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Diagnosis, Treatment, and Prevention of Acute-on-Chronic Liver Failure with Bacterial Infections

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Abstract: *Acute-on-chronic liver failure (ACLF) is a syndrome that can lead to severe dysfunction and decompensation of liver synthesis, metabolism, detoxification, and biotransformation. ACLF with bacterial infections can lead to making the disease worse and increasing short-term mortality. However, the clinical manifestations of patients are not typical and the waiting time for bacterial culture is long. Finding reliable early diagnostic indicators, starting effective treatment, and giving timely preventive measures can reduce the mortality of patients and improve the clinical prognosis. This article describes the mechanism of acute-on-chronic liver failure with bacterial infections, summarizes its early diagnostic indicators, and reviews the treatment and prevention methods.*

Keywords: *acute-on-chronic liver failure, bacterial infections, diagnosis, therapy, prevention*

1. Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute jaundice and coagulation dysfunction caused by various triggers on the basis of chronic liver disease and can be combined with complications including hepatic encephalopathy, ascites, electrolyte disturbances, infections, hepatorenal syndrome, hepatopulmonary syndrome, extra-hepatic organ failure [1]. Patients with ACLF are prone to bacterial infections within a short follow-up period. Bacterial infections are associated with more severe systemic inflammation, worse clinical course, and higher mortality, and are essential determinants of prognosis for patients with ACLF. Studies have reported lower 90-day survival and higher short-term mortality in ACLF patients with bacterial infections compared to ACLF patients without bacterial infections [2, 3]. Infections in ACLF patients exacerbate liver damage, leading to deterioration, longer hospital stays increased difficulty in treatment and increased burden on the patient's family. Therefore, it is important to understand the early diagnosis and methods of treatment and prevention for patients with secondary infections in ACLF.

2. Pathogenesis of bacterial infections

2.1 Intestinal bacterial translocation

Intestinal bacterial translocation is defined as the migration of bacteria or bacterial products from the intestinal lumen to the mesenteric lymph nodes. Altered intestinal permeability, changes in the intestinal microbiota, and portal shunts predispose bacteria and bacterial products such as lipopolysaccharides, flagellin, or peptidoglycan to spread outside the intestinal lumen and bacterial translocation occurs. Alteration of intestinal permeability:Downregulation of tight junction proteins and antimicrobial lectins affects intestinal barrier integrity [4], secretory mediators such as immunoglobulin A (IgA) restrict direct contact of intestinal bacteria with the epithelial surface, biliary lipids and antimicrobial peptides are deficient and portal hypertension. These factors increase intestinal permeability and constitute a prerequisite for the translocation of intestinal bacteria [5]. Changes in intestinal microbiota:Decreased intestinal dynamics, dysregulation of the mucosal immune system, reduced secretion of antimicrobial proteins and reduced secretion of gastric and bile acids lead to an overgrowth of intestinal bacteria. Change in intestinal flora from beneficial to potentially pathogenic

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flora resulting in dysbiosis of intestinal ecology. Quantitative changes (intestinal bacterial overgrowth) and qualitative changes (intestinal ecological dysbiosis) cause a change in the intestinal microbiota in a negative direction [6, 7].

2.2 Immune dysfunction

The concept of cirrhosis-associated immune dysfunction (CAID) includes two conditions: 1) immunodeficiency: immunodeficiency caused by impaired local immune surveillance in the liver, reduced synthesis of pattern recognition receptors, and impaired function of immune response cells. 2) Systemic inflammation: sustained but inadequate stimulation of the immune system leading to systemic inflammation [7, 8]. CAID represents a reversible series of dynamic events that occur during the course of cirrhosis, with a tendency for immunodeficiency to predominate as the disease progresses into advanced stages. In summary, the immune response pattern shifts from a predominantly 'pro-inflammatory' to a predominantly 'immunodeficient' phenotype due to sustained pathogen-associated molecular pattern stimulation [8]. This makes patients with the liver disease more susceptible to bacterial attack.

2.3 Genetic predisposition

Genetic variants in pattern recognition receptors, such as Toll-like receptor variants that lead to impaired innate host defense mechanisms, are associated with susceptibility to spontaneous bacterial peritonitis and more severe systemic inflammation in patients with cirrhosis [7]. Studies have also shown that activation of the systemic inflammatory response syndrome and circulating pathogen-associated molecular patterns trigger the expansion of Myeloid-derived suppressor cells (M-MDSCs) in patients with ACLF [9].

