Treatment of AECHB and Severe Hepatitis (Liver Failure)

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Abstract

This chapter describes the general treatment and immune principles and internal management for AECHB and HBV ACLF, including ICU monitoring, general supportive medications/nutrition/nursing, immune therapy, artificial liver supportive systems, hepatocyte/stem cell, and liver transplant, management for special populations, frequently clinical complications and the utilization of Chinese traditional medicines.

1. Early clinical indicators of severe hepatitis B include acratia, gastrointestinal symptoms, a daily increase in serum bilirubin >1 mg/dL, toxic intestinal paralysis, bleeding tendency and mild mind anomaly or character change, and the presence of other diseases inducing severe hepatitis. Laboratory indicators include

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T-Bil, PTA, cholinesterase, pre-albumin and albumin. The roles of immune indicators (such as IL-6, TNF-α, and fgl2), gene polymorphisms, HBV genotypes, and gene mutations as early clinical indicators.

2. Intensive Care Unit monitor patients with severe hepatitis include intracranial pressure, infection, blood dynamics, respiratory function, renal function, blood coagulation function, nutritional status and blood purification process. Nursing care should not only include routine care, but psychological and special care (complications).
3. Nutrition support and nursing care should be maintained throughout treatment for severe hepatitis. Common methods of evaluating nutritional status include direct human body measurement, creatinine height index (CHI) and subject global assessment of nutrition (SGA). Malnourished patients should receive enteral or parenteral nutrition support.
4. Immune therapies for severe hepatitis include promoting hepatocyte regeneration (e.g. with glucagon, hepatocyte growth factor and prostaglandin E1), glucocorticoid suppressive therapy, and targeting molecular blocking. Corticosteroid treatment should be early and sufficient, and adverse drug reactions monitored. Treatments currently being investigated are those targeting Toll-like receptors, NK cell/NK cell receptors, macrophage/immune coagulation system, CTLA-4/PD-1 and stem cell transplantation.
5. In addition to conventional drugs and radioiodine, corticosteroids and artificial liver treatment can also be considered for severe hepatitis patients with hyperthyreosis. Patients with gestational severe hepatitis require preventive therapy for fetal growth restriction, and it is necessary to choose the timing and method of fetal delivery. For patients with both diabetes and severe hepatitis, insulin is preferred to oral antidiabetic agents to control blood glucose concentration. Liver toxicity of corticosteroids and immune suppressors should be monitored during treatment for severe hepatitis in patients with connective tissue diseases including SLE, RA and sicca syndrome. Patient with connective tissue diseases should preferably be started after the antiviral treatment with nucleos(t)ide analogues.
6. An artificial liver can improve patients' liver function; remove endotoxins, blood ammonia and other toxins; correct amino acid metabolism and coagulation disorders; and reverse internal environment imbalances. Non-bioartificial livers are suitable for patients with early and middle stage severe hepatitis; for late-stage patients waiting for liver transplantation; and for transplanted patients with rejection reaction or transplant failure. The type of artificial liver should be determined by each patient's condition and previous treatment purpose, and patients should be closely monitored for adverse reactions and complications. Bio- and hybrid artificial livers are still under development.
7. MELD score is the international standard for choosing liver transplantation. Surgical methods mainly include the in situ classic type and the piggyback type; transplantation includes no liver prophase, no liver phase or new liver phase. Preoperative preparation, management of intraoperative and postoperative complications and postoperative long-term treatment are keys to success.

8. Severe hepatitis belongs to the categories of “acute jaundice”, “scourge jaundice”, and “hot liver” in traditional Chinese medicine. Treatment methods include Chinese traditional medicines, acupuncture and acupoint injection, external application of drugs, umbilical compress therapy, drip, blow nose therapy, earpins, and clysis. Dietary care is also an important part of traditional Chinese medicine treatment.

4.1 Acute Exacerbation of Chronic Hepatitis B: Early Prediction, Diagnosis and Clinical Management

Yuming Wang

Acute exacerbation of chronic hepatitis B (AECHB) usually occurs with an acute course and unpredictable outcomes, making it complicated for the poor treatment efficacy. If an early prediction can be made with specific clinical signs before the occurrence of AECHB, the disease progression may be interrupted by a timely effective management. Currently, although researches have been focused on prognosis of estimation and prediction on AECHB, there is no obvious progress due to lacking sensitive, reliable and systematic markers and grading systems for early prediction of AECHB. Establishment of AECHB staging system by a combination of clinical evaluation, laboratory tests, mutation of HBV genome, host immune response and genetic susceptibility to evaluate various risks, may be useful for specific early intervention and treatment to elevate curative effect, and therefore to reduce morbidity and mortality in these patients.

4.1.1 Markers for Early Prediction of AECHB

4.1.1.1 Relevant Clinical Signs for Early Prediction

Obvious fatigue, severe gastrointestinal symptoms, progressive jaundice, hepatic encephalopathy level II or above are typical clinical manifestations in severe hepatitis. As a matter of fact, certain clinical symptoms have suggested the coming up or occurrence of severe hepatitis before typical change in laboratory test results. Some of these clinical manifestations are as follows: (a) obvious fatigue, mental fatigue and insomnia; (b) nausea, hiccup, emesis; (c) jaundice: serum total bilirubin (T.Bil) less than ten times upper limit normal, but with a rapid elevation of more than 1 mg/dL (17.1 μmol/L) per day, or aggravation of certain symptoms accompanied by continuous jaundice; (d) abdominal distension, tenderness, rebound tenderness, occurrence of ascites; (e) aggravation of abdominal tenderness, bowel sound weakening and vanishing in some patients indicated toxic enteroparalysis caused by entotoxemia, or signs of spontaneous bacterial peritonitis hemorrhagic tendency: purpura, ecchymosis, gingival bleeding, indicating coagulation dysfunction; (f) mild mental abnormal, personality or behavior change; asterixis and hepatic fetor

may be also an important sign; (g) accompanied with other diseases that may induce severe hepatitis, such as viral super-infections, immune suppression or co-infected with bacteria.

4.1.1.2 Relevant Laboratory Markers for Early Prediction

Currently, effective assessment of AECHB is still on its way to fulfill the anticipation of clinicians and researchers around the world. Several common clinical markers may contribute to early diagnosis of AECHB, including T.Bil, prothrombin activity (PTA), cholinesterase (CHE), serum albumin and pre-albumin et al. According to the definition of liver failure by the Acute-on-Chronic Liver Failure Study Group of Asia-Pacific Liver Congress in 2008, serum T.Bil ≥5 mg/dL (85 μmol/L) and coagulation dysfunction including international normalized ratio (INR) ≥1.5 or PTA <40% are considered as necessary points for the diagnosis. So, T.Bil and PTA are the most frequently used markers to evaluate the severity and prognosis of patients with severe hepatitis. Synthesis of serum albumin and CHE reduced when hepatocytes were injured, and CHE is more sensitive than albumin in reflecting hepatic synthesis function Researches have reported that CHE level can predict the degree of severe hepatitis recovery. The half-life of serum pre-albumin is much shorter than serum albumin (1.9 days vs. 20 days), and the two proteins share similar metabolism pathways. So, serum pre-albumin may be more sensitive to reflect albumin metabolic function in the liver. Researchers have observed the dynamic change of serum pre-albumin levels in patients with severe hepatitis, and found that serum pre-albumin levels decreased at early stage of liver injury. Another study compared serum pre-albumin levels between patients with different liver diseases, and found that serum pre-albumin levels restored rapidly along with the recovery in those who suffered mild hepatocyte necrosis and with a favorable prognosis, while serum pre-albumin levels always stayed low in patients with severe hepatitis. Sustained serum pre-albumin levels <100 mg/L can be regarded as one of the markers for early diagnosis of severe hepatitis in clinical practice. Other researchers have found that serum thymosin β4 can be used as one of the markers for early prediction of hepatitis B related liver.

Hepatic encephalopathy is required for the diagnosis of liver failure, and early diagnosis of hepatic encephalopathy contributes to early prediction of liver failure. Early stage of hepatic encephalopathy can be realized not only by clinical manifestations such as mild personality change or abnormal behavior, but also by laboratory test results. Patients with abnormal electroencephalogram, special intelligence quantitative test or evoked potentials were usually checked out with subclinical hepatic encephalopathy. Bernal et al. found that arterial blood ammonia level (>100 μmol/L) is an independent risk factor for severe hepatic encephalopathy in patients with acute liver failure (ALF) with a prediction accuracy of 70%, MELD score is also a risk factor. Furthermore, the two combinations, blood ammonia level and MELD score, can elevate specificity and accuracy for prediction. Takikawa et al. established models for acute severe hepatitis progressing to hepatic encephalopathy by Logistic regression analysis, and their results indicated that older age, prolonged PTA, elevated T.Bil levels, viral hepatitis (except hepatitis A or E) were risk factors for hepatic encephalopathy.

Although above mentioned markers have important implications for the diagnosis of severe hepatitis, they cannot reflect the course, and it is hard to make accurate diagnosis according to a single marker, thus they cannot be regarded as prediction markers to fulfill clinical demands. Yoshiba et al. enrolled acute severe hepatitis patients without hepatic encephalopathy, but with PTA <40%. Viral type, T.Bil level and CHE were selected from 13 clinical and laboratory markers to establish a prediction model. Their results showed that T.Bil level is positively correlated to the incidence of liver failure, while CHE level exhibited a negative correlation. Then researchers confirmed that the judging formula showed a satisfied efficacy in early diagnosis of liver failure. The specificity, sensitivity, accuracy, positive predictive value and negative predictive value were 83.3%, 98.3%, 94.7%, 95.0%, 93.8%, respectively.

4.1.1.3 Potential Markers for Early Prediction

The occurrence and progression of AECHB reflects the interaction between host and virus. Therefore, we can dig out potential markers from their interactions.

