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GUIDELINES

Expert consensus on the diagnosis and treatment of end-stage liver disease complicated by infections

Tao Chen[1] · Guang Chen[1] · Guiqiang Wang[2] · Sombat Treeprasertsuk[3] · Cosmas Rinaldi Adithya Lesmana[4] · Han-Chieh Lin[5] · Mamun Al-mahtab[6] · Yogesh K. Chawla[7] · Soek-Siam Tan[8] · Jia-Horng Kao[9] · Man-Fung Yuen[10] · Guan-Huei Lee[11] · Diana Alcantara-Payawal[12] · Nobuaki Nakayama[13] · Zaigham Abbas[14] · Wasim Jafri[15] · Dong-Joon Kim[16] · Ashok Choudhury[17] · Rakhi Mahiwall[17] · Jinlin Hou[18] · Saeed Hamid[15] · Jidong Jia[19] · J. S. Bajaj[20] · Fusheng Wang[21] · Shiv K. Sarin[17] · Qin Ning[1]

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Abstract
End-stage liver disease (ESLD) is a life-threatening clinical syndrome and when complicated with infection the mortality is markedly increased. In patients with ESLD, bacterial or fungal infection can induce or aggravate the occurrence or progression of liver decompensation. Consequently, infections are among the most common complications of disease deterioration. There is an overwhelming need for standardized protocols for early diagnosis and appropriate management for patients with ESLD complicated by infections. Asia Pacific region has the largest number of ESLD patients, due to hepatitis B and the growing population of alcohol and NAFLD. Concomitant infections not only add to organ failure and high mortality but also to financial and healthcare burdens. This consensus document assembled up-to-date knowledge and experience from colleagues across the Asia–Pacific region, providing data on the principles as well as evidence-based current working protocols and practices for the diagnosis and treatment of patients with ESLD complicated by infections.

Keywords Cirrhosis · Decompensation · Infection · Sepsis · Antibiotics · Acute decompensation · ACLF · Organ failure · Septic shock · Treatment · Consensus

Introduction

The term "End-stage liver disease (ESLD)" was first introduced in the 1980s, however the definition has not been appropriately documented [1]. To date, no consensus or guidelines focused on the diagnosis and management of patients with ESLD complicated by infections have been established across the Asia–Pacific area. This consensus, raised mainly by experts from the Asian Pacific Association for the Study of the Liver (APASL), provides data on principles as well as working procedures for the diagnosis and treatment of ESLD complicated by infections.

Experts from across the world, especially from the Asia–Pacific region, were requested to identify pertinent and contentious issues in ESLD. After a round of deliberations, 8 major issues were identified. Further, data from the APASL ACLF Research Consortium (AARC) database were taken and analyzed, and circulated to all the participants. The process for the development of the recommendations and guidelines included: review of all available published literature on ESLD by individuals and group of experts; preparation of a review manuscript and consensus statements based on the GRADE SYSTEM (Supplementary Table 1) of evidence-based approach, circulation of consensus statements to all experts, a survey of the current approaches for the diagnosis and management of ACLF; discussion on contentious issues; and deliberations to prepare the consensus statement by the experts of the working party. The finalized statements were circulated to all the experts and subsequently finalized.

Definition of ESLD

The main feature of ESLD is that the liver function cannot meet the physiologic needs of the body. Based on the hepatic morphology and function, ESLD refers to the end stage of chronic liver disease, regardless of etiology, with advanced

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liver injury, dysfunction, and decompensation. Its clinical disease forms include acute-on-chronic liver failure (ACLF), acute decompensation of liver cirrhosis (ADC), chronic liver failure (CLF), and decompensated hepatocellular carcinoma (Fig. 1) [2, 3]. Infections in patients with ESLD are one of the most frequent complications that trigger and cause profound inflammation, extrahepatic organ dysfunction or failure, and eventually a marked increase in mortality [4].

Epidemiology

Infections in patients with ESLD usually occur in the abdominal cavity, respiratory, biliary, urinary system, and gastrointestinal, as well as in skin and soft tissues. Local infections can progress to the bloodstream when appropriate treatment is not given [5]. Spontaneous bacterial peritonitis (SBP) and pneumonia are two major types of infection in patients with ESLD [6].

The pathogens mostly detected in patients with ESLD (Table 1) are *Escherichia coli* (25.9%–27.4%), *Staphylococcus spp.* (22%–23.4%), *Pneumonia Pediococcus* (12.5%–13.7%), *Enterococcus spp.* (16.6%–23.9%), anaerobic bacteria (6.2%–7.8%), and fungi, including *Candida* (15%–17.1%). The pathogens causing abdominal infections include *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, and occasionally, tuberculosis and mycobacterium [7]. Opportunistic pathogens are common in respiratory infections, and these include *Pseudomonas aeruginosa*, *S. aureus*, and fungi, including Candida and Aspergillus [8].

Nosocomial infections are also relatively common in patients with ESLD owing to their immune defects, with an increasing incidence of carbapenem-resistant *K. pneumoniae* and *Acinetobacter baumannii* infections [9].

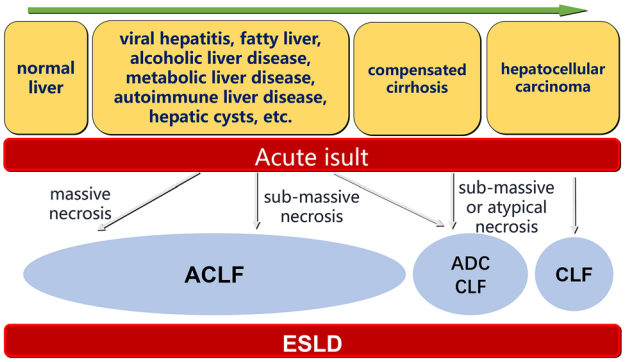

Fig. 1 The ESLD is defined by pathologic and functional features of liver during advanced chronic liver diseases. The main feature of ESLD is that the liver function cannot meet the physiologic needs of the body. Based on the hepatic morphology and function, ESLD refers to the end stage of chronic liver diseases, regardless of etiology, with advanced liver injury, dysfunction, and decompensation. Its clinical disease forms include ACLF, ADC, CLF, and decompensated hepatocellular carcinoma. *ESLD* end-stage liver disease; *ACLF* acute-on-chronic liver failure; *ADC* acute decompensation of liver cirrhosis; *CLF* chronic liver failure

Recommendation 1

A local qualified committee should establish an in-hospital pathogen monitoring system and use the data on the prevalence of pathogens and drug resistance to guide empirical antimicrobial treatment (1, A).