Bacterial infections result from the interaction between the intestinal microbiota, intestinal permeability, bacterial translocation and defective immune function, which may be the result of genetic susceptibility.

3. Diagnosis

3.1 Diagnostic biomarkers

The diagnosis of concomitant bacterial infections in patients with ACLF is difficult, the clinical presentation is atypical and there are many associated risk factors. Early clinical signs such as fever, tachycardia, tachypnoea, and hypotension are not specific and some of these may be present in patients with liver failure without infection. Hyperbilirubinemia, higher cytokine levels, hyponatremia, and low serum globulin are risk factors for bacterial infections in patients with ACLF [2,10,11]. Although bacterial culture is the gold standard for the diagnosis of bacterial infection, its low culture rate and time-consuming nature cannot guide the rapid and effective treatment. Therefore, it is very important for patients to find early, fast and reliable indicators of bacterial infection.

C-reactive protein (CRP) is mainly produced by hepatocytes, while procalcitonin (PCT) can be produced by many organs and tissues throughout the body, including the liver. Zhang et al. found that CRP was a reliable marker for the diagnosis of bacterial infection in patients with ACLF, with a sensitivity and specificity of 96.6% and 83.3%, respectively [12]. In a meta-analysis of the diagnostic accuracy of PCT in patients with liver failure, it had a sensitivity of 77% and a specificity of 76% when diagnosing bacterial infections [13]. Although CRP and PCT are well accurate for diagnosing infection, the diagnostic thresholds for PCT, as well as CRP in patients with ACLF co-infection, are different from those in patients with the infection without underlying disease. In patients with advanced liver disease, baseline PCT levels may be elevated even in the absence of bacterial infection, and CRP levels are negatively correlated with the degree of liver failure [14,15]. Lin et al. found that in patients with ACLF, baseline PCT levels were elevated in both the infected and uninfected groups (1.47 ng/mL ± 1.83 ng/mL and 0.75 ng/mL ± 0.60 ng/mL, respectively). However, levels were significantly higher in the infected group than in the uninfected group. Compared to the 0.5 ng/mL threshold for diagnosing bacterial infections in the general population, the best diagnostic results were obtained with a PCT threshold of 1.01 ng/mL, and the highest diagnostic value for bacterial infections complicated by ACLF was obtained with a CRP threshold of 17.50 mg/L [16]. In patients with ACLF, the diagnostic value of the PCT and CRP thresholds will be reduced if the common values employed to differentiate between

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bacterial infections are still used. Further redefinition of PCT and CRP thresholds for patients with different stages of liver disease and the combination of other biomarkers are needed to improve their diagnostic value.

An increasing number of new tests are now being discovered. (1) Interleukin-6 (IL-6) is a highly active immunomodulatory factor that can be significantly elevated within hours of the onset of infection [17]. In patients with cirrhosis, IL-6 has a sensitivity of 97.5% and a specificity of 80.6% for the diagnosis of bacterial infections and is elevated earlier than PCT [18]. Therefore, IL-6 can also be used as a reliable diagnostic indicator of bacterial infection in patients with ACLF. (2) Neutrophil CD46 (nCD46), a crystallizable fragment receptor for immunoglobulin G, is elevated in the presence of bacterial infection and is a reliable biomarker for identifying bacterial infections [19,20]. Xiong Kegong et al. found that nCD46 had a sensitivity of 82.22% and a specificity of 73.3% for the diagnosis of bacterial infections complicated by ACLF, and that nCD46 combined with PCT was more accurate for diagnosis when compared to a single indicator [21]. (3) In addition, interleukin 10 and the tryptophan metabolite quinolinic acid [22], ascites lactoferrin, serum anti-neutrophil cytoplasmic antibodies [23] and D-dimer [24] are useful new diagnostic indicators. However, the diagnostic value, sensitivity and specificity of these novel assays need further study.

3.2 Diagnostic models

A single indicator is flawed in diagnosing infection and combining two or even more, indicators can improve the accuracy of early diagnosis. Some have integrated these predictors to form a scoring system, such as Su Lin et al. who developed a scoring system for the diagnosis of ACLF complicated by bacterial infection that consisted of neutrophil percentage, PCT and CRP, with a significantly higher area under the curve than any other indicator used alone [25]. Zhongwei Zhang et al. also developed a diagnostic model for ACLF with CRP, IL-6 and globulin as parameters for concurrent bacterial infections [11]. These models have shown good reproducibility and reliability in validation. However, bacterial infection is a complex pathophysiological process that cannot be assessed by a single measurement. Therefore, either a single diagnostic indicator or a diagnostic model consisting of several indicators needs to be combined with a detailed history, physical examination, radiological examination, laboratory tests and microbiological examination.