Host Factors

Host Immune Markers

It is known that molecules and intrinsic modulation factors are involved in the course of ALF. For example, these host immune factors can cause severe liver *in situ* inflammatory injury and systematic inflammatory reaction syndrome, which indicate progression to multiple organ failure and final poor outcomes. Mononuclear macrophages release abundant pro-inflammation and anti-inflammation cytokines after activation, the severity degree of the diseases are closely related to pro-inflammation cytokine levels of peripheral blood in patients with ALF. In peripheral blood, levels in tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) are much higher in ALF patients who failed to survive or urgently needed to perform liver transplantation than those who survived. Human fibrinogen-like protein 2/fibroleukin (fgl2), produced from activated macrophage, belongs to fibrinogen super-family. This protein can catalyze prothrombin to thrombin directly, thus initiate coagulation process rapidly and lead to thrombus formation. Recently, researchers have found that fgl2 was specifically highly expressed in peripheral monocytes and liver tissues in AECHB patients, and its level was closely correlated to the severity of the disease. The above findings indicated that peripheral pro-inflammation cytokine levels may be helpful for prognosis prediction in patients with ALF. Except for secreting inflammatory cytokines, mononuclear macrophage initiate acquired immune response through antigen presentation, the expression of human leukocyte antigen II molecules, especially the human leukocyte antigen-DR, which are responsible for antigen presentation, are vital to monocyte activation. Antoniades et al. noticed a significant decrease of human leukocyte antigen-DR expression in peripheral monocytes accompanied by a significant increase of serum anti-inflammatory cytokine interleukin 10 (IL-10) expression levels in patients with ALF, suggesting that function states of peripheral monocytes in patients with ALF can be used for monitoring

disease progression and predicting clinical outcomes. The concept of Th17 cell was proposed in 2005, the biological function, differentiation process and cytokines expressed from Th17 cells were totally different from Th1 and Th2 cells, by recruiting and activating neutrophil granulocyte to mediate inflammation effectively by secretion of cytokines such as interleukin 17 (IL-17), interleukin 6 (IL-6) and TNF-α. Zhang et al. found that Th17 cells gathered in peripheral blood and liver in chronic hepatitis B patients with acute on chronic liver failure, the increase frequency of Th17 cells are closely correlated to HBV virus titer, serum ALT levels and inflammatory activity of liver tissue, indicating that Th17 may play a role in predicting the prognosis of chronic hepatitis B patients with acute on chronic liver failure. PD-L/PD-1 signal pathway can inhibit activation of T and B lymphocytes in the initial sites and target sites during immune responses, which is important to maintain peripheral immune tolerance. Zhang et al. analyzed different types of hepatitis B patients by modern immune technologies including pentamer staining, signal pathway blockade, to investigate the expression of PD-1 molecule on viral specific $CD8^+$ T cells and the relationship between PD-1 and disease progression. They found that high expression of PD-1 in early stage can specifically inhibit host immune response to reduce liver injury, while low expression in delayed stage leads to a loss of inflammation control, and by this way it may induce ALF. This study uncovered the protective modulation mechanism of the negative regulation molecule PD-1 in the course of ALF, and indicated that PD-1 may be one of the important markers in predicting prognosis of acute hepatitis B or ALF.

Polymorphism of Host Genetic Susceptible Genes

There were few studies in genetic susceptibility of severe hepatitis B patients, all these subjects came from Asia, target genes were focused on host immune responses in chronic hepatitis B, such as TNF-α, TNF-β, fgl2, IL-10, interferon induced protein 10 (IP-10), vitamin D receptor, HLA. Studies showed that polymorphism of these genes were related to AECHB.

Viral Factors

Although the mechanism of HBV involved in AECHB was complicated, replication of viruses usually plays essential role and is the major cause for the occurrence and progression of the disease. Thus, further studies on the relationship between HBV genotype and AECHB, the mechanism on occurrence of HBV mutated strains, biological characteristics and the role of the modulation of HBV transcription and replication by host transcription factors in the course of AECHB, will offer clues for finding out new markers in predicting and monitoring the occurrence and progression in AECHB.

HBV Genotypes and Subtypes

So far, ten HBV genotypes have been found from A to J, and their distributions have distinct regional characteristics. More and more evidences showed that disease progression and prognosis are correlated with HBV genotypes in patients with chronic hepatitis B. While the result of studies in the relationship between HBV genotype

and AECHB from different regions varies. In worldwide, researchers pointed out that the patients with HBV genotype A and B are easier to achieve HBeAg seroconversion and suffer milder liver lesions than those with HBV genotype D and C, respectively. While divergence still exist in studies from different regions. Imamura et al. found that detection rate of genotype B is significant higher in the population with fulminant hepatitis B than in population with acute self-limited hepatitis B. A multi-center study from Japan showed that in 301 patients with acute HBV infection, genotype B is the independent prediction factor for acute fulminant hepatitis by multivariate regression analyses. While another multicenter study also from Japan showed that patients with genotype C occupied 80% and 69% in patients with fulminant liver failure and acute fulminant liver failure on the basis of hepatitis B reactivation, respectively. These results indicate that patients with genotype C are more likely to suffer from fulminant liver failure. Recently, we have found that the proportion of severe hepatitis in patients with genotype B was not lower than those with genotype C, indicating a complicated relationship between genotype and severity or prognosis, which needs further investigation.

Mutation of HBV Genes

It is believed that most HBV gene mutations are found in pre-C and promoter of C gene. "1896 G to A" is the major mutation site in pre-C gene, this mutation turns codon TGG that encoding tryptophan to terminal codon TAG, leading to the failure of HBeAg synthesis. Major mutations in the promoter of C gene are ntA1764T/A1766G and A1762T/G1764A site mutations. Currently, the major sites reported to be related with AECHB are the terminal mutation at 1896 in pre-C gene and 1762/1764 double mutations in promoter of C gene. Imamura et al. performed a study on 61 patients with hepatitis B in Chiba Japan, and found that site mutation rates of 1896 in pre-C gene and 1762/1764 in promoter of C gene are much higher in patients with fulminant hepatitis than in patients with acute self-limited hepatitis. A study performed by Sainokami also indicated that G1896A and (or) G1899A in pre-C region and T1753A/C and (or) T1754C/G and (or) A1762T/G1764A in C region were correlated to fulminant hepatitis. In Japan, therefore, site 1896 terminal mutation in pre-C region was considered as one of the independent prediction factors for fulminant liver failure. However, this correlation did not seem to be the same in different areas due to differential genotype distribution. For example, studies from Taiwan, China showed that site 1896 terminal mutation in pre-C region of HBV plays a protective role in liver function decompensation.

4.1.2 Urgent Need for Establishing AECHB Early Prediction Score System

As above mentioned, current markers for early prediction of AECHB are not enough predictive, and effective early prediction score systems is still needed. Establishment of the system can contribute to the early intervention and treatment, so as to improve efficacy, decrease morbidity and mortality. The system should take a comprehensive

consideration in all aspects, including clinical manifestations, laboratory tests, HBV genotypes, HBV subtypes and mutations, host immune responses and genetic susceptibility, so as to screen candidate markers for early prediction and monitoring, and establish early prediction score system for AECHB through analyzing the weight of each candidate markers by bio-information technologies, and finally identify the specificity and sensitivity of the system through an independent cohort of patients with chronic hepatitis B.

Relevant studies have indicated that the development of systematic biology provide various ways for early diagnosis of severe hepatitis, through analyzing relevant gene expression and characteristics of protein change in different time point during the course of severe hepatitis by the technologies of genomics and proteomics, and searching target molecules for prediction, early diagnosis, outcome and efficacy of severe hepatitis by combining with bio-arrays, quantitative PCR, novel immune diagnosis, bio-informatics. It will achieve the goal of individualized diagnosis.

Rapid progression on the knowledge of AECHB has been made in China in the past few years, it is expected to establish a set of mature prediction score system of AECHB for Chinese patients on the basis of these progressions. Establishment of the system will bring a significant difference in prevention and treatment of AECHB. This should be a huge work and difficult for a singer center to finish, nationwide research centers should cooperate and share resources to complete the system to benefit patients with chronic hepatitis B.

4.1.3 Society and Economic Significance in Operating Fundamental Researches on Establishing AECHB Early Prediction, Course Surveillance and Assessment System, Finding New Ways to Prevention and Treatment

To establish a disease score system is important goal in clinical research, a good system will make an extensive impact on clinical management in theory and practice. Several systems, including diagnosis score system for auto-immune hepatitis and primary choleric liver cirrhosis, Child-Pugh score system for the prognosis of liver failure, model for end-stage liver disease (MELD) system, liver tissue pathological inflammation/fibrosis score system, are widely used for liver diseases in clinical practice. While in severe hepatitis, sensitive and reliable markers for early prediction and surveillance are still lacking, establishing a score system by assessing the risk of factors including viral mutation, host immune responses and genetic susceptibility to occurrence of AECHB, shall contribute to early intervention and treatment. Due to the different including strategies in different period of severe hepatitis, accurate diagnosis on the severity and period of the course may help clinicians making optimal individualized therapeutic schedule for each patient. Early prediction and course surveillance show important significance for clinical guidance.

Management in severe hepatitis B is a big issue for medical and health enterprises in China. Meanwhile, organ transplantation was limited by various factors,

shortage of liver donor, immune rejection and lifetime intake of immune suppressive drugs after transplantation significantly reduce long-term survival in these patients. Thus, it is necessary to find an effective therapeutic approach to fit our national conditions. It is important to find the key target of anti-virus gene therapy and host immune mediated gene therapy for severe hepatitis B, so as to establish gene therapy cell models, animal models and pre-clinical research system, to construct bone marrow stem cell components of functional liver tissue and investigate its short-term and long-term efficacy. The launch of relevant researches may provide novel ways for the management of severe hepatitis, and increase survival rate and quality of life of patients with severe hepatitis B, meanwhile slowdown the demands for transplantation and create huge economic value, which will draw significant influence to the society and human being.

4.1.4 Clinical Management Strategies

4.1.4.1 Multiple Ways in Early and Moderate Stage to Prevent Infection by Antibiotics

Abdominal infection is the most common co-infection of severe hepatitis, it is recommended to use antibiotics specific to gram-negative bacteria with low drug-resistance rate for prevention, long-term, huge dose and single use of strong antibiotics should be avoided. Meanwhile, it is suggested to take lactulose and bifid bacteria orally to clean intestine, to avoid alteration of intestinal flora, to reduce endotoxemia, to avoid drug-resistant strains and superinfection. Regimen of Penicillin or second or third generation of cephalosporins combined with β2 lactamase inhibitors can enhance the efficacy of anti-infection. Quinolones also show satisfied efficacy in clinical treatment of SBP with a broad spectrum and good tolerance.

4.1.4.2 Antiviral Therapies

Safe and effective antiviral therapies can lead to rapid suppression of viral replication, so as to termination of fierce cellular and innate immune responses, and save time for hepatocytes regeneration and restoration.