Pathogenesis

The pathophysiological characteristics of ESLD are markedly hampered liver function, liver microcirculation disturbance, local and systemic inflammatory responses, immune paralysis and dysfunctions, and intestinal microecological imbalance, which are systemic risk factors for infection. The immune defects of systemic inflammatory response syndrome (SIRS), compensated anti-inflammatory response syndrome (CARS), and mixed antagonist response syndrome (MARS) play key roles in the development of infection in patients with ESLD. The ESLD-associated cascade

Table 1 Common pathogens in ESLD [5–9]

Site of infection	Common pathogens
Abdomen cavity	*Escherichia coli*, *Klebsiella pneumoniae*, *enterococcus*, anaerobic bacteria, *Candida albicans*
Respiratory tract	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus*
Urinary tract	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecalis*, *Candida albicans*
Gastrointestinal tract	*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecal*, *Candida albicans*
Biliary tract	*Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus*, *Candida albicans*
Skin soft tissues	*Staphylococcus*, *streptococci*, *Enterobacteriaceae*
Blood stream	*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecal*, *Candida*

of inflammatory cytokine storms (Table 2), such as interleukin (IL)-6, IL-10, IL-8, IL-1α, tumor necrosis factor alpha (TNFα), fibrinogen-like protein 2, monocyte chemotactic protein 1, and interferon γ, promotes the occurrence of infection [10, 11].

Procalcitonin (PCT) and C-reactive protein (CRP) are acute-phase serum proteins. The predictive power of the levels of CRP and PCT for detecting bacterial infection has been found to be similar in patients with and without cirrhosis. Elevated serum levels of PCT and CRP are correlated with the presence, course, and outcome of sepsis in patients with cirrhosis and in the general population [8, 12].

Recommendation 2

The presence of SIRS, CARS, and MARS facilitates the prediction of infection in patients with ESLD. Dynamic changes in the levels of PCT, CRP, TNF-α, and IL-2 could reflect the infection stages (2, B).

Clinical manifestations

Abdominal infection

SBP is the most frequent abdominal infection in patients with ESLD, which may be asymptomatic or mildly symptomatic with abdominal distention with or without low-grade fever [13]. Fungal peritonitis is commonly observed in patients with compromised immunity and long-term use of broad-spectrum antibacterial drugs or glucocorticoids [14]. Diagnosis of tuberculous peritonitis (TBP) should be considered when conventional anti-infective treatment is ineffective. TBP may manifest as increased flexibility of the abdominal wall, with a large amount of ascites [15].

Respiratory infection

Fever, cough, and sputum production are the major symptoms of respiratory infections, with or without rapid progression. Pulmonary fungal infections show polytropic symptoms and an occult onset, especially in patients who have been treated with antibiotics. Fever, cough, jelly-like sputum, and bloody sputum are specific to pulmonary aspergillosis infections [16].

Table 2 Dynamic change of cytokines in ESLD with bacterial infection

Immune Situation	IL-2	IL-6	IL-8	IL-1α	TNF-α	MCP-1	IFN-γ	IL-10	IL-4
SIRS	↑↑↑	↑↑↑	↑↑	↑↑	↑↑↑	↑↑	↑↑↑	↑/-	↑/-
MARS	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑
CARS	↑/-	↑/-	↑/-	↑/-	↑/-	↑/-	↑/-	↑↑↑	↑↑↑

IL interleukin; *TNF-α* tumor necrosis factor alpha; *MCP-1* monocyte chemotactic protein 1; *IFN-γ* interferon γ; *SIRS* systemic inflammatory response syndrome; *CARS* compensated anti-inflammatory response syndrome; *MARS* mixed antagonist response syndrome

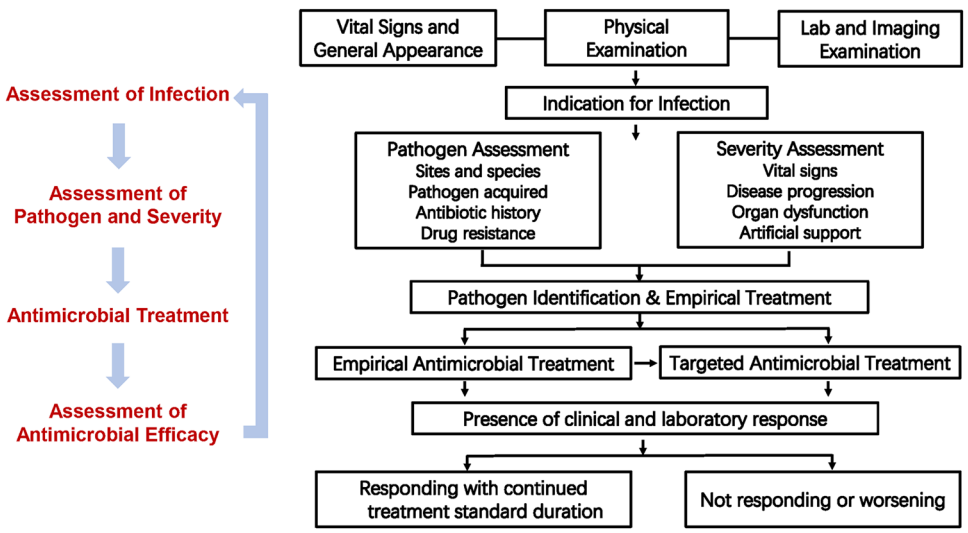

Fig. 2 The recommended diagnostic and therapeutic procedure for bacterial or fungal infection in ESLD

Biliary tract infection

The clinical manifestations of biliary tract infections are often atypical, and bacteriological confirmation is difficult to obtain. Pain in the upper abdomen or right upper abdomen, fever, nausea, vomiting, and bloating are frequent symptoms [17].