3.3 New bacteria detection methods

The new bacterial detection technique is faster than conventional culture and can find pathogenic bacteria in secretions more efficiently and quickly. For example: (1) chemically modified microbeads can be used to bind and isolate bacteria by magnetic force, gravity or filtration, and immunoassays coupling the microbeads to the appropriate ligands can be used to isolate specific pathogens. It has been found that glycosaminoglycans (such as heparin or acetyl heparan sulfate) are distributed in all human tissues and can specifically bind certain bacteria. Heparinized polyethylene microbeads on the surface were able to capture Staphylococcus aureus from the blood with an efficiency of over 65% [26,27]. (2) The integrated comprehensive droplet digital detection (IC3D) produces a microliter size droplet mixing untreated whole blood with digital PCR reagents in a special device. After digital PCR, droplets containing the target bacteria fluoresce and are then detected and quantified by a high-throughput 3D particle counting system (minimum detection concentrations of up to 10 CFU/mL can be achieved.) The IC3D system can also detect drug-resistant bacteria from blood samples in less than an hour with specific primer designs [28-30]. (3) Taalin R Hoj et al. also proposed a real-time PCR-based assay for the rapid identification of the most common beta-lactamase genes in patient blood specimens (including Klebsiella pneumoniae carbapenemase (KPC),New Delhi metallo-beta-lactamase (NDM), cefotaximase-Munich (CTX-M), cephamycin AmpC beta-lactamases (CMY), Oxacillinase-48 (OXA-48)) [31].

4. Antibiotic therapy

Timely and judicious use of antibiotics is the first line of anti-infective measures. Until bacterial culture results are available, empirical antibiotics should be selected according to the type and site of infection, local epidemiology and bacterial resistance. Common types of bacterial infections in patients with ACLF include SBP, urinary tract infections, pneumonia, spontaneous/secondary bacteremia, skin and soft tissue infections, intestinal infections and Clostridium difficile infections, while other infections include secondary peritonitis, biliary tract infections, appendicitis, endocarditis and pleurisy

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[23,32,33]. In patients with ACLF, common bacteria are Gram-negative, such as Escherichia coli and Klebsiella pneumoniae, and Gram-positive, such as Staphylococcus aureus and Enterococcus, are also seen [23,34]. Current guidelines recommend third-generation cephalosporins, beta-lactams/beta-lactamase inhibitors, or carbapenems as the first choice for empirical treatment. The treatment regimen should also be adjusted according to the severity of the disease and the site of infection, such as the addition of a respiratory quinolone for secondary pulmonary infections, carbapenems plus daptomycin for combination therapy in the presence of sepsis in SBP, and anti-anaerobic agents such as metronidazole for biliary tract infections [35-37]. The prevalence of drug-resistant bacteria has become one of the global public health problems in recent years due to increased invasive operations, repeat hospitalizations, and irrational application of antibiotics. Currently, the main drug-resistant bacteria are methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and ultra-broad-spectrum β-lactamase-producing Enterobacteriaceae, most of whom are resistant to third-generation cephalosporins [23]. The prevalence of multidrug resistance leads to the failure of recommended antibiotic therapy and increases the difficulty of anti-infective treatment. Empirical antibiotic regimens against multi-drug resistant bacteria, therefore, need to be appropriately and promptly adapted to local epidemiological patterns.

5. Prevention

5.1 Antibiotic prophylaxis strategies

ACLF patients have a high rate of bacterial infection. xiao-Qin Liu et al. found that among 140 patients with HBV-ACLF, those treated with prophylactic antibiotics had a lower probability of infection than those who did not receive prophylactic antibiotics, regardless of the HBV-ACLF grading level. In addition, patients who received prophylactic antibiotics showed a higher 90-day transplant-free survival rate than those who did not receive prophylactic antibiotics [3]. Given the potential for multidrug-resistant bacteria to develop with long-term prophylactic antibiotics, the current main strategy is to target prophylactic antibiotics to patients at high risk of infection, including 1) Patients at high risk of SBP: patients with ascites and low ascites protein concentration (< 15 g/L) with high serum bilirubin (> 3 mg/dL) or renal insufficiency (serum creatinine > 1.2 mg/dL) or low platelet count (< 98◊109/L); 2) patients with a history of SBP; and 3) patients with gastrointestinal bleeding[38] .