With better understandings to the pathogenesis of severe hepatitis and mechanism of antiviral drugs, more and more experts and scholars propose antiviral therapy to patients with severe hepatitis B. Nucleot(s)ides are safe with powerful inhibiting effect to HBV and show quick curative effect, these features draw wide attention by experts and scholars. The results from experimental and clinical studies on antiviral therapies to chronic hepatitis B indicate that selection of drugs with potent antiviral activity, low drug-resistance rate and high safety profile is important mean to elevate antiviral efficacy in naïve patients. However, in some NUCs resistant patients, the combination of two drugs with different antiviral mechanisms including nucleoside and nucleotide will be the only choice. In the future, strategy for eradication of HBV will be the direction for antiviral therapies on patients with severe hepatitis B.

4.1.4.3 Supporting Therapies

As so far there is no cure drug for chronic severe hepatitis B, multiple supporting therapies are needed to control the disease progression, including the use of pro-hepatocyte growth factor (pHGF), transfusion of plasma and human albumin, and in some severe patients, artificial liver including plasma replacement may be necessary.

Application of pHGF

pHGF can initiate the synthesis of hepatocyte DNA, promote hepatocyte regeneration, enhance the function of Kupffer cells, inhibit activity of TNF-α and reduce the incidence of endotoxemia, and therefore is widely used in clinical practice of China. Nevertheless, there is some different opinions on the application of pHGF, particularly in western countries.

Application of Plasma and Human Albumin

Supporting therapies play key role in chronic severe hepatitis, especially the supplement of plasma and human albumin. Plasma contains albumin, globin, antibodies, coagulation factors, opsonin etc., these components can enhance the immune modulation ability and restore coagulation factors in such patients. Albumin can be used directly by the human body to correct hypoproteinemia, elevate colloid osmotic pressure, promote diuresis, reduce ascites, prevent hydrocephalus, absorb endotoxin, thus help to prevent hepatocyte necrosis and promote hepatocyte regeneration. Patients were treated with plasma 200 mL or 20% human albumin 30 mL per day/2 days through intravenous injection.

Plasma Replacement

Plasma replacement can eliminate continuously generated toxic and inflammatory substances including endotoxin, TNF, bilirubin, blood ammonia, and help restore bio-active substances such as albumin and coagulation factors, so as to contribute to improvement of internal environment for hepatocyte regeneration. Plasma replacement is one of the routine therapies for artificial liver support.

4.2 Intensive Care for Severe Hepatitis B (Liver Failure)

Ke Li

Intensive care medicine or critical care medicine is a branch of medicine concerned with the diagnosis and management of life-threatening conditions requiring sophisticated organ support and invasive monitoring.

Patients requiring intensive care may require support for instability (hypertension/hypotension), airway or respiratory compromise (such as ventilator support), acute renal failure, potentially lethal cardiac arrhythmias, or the cumulative effects of multiple organ failure, more commonly referred to as multiple organ dysfunction syndrome. They may also be admitted for intensive/invasive monitoring, such as the

crucial after major surgery when deemed too unstable to transfer to a less intensively monitored unit. Intensive care is usually only offered to those whose condition is potentially reversible and who have a good chance of surviving with intensive care support. A prime requisite for admission to an intensive care unit (ICU) is that the underlying condition can be overcome [1, 2]. ICU, equipped with monitoring and support facilities and medical staffs received strict and scientific training for management of critically ill patients, provide more intensive care than general ward to improve the survival rate of critically ill patients [3].

In regards to patients with severe hepatitis B or liver failure, since most of their livers have been severely damaged, in hence losing their proper function, many other complications of multi-organ dysfunction often arise, of which could lead to a high risk of mortality [4]. In principle, the patients with severe hepatitis B or liver failure should be admitted in the ICU for monitoring and management in order to raise the rescue rate. However, in practice, we should consider, especially doctors working within the Chinese medical care system, several factors including but not limited to the pathophysiology of the patient, controllability of the disease, the financial state of the patient of the family, and, due to the novel nature of the concept of intensive care, the comprehension of family regarding to this phenomenon as well as to the idea of liver transplantation.

"The first liver critical care unit was established in the King's college hospital in 1973, then up to 2006, 2017 cases of acute liver failure (ALF) (hepatic encephalopathy III–IV degree) had been admitted to the unit, the survival rate increased from 20% to 60%. Moreover, in recent 25 years, with the development of monitoring and treatment technology, the ALF mortality rate decreased from 80% to 33% in the United States [5]". These statistics undoubtedly imply that through employing the intensive care methods on liver failure patients could improve patient survival and gain valuable time for the liver transplantation [6]. However, due to liver failure patient's condition as well as the complexity associated with multiple organ failure (multiple organ dysfunction syndrome, MODS), often makes the treatment of liver failure in the ICU become challenging work. The recommendations from US Acute Liver Failure Study Group (US Acute Liver Failure Study Group, ALFSG) for ALF patients in intensive care indicated that when accompanied by a significant lack of hepatocyte function (international normalized ratio >1.5), the patients with acute liver injury should be hospitalized, and patients with hepatic encephalopathy should be immediately transferred to ICU. One of reasons is that some ALF patients require immediate etiological treatment, such as acetaminophen overdose, poisonous mushroom induced fulminant hepatic failure patients [7, 8].

Another reason is that liver failure is often accompanied by multiple organ dysfunction, such as systemic inflammatory response syndrome (SIRS), infection, hepatic encephalopathy, hypotension, heart failure caused by inadequate vascular tone, hypoglycemia, acute lung injury (acute lung injury, ALI)/acute respiratory distress syndrome (acute respiratory distress syndrome, ARDS), gastrointestinal bleeding, acute renal dysfunction and disseminated intravascular coagulation. MOF patients with liver failure is the most common cause of death (>50%). The severity is highly correlated with mortality and other causes of death are infection, GI bleeding and intracranial hypertension (ICH) [9, 10].

Therefore, the monitoring methods and the approach in order to maintain the organs stable used in critical care medicine play a crucial role for the liver function recovery and bridging to the liver transplantation [6].

However, due to the special nature of severe hepatitis and liver failure, such as hemodynamics, blood coagulation and liver metabolism, in the treatment of liver failure, the methods and approaches can not be completely applied, there must be specialized. In addition, according to histological characteristics and speed of development of the disease, the liver failure is characterized as acute liver failure (ALF), sub-acute liver failure (SALF), acute-on-chronic liver failure (ACLF) and chronic liver failure (CLF) (The guideline for the diagnosis and treatment of the liver failure, Chinese Medical Association in October 2006) [4]. For acute on chronic liver failure as a distinct clinical entity with clear clinical, laboratory, and pathophysiological features. A new definition has been proposed from World Congress of Gastroenterology, it is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of INR and one or more extrahepatic organ failure that is associated with increased mortality within a period of 28 days and up to 3 months from onset).

There are greater differences in the pathophysiological characteristics among them, especially for CLF which is occurring in the style of progressive decomposition superimposed on the liver cirrhosis and showing different pathophysiological processes, the prominent feature is the complications of portal hypertension, therefore, severe liver disease in routine care project basis, should take appropriate, targeted measures for monitoring and management, respectively. Due to space limitations, this article does not involve in the chronic liver failure.

4.2.1 Regular Monitoring of Severe Hepatitis B

And minimize the activity to reduce the consumption of the energy, help the patient to adapt the liver dysfunction and reduce the patient exposure to the psychological stress as soon as possible in order to establish the confidence for recovery from the disease. The patient should be also encouraged to comply with the treatments such as Antiviral therapy, artificial liver support and blood purification.

It should be noted that the above managements is based on studies of the progressive stage of acute and sub-acute severe hepatitis and liver failure. The nutritional risk screening the enteral and parenteral nutritional support should be considered in the patients of ACLF and CLF with longer duration based on the recommendations of guideline from European Society of Parenteral and Enteral Nutrition [11].

On the limited experience showed that nutritional risk screening for all patients with severe hepatitis [12] and maintaining the patient's basic caloric intake (30–300 kcal/kg/day) regardless of enteral or parenteral nutrition (late evening snack, LES) in order to keep the body weight stable, may prevent the risk of infection, wasting disease and other complications and promote liver function recovery. The parenteral nutrition support only be given to the patients who can not tolerate enteral nutrition to guarantee the energy needs of the patients.

Serum electrolytes, glucose blood gas analysis, prothrombin time, transaminases, bilirubin must be ordered, and electrolytes and glucose should be monitored twice daily. The metabolic derangements must be promptly corrected especially for hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypomagnesemia, metabolic acidosis and respiratory alkalosis. When the liver cells which are sensitive to the hypoxia are severely damaged, that their ability to uptake the oxygen is impaired leads to the further degeneration, necrosis [13]. The mortality is negatively correlated with the low oxygen saturation. Therefore, hypoxia, which showed the illness in the severe conditions and further detritions, is one of the important prognostic factors, oxygen uptake is one of the effective ways to improve the hypoxia, and the better way is to maintain 95% or more of the SaO_2 through inhaling 1–3 L/min of the oxygen flow. Protein restriction is not indicated [13]. Specific amino acid formulations (branched chain) appear to be no more effective than standard supplements. Rapid development of hypoglycemia, which can confound the hepatic encephalopathy, should be managed with continuous intravenous glucose infusion. Hyperglycemia should also be avoided because it may contribute to poor ICP control. Prophylactic infusion of 3% or 10% hypertonic saline to keep serum sodium 145–155 mmol/L in patients with severe encephalopathy is associated with fewer episodes of intracranial hypertension. Trials are now conducted in our center to test its efficacy.

Malnutrition in severe hepatitis, liver failure patients is related to impaired immunocompetence. Infections and sepsis are also associated with severe hepatitis, liver failure and malnutrition. Therefore, In order to reverse the course of liver failure and reduce the complications, the better way to give the specific nutritional support to the patients is based on the diet survey and metabolism measurement [13]. The clotting factors and the level of poisoning supplemented by appropriate, adequate infusion of fresh frozen plasma, albumin, and fresh whole blood may contribute to the prevention of bleeding, secondary infection and other complications [14].

Throughout the whole course of severe hepatitis, the complications and the occurrence time of the complications are the important factors for the prognosis of the severe hepatitis. The early complication are prone to be overlooked and they usually influence and reinforce each other then make the prognosis worse. Therefore, early detection, close monitoring and aggressive treatment of complications, are the key to successful treatment of severe hepatitis.