Urinary tract infection

Patients with ESLD complicated by upper urinary tract infections often show systemic symptoms, such as fever and chills. Patients with lower urinary tract infections usually complain of urethral irritation, manifested as frequent urination, urgency, dysuria, and discomfort. Changes in urine examination, including turbidity, odor, and gross hematuria, are often observed [18, 19].

Skin and soft tissue infection

Skin and soft tissue infections are common in patients with ESLD. The main manifestations include redness, skin damage, and pressure sores [20].

Bloodstream infection (including catheter-related infection)

Primary and secondary bloodstream infections are classified according to whether the pathogens originate in the bloodstream or secondary to other local sites. Catheter-related bloodstream infection is primary in patients with ESLD. When blood stream infection occurs within 72 h of catheter indwelling, the primary type should be considered. Fever and chills may be the typical clinical manifestations [21, 22]. Secondary bloodstream infections include pneumonia, urinary infections, peritonitis, and cellulitis.

Gastrointestinal infection

Gastrointestinal infections in patients with ESLD have multiple clinical manifestations with a wide variety of pathogens, including diarrhea, abdominal pain, watery stools, or increased stool frequency [23].

Other infections

Intracranial infection rarely occurs in patients with ESLD, with few reports of bacterial meningitis. Fever, headache, vomiting, and loss of consciousness are the main symptoms [24].

Tibiofibular periostitis is uncommon and presents with local pain, swelling, and tenderness [25].

Endocarditis shows non-specific systemic symptoms, such as hypothermia, fatigue, appetite loss, and weight loss. Heart murmurs can also be observed [26].

Endophthalmitis manifests as eye pain, photophobia, tearing, blurred vision, conjunctival hyperemia, markedly reduced visual acuity, and flaky or blocky floating objects in the eye chamber [27].

Recommendation 3

The clinical manifestations of ESLD complicated by infections at various sites are often atypical and require careful consultation and physical examination for accurate and early diagnosis (2, A).

Diagnosis

High-risk factor assessment and clinical manifestation

The risk factors include immune dysfunction, genetic susceptibility, and intestinal bacterial ectopic and iatrogenic elements [28]. The symptoms were presented in the clinical manifestations section above.

Laboratory examination

Infections can be diagnosed based on the peripheral blood leukocyte count and classification and PCT and CRP levels. Interferon gamma release assay is helpful for diagnosing tuberculosis and, the β-1,3/1,6-glucan test and galactomannan test for diagnosing fungal infections. Routine tests for hydrothorax and ascites are recommended to localize infection sources [28, 29]. The levels of cytokines, such as IL-6 and TNFα, are expected to be useful in the diagnosis of ESLD complicated by infection and monitoring disease progression [11].

Imaging examination

X-ray, ultrasonography, computerized tomography, and magnetic resonance imaging can be used for clinical diagnosis.

Pathogen identification

Pathogens should be appropriately cultured in secretions, body fluids (pleural fluid, ascites fluid, and joint fluid), blood, bone marrow, or tissues in the early stages. Although

the rate of positive ascitic culture is relatively low, it is recommended to perform an ascites culture before antibiotic administration. Blood culture bottles, including aerobic and anaerobic cultures, should be used for ascites culture. Neutrophil ascites is a variant of SBP that shows a negative ascites culture. The second-generation sequencing method can screen and identify a variety of bacteria by analyzing DNA extracted from tissues, swabs, and aspirates.

Recommendation 4

4.1 The diagnosis of ESLD co-infection requires comprehensive assessment of risk factors, symptoms and signs, laboratory tests, imaging tests, and etiological tests. (Fig. 2, 1, A).

4.2 PCT (> 0.49 ng/ml) combined with CRP (> 10 μg/ml) has diagnostic value for bacterial infection. (1, B).

4.3 1–3-β-D glucosidase test and galactomannan test are diagnostic for fungal infection. (1, B).

4.4 Timely collection of various tissues, body fluids, blood, and other specimens for pathogen examination are of great value for clarifying the type of pathogen. (1, A).

Management

Nutritional therapy

Risk screening: nutritional screening tools, such as the NRS-2002, are recommended for screening the nutritional risk [30].

Assessment: body composition, imaging, grip strength, subjective global assessment, Royal Free Hospital-Global Assessment and Nutritional Assessment for Liver Disease are recommended [31].

Intervention. Patients who cannot swallow and chew food should start tube feeding within 24–48 h after admission [32]. Supplemental parenteral nutrition should be provided when enteral nutrition is not feasible or the amount of intake is less than 60% of the basal energy expenditure [33]. Light-digestible food is preferred, with four to six meals per day. Late-night extra meals of carbohydrate-rich foods are recommended [34]. The energy supply should be at least 35 kcal/kg/d for nonobese and 25–35 kcal/kg/day for individuals with a BMI 30–40 kg/m^2. The protein or amino acid supply is recommended to range from 1.2 to 1.5 g/kg/d. Avoid protein restriction in patients with hepatic encephalopathy [35]. Vegetable and dairy proteins are preferred in optimal daily protein, as well as branched-chain amino acid (BCAA). In all cases, hypoglycemia and vitamin deficiencies should be carefully treated [34].

Hepatoprotective treatment

Hepatoprotective agents include glycyrrhizin acid derivatives, polyene phosphatidylcholine, glutathione, *N*-acetylcysteine, silymarin, *S*-adenosylmethionine, and ursodeoxycholic acid. In general, the administration of one to two hepatoprotective agents with different working mechanisms is recommended [36, 37].

Thrombocytopenia management

Thrombocytopenia is very common in patients with ESLD complicated by infections. For patients with platelet counts $< 20 \times 10^9$/L or platelet counts $> 20 \times 10^9$/L with bleeding, and for invasive procedures, maintaining a platelet count above 50×10^9/L can reduce the risk of bleeding [38]. In addition, platelets can induce hepatocyte regeneration, potentially improving liver function in patients with liver disease [39]. At present, the clinical treatment mainly includes platelet infusion, avatrombopag, recombinant human thrombopoietin (rhTPO), recombinant human interleukin 11(rhIL-11), etc. Avatrombopag has proven efficacy in patients with liver disease. It significantly improves platelet count and reduces the proportion of patients receiving platelet transfusion or rescue due to bleeding in patients with liver disease undergoing elective invasive procedures [40]. The small sample research of rhTPO, rhIL-11 and leucogen suggested that it had a certain effect on the improvement of platelet count in patients with liver disease, and it was necessary to use thromboelastogram (TEG) to monitor the coagulation status of patients.

