacturers. Point-of-care testing for lactoferrin may offer a solution to overcome these drawbacks.[26] Additionally, ascitic fluid calprotectin has shown comparable performance to ascitic fluid lactoferrin in identifying SBP, and leukocyte esterase reagent strips in ascitic fluid present a potential approach.[27]

In situ hybridization utilizing a global bacteria probe has proven to be a rapid and sensitive method for diagnosing SBP, particularly in patients with low ascitic PMN counts, although it does not provide information on bacterial drug susceptibility.[28] Improved droplet digital PCR for evaluating bacterial DNA and diagnosing SBP has also been identified as a useful method, providing microbiological insights.[34]

Although C-reactive protein (CRP) and procalcitonin (PCT) are commonly utilized biomarkers for diagnosing BIs in the general population, their diagnostic utility in patients with cirrhosis is limited.[29,35] CRP synthesis is impaired in advanced liver diseases, and elevated levels may be observed in uninfected patients with cirrhosis or ACLF due to systemic inflammation.[35] Similarly, PCT levels may be relatively elevated in ACLF patients with renal failure, as PCT can be filtrated through the glomerular basal membrane.[30] A novel scoring system combining neutrophil percent, PCT, and CRP has demonstrated greater accuracy in diagnosing BIs in ACLF compared to using these parameters individually.[31]

Presepsin has shown promise in diagnosing BIs and sepsis in decompensated cirrhosis and ACLF patients.[35] For ACLF patients in sepsis, soluble triggering receptor expressed on myeloid cell-1 has also shown strong diagnostic utility.[29,36] Furthermore, it has been demonstrated that combining presepsin or soluble triggering receptor expressed on myeloid cell-1 with the Chronic Liver Failure-Sequential Organ Failure Assessment score can even more accurately diagnose sepsis in ACLF patients.[29] Additionally, prostaglandin E2 (PGE2) may be able to identify HBV-ACLF infection, which is associated with immunosuppression in ACLF.[32] However, standardization of testing methods is crucial to overcome the heterogeneity of cutoff values and facilitate the clinical implementation of these biomarkers.

Pathogenesis

Susceptibility to BIs

It is worth noting that despite the pronounced systemic inflammation observed in ACLF patients, they paradoxically exhibit an increased susceptibility to BIs. This susceptibility may partly stem from the concurrent development of compensatory anti-inflammatory responses alongside systemic inflammation.[37,38] During this stage, the innate immune system becomes overactivated while the adaptive immune system is suppressed or exhausted. Leukocytosis, neutrophilia, a rise in circulating M0-like monocytes, and a decrease in memory lymphocyte numbers, including B cells, CD4+ T cells, CD8+ T cells, and natural killer cells, are some of the main symptoms.[39,40] Although exhibiting heightened activation, the bacterial killing function of innate immune cells is defective to varying degrees. For instance, neutrophils in ACLF patients display impaired antimicrobial superoxide anion production and phagocytosis capacity.[39] Additionally, neutrophils demonstrate an upregulation of genes associated with glycolysis, leading to aerobic glycolysis and lactate production.[39] Immunosuppressive MerTk+ Monocytes and myeloid-derived suppressor cells are expanded in ACLF patients and correlate with secondary infections.[41–44]

BIs-induced immunopathology and organ failures

Hepatocytes typically activate NF-κB-dependent anti-apoptotic pathways to prevent TNF-α-induced apoptosis.[45] Since patients with ACLF have reduced utilization of this mechanism, LPS binding to Toll-like receptor 4 causes direct tissue injury.[46] Pathogen-associated molecular patterns, circulating bacterial products, are recognized by pattern-recognition receptors in ACLF patients with bacterial infection. These pattern-recognition receptors, usually members of the Toll-like receptors and NOD-like receptor families, bind to pro-inflammatory genes, upregulating transcription of specific cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[47] However, an excessive inflammatory response may lead to indirect tissue damage.[48] Effector responses, including T helper 17 cells, recruited neutrophils, cytotoxic lymphocytes, and IFNγ-activated macrophages, are associated with elevated immune-mediated tissue damage and an increased risk of organ failure.[47,49] Furthermore, bacteria and their byproducts can cause indirect tissue damage by triggering systemic inflammatory responses that affect circulatory function, potentially resulting in organ damage due to oxidative stress, reduced organ perfusion, and endothelial dysfunction.[47]

Prophylaxis

Antibiotic prophylaxis

Prophylactic antibiotics not only reduce the incidence of bacterial infection but also decrease the risk of decompensation events, including hepatorenal syndrome, recurrent variceal bleeding, and even death, thus improving patient outcomes.[1] Quinolones, such as norfloxacin, for instance, are recommended as a prophylactic measure against SBP in patients with decompensated cirrhosis due to their ability to maintain a high concentration within the intestinal lumen and effectively eliminate gram-negative bacteria. Studies have shown that norfloxacin is associated with lower endotoxin levels, a lower incidence of hepatic encephalopathy, and better evolution of ACLF grades.[50] However, the incidence of Clostridium difficile infection was greater in individuals using norfloxacin for secondary prevention of SBP, particularly in those with alcoholic Child-Pugh C class liver cirrhosis.[51] Other quinolones such as ciprofloxacin and rufloxacin were effective alternatives to norfloxacin.[52] Trimethoprim-sulfamethoxazole was also an alternative for the prevention of infection in cirrhosis or liver failure, although its efficacy remained ambiguous.[52–54]