4.2.2 Severe Hepatitis B Liver Failure Complications Guardianship

4.2.2.1 Cerebral Edema and Intracranial Pressure Monitoring

Intracranial Pressure Monitoring

Severe hepatitis is associated with the cerebral edema, which can lead to the intracranial hypertension (ICH), one of the common serious complications. The rate of ICH in acute liver failure is as higher as 20–30%, which is greater than that in the

chronic liver failure and can result in fatal cerebral herniation. One thing should be noted that patients with hepatic encephalopathy, does not mean that there is ICH, such as there is no cerebral edema in most of the decompensated cirrhotic patients with HE. Higher grades of encephalopathy correlate with a higher risk of ICH, and 20–25% of ALF deaths have been attributed to ICH historically, though more recent data show significantly fewer deaths (5–13%) directly resulting from ICH [10].

The pathological mechanism of cerebral edema is not completely understood, it is appeared that the rapid rise of the ammonia may played a critical role in development of the cerebral edema. Ammonia crosses the blood-brain barrier to be taken up by the astrocytes, where it converts to the osmotically active glutamine, water passively diffuse into the astrocyte, causing edema. In addition, inflammatory cytokines exacerbate vasodilation, resulting in the swelling worse. In contrast, Inpatients with liver cirrhosis complicated hyperammonemia, glutamine accumulated in astrocytes in relatively slow speed since the organic permeable material can be discharged from the cell, so that it can be maintained intracellular osmotic pressure relative balance with outside, which may explain why the less cerebral edema and ICH in patients with liver cirrhosis. In addition, in patients with acute liver failure, the enhanced anaerobic glycolysis could easily lead to the accumulation of lactic acid in the body, as well as mitochondrial dysfunction, which can promote the formation of cerebral edema, increased intracranial pressure (intracranial pressure, ICP) [15].

When ICP >20 mmHg called ICH, when significant ICH ICP >25 mmHg longer than 10 min. Another important indicator for the diagnosis and treatment cerebral perfusion pressure (CPP, CPP = MAP-ICP), the normal range of CPP is 60–80 mmHg. Thus, when the occurrence of ICH, this formula can be used to guide the application of vasoactive drugs increased MAP maintain adequate CPP, in order to maintain effective blood supply to the brain. Some studies demonstrated that when ICP >25 mmHg and CPP <40 mmHg longer than 2 h in liver failure patients, nervous system function is difficult to recover, the prognosis is poor, these patients should not be listed for liver transplantation. But there is a contrary report, four cases with ALF ICP >35 mmHg and CPP <50 mmHg longer than 24 h, the nervous system function returned to normal after recovery, which is undoubtedly a challenge to previous report. But most clinicians the Goal ICP is less than 20 mmHg, with a cerebral perfusion pressure (CPP) of greater than 50–60 mmHg.

ICP monitoring has been a controversial problem in liver failure patients due to the severe coagulopathy since the risk of intracranial bleeding may endanger the patient's life, the invasive ICP monitoring is center dependent in the clinical practice. Some studies showed that the risk of intracranial hemorrhage is usually associated with where to place the sensor (such as epidural, subdural, intraventricular, etc.) and what kind of the sensor to use. The rate of occurrence of death due to intracranial hemorrhage is 1–3%. But intracranial pressure monitoring can indeed provide reliable information for clinicians and guidance for intracranial hypertension management. A few non-randomized studies from Liver Center of European countries showed that the usage of intracranial pressure monitoring to guide treatment can improve prognosis of acute liver failure

patients with intracranial hypertension. Therefore, the USA acute Liver Failure Study Group recommends invasive ICP monitoring should be placed in patients with acute liver failure at high risk of ICH (such as patients with severe hepatic encephalopathy).

In China, invasive ICP monitoring could not be performed in the majority of general ICU except in a few of academic neurological institute. With the aide of non-invasive monitoring techniques such as cranial CT, MRI, positron emission tomography, electroencephalogram (EEG) (transcranial Doppler) brain flow diagrams, and with a variety of clinical evaluation tools of nervous system, such as a variety of physiological and pathological reflexes and others to evaluate the brain function, the treatment, prognosis of patients and the feasibility of liver transplantation could be determined. However, compared with invasive ICP monitoring, it is not as intuitive and accurate as invasive ICP monitoring and has a lower sensitivity to early intracranial pressure elevation, when the ICH is diagnosed, the brain has been significantly damaged, which leaves no chance of liver transplantation. For this reason, for patients with liver failure, on the one hand, a prospective, randomized, controlled multi-center clinical trial should be conducted to compare invasive and non-invasive ICP monitoring to decide which one is better in guidance to reduce the ICH and improve the prognosis. On the other hand, a new less invasive or even non-invasive monitoring techniques should be developed to be used in liver failure patients with ICP who have high risk of hemorrhage.

Brain Edema and Intracranial Hypertension Treatment

For severe hepatitis B with ICH treatment, the general management of ICH should combine with the pathophysiology of liver failure. These include limiting stimulation, elevating the head to 30°; the goal of MAP is above 65 mmHg, CPP is 60–80 mmHg and ICP <25 mmHg; hypotension and hypoxemia should be corrected, normal blood volume be maintained; correcting aggravating factors such as hypoxic brain edema, high hypercapnia, hypotension, hypoglycemia and metabolic derangement; the painful stimuli (including suctioning) should be avoided or reduced [16]. Propofol is a reasonable choice for adequate sedation because it may reduce ICH. For treatment of pain, fentanyl is preferred as the first-line agent for whom is put on mechanical ventilation, the hyperventilation mode can be used in order to maintain the partial pressure of carbon dioxide from PCO_2 30–35 mmHg; the use of sedation, analgesics can significantly reduce intracranial pressure of patients who receive painful stimuli, but the daily interruption should be applied in these patients. The brain edema is highly correlated with increased ammonia (>150–200 mol/L), so the corresponding intestinal decontamination agents can be administered, but application of aspartate—ornithine formulations, arginine to promote ammonia metabolism leading to reduce blood ammonia, are proved to be ineffective; albumin infusion and nutritional support may correct the edema caused by hypoalbuminemia.

There were a few evidences of hypothermia therapy can reduce the ICP, but the outcomes were controversial, in consideration of the complication of coagulation, we still do not carry out this method in clinical practice.

In addition, in resuscitation of patients with hepatic encephalopathy, due to the presence of hyponatremia, infusion of appropriate hypertonic saline to target the serum sodium concentration to the upper limit of normal (145–155 mmol/L) is conducive to the prevention and mitigation of brain edema, but hyperchloremic acidosis also should be noted due to the infusion of high dose of the sodium chloride. The methods of the specific application of some drugs for the treatment of ICH. For renal impairment or failure in patients with ICP or hepatic encephalopathy, continuous veno–venous hemofiltration (CVVH) or albumin dialysis, may play a role in lowering intracranial pressure, reducing ammonia and eventually improve the outcome of the patients with liver failure [17].

4.2.2.2 Infection and Sepsis Monitoring and Prevention

Compromised immune system, the impairment of the intestinal mucosal barrier, the translocation of bacteria and endotoxin from the intestine and invasive procedures (catheters, endotracheal tube, et cetera) for patients with severe hepatitis B in ICU make the patients more susceptible to the infection including bacterial and fungal infection even lead to sepsis or septic shock [18]. Statistics showed more than 50% of patients with liver failure have bacterial infection; the occurrence of fungal infection is 12–30%. The common sites of the infection are located in the abdominal cavity, respiratory system, urinary and biliary system. The common pathogens of infection include E. Coli, klebsiella pneumonia, Staphylococcus, and Streptococcus. The most commonly seen fungal infection are candida and aspergillus.

The differential diagnosis between clinical manifestation in patients with liver failure and sepsis is difficult since the patients have the SIRS- like symptoms due to the tissue necrosis and inflammation in the liver, a lower baseline value of WBC, a quick heart and respiratory rate from the hyper dynamic circulation, hyperventilation [19]. Once infection occurs in patients with liver failure, it will lead to rapid disease progression, significantly increased mortality. The infection is also the contraindication of liver transplantation. Thus, close surveillance for infection should be given to all liver failure patients, with each day chest radiographs and frequent cultures of blood, urine and sputum. Empirical antibiotics should be administered when the results showed the signs and symptom of infection are positive (increased PCT, cultures positive, G and GM positive, high body temperature). Immediate prevention and treatment of infection are the main measures for liver failure patients. EGDT [20] should be used as a tool to treat the patients with severe sepsis or septic shock.

This guideline's aim is to significantly reduce mortality in patients with sepsis. During the first 6 h of resuscitation, the goals of initial resuscitation of sever sepsis and septic shock should include all of the followings:

- CVP (central venous pressure, CVP) 8–12 mmHg (1 mmHg = 0.133 kPa),
- MAP (mean arterial pressure ≥60 mmHg),
- Urine output ≥0.5 mL/kg/h,
- Superior venous cava oxygen saturation ($ScvO_2$) ≥70% or mixed venous oxygen saturation (SvO_2) ≥65%.

Targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue perfusion [13, 20].

The guidelines for critically ill patients with sepsis have universal significance, but one must pay attention to the particularities of patients with liver failure. Due to the presence of liver failure patients with low albumin, and for spontaneous bacterial peritonitis (SBP) and human studies put the amount of ascites showed that human serum albumin for expansion instead of conventional fluid resuscitation, can significantly reduce the mortality of patients, and therefore, in regards to liver failure complicated by septic sera levy early fluid resuscitation should be added human blood albumin. Liver failure patients vasoactive drugs should use norepinephrine, dopamine is not recommended. Because liver failure patients with a weak response to dopamine, and dopamine could possibly go through the expansion of the superior mesenteric artery, thereby theoretically lead to a further increase in portal pressure [21]. Due to the high power cycle liver failure patients, oxygen transport unit time is relatively high, venous oxygen saturation tend to look high, resulting in critically ill patients for general standard may not apply to patients with liver failure recovery float estimates. CVP may have been affected by the presence of ascites and pleural effusion. In addition, increased lactate concentration reflects the severity of critically ill patients, but due to liver failure patients with impaired liver function, lactate metabolism, blood lactate concentration within even in the absence of anaerobic metabolism situation has also been increased. In summary, EGDT, in principle, should be analyzed and used in conjunction with severe hepatitis, liver failure specific pathophysiological conditions.