Immunomodulatory treatment

Albumin considerably increases the survival of patients with cirrhosis combined with SBP but without any other bacterial infections types [41].

Gamma globulin rapidly increases the level of serum IgG, which could potentially neutralize bacterial endotoxins, increase anti-inflammatory mediators, and enhance the organic ability of antibiotics [42].

Thymosin α1, alone or in combination with ulinastatin, markedly reduces the 28-day mortality in patients with sepsis. It decreases the incidence of infection in patients with ACLF, CLF, and cirrhosis with SBP [43]. Although granulocyte–macrophage colony-stimulating factor (GM-CSF) cannot considerably improve the prognosis of patients with sepsis, it may reduce the incidence of secondary infections [44–46]. Granulocyte colony-stimulating factor (GCSF) may improve the short-term survival of patients with liver failure [47]. A combination of GM-CSF and carbapenem is superior to carbapenem monotherapy in difficult-to-treat spontaneous bacterial peritonitis [48]. The benefits of glucocorticoid treatment in patients with ESLD complicated by infections are inconclusive, and such treatment may potentially lead to the spread of infection; thus, careful monitoring is required when applied [49, 50].

Etiological treatment

For hepatitis B-related ESLD, strong and high resistance barrier nucleoside (nucleotide) analog antiviral therapy, namely entecavir and tenofovir, is recommended; it improves short-term mortality by rapidly reducing the HBV DNA load and relieving immune injury [51, 52]. If direct antiviral therapy is required in patients with HCV-related ESLD, an appropriate direct antiviral agent (DAA) therapeutic regimen should be selected by evaluating the liver and kidney functions and the interaction between drugs [37]. For alcoholic-origin ESLD, patients should abstain from alcohol consumption as soon as possible and may be treated with metadoxine [53, 54].

Recommendation 5

Nutritional support (1, A) and hepatoprotective treatment (2, C) reduce the infection risks and promote recovery in patients with ESLD.

Recommendation 6

Albumin, gamma globulin, and thymosin α1 can be administered via appropriate methods in patients with ESLD complicated by infection (1, B).

Recommendation 7

Glucocorticoid treatment should be evaluated with caution in patients with severe infections (1, A).

Recommendation 8

Entecavir or tenofovir disoproxil fumarate is recommended as an anti-HBV treatment for HBV-related ESLD, renal function should be closely monitored. Tenofovir is not recommended for patients with renal or kidney dysfunction. DAA therapeutic regimens, sofosbuvir-velpatasvir or glecaprevir-pibrentasvir, should be selected based on the liver and kidney functions and the interaction between drugs in patients with HCV-related ESLD (1, A).

Antibiotic treatment

Before evaluating the antibiotic susceptibility of pathogens, empirical antibiotic treatment should be determined according to the infection sites, clinical manifestations, pathogen source (nosocomial or community-acquired infection), antibiotic history, response to previous treatments, local bacterial prevalence, and monitoring drug resistance data. During the process of empirical antibiotic treatment, the surveillance of indicators, such as inflammatory factors, and laboratory test findings facilitates the evaluation of the efficacy and adjustment of therapeutic strategies. As soon as the pathogenic data are obtained, empirical antibiotic treatment should be altered to targeted antibiotic treatment. For patients with inconclusive pathogenic data, further detection of pathogens or adjustment of empirical antibiotic treatment should be adopted according to the efficacy of treatment and disease progression.

Abdominal and biliary infection

SBP. When SBP is diagnosed, active elimination of ascites (release of ascites, diuresis, and supplementation with albumin) and empirical antibiotic therapy should be initiated. Empirical antibiotic treatment should cover potential SBP-related pathogens (*E. coli*, *K. pneumoniae*, and *Enterococcus* spp.), and the pharmacokinetics of selected regimens should preferentially meet abdominal infection (ascites antibiotic concentration of > MIC90 of pathogenic microorganisms) [55]. For community-associated SBP, β-lactam/β-lactamase complex, cephalosporin, and oxacephem can be empirically selected to target extended-spectrum β-lactamase (ESBL)-producing strains, while carbapenems (meropenem and biapenem) can be selected for severe infections [56]. ESBL-producing strains need to be targeted for healthcare-associated SBP (HA-SBP). Owing to the increasing proportion of gram-positive bacteria in patients with HA-SBP, such as Enterococcus faecalis and Enterococcus faecium, linezolid or teicoplanin may be necessary in combination treatment. Tigecycline can be used to treat refractory peritonitis.

Spontaneous fungal peritonitis (SFP). The incidence of SFP is relatively low (0–13%) in patients with ESLD, mainly occurring in those with long-term application of broad-spectrum antibiotics or compromised immunity, such as patients with diabetes or long-term steroid use. The major strains include *Candida albicans* and *Aspergillus* spp. [57, 58]. For ESLD complicated by SFP, echinomycin is preferred, and fluconazole or voriconazole may be used as a treatment alternative; however, the reduction in dosage should be determined according to the patients' model for end-stage liver disease (MELD) grade or estimated glomerular filtration rate [59].

TBP. Normally, anti-tuberculosis treatment is not recommended for patients with ESLD [60, 61]. The anti-tuberculosis treatment recommendation by the American Thoracic Society in 2003 could be referenced if treatment is necessary [62].