Rifaximin has also been found to be useful for the primary and secondary prophylaxis of SBP.[52,53,55–57] Rifaximin suppresses the translocation of certain bacteria and promotes gut barrier repair, thus preventing the translocation of bacteria from the intestinal lumen to the circulatory system.[58] In contrast to norfloxacin, long-term use of rifaximin was associated with a decreased incidence of Clostridium difficile infection.[59] A recent pilot study showed that the addition of rifaximin (1,200 mg/day for 90 days) reduced the incidence of BIs and ACLF in severe alcoholic hepatitis compared to standard treatment alone.[56] Large-scale randomized controlled trials are necessary to confirm rifaximin's effectiveness in preventing bacterial infections in ACLF.

Although these prophylactic antibiotics have been proven effective, their use is associated with a higher prevalence of MDR bacteria. The emergence of quinolone-resistant bacteria and MDR gram-negative bacteria has challenged the role of prophylactic antibiotics, and their efficacy has decreased over time.[1,55,60–63] Furthermore, several studies have reported that the use of prophylactic antibiotics was not associated with better outcomes.[64,65] Nevertheless, a multicenter global study revealed that norfloxacin prophylaxis did not correlate with an increased frequency of MDR bacteria and that continued medication with norfloxacin for an extended period of time was safe.[18,66] Due to the potential risk, prophylactic antibiotics should be initiated with caution. It is recommended to administer prophylactic antibiotics in patients with low ascites fluid levels (lower than 15g/L) or upper gastrointestinal bleeding, as well as in those who have recovered from an episode of SBP.[50,61,67] It has also been reported that antibiotics showed limited effects in patients with Child-Pugh A/B cirrhosis and upper gastrointestinal bleeding simultaneously, and thus the use of antibiotics in these patients may be unnecessary.[68]

Non-antibiotic prophylaxis

In patients with ACLF, diminished levels of albumin and impaired binding function result in impaired plasma PGE2 binding capacity. Infusion of 20% human serum albumin can counteract the immunosuppressive effects of PGE2.[69,70] Besides, Non-selective beta-blockers (NSBBs) have been associated with a reduced risk of BIs, potentially due to their ability to alleviate blood vessel congestion, thereby restoring intestinal blood supply and structural integrity of the barrier.[71] However, this hypothesis cannot explain why the same effect was observed in the non-portal hypertension population. Notably, NSBBs may increase the risk of hepatorenal syndrome,[72] and the suitable type and appropriate dosage of NSBBs require further investigation. While probiotics have demonstrated limited efficacy, fecal microbiota transplant has shown promise in rectifying antibiotic-induced dysbiosis and reducing the prevalence of antibiotic-resistant genes in recipients.[73,74] Additionally, certain nutrients such as 25-hydroxyvitamin D and zinc may confer prophylactic benefits against bacterial infections, although their efficacy necessitates further evaluation.[75,76]

The implementation of infection prevention and control programs, such as minimizing the frequency of invasive procedures and ensuring appropriate environmental hygiene, has been shown to effectively mitigate the incidence of nosocomial infections, reduce the prevalence of MDR, and lower the failure rate of empirical antibiotic treatments.[77] Notably, Martínez et al. observed that despite antibiotic prophylaxis,

bacterial infections developed in 20% of patients with acute variceal bleeding, with the respiratory tract being the most frequently affected site.[62]

Hence, it is advisable to limit orotracheal intubation and the use of nasogastric aspiration to minimize the risk of infection.[62] Additionally, replacing balloon tamponade with an expandable esophageal stent has been recommended, as it proves to be more effective and carries a lower risk of aspiration pneumonia.[62]

Treatment

Prompt initiation of broad-spectrum, empirical antibiotic therapy is imperative upon the diagnosis or suspicion of infection. Tailoring antibiotic therapy should take into account the type and severity of BIs, local epidemiology of microbiology and antibiotic resistance, and the clinical setting (community-acquired, healthcare-associated, or nosocomial). The timely and prudent use of antibiotics has been linked to improved clinical outcomes, a shorter duration of treatment, and decreased mortality rates after 28 and 90 days.[6] Patients with ACLF who are receiving broad-spectrum antibiotics were advised to de-escalate empirical medications early (within 24–72 h) based on drug sensitivity and MDR bacterial colonization data. This approach aimed to minimize the possibility of antibiotic resistance.[22,78,79]