Liver failure patients once diagnosed a bacterial infection, anti-infective therapy should be carried out within 1 h. Based on epidemiological and drug-resistant bacterial infections in the region, choose efficient, broad-spectrum antibiotics before anti-infection treatment censorship blood or other specimens for bacterial culture after culture results and drug sensitivity test results are reported in a timely manner to adjust to a relatively narrow spectrum of antibiotics target therapy. 48–72 h evaluate the effect of each anti-infection treatment, specifically water evaluation include changes in the patient's symptoms and signs of infection, bacterial culture, blood and leukocyte classification, endotoxin detection, serum procalcitonin (procalcitonin, PCT) detection. In addition, by means of imaging to determine the foci, radiographic change certain pathogen infection displayed characteristic has important implications for determining the nature of the infection. Suspected invasive fungal infection, do as histology clear, but there are certain difficulties in clinical practice. Focus is to assess whether the patient has risk factors for fungal infections, anti-infection treatment process and effect, it is necessary to censorship G test (1,3-β-D-glucan detection) and GM test (galactomannan detection) whether it is clinically diagnosed fungal infection evidence and evaluate the efficacy of anti-fungal infections. It should be noted that, in the choice of anti-infective drugs, antibiotic-induced liver injury should be avoided.

4.2.2.3 Hemodynamic Abnormalities

Hemodynamic changes induced by severe acute liver failure and is similar to toxemia septic-shock, showing a significant characteristic of abnormal blood flow distribution, the specific performance of internal organs and portal vein blood flow, increased portal pressure back efforts to reduce central venous flow, vital organs heart, brain, kidney and other blood supply is reduced. Therefore, it is necessary to fluid resuscitation and vasoactive drugs increased MAP (>65 mmHg) to improve vital organ perfusion. To this end, (CVP) and $ScvO_2$ or SvO_2, has an important significance in guiding fluid resuscitation and vasoactive drugs application through a central venous catheter inserted central venous pressure monitoring. In conditional ICU, you can float into the lungs through a catheter (Swan-Ganz catheter) or by pulse wave contour analysis indicative continuous cardiac output monitoring (PiCCO), which are spotted sword hemodynamics monitoring technology to monitor more than the CVP Value can be more precise guidance capacity of some hemodynamic recovery. Studies have shown that, with the stroke volume variation PiCCO monitoring (SVV) and intrathoracic blood volume index (ITBI) for the evaluation of mechanical ventilation capacity of the state of hemorrhagic shock, obviously superior to heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), SVV continuous monitoring can be more accurately guide fluid resuscitation.

Almost all patients with severe hepatitis exhibit vasoconstrictor effects on α-adrenergic receptor agonists (such as adrenaline, high doses of vasopressin, terlipressin, etc.) is reduced [22]. Adrenaline agonists could reduce oxygen delivery to surrounding tissue and visceral blood flow, and cause ischemia due to loss of self-regulation of brain blood vessels, terlipressin enables increased cerebral blood flow and also makes ICP high. In acute liver failure, it seems that β-adrenergic sensitivity does not drop, dopamine and norepinephrine can increase cardiac output at the same time, and increase blood flow to the liver, but dopamine can also increase heart rate and myocardial oxygen consumption, noradrenaline is not significantly increase heart rate [21]. Therefore, norepinephrine often uses as first-line vasoactive drugs in acute liver failure when hemodynamic adjustment needed.

In acute and sub-acute severe hepatitis or liver failure, deficiencies of relative adrenal function is a common situation, a stress doses of glucocorticoids can reduce the amount of norepinephrine. When patients after adequate fluid resuscitation and high dose of vasoactive drugs to support still showed persistent hypotension, please consider glucocorticoids [23, 24].

4.2.2.4 Monitoring of Respiratory System

Occur in patients with severe hepatitis liver failure often hypoxemia (hypoxemia), lung injury (acute lung injury, ALI)/acute respiratory distress syndrome (acute respiratory distress syndrome, ARDS). Patients with liver failure and III–IV hepatic encephalopathy, because of the reduced gig reflex and respiratory function suppression, should be given selective intubation to protect the airway (mechanic ventilation, MV) [25] Propofol sedation is preferred in this situation. Sprayed endotracheal lidocaine may help to reduce the surge of ICP during intubation. For the successful

endotracheal intubation, cisatracurium as a muscle relaxant may be preferred to induct of anesthesia, because as a non-depolarizing muscle relaxants along with rapid onset (1 min), duration short (15 min), the drug does not affect the heart, liver and kidney function, and no accumulation and after a single intravenous injection of 40–60 min to evaluate neurological function and so on. The recommended dose of this product for adults of 0.15 mg/kg of body weight or as directed. After induction of anesthesia with propofol, we can achieve good to excellent intubating conditions after 120 s.

There is no consensus for the selections of mechanical ventilation mode in patients with acute and chronic liver failure patients at present. Volume-controlled (VC) or pressure controlled (PC) mode can be used either. In liver failure patients, hypoalbuminemia, low colloid osmotic pressure can facilitate the occurrence of lung edema and chest wall edema, pleural effusion and ascites will further reduce the chest wall compliance. Therefore, low tidal volume lung protective ventilation strategy should be adopted, tidal volume of 4–6 mL/kg, plateau pressure ≤30 mmHg may be considered in these settings. Its purpose is to minimize barotrauma caused by mechanical ventilation (barotrauma) and biological injury (biotrauma) and reduce ventilator-associated ALI/ARDS. However, in the implementation of such lung protective ventilation strategy, increased P_{CO2} and hypercapnia may be occurred due to hypoventilation, leading to dilatation of brain's blood vessels and increased ICP, the appropriate respiratory rate would be used to maintain adequate minute ventilation to prevent this from happening. In addition, conservative fluid administering can reduce the occurrence of pulmonary edema, an appropriate PEEP can facilitate the lung recruitment and improve the hypoxemia, but it is possible to lead the reduction in blood flow returning and liver. Therefore, respiratory support modes and parameters should be considered in these scenaria to benefit the patients with liver failure from the mechanic ventilation [26].

4.2.2.5 Coagulation Abnormalities

Coagulation abnormalities are seen in nearly all patients with liver failure [27], 50–70% of patients with acute liver failure have thrombocytopenia. The reason for low platelet counts has not been elucidated, such as, thrombopoietin levels are not uniformly low and not correlated with platelet levels. It seems there is a high risk of bleeding in liver failure patients, but clinically significant bleeding occurs rarely (about 5% of cases) unless the platelet count is very low, and recent data suggest that the defects are balanced between the coagulation and the fibrinolytic pathways, the bleeding risk based upon INR may be overestimated. Bleeding generally occurs from superficial mucosal lesions, especially gastric erosions. It is very rare for the patients with liver failure have spontaneous intracranial hemorrhage. In general, fresh frozen plasma (FFP), cryoprecipitate or platelets is reserved for active bleeding or the count of platelet <10,000/mm^3 and If infection or sepsis occurs, it is recommended to maintain a platelet count >20,000/mm^3, if an invasive procedure is planned, a platelet count >50,000/mm^3.

It is not recommended to administering the FFP to the patients with liver failure to normalize the INR if without active bleeding. Current data showed plasma

transfusion cannot improve the prognosis and can interfere in using INR as a continuously available and reliable measure of hepatic synthetic function. Vitamin K should be considered for all the patients with liver failure since the deficiency can occur in 25% of the patients, however vitamin K applications may affect or even damage the liver function, small dose and 3-day regimen may be a reasonable choice (such as 5–10 mg subcutaneous daily for 3 days). On the condition of using broad-spectrum antibiotics, administration of vitamin K is appropriate [26, 28]. FFP infusion and plasmapheresis (plasma, exchange, PE) has the potential to cause volume overload and transfusion-related ALI in patients with acute liver failure. There are fierce controversies in these viewpoints for Chinese scholars who advocate for selective infusion of fresh frozen plasma, vitamin K and plasma exchange in patients with liver failure. These may be due to the difference of the type of severe hepatitis, the course of disease and pathophysiology of the liver failure. It is needed to accumulate more evidence to elucidate the controversies.

If an invasive procedure is planned, for example, ICP monitoring or placement of artery or vein lines, INR can be corrected by temporary administration of recombinant activated factor VII (Novo-7) or FFP.

4.2.2.6 Upper GI Bleeding

A multicenter study showed longer than 48 h Mechanical ventilation and coagulation abnormalities are independent risk factor for gastrointestinal bleeding in critically ill patients, respectively. The presences of severe coagulopathy and SIRS or sepsis in patients with liver failure especially for acute liver failure are vulnerable to stress ulcer and bleeding. Therefore, the patients with liver failure are at high risk of gastrointestinal bleeding. For these patients, we have to pay more attention to the bleeding signs at skins, mucosa and cavities and to retest the CBC, stools and may need endoscopies or imaging facilities to detect the cause and sites of bleeding in order to give targeted therapy [29].

Prophylactic administration of H2 blockers and sucralfate can significantly reduce the incidence of upper gastrointestinal bleeding. H2 blockers may be more effective in preventing hemorrhage, but further evidences are needed, sucralfate can be used as second-line preventive medication. It is recommended that patients with liver failure should receive H2 blockers or proton pump inhibitors (or sucralfate as a second-line drug) to prevent gastrointestinal bleeding from stress ulcers. In fact, the best measures to protect the gastrointestinal mucosa are the early use of enteral nutrition (EN) if there is no contraindication (gastrointestinal obstruction) [29].

4.2.2.7 Monitoring of Renal Failure

The incidence of Acute kidney injury or acute renal failure in severe hepatitis and liver failure is as high as 50–70%, and it is a common cause of ICU admission and also one of the important factors negatively affect the prognosis of patients. Common causes of injury are SIRS or sepsis, low renal perfusion (bleeding, hypotension), direct renal toxicity (drug overdose), hepatorenal syndrome. In addition, development of abdominal compartment syndrome, due to ascites, intra-abdominal hemorrhage or severe abdominal and gut wall edema, leads to hypoperfusion of

kidney, is a common cause of renal impairment in ALF. Once renal failure occurs, Patients with liver failure would have significantly worse prognosis and increased risk of death. Therefore, 24 h intake and output volume and hourly changes of urine output should be recorded, daily biochemistry, creatinine and urea nitrogen, urinalysis should be monitored for the early detection of renal damage, if necessary, by means of imaging techniques to exclude parenchyma damage. Promptly correct these vicious factors is the major premise for management of acute renal dysfunction [30].