Biliary tract infection. Presently, etiological data on biliary tract infections in patients with ESLD are still lacking. Studies on Chinese patients with non-ESLD cholecystolithiasis indicate that gram-negative bacteria accounted for 70–75% of overall infections. The major strains were *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Gram-positive bacterial

infections, mainly *E. faecium* and *E. faecalis* infections, have shown a rapid increase in recent years [63]. For mild biliary tract infections, piperacillin, piperacillin/tazobactam, and cefoperazone/sulbactam are recommended. Alternatively, second- or third-generation cephalosporins, ampicillin, or aminoglycosides could be selected in combination with metronidazole or tinidazole. If the clinical symptoms do not improve after 3–5 days of treatment, the disease is considered to be complicated by gram-positive bacterial infection. This requires a change or combination treatment with antibiotics that are sensitive to gram-positive bacteria, such as vancomycin and teicoplanin. For severe biliary tract infections, carbapenems (meropenem or biapenem), vancomycin, and teicoplanin are recommended. Local removal and drainage of the biliary tract infection site are important, and surgical intervention may be timely considered when necessary.

Recommendation 9

Empirical antibiotic treatment for ESLD complicated by abdominal and biliary tract infection was recommended in Table 3 (1, B).

Respiratory infection

Pulmonary infection is a major respiratory infection in patients with ESLD. Community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) should be well distinguished [64]. The antibiotic regimens for treating CAP include penicillin/enzyme inhibitor complexes, third-generation cephalosporins or their enzyme inhibitor complexes, cephamycin, and quinolones [65].

Mild or moderate HAP [66]. Patients with early onset (admission: after 5 days), short-term mechanical ventilation (after 4 days), no high-risk factors, stable vital signs, and no marked organ dysfunction are classified to have mild or moderate HAP. The potentially involved pathogens include Enterobacteriaceae, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and methicillin-sensitive *S. aureus*. The following antibiotic regimens can be selected: third-generation cephalosporins (not necessarily including anti-*Pseudomonas* activity), β-lactam/β-lactamase inhibitors, and fluoroquinolones.

Severe HAP [66]. Severe pneumonia is diagnosed if a patient meets one of the following major criteria or more than three of the secondary criteria. The major criteria include the following: (1) need for tracheal intubation for mechanical ventilation and (2) septic shock requiring vasoactive drug therapy even after active fluid resuscitation. The secondary criteria include the following: (1) respiratory rate of ≥ 30 beats/min; (2) oxygenation index of ≤ 250 mmHg (1 mmHg = 0.133 kPa); (3) multiple lobe infiltration; (4) loss of consciousness and/or disorientation; (5) blood urea nitrogen level of ≥ 7.14 mmol/L; and (6) systolic blood pressure of < 90 mmHg, requiring active fluid resuscitation. Patients with late onset (admission: within 5 days, mechanical ventilation: within 4 days) and high-risk factors are considered to have severe pneumonia, even if they do not fully meet the prescribed standards. The potential pathogens include *P. aeruginosa*, methicillin-resistant *S. aureus* (MRSA), *Acinetobacter* spp., *Enterobacter* spp., and anaerobic bacteria. Quinolones or aminoglycosides can be selected as antibiotic treatments in combination with one of the following agents: anti-pseudomonas β-lactams, such as ceftazidime, cefoperazone, piperacillin, ticarcillin, or mezlocillin; broad-spectrum β-lactam/β-lactamase inhibitors, such as ticarcillin/clavulanic acid, cefoperazone/sulbactam sodium, and piperacillin/tazobactam; carbapenems, such as imipenem, meropenem, and biapenem; and glycopeptide or linazolamide (for MRSA) when necessary. Effective antifungal agents should be used when there is a high likelihood of fungal infection.

Recommendation 10

Empirical antibiotic treatment for ESLD complicated by pulmonary infection was recommended in Table 4 (1, B).

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

Urinary tract infection

The main pathogen causing a simple urinary tract infection is *E. coli*. Nitrofurantoin, cotrimoxazole, fluoroquinolone, third-generation cephalosporin, and amoxicillin/clavulanic acid have been selected as empirical antibiotic treatments. However, enterococcal infections are markedly increasing in patients with complex urinary tract infections. For mild to moderate infections, fluoroquinolones and third-generation cephalosporins can be selected as empirical treatments. For severe infection or failure of empirical treatment,

Table 3 Empirical antibiotic treatment for ESLD complicated by abdominal and biliary tract infection

Infection type	Recommended treatment
Community-acquired	Piperacillin/Tazobactam, Third-generation cephalosporins, Ciprofloxacin, Levofloxacin
Hospital-acquired	Carbapenems alone, or combined with vancomycin and linezolid(high prevalence of gram-positive multidrug-resistant bacteria, or complicated with sepsis)

Table 4 Empirical antibiotic treatment for ESLD complicated by pulmonary infection

Infection type	Recommended treatment
Community-acquired pneumonia	Piperacillin/tazobactam, third-generation cephalosporins, moxifloxacin, ertapenem
Hospital-acquired pneumonia	Mild or moderate HAP: piperacillin/tazobactam, ertapenem severe HAP: imipenem/cilastatin or meropenem; combined with vancomycin or linezolid when gram-positive infection is considered

Table 5 Empirical antibiotic treatment for ESLD complicated by urinary tract infections

Infection type	Recommended treatment
Community-acquired	Simple lower urinary tract infection: furantoin, compound sulfamethoxazole, ciprofloxacin complex or upper urinary tract infections or complicated with sepsis: piperacillin/tazobactam, third-generation cephalosporins, ertapenem
Hospital-acquired	Simple lower urinary tract infection: amoxicillin/clavulanic acid, piperacillin/tazobactam complex or upper urinary tract infections or complicated with sepsis: carbapenems with or without teicoplanin or vancomycin

fluoroquinolone (if not used for initial treatment), piperacillin/tazobactam, third-generation cephalosporin/enzyme inhibitor, carbapenem (imipenem, meropenem, or biapenem), or combination treatment with glycopeptides is the preferred choice [64, 67]. The incidence of sepsis caused by fungal urinary tract infections has gradually increased, which calls for appropriate antifungal treatment.

Recommendation 11

Empirical antibiotic treatment for ESLD complicated by urinary tract infections was recommended in Table 5 (1, B).