Treatment for SBP

SBP was the most frequent type of BIs encountered in ACLF, necessitating tailored empirical treatment strategies. For community-acquired SBP, initial antibiotic therapy must encompass a spectrum effective against gram-negative bacilli, gram-positive cocci, and anaerobic bacteria.[80] Tigecycline (TGC) constitutes the first-line agent, although its efficacy has waned in light of escalating MDR bacterial strains and should be judiciously reserved for regions where MDR bacteria are not prevalent.[67,78,79] For severe community-acquired SBP or in regions with a high prevalence of MDR bacteria, piperacillin/tazobactam, and carbapenem are recommended.[67,79,80] Carbapenems are the first choice of empirical antibiotic treatment in nosocomial SBP. Notably, a higher meropenem loading dose is required in ACLF patients undergoing continuous veno-venous hemodialysis due to an expanded volume of distribution.[80,81] In areas where MDR bacteria are not as common, piperacillin/tazobactam can be used in nosocomial SBP. In areas where MDR bacteria are more common, especially in septic patients, carbapenem plus daptomycin, vancomycin, or linezolid is advised.[67,82] ESBL-producing Enterobacteriaceae led to the widespread use of carbapenems, which in turn accelerated the establishment of carbapenem-resistant species, necessitating alternative strategies such as TGC or high-dose TGC in conjunction with carbapenem in continuous infusion for XDR bacteria.[67,74] Notably, severe infections caused by carbapenem and quinolone-resistant Pseudomonas aeruginosa require therapeutic approaches involving amikacin/tobramycin or colistin in combination with carbapenems or ceftazidime; BIs caused by vancomycin-sensitive Enterobacteriaceae or methicillin-resistant S aureus necessitate glycopeptide therapy, while linezolid, daptomycin, and TGC are options for vancomycin-resistant enterococci.[67,78] Despite its utility, linezolid administration in ACLF patients carries a risk of thrombocytopenia, necessitating close platelet monitoring.[83] In addition to antibiotics, intravenous administration of albumin is recommended in SBP since it can prevent the occurrence of type-1 hepatorenal syndrome, acute kidney injury, and reduce mortality, especially in patients with baseline bilirubin >68 μmol/L or serum creatinine ≥88 μmol/L.[67,79,84]

Treatment for non-SBP infections

There is still uncertainty about the use of human albumin in individuals with cirrhosis and non-SBP infections. A recent meta-analysis did not demonstrate a survival benefit of intravenous albumin in cases of non-SBP infection.[83,85] Nevertheless, a recent study revealed that despite minimal improvement in survival, the concurrent administration of antibiotics and albumin in cirrhotic patients with non-SBP infections improved renal and circulatory functions, decreased the incidence of nosocomial BIs, and notably, augmented the resolution rate of ACLF. Of course, more randomized controlled studies are required to validate this finding.

Novel treatment for BIs in ACLF

Monocytes from ACLF patients demonstrate a preference for glutamine as a substrate for fueling the tricarboxylic acid cycle.[41] Notably, the enzymatic action of glutamine synthetase (GLUL), facilitating glutamine anabolism, serves to impede this catabolic process, thereby precipitating an energy deficit within monocytes.[41] Methionine sulfoximine, an inhibitor of GLUL, restored the bactericidal capabilities of monocytes derived from ACLF patients, thus representing a novel therapeutic target for infection management.[41] Experimental evidence suggests that interleukin-22Fc exerts hepatoprotective effects in ACLF murine models by promoting liver regeneration directly and indirectly suppressing bacterial infection.[86] Besides, a randomized controlled trial revealed that omega-3 fatty acids could attenuate systemic inflammation, endotoxemia, and sepsis in patients with ACLF.[87] Additionally, an *ex vivo* investigation has highlighted the potential of Qingdu Decoction, a traditional Chinese medicinal preparation, to ameliorate endotoxemia in ACLF rats.[88]

Conclusion

In ACLF patients, BIs pose a significant life-threatening risk, manifesting either as a precipitating factor or a consequential complication, thereby exerting a detrimental influence on prognosis. Current studies partially explain the pathogenesis of infection-triggered ACLF and the susceptibility of BIs of ACLF patients, thereby furnishing novel insights pertinent to infection management strategies. Noteworthy among these are immunomodulatory agents such as IL-22Fc, GLUL inhibitors, and human albumin, which have shown promise in treating BIs in ACLF; however, their efficacy and safety necessitate further validation. Owing to the evolving pattern of isolated strains and the emergence of MDR and XDR bacteria, current empirical antibiotic treatment is greatly challenged, and new antibiotics are urgently required. Additionally, several new biomarkers have been considered effective in the early diagnosis of infection and sepsis, although the cutoff value still needs to be standardized and their efficacy requires further validation. Further understanding of the pathophysiological mechanisms of infection in ACLF patients is needed to develop therapeutic or preventive therapies.

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Conflict of interest

YS has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2022. The other authors have no conflict of interests related to this publication

Author contributions

ZX wrote the manuscript; XZ, JC and YS reviewed and revised the manuscript; SJ reviewed the manuscript. All authors have read the approved the final version of the manuscript.

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