When acute renal failure develops, continuous renal replacement therapy with bicarbonate buffer is recommended, because most patients with ALF tolerate intermittent hemodialysis poorly due to circulatory instability, precipitous fluid shifts, and a rise in ICP. There is no more evidence to use other modalities to treat the patients (continuous hemofiltration, plasma hemodiafiltration, molecular adsorbent recirculating system, MARS). For type I hepatorenal syndrome, the measures should be carefully chosen to restore effective circulating volume, it is recommended to administrate 20% of albumin solution, and terlipressin is the effective methods pared with management with vasopressin, norepinephrine or octreotide. The large volume paracentesis can alleviate intra-abdominal pressure while ensuring effective blood volume,

4.2.2.8 Metabolic Derangements

Metabolic disorders in patients with severe hepatitis are occurred frequently. Due to decline in the ability of the liver to metabolize lactic acid to pyruvate in patients with liver failure and inadequate tissue hypoperfusion related to hypotension and hypoxemia, lactic acidosis develops in 1/3 of patients with stage III encephalopathy. Poor response to treatment and high mortality is associated with the lactic acidosis, therefore, prevention is the same important as treatment. The main measures include effective tissue perfusion (e.g. Oxygenation and normovolume), adequate, appropriate amount of nutritional support and avoiding precipitating factors. Patients are prone to develop hypoglycemia because of glycogen depletion and defective glycogenolysis and gluconeogenesis. Rapid development of hypoglycemia should be treated vigorously and increase the times of monitoring blood glucose (time/2–4 h). Enteral feedings should be initiated as early as possible unless contraindicated. Hyperglycemia should also be avoided because it is contributable to poor ICP control. It is also needed to promptly correct the common seen complications of hyponatremia, hypokalemia, and hypomagnesemia. Hypophosphatemia are also common in patients with liver failure, especially when the patients with metabolic or respiratory alkalosis, the patients may be manifested with hemolysis, fatigue, weakness and seizures or convulsions, et cetera. Administration of fructose phosphate can be used as management of Hypophosphatemia [31].

In addition, ALF patients with hypophosphatemia should be replenished with phosphate due to increased demand for phosphate in regeneration showed better prognosis.

Characteristics of metabolism in patients with ALF is not yet entirely clear, but it is certain that the majority is in hypermetabolic states. But in terms of hepatitis,

Beijing You An Hospital study showed that different for chronic severe patients with energy metabolism which showed reduced resting metabolic rate (REE), the oxidation rate of glucose and respiratory quotient (RQ), while relatively higher oxidation rate of fat and protein, especially much higher fat oxidation rate. to predict the energy expenditure with the Harris-Benedict equation in patients with liver failure is not accurate enough [14].

For ALF or ACLF, more accurate energy expenditure can be measured at bedside by indirect calorimetry; this technique is useful in patients with hypermetabolic status from sepsis or trauma and whose bodyweight cannot be ascertained accurately. Sufficient supply of energy and nutrients is conducive to the liver regeneration and repair, overloads would increase the burden on the liver and exacerbate the metabolic derangements, have detrimental effects on restoring liver function. Early enteral feedings can reduce infectious complications, stress ulcer and bleeding. Protein intakes of 1.2–1.4 g/kg (up to 1.5 g/L) should be provided as long as encephalopathy due to protein intolerance does not occur. In the presence of protein intolerance, formulas containing 33–50% branched chain amino acids are available can be provided at the 1.2–1.4 g/kg level. For normally nourished patients, the total energy expenditure is 30–35 kcal/kg (up to 40–45 kcal/kg when in sepsis), using dextrose provide 55–60% of the energy expenditures, the remaining is supplied by fat. If intolerance of enteral feeding, parenteral feeding can be used in this situation. TPN (total parenteral nutrition) via a peripheral vein is generally intended as a supplement to oral feeding. At the same time, micronutrients (minerals and vitamins) requirements should be supplemented [31].

To normalize and to avoid sharp fluctuation of blood glucose level with insulin in continuously intravenous infusion of glucose is important.

In continuous intravenous infusion of glucose, while administered insulin therapy, blood glucose control in the normal range. Avoid sharp fluctuations in blood sugar. Inpatients with liver failure, the branched-chain amino acids did not show superiority over other amino acid formula. L-ornithine-L-arginine has had controversial outcomes in reduction in ammonia and prevention of hepatic encephalopathy, but may help patients with liver reserve function. Avoid preparations containing glutamine for it will exacerbate cerebral edema in patients with liver failure [32].

4.2.2.9 How and When to Use the CBP (Continuous Blood Purification) Technique in Patients with Liver Failure

Since 1977, Krameretct first proposed the concept of continuous arterio-venous hemofiltration, CBP has quickly widely used in treatments of acute and critically ill patients, it has developed from the initial increase of the therapeutic effects in critically ill patients with acute renal failure to the treatment of a variety of commonly seen urgent situations, and has achieved a significant success, such as acute liver failure, hepatorenal syndrome, systemic inflammatory response syndrome, sepsis, multiple organ dysfunction syndrome and among others. This treatment usually tends for patients with hemodynamic instability and severe high catabolism. It can control the water, electrolyte and acid-base balance, maintain homeostasis, and ensure that the large volume of fluid can be delivered and intake adequate amounts

of protein and energy. CBP is preferred to IHD (intermittent hemodialysis) because of the hemodynamic stability in patients with liver failure can avoid the rising of ICP and reducing IPP. In china, CBP sometimes include the artificial liver support system.

High Volume (HV)-CVVH >90 mL/kg/day can reduce the dosage of vasopressors by effectively decreasing the level of the inflammatory factors (IL-2, IL-6, IL-8, IL-10, TNF, C3a and C5a, etc.) of a patient in sepsis. The animal experiments demonstrated this method have significantly improved the survival rate of the animals with sepsis. When the patients with ALF, SALF and ACLF have the complications of severe SIRS or sepsis, acute renal dysfunction or failure, cerebral edema, or ICP, hepatic encephalopathy, CBP are indicated. Due to the severe coagulopathy in liver failure patients, reduced doses of heparin, or complete withdraw of heparin may be the reasonable choice. Studies have failed to show high dose CRRT is superior to low dose of CRRT and large dose may aggravate the already existed hemodynamic abnormalities, hypotension, cerebral edema and ICH. In my practice, HV-CVVH can also facilitate the elimination of ammonia in hepatic encephalopathy patients of liver failure.

There is a technique using regional citrate anticoagulation method, infusion of 4% trisodium citrate proximal to the filter (at a rate of 3–7% of the blood flow) and to neutralizing it at distal side with calcium chloride to maintain serum-ionized calcium level of 1.0–1.1 mmol. In order to avoid metabolic alkalosis and hypernatremia, the constituents of the replacement fluid are sodium chloride 113 mmol/L, magnesium chloride 0.797 mmol/L, calcium gluconate 1.6 mmol/L, and glucose 10.6 mmol/L. In addition, the artificial liver support systems have now widely in patients with liver failure (plasma exchange, hemodiafiltration, molecular adsorbent recirculating system), in a broad sense, they also belong to the category of blood purification technology. It has become the main methods to treat the patients with liver failure.

4.2.2.10 Prognostic Evaluation of Patients with Liver Failure

There are many scoring systems can be used to assess the severity of patients, such as acute physiology and chronic health evaluation (acute physiology and chronic health evaluation, APACHE), Sequential Organ Failure Assessment Scoring System (sequential organ failure assessment scoring system, SOFA) and other universally valid applications for prognostic evaluation in ICU patients, but for acute and chronic severe hepatitis patients temporarily, if applicable, require further study [33]. For patients with liver failure, to assess patient function of various organs and the prognosis is very important. Its greatest value lies indistinguishing those patients without spontaneous recovery or death, so those who can not spontaneously recover as early as possible for the liver transplant to save the lives of patients. Pathogens may provide important information for determining prognosis, such as the ALF acetaminophen poisoning, viral hepatitis, shock liver and liver disease due to pregnancy. While not receiving liver transplants, there are more than 50% survival rate, while other etiologies such as ALF, only less than 25%.

Some special assessment system used in patients with liver disease, such as Child-Turcotte-Pugh (CTP), model for end-stage liver disease (MELD) for liver cirrhosis and king's college criteria for ALF. The King's College criteria are widely used to assess of the severity of ALF and the potential variability of the prognosis, with a sensitivity of 68–69% and a specificity of 82–92%. Recent addition of lactate level in patients with ALF has been found to improve the sensitivity and specificity for the prognosis.

Using King's College hospital criteria to predict mortality is not accurate, the specificity for patients with ALF is about 92%. But the sensitivity is only 69%, which may lead to the patients who should receive liver transplantation lose the opportunity and who do not need liver transplantation receive the operation. On the one hand this will undoubtedly result in a waste of medical resources, on the other hand, it lead to patents' family having to pay a heavy price. So the criteria must be amended to improve its accuracy of prediction, or more effective and accurate evaluation criteria should be established to predict the prognosis of ALF.

With the extensive development of liver transplantation, United Network for Organ Sharing (UNOS) has developed a scoring system known as the Model for end stage liver disease, or MELD, in which the sickest patients are given priority for organ allocation. MELD has four parameters: $3.8 \times \ln$ [bilirubin (mg/dL)] + $11.2 \times \ln$ (lNR) + $9.6 \times \ln$ [creatinine (mg/dL)] + $6.4 \times$ (etiologies: biliary or alcoholic 0; the other 1). Initially it is used to successfully assess short-term survival in the patients who received the jugular vein portosystemic shunt (TIPS). The MELD scoring system is more objective in evaluation of the severity for patients with liver disease than CTP does [34]. Since 2002, UNOS has used this system to assess the severity of the patients and to allocate the organs and widely used in the other countries. The system gives each person a score based on how urgently he or she needs liver transplantation within the next 3 month and no longer based on principle of "first come, first served". The unreasonable allocation of the organ is avoided to the maximum. But there are still some disadvantages for MELD scoring system:

First, although variables are finally included in the MELD scoring system is determined by the multivariate analysis, these variables were first selected empirically for their potential impact on the prognosis of the patients, thus some important variables may not be included. Second, the variables in MELD scoring system theoretically are objective, it incorporates laboratory parameters that are easily available and reproducible, but some of them (creatinine, bilirubin) are varied with the treatment and complications (diuretic, sepsis or hemolysis). Third, In studies in which liver patients' plasma samples were tested using different prothrombin reagents, there was a substantial degree of variation in INR values. In china, not all of the liver centers use INR as a marker for liver failure patients. Fourth, the MELD score, which was initially created to predict survival rate in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts (TIPS), is used as a predictor for decompensated liver cirrhosis and ACLF except ALF. Fifth, this system, which is created from individuals with alcoholic liver disease and hepatitis C, should be verified in china, where the majority of the patients is infected with hepatitis B virus.