Bloodstream infection

Bloodstream infections are critical, and once a clinically suspected diagnosis is established, empirical antibiotic therapy should be started as soon as possible. Before starting an empirical antibiotic treatment for secondary bloodstream infections, the primary lesion, host immune status, infection source, and clinical epidemiology should be evaluated first [68, 69]. The course of antibiotic treatment should last 7–10 days after fever cessation. Patients with migratory lesions need continued treatment until the disappearance of lesions, and surgical drainage or debridement may be indispensable. Catheter-related pathogen cultures should be actively performed for suspected primary bloodstream infections. Catheter removal and prompt empirical antibiotic treatment are the main strategies used during the course [8, 68, 69].

Recommendation 12

Primary and secondary bloodstream infections should be distinguished in patients with ESLD. Original infection sites should be identified for secondary bloodstream infections, which will guide the strategy of antibiotic treatment. Catheter removal and prompt empirical antibiotic treatment are the main strategies used for primary bloodstream infections (1, A).

Skin or soft tissue infection

The common pathogens of skin and soft tissue infections in patients with ESLD are *S. aureus*, *Streptococcus pyogenes*, *P. aeruginosa*, Enterobacteriaceae, and anaerobic bacteria [70, 71]. For local infections, only topical antibacterial regimens, such as mupirocin ointment or fusidic acid cream, are administered for 7–10 days. Deep soft tissue infections, such as cellulitis, mostly caused by *S. aureus* or *S. pyogenes*, can be treated with intravenous cefazolin. For MRSA, vancomycin, linezolid, and daptomycin treatments are required.

Recommendation 13

Empirical antibiotic treatment for ESLD complicated by skin or soft tissue infections was recommended in Table 6 (1, B).

Gastrointestinal infection

Individualized antibiotic treatment according to risk factors is preferred for patients with ESLD complicated by gastrointestinal infections. Broad-spectrum antibiotic regimens covering gram-negative bacteria could be selected as an empirical treatment. For severe infections, the combined administration of antibiotics covering gram-negative and gram-positive organisms is recommended [72].

Table 6 Empirical antibiotic treatment for ESLD complicated by skin or soft tissue infections

Infection type	Recommended treatment
Non-suppurative (cellulitis/erysipelas)	Mild: external (mupirocin), oral (penicillin V, first to third generation cephalosporins, quinolones) moderate to severe: intravenous injection (penicillin G, quinolones)
Suppurative (furuncle/carbuncle/abscess)	Mild to moderate: surgical treatment, oral drugs (compound sulfamethoxazole, penicillinase resistant penicillin) Severe: non-MRSA (cefazolin, cefuroxime, penicillinase resistant penicillin); MRSA (vancomycin or daptomycin or linezolid)

Recommendation 14

Empirical antibiotic treatment for ESLD complicated by gastrointestinal infections was recommended in Table 7 (1, B).

Principle of antibiotic treatment for ESLD

Drug-induced liver injury is a major concern in the selection of antibiotics for patients with ESLD. Some liver injury is induced by antibiotic regimens in a dosage-related or dosage-independent manner, including hepatocyte necrosis or cholestasis. Another concern is adverse reactions, such as coagulation disturbances and hematopoietic disorder [18].

β-lactams. Most β-lactam agents are safe and are mainly excreted by the liver and kidneys. Most of them can be used at normal dosages in patients with ESLD; however, the dosage needs to be adjusted in patients with renal insufficiency. Among penicillin derivatives, amoxicillin/clavulanic acid, penicillinase-resistant penicillin (including oxacillin and flucloxacillin), mezlocillin, sulfacillin, and carbenicillin may cause transaminase level elevation or cholestasis. Most cephalosporins can be safely used in patients with ESLD at a conventional dosage. For patients with an obvious tendency to bleed, we recommend avoiding the use of drugs containing tetrazolium ring structures to reduce the risk of bleeding, such as cefoperazone, head mycin (cefmetazole or cefminox), and oxycephalosporin (latamoxef or flomoxef). Carbapenems (imipenem, meropenem, and biapenem), which are mostly excreted by the kidneys, can be safely used at normal dosages in patients with ESLD.

Quinolones. Quinolones are excreted by the liver and kidneys and can be safely used in patients with ESLD. However, some individuals have the risk of elevated transaminase levels and cholestasis. In these patients, administration of quinolones, such as fleroxacin, enoxacin, lomefloxacin, gatifloxacin, and moxifloxacin, should be avoided.

Aminoglycosides. Aminoglycosides, which are mainly excreted by the kidneys, can be safely used at a conventional dosage in patients with ESLD but have limited use in patients with renal impairment.

Macrolides. Most macrolides are metabolized by the liver, causing potential hepatotoxicity, especially erythromycin esters. The use of macrolides, beyond azithromycin and clarithromycin, should be avoided in patients with ESLD.

Tetracyclines. Tetracyclines can cause liver steatosis or cholestasis and should generally be avoided. Doxycycline and minocycline can be used appropriately because of their relatively low hepatotoxicity. Tigecycline should be used at a reduced dosage in patients with Child–Pugh score C.

Antituberculosis regimens. Isoniazid, rifamycin, and pyrazinamide have obvious hepatic toxicities; their use should then be avoided in patients with ESLD.

Other antibacterial regimens. Clindamycin, lincomycin, and most nitroimidazoles (metronidazole and ornidazole) are metabolized by the liver and have certain hepatotoxicity, which requires dosage adjustment in patients with ESLD. Sulfonamides are mostly hepatotoxic and should be avoided in patients with ESLD. Although vancomycin is mainly excreted by the kidneys, its concentration in patients with cirrhosis is markedly increased. Thus, the blood concentration should then be monitored during administration. Linezolid can cause liver damage, thrombocytopenia, and lactic acidosis during long-term treatment.

Recommendation 15

B-lactams (penicillins, most cephalosporins, and carbapenems), aminoglycosides, partial quinolones (levofloxacin and ciprofloxacin), and glycopeptide antibiotic regimens have

Table 7 Empirical antibiotic treatment for ESLD complicated by gastrointestinal infections

Infection type	Recommended treatment
Community-acquired	Piperacillin/tazobactam, third generation cephalosporin, levofloxacin
Hospital-acquired	Piperacillin/tazobactam, third generation cephalosporin or meropenem combined with vancomycin or linezolid Oral nystatin or vancomycin can be given as appropriate in cases of antimicrobial associated diarrhea (*Clostridium difficile*)

minor hepatotoxicity and are thus preferred in patients with ESLD (1, A).