Fluoroquinolones (norfloxacin and ciprofloxacin), third-generation cephalosporins (ceftriaxone and cefotaxime) and meperidine-sulfamethoxazole are currently recommended for the prevention of infection in patients with liver failure [39]. In areas where norfloxacin is not available, ciprofloxacin or meperidine-sulfamethoxazole is recommended as an alternative [35]. Rifaximin is an antibiotic with low gastrointestinal absorption and broad-spectrum antibacterial activity, which is highly bioavailable in the gastrointestinal tract and has a low risk of inducing drug resistance [40]. Studies have shown that the use of rifaximin is associated with a lower incidence of SBP [41]. In theory, rifaximin could be a reasonable alternative antibiotic to quinolones for the prevention of SBP, but current studies do not strongly support its use for the prevention of bacterial infections and only recommend it for the prevention of recurrent hepatic encephalopathy, and more follow-up studies are expected to give strong evidence for the prevention of bacterial infections with rifaximin [40].

Antibiotic prophylaxis is a double-edged sword, as it can prevent bacterial infections while also triggering multidrug resistance, direct antibiotic-related toxicity, Clostridium difficile infections, and drug interactions. Therefore, prophylactic antibiotic use needs to be assessed on a patient-by-patient basis.

5.2 Other prevention strategies

The widespread and prolonged use of antibiotic prophylaxis will lead to multi-drug-resistant bacterial infections, so new non-antibiotic prophylactic strategies are now recommended. Novel prevention strategies are as follows: (1) Modulation of intestinal flora (intestinal microecological therapy): probiotics and faecal microbiota transplantation. Probiotics can regulate the patient's intestinal flora, improve intestinal permeability and reduce bacterial translocation [42]. Faecal microbiota transplantation involves the injection of healthy donor faeces into the patient's gut with the aim of reversing ecological dysbiosis by rebalancing the normal gut microbiota [43]. (2) Enhancement of host defense: statins. In addition to their lipid-lowering properties, statins have a variety of

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anti-inflammatory, immunomodulatory, antioxidant, anti-apoptotic, and portal hypotensive effects. Statins help to inhibit the recognition of pathogenic microorganisms by immune cells, reduce pro-inflammatory cytokines and endothelial dysfunction, and reduce the pro-thrombotic effects of sepsis on coagulation [43]. (3) Promotion of intestinal motility: non-selective beta-blockers (NSBBs). NSBBs increase intestinal motility and improve bacterial translocation in ACLF and reduce the incidence of SBP [44]. (4) Immunomodulation: albumin, granulocyte colony stimulating factor (G-CSF). Human serum albumin is a multifunctional protein involved in immune regulation and antioxidant responses [23]. A multicenter trial of 118 patients showed that patients with ACLF complicated by non-SBP infections who received a combination of albumin and antibiotics had a better prognosis than those who received only antibiotics [45]. G-CSF is an immunomodulatory agent that can be used to prevent bacterial infections in patients with advanced cirrhosis. Studies have shown that the incidence of sepsis is lower in ACLF patients treated with G-CSF than in those treated with a placebo [23].

6. Conclusion

Patients with ACLF are prone to infections due to immune dysfunction. At the same time, the body of such patients is chronically irritated by inflammation and the symptoms of early infection, such as rapid heart rate and shortness of breath, can be masked by the disease itself. Therefore, there is an urgent need for new and reliable methods to improve the accuracy of diagnosis. ACLF patients are at high risk of multi-drug resistant infections due to the number of invasive procedures performed during their hospital stay, and it is particularly important to keep the antimicrobial spectrum up to date according to local epidemiology. At the same time, appropriate antibiotic prophylaxis in high-risk groups can also reduce the incidence of infections. However, there are two sides to everything, and prophylactic use of antibiotics can lead to an increase in infections with drug-resistant bacteria. The search for drugs that are effective in preventing infections but less prone to side effects such as multidrug resistance and drug toxicity reactions, as well as rational non-antibiotic prophylactic strategies, has become a new proposition for the future.

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