In short, severe hepatitis B can not be regarded simply as a simple disease, it should be think of it as a syndrome. Currently, there is no accurate model of prognosis with both high sensitivity and specificity to discriminate who are going to recover and who need emergency liver transplantation. For liver failure patients, not only is the MELD system needed but also certain specialists (e.g. Hepatologist, surgeon for liver transplantation and intensivist) should be referred to determine who need liver transplantation accurately and precisely. Standard care of the patients and use of liver support modalities may bridge the patient to liver transplantation.

4.2.3 ICU Nursing Care of Severe Hepatitis

4.2.3.1 How to Observe the Severity of the Illness

The most common causes of death are the complications of the liver failure, which is the presence of hepatic encephalopathy, bleeding, hepatorenal syndrome, endotoxemia, and electrolyte imbalance are the most critical stages for acute or chronic hepatitis. It is very important for early detection and timely treatment to save the patient's life. 24 h nursing care in ICU at the bedside for critically ill patients is truly the first line of care, the observational level of details, early alert capabilities, expertise on the disease and the responsibility of the nurses would all have strong impact on the nursing quality of the critically ill patients [35]. Below described the contents of disease observation and nursing in ICU:

Disease Observed-Observation of Consciousness and Speech and Behavior of Patients

Hepatic encephalopathy can occur in chronic or acute liver failure, life-threatening complication of cerebral edema occurs in 3/4 of patients with grade 4 encephalopathy. The nurses have to pay more attention to the any changes of the consciousness, personality and behavior, such as crying, laughing for no reason, apathy, drowsiness or talking endlessly, slurred or low speech. It is an overt hepatic encephalopathy; if it develops from agitation to confusion, very drowsy and not reusable or even coma, and presence of apathy, pallor, sweating may prompt the patient in the shock state and should report to the doctor to manage the situation promptly.

Observe the Patient's Respiratory Abnormality

Respiratory abnormality often occurs in patients with hepatic encephalopathy, bleeding or secondary infection, the changes of respiratory rate, rhythm may reflect the degree of the brain edema, and therefore should be given close surveillance. The presence of fetor hepaticus, which is attributed to the presence of mercaptans, does not correlate with the degree and duration of the encephalopathy but reflect the mass necrosis of the liver. These should be notified to the doctors as soon as possible.

Body Temperature Changes

Patients with severe hepatitis due to liver cell necrosis often have persistent low fever, if the patient's body temperature gradually and continuously rises, it often

suggest the possibility of secondary infection, if physical cooling or cooling drugs used, the body temperature should be measured every half-hour and should be documented to provide the evidence for treatment.

Changes in Blood Pressure and Pulse

Hypotension and tachycardia may often suggest hemorrhagic shock. Hypertension, bradycardia and deep breathing may suggest the high ICP. After paracentesis and other invasive procedures, timing measure of blood pressure and documentation should be conducted.

Accurate Documentation of Daily Fluid Balance

To observe the changes in urine output, color and nature, such as a sudden oliguria or anuria may be the results of renal failure or great hemorrhage or shock, should alert to doctors to handle them.

4.2.3.2 Life Health Care

Maintain good hygiene. Disinfection of environmental and related items regularly; wash with mild soap and water, rinse well, pat dry carefully and gently. Do not rub vigorously directly over wounds. Keep the patients breathing smoothly, turning and knocking back frequently, apply suction to prevent respiratory tract infection and the occurrence of hypostatic pneumonia. Increase the times of teeth brushing for the patients who are awake and increasing oral care for the coma patients sometimes help with mouth gag.

4.2.3.3 Diet

The diet for severe hepatitis should be, principally, rich in sugar and vitamins and the adequate amount of protein. Avoid any injuries of esophageal mucosa from the eating solid, fried or spicy foods. The ability to eliminate the ammonia decreased due to the reduced liver function, the food containing large amount of protein should be properly controlled, especially those containing aromatic amino acids (animal proteins) to reduce the possibility of occurrence of hepatic encephalopathy. Prohibition of protein intake in patients with encephalopathy is controversial, vegetable protein is better tolerated than animal protein; the benefits related to the effects of dietary fiber on colonic function which include decreases in the transit time and intraluminal pH and an increase in fecal ammonia excretion, at the same time the intake of sodium and water should be balanced.

4.2.3.4 Psychological Care

Since it is difficult to treat the patients with severe hepatitis who is in the critical illness, pessimism, fear, despair, loneliness and other negative emotions will often be produced, nurses should pay more attention to the psychological needs of patients, appropriate words and behaviors to comfort the patients are necessary and clear explanation of the progress in the treatment and in nursing procedures should

be applied so that patients understand the best results can be obtained from compliance, regulated negative emotions and to finally overcome the disease [35].

4.2.3.5 Special Care

Hepatic Encephalopathy Care

the common complication in patients with severe hepatitis is encephalopathy due to the reduction in elimination of toxicity, it is important to keep the airway open, elevating the head to 30°; when in stage III encephalopathy, obtunded patients should be electively intubated for airway protection. Using nasogastric tube to feed the patients to meet the needs of nutrition. When needed, restriction measures to prevent the patients from fall and injuring themselves. Urinary catheter is often used to the patients with urine incontinence or retention, and it is convenient to observe the changes of urine output, color and nature. Urine test should be conducted regularly; keeping genitals clean and avoiding injuries in perianal and perianal skins.

Gastrointestinal Bleeding Care

Upper gastrointestinal bleeding is one of the major causes of death in patients with severe hepatitis. With active hematemesis, a nasogastric tube should be paced to reduce the risk of aspiration. Endotracheal intubation is indicated with hematemesis and decreased mental status, prior to endoscopy for active hematemesis, prior to insertion of esophageal tamponade tube and in the setting of shock. Continuous hemodynamic monitoring should be performed for the patients with hemorrhagic shock and the risk of rebleeding. When any signs of shock such as sweating, irritability or tachycardia appeared, the doctors should be notified; pay attention to the color and quantitative changes of stools, lactulose or vinegar enema can be administered in this scenario, but alkaline solution is prohibited since it can increase the absorption of ammonia. Hematemesis can stimulate the patients to produce the negative emotions such as fear, depression, despair, nurses should comfort the patients to establish the confidence of overcoming the disease.

The successful treatment of this severe quickly changing disease with many complications Nursing care should be accurate and targeting. Early detection, diagnosis and treatment are the key for the prognosis of the disease. As long as the medical team dedicate themselves to the treatment of the patients, many complications would be avoided, thereby mortality of the patients would be improved.

With the rapid development of critical care medicine, the survival rate of critically ill patients has been significantly improved; the new monitoring modalities and treatment methods have been invented and updated. All of those can be used to manage the patients with severe hepatitis to improve the prognosis, despite the difficulty of reaching a complete cure of liver function, valuable time can be earned to bridge the patients to liver transplantation.

4.3 General Treatment for AECHB and Severe Hepatitis B (Liver Failure) (Supportive Treatment, Nutrition Support and Nursing Care)

Xiao-Guang Dou Han Bai

4.3.1 Purpose and Significance of General Treatment

HBV infection mostly occurred in infancy and childhood in China. The majority of severe hepatitis B patients are acute attacks on chronic hepatitis B patients, except for a few acute severe hepatitis B patients. Since the majority of the patients are in the middle or later stage of chronic HBV infection, the treatment of these diseases is difficult and should be prolonged. Therefore, except for drug treatment, general supportive treatment, nutrition support and nursing care play very important role in the treatment of severe hepatitis B, and are the key points deciding the outcome of the diseases.

4.3.1.1 General Treatment Provides basic and Guarantee for All Treatments

First of all, medical workers should understand that general treatment is the basis and ensurence of the whole treatment for severe hepatitis B. The supportive treatment should be given to the patients once they are admitted, which including a necessary amount of carbohydrate, fat and protein to keep adequate intake of calories, blood products are also very important for supportive treatment. Eternal nutrition is necessary for patients with poor eating and dysfunction of pancreatic to reduce heart burden, systemic edema and pathoglycemia resulting from large amount of infusion. In addition, the emotional changes of the patients should also be noticed. Oral and skin care should be conducted to prevent fungal infections, limb function exercise is important to prevent muscle atrophy.

4.3.1.2 General Treatment Is Throughout the Course of the Treatment

Supportive treatment, nutrition support and nursing care should be given to the patients throughout the course of the treatment, rather than only in the critical conditions. The guides of nutrition support and nursing care are easy to be ignored once the diseases remission, especially when the patients can have normally diet. However, since recurrence of the disease usually occurs, nutrition support and nursing care should never be ignored. Oral nursing problems or fungal infection are usually the causes of death. Improving supportive treatment, positive and reasonable nutrition prescription, uninterrupted nursing care and correct etiological and symptomatic treatment may help the patients to recover earlier and better.

4.3.2 Methods and Significance of General Treatment

We used to rely too much on medication in the treatment of severe hepatitis B, but ignored the importance of supportive treatment in the recovery of the disease. The insufficiencies of general supportive treatment are the common reasons for unsatisfied outcomes or missing the best treatment time. General supportive treatment includes nutrition supportive, calories maintenance, electrolyte balance and the essential materials for the metabolism of the liver (such as amino acids, vitamins, fat and protein supplements). Prevent constipation and ensure the daily urine volume is essential to reduce the absorption of ammonia, urea and other metabolic poisons. Nutritional support is the most important but the most likely to be overlooked clinical issues. It is easy to be neglected in clinical practice that abnormal nutrition and metabolism (including sugar, lipids, and proteins) can even occur in patients with compensated liver function. Meanwhile, it is a major complication of the end-stage liver disease and is a significant risk factor affecting the short-term prognosis and long-term survival of the patients, especially in patients with severe hepatitis B. Many factors can lead to malnutrition in patients with severe hepatitis B. The patients usually have decreased appetite, nausea and abdominal distension, which result in the lack of dietary intake and poor digestion, at the same time, the complications such as infection or bleeding will increase the energy requirement. In particular, the hepatic and extra-hepatic abnormal metabolism in patients with severe hepatitis B will further aggravate the nutrition deficiency.