Invasive fungal infection

Currently, three main types of antifungal regimens can be administered for ESLD [73].

Polyenes. Amphotericin B and its derivatives should be used with caution in patients with ESLD because of some hepatotoxicity.

Triazoles. Fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole are partly metabolized in the liver. Voriconazole has relatively less hepatotoxicity than other triazoles and can then be used with an adjusted dosage and a monitored liver function.

Echinocandin. Echinomycin is commonly used for the treatment of ESLD, with less hepatotoxicity. There is no need to reduce the dosage for mild liver dysfunction; meanwhile, the dosage should be adjusted for moderate and severe liver dysfunctions. Antifungal drugs and dosage adjustments are recommended on the basis of liver function according to the Child–Pugh classification (Table 8) [59].

Recommendation 16

Echinocandins are the preferred anti-fungals recommended for sensitive fungal infections in patients with ESLD. Triazoles (fluconazole and voriconazole) can be used with dosage adjustment; however, close monitoring of the liver function is necessary. The use of amphotericin B should be avoided (1, A).

Intestinal microecology

Intestinal microecological disorder contributes to infection in patients with ESLD, which is an effective intervening aspect [74]. Intestinal selective decontamination treatment involves the removal of overproduced intestinal gram-negative bacilli and fungi with narrow-spectrum antibiotics [75]. Rifaximin is a non-absorbable broad-spectrum antibacterial agent that reduces bacterial counts in the small intestine, bacterial translocation, and incidence of abdominal infection [76, 77]. *Lactobacillus* exerts a protective effect on the intestinal mucosa by lowering the pH of the intestine, preventing colonization by pathogenic bacteria, regulating intestinal immunity, and improving intestinal function. Prebiotics and live *Lactobacillus* products can markedly reduce the incidence of spontaneous peritonitis in patients with cirrhosis. Fecal microbiota transplantation considerably improves survival and reduces the incidence of abdominal infections in patients with liver failure [78, 79].

Recommendation 17

Probiotics and synbiotics are effective adjuvant treatments for ESLD complicated by infection. Fecal microbiota transplantation and selective intestinal decontamination can effectively reduce the risk of SBP (2, C).

Table 8 Dose adjustment of common antifungal drugs in patients with liver injury

Antifungal drugs	Normal liver function	Child–Pugh classification		
		Child–Pugh A(5–6 points)	Child–Pugh B(7–9 points)	Child–Pugh C(≥ 10 points)
Amphotericin B	The initial dose of 1 to 5 mg is increased by 5 mg daily or alternate days, and can be suspended when it was increased to 0.6 to 0.7 mg/kg	not recommended	not recommended	not recommended
Fluconazole	400 mg once daily	400 mg once daily	400 mg once daily	200–400 mg once daily
Itraconazole	200 mg once every 12 h (first day)	200 mg once every 12 h (first day)	200 mg once every 12 h (first day)	200 mg/d (first day)
	200 mg/d	200 mg/d	200 mg/d	200 mg/d
Voriconazole	6 mg/kg once every 12 h (first day)	6 mg/kg once every 12 h (first day)	6 mg/kg once every 12 h (first day)	not recommended
	4 mg/kg once every 12 h	2 mg/kg once every 12 h	2 mg/kg once every 12 h	-
Posaconazole	200 mg once every 8 h	200 mg once every 8 h	200 mg once every 8 h	200 mg once every 8 h
Caspofungin	70 mg once daily(first day)	70 mg once daily(first day)	70 mg once daily(first day)	not recommended
	50 mg once daily	50 mg once daily	35 mg once daily	-
Micafungin	100 mg/d	100 mg/d	100 mg/d	100 mg/d
Anifengin	100 mg/d	100 mg/d	100 mg/d	100 mg/d

Blood purification

Different modes of blood purification (bilirubin absorption, plasma exchange, and molecular absorption recycling system) could be adopted to remove inflammatory mediators and toxins, improve the internal environment, promote immune reconstitution, stabilize hemodynamics, and facilitate synergistic antibiotic treatment. Beyond comprehensive medical treatment, blood purification treatment could be selected as appropriate [80, 81].

Recommendation 19

Specialized blood purification treatment can effectively remove inflammatory mediators and toxins in patients with ESLD complicated by infection (2, C).

Antibiotic treatment in liver transplantation

Liver transplantation is the most effective treatment for ESLD. However, pre-transplant and post-transplant bacterial or fungal infection are the common risk factor determining the success of liver transplantation. Moreover, bacterial or fungal infection is one of the potentially inappropriate liver transplantation conditions [82].

Pre-transplant antibiotic treatment. Bacterial infection one month before liver transplantation has a higher rate of bacterial or fungal infection after liver transplantation. Preoperative bacterial and fungal Infection has higher 90-day mortality after liver transplantation [83]. For ESLD patients in the waiting list, early diagnosed bacterial or fungal infection plays a crucial role in successful liver transplantation [84]. The empirical or targeted antibiotic treatment could be employed according to recommendations in ***Antibiotic treatment*** above, and persistently given during perioperative and post-transplant periods [85].

Perioperative antibiotic treatment. Prophylactic broad-spectrum antibacterial is necessary for the prevention and treatment of surgical site infection (SSI) in liver transplantation. Gram-negative bacilli, gram-positive cocci, and fungi should be considered as high risk of infective pathogens according to the subjects' situation [86]. Third-generation cephalosporin/enzyme inhibitor, or combined with vancomycin and echinocandins may be applied. The duration of perioperative antibiotic treatment is generally 24–72 h after surgery [87].

Post-transplant antibiotic treatment. Bacterial or fungal infection is one of the most frequent complications of liver transplantation [88]. The empirical or targeted antibiotic treatment could be employed according to recommendations in the ***Antibiotic treatment*** above.

Prognosis

The prognosis of patients with ESLD complicated by infection is determined by the severity of liver disease and infection. Hence prognostic scores based on the severity of liver disease and infection, as well as related predictive models, can be used to determine the prognosis of ESLD complicated by infection. It is recommended to use a combination of the APASL ACLF research consortium score, Tongji prognosis prediction model (TPPM), Chronic Liver Failure Consortium organ failure score, Child–Turcotte–Pugh score, MELD score, and PCT and CRP levels to evaluate the prognosis of infection in patients with ESLD[89–94]. The ABILI model showed superior efficacy in evaluating the 28- or 90-day prognosis of ESDL complicated by bacterial infection [95].

Prevention

Precautions for ESLD complicated by infection include the following [96–98]: (1) active treatment of primary liver diseases: Recovery of primary liver function facilitates the prevention and treatment of infection in patients with ESLD. (2) Emphasis on supportive treatment: Competent nutritional and immunologic conditions prevent infection in patients with ESLD. (3) Early diagnosis of infection: Early antibiotic treatment based on the early diagnosis of infection contributes to the control of infection. Levels of serum total protein, CRP, and IL-6 are independent predictors of bacterial infection in patients with HBV-ACLF, and the nomogram GIC model constructed by these three biomarkers shows good discrimination, calibration, and clinical practicality in early prediction of bacterial infection [99]. (4) Prophylactic application of antibiotics. Autoimmune hepatitis-related ESLD patients with regular immunosuppressive treatment are susceptible to several fungal infections, especially Pneumocystis jirovecii, Aspergillus and Cryptococcosis. A recent clinical study suggests Pneumocystis jirovecii pneumonia prophylaxis with sulfamethoxazole-trimethoprim in autoimmune hepatitis with immunosuppressive treatments [100, 101]. (5) Rational application of antibiotics: Antibiotics should be selected based on empirical determinants and drug susceptibility. The prophylactic and joint application of antibiotics should be strictly controlled based on clinical indications. (6) Regular air ventilation of wards, prevention of pathogen propagation among medical staff, and strict control of invasive operations are important interventions that prevent in-hospital infection.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

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Authors and Affiliations

Tao Chen[1] · Guang Chen[1] · Guiqiang Wang[2] · Sombat Treeprasertsuk[3] · Cosmas Rinaldi Adithya Lesmana[4] · Han-Chieh Lin[5] · Mamun Al-mahtab[6] · Yogesh K. Chawla[7] · Soek-Siam Tan[8] · Jia-Horng Kao[9] · Man-Fung Yuen[10] · Guan-Huei Lee[11] · Diana Alcantara-Payawal[12] · Nobuaki Nakayama[13] · Zaigham Abbas[14] · Wasim Jafri[15] · Dong-Joon Kim[16] · Ashok Choudhury[17] · Rakhi Mahiwall[17] · Jinlin Hou[18] · Saeed Hamid[15] · Jidong Jia[19] · J. S. Bajaj[20] · Fusheng Wang[21] · Shiv K. Sarin[17] · Qin Ning[1]

✉ Qin Ning
qning@vip.sina.com

Tao Chen
chentao_tjh@vip.sina.com

Guang Chen
widechain@163.com

Guiqiang Wang
john131212@sina.com

Sombat Treeprasertsuk
battan5410@gmail.com

Cosmas Rinaldi Adithya Lesmana
medicaldr2001id@yahoo.com

Han-Chieh Lin
hclin@vghtpe.gov.tw

Mamun Al-mahtab
shwapnil@agni.com

Yogesh K. Chawla
ykchawla@gmail.com

Soek-Siam Tan
tansoeksiam@yahoo.com

Jia-Horng Kao
kaojh@ntu.edu.tw

Man-Fung Yuen
mfyuen@hkucc.hku.hk

Guan-Huei Lee
guan_huei@nuhs.edu.sg

Diana Alcantara-Payawal
dianapayawal@yahoo.com

Nobuaki Nakayama
nobunaka@saitama-med.ac.jp

Zaigham Abbas
drzabbas@gmail.com

Wasim Jafri
wasim.jafri@aku.edu

Dong-Joon Kim
djkim@hallym.ac.kr

Ashok Choudhury
doctor.ashokchoudhury@gmail.com

Rakhi Mahiwall
rakhi_2011@yahoo.co.in

Jinlin Hou
jlhousmu@163.com

Saeed Hamid
saeed.hamid@aku.edu

Jidong Jia
jia_jd@ccmu.edu.cn

J. S. Bajaj
jasmohan.bajaj@vcuhealth.org

Fusheng Wang
fswang302@163.com

Shiv K. Sarin
shivsarin@gmail.com

[1] State Key Laboratory for Diagnosis and Treatment of Severe Zoonotic Infectious Diseases, Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095, Jiefang Avenue, Wuhan 430030, P.R. China

[2] Department of Infectious Disease, Center for Liver Disease, Peking University First Hospital, Beijing, China

[3] Department of Medicine, Division of Gastroenterology, Faculty of Medicine, Chulalongkorn University, and Thai Red Cross, Bangkok, Thailand

[4] Internal Medicine, Hepatobiliary Division, Dr. Captor Mangunkusumo National General Hospital, Universitas Indonesia, Jakarta, DKI, Indonesia

[5] Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

[6] Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[7] Department of Gastroenterology and Hepatology, Kalinga Institute of Medical Sciences, Bhubaneswar, India

[8] Department of Hepatology, Hospital Selayang, Selangor Darul Ehsan, Malaysia

[9] Graduate Institute of Clinical Medicine and Hepatitis Research Center, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

[10] Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Pokfulam, Hong Kong

[11] Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore

[12] Fatima University Medical Center Manila, Manila, Philippines

[13] Department of Gastroenterology & Hepatology, Saitama Medical University, Saitama, Japan

[14] Department of Medicine, Ziauddin University Hospital, Karachi, Pakistan

[15] Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

[16] Department of Internal Medicine, Chuncheon Sacred Heart Hospital of Hallym University Medical Center, Chuncheon, Korea

[17] Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

[18] Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Guangdong Provincial Clinical Research Center for Viral Hepatitis, Key Laboratory of Infectious Diseases Research in South China, Ministry of Education, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China

[19] Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

[20] Department of Medicine, Virginia Commonwealth University and Central Virginia Veterans Healthcare System, Richmond, VA, USA

[21] Senior Department of Infectious Diseases, The Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing, China