Malnutrition is common in patients with severe hepatitis B, which can severely weaken the reserve and regenerative capacity of the liver, and is an independent risk factor for poor prognosis. General supportive treatment can not only improve the nutritional status, but also improve the liver function, reduce the incidence of complications and improve prognosis of the patients.

Therefore, as an integral part of clinical treatment, the general supportive treatment is getting more and more important in clinical works.

General supportive treatment includes providing a quiet, ventilated and warm environment, regular air disinfection, ensure the patients with adequate supplement of water and no less than 1000 kcal of daily intake, with supplement of essential amino acids, sugar, fat and protein. Insulin should be added appropriately to patients with abnormal glucose metabolism. Properly administration of laxatives could reduce the intestinal absorption of ammonia. Supplement of blood coagulation factors, other blood products and some cytokines may helpful to increase in the body's immune function.

4.3.3 Evaluation and Treatment for Malnutrition

4.3.3.1 The Cause and Evaluation of Malnutrition

Patients with severe hepatitis B appear acute or sub-acute onset on the basis of chronic liver disease. Since the relatively long duration of the disease, it is widely accepted that most patients are accompanied with different nutritional deficiencies.

Malnutrition affects not only the prognosis of the disease, but also the regeneration of hepatocytes. Severe malnutrition leads to poor regeneration of hepatocytes, increase the basal metabolic rate which further accelerate the energy consumption, and worsen nutritional deficiencies.

Nutritional evaluation index mainly depends on the height, weight, BMI, fat thickness and other indicators, and Liver function has a great influence on these indexes. Therefore, in order to give a reasonable nutritional support, first of all, we must make a correct evaluation of the nutritional status of the patients.

Single Method Cannot Accurately Evaluate the Nutritional Status of Patients with Severe Hepatitis B

At present, the commonly used methods of nutritional status evaluation include human body measurement, creatinine height index (CHI) and subjective global assessment (SGA). Direct human measurement is convenient and economy, which include arm muscle circumference (AMC), arm circumference (AC) and triceps skinfold thickness (TSF), is usually used for the analysis of body tissue and fat storage. Since this method is not affected by ascites or lower extremity edema, it is suitable for all patients with liver disease. However, these indicators are less sensitive because it shift in the rear a few months after the occurrence of malnutrition. When body weight and body mass index as evaluation standard, it's easy to overestimate, and lead to underestimation of protein energy malnutrition, since the patients with chronic severe hepatitis B often had fluid overload and ascites. CHI is a sensitive indicator for protein nutrition in somatic cells. The 24 h excretion of urine creatinine of adult was consistent with the amount of lean body tissue (LBM). CHI was not affected by water and sodium retention, so it is a sensitive indicator of malnutrition in patients with chronic severe hepatitis B with normal renal function and no complications such as infection. For comprehensive nutritional assessment (SGA), the nutritional status of the patients was evaluated by evaluating the indexes such as weight and dietary changes, gastrointestinal symptoms, subcutaneous fat and muscle reduction, but since it is lack of quantitative indicators, the subjective impression is prone to bias, and also loss of appetite is one of the main symptoms of liver disease and ankle edema is common signs in patients with chronic severe hepatitis B. There for single SGA indicator does not apply in patients with chronic severe hepatitis B.

Overall, liver function of the patients with chronic liver disease will affect directly on the effectiveness of any indicators of nutrition evaluation. For patients with acute exacerbation of chronic hepatitis B are usually accompanied by the following situations: different degrees of fluid retention, edema and ascites, which will have great influence on the indexes of body weight and AMC, AC, BMI, TSF; the administration of human serum albumin or plasma to the patients will interfere with the evaluation on patients' nutrition status, so the serum albumin, pre albumin, lymphocyte counts may not reflect the actuarial nutritional status of the patients. This indicated that combined multiple nutritional evaluation indicators should be applied to patients with severe hepatitis B to make a comprehensive evaluation of nutrition status, rather than using a single index.

4.3.3.2 Reasons for Malnutrition

The main reason for malnutrition of patients with chronic hepatitis B is long-term insufficient dietary intake, coupled with impaired liver function, reduced ability of absorption and usage of sugar and fat, that leading to imbalanced energy metabolism. Meanwhile, majority of the patients were combined with infection, bleeding or suffering from diabetes, hyperthyroidism and other diseases, these will further aggravate the malnutrition. A large number of studies have shown that the metabolic rate of the patients with chronic liver disease was significantly increased by the lack of nutrition. Glucose metabolism induced thermogenesis and respiratory effort caused by ascites further increased the resting energy consumption. Infection or cytokine mediated acute phase inflammatory reaction of severe liver disease will also result in increased resting energy consumption that led to increased demand of energy. After 8 years follow-up of patients with liver cirrhosis, Tajika et al. reported that the decrease of non-protein respiratory quotient is associated with the lower survival rate; while the survival rate is higher in normal resting energy expenditure patients than those in lower or higher resting energy consumption.

In addition, the shortage of protein is common in severe hepatitis B patients. Since some of the patients were accompanied with hepatic encephalopathy, the dietary protein is strictly controlled at very low level, which makes it more difficult to increase protein and energy intake for the patients. Branched chain amino acids (BCAA) was used to be applied in the treatment of hepatic encephalopathy caused by imbalance of amino acid and neurotransmitter, since the metabolism of branched chain amino acids was mainly in skeletal muscle, it can reduce the burden on the liver and decrease the level of aromatic amino acids in the liver, rich in arginine, BCAA can also reduce the level of aromatic amino acids.

In conclusion, according to the multiple reasons for malnutrition in clinic, a targeted nutritional therapy must base on the specific circumstances.

The Intervention of Malnutrition

It has been widely accepted that nutritional support plays a very important role in the treatment of chronic severe hepatitis; however a few doctors are still worried that nutritional supplements will add the burden on the liver. Yet excessive control of the diet, especially protein diet, may aggravate malnutrition and impact the recovery of patients. Some other doctors who pay too much attention on intravenous nutrition supplement but ignoring the enteral nutrition, that will result in insufficient supplement and the deficiency of total calories.

4.3.3.3 Enteral Nutrition Support

The selection of nutritional components is very important for enteral nutrition in patients with chronic severe hepatitis B; enteral nutrition should especially be encouraged to carry out in patients with appetite. Besides replenish nutrients, modulates the supplementary food should also be included. Due to severe gastrointestinal symptoms at the onset of the disease, the main choice is digestible food, such as porridge, noodles, lotus root starch, soymilk, tofu, egg, milk, soft rice and so on, and appropriate vegetable oil and salt should be added according to the symptoms of

jaundice and the complications. During the recovery period, protein foods can be added gradually, such as lean meat, fish, etc., with appropriate adjustments according to the patient's taste. Protein intake should base on the severity of the disease and metabolic overload should be avoided.

In particular, it is encouraged to take a small amount of evening meal that is not only to provide carbohydrate and other energy supplements, but also have food rich in branched chain amino acids can enhance the night time protein synthesis, improve nutrition and glucose tolerance, correct amino acid imbalance, and reduce the body's consumption of fat and protein. Dietary supplements of antioxidant vitamins (such as vitamin A, vitamin C and vitamin E, etc.) can prevent the progress of liver disease; daily intake of 150–200 g green vegetables is recommended. Deficiency of Zinc can reduce appetite and immune function, excessive iron can promote the progression of liver disease and fibrosis, therefore, animal blood products rich in iron should be strictly limited, and increase Zinc rich food properly. For patients who can't intake adequate energy and protein by dietary, it is necessary to supply standard elemental diet by nasogastric feeding. Nasogastric feeding of liquid elemental diet can improve liver function, and increase the rate of survival. It is only necessary to change to total parenteral nutrition when the patients cannot intake any enteral nutrition [36].

Recent studies have showed that eating a diet rich in branched chain amino acid can ameliorate glucose intolerance, especially with night meal. After 1 week's treatment, non-protein respiratory quotient increased and oxidation decreased significantly, nitrogen balance and energy metabolism state can also be improved. It is accepted that enteral nutrition is the main route of nutrition supplement, because enteral nutrition is corresponding to normal physiological characteristics of the human body, easy to be accepted by the patients, and it can maintain gastrointestinal function in the patients, prevent bacterial translocation and the production of endotoxin. In short, the correct usage of enteral nutrition can significantly relive the symptoms; improve the effective rate and the nutritional status of the patients.

4.3.3.4 Parenteral Nutrition Support

Parenteral nutrition plays a vital role in the nutritional support of patients with chronic severe hepatitis B, despite the shortcomings such as for patients with diabetes, excessive intravenous infusion of glucose will increase blood glucose and make diabetes difficult to control, too much fat emulsion will worsen liver damage, extend the length of hospital stay and increase spending, etc. There is malnutrition or a risk of malnutrition when patients are unable or unwilling to eat normally because of different reasons. Parenteral nutrition can play a major role in providing valuable energy, improving nutritional status and maintenance of life.

In one word, the researches on nutrition support for severe hepatitis are still at the initial stage in China, there are some treatment principles but they are still lack of systematic research. Because of the differences in nomenclature, classification and etiology, the aboard research methods and results can only be used as references in our country. When using the parameters to evaluate nutritional status, it is required to not only pay attention to the research methods, but also to the special pathological

and physiological status of the liver. Use the indicators including nitrogen balance, CHI, etc. to replace the traditional indicators and avoid the limitations of the indicators. At the same time, establish a complete and standardized nutritional support scheme for the treatment of severe hepatitis B by correcting dietary changes and index of gastrointestinal symptoms.

4.3.4 Nursing Care

Nursing care plays a very important role in the treatment of patients with severe hepatitis B during the process of the whole treatment. Correct and in place nursing is the key to the success of the rescue, which including general nursing, psychological nursing, observation and nursing care of complications, reasonable dietary guidance, life care, skin care and skin care guidance after discharged, and so on.

4.3.4.1 General Nursing

General nursing includes the guidance of activity and rest for patients. Proper rest can promote the recovery of liver cells, due to 40% increased liver blood flowing when taking bed rest than standing. The liver gets more nutrients with more amount of blood flowing, at the same time; stay in bed can also reduce the energy consumption of the liver and accelerate the recovery of liver cells. In the case of the patients with a tendency of severe hepatitis B, they should be required to stay in bed, auxiliary passive activities, ensure an adequate sleep and appropriate protective isolation.

4.3.4.2 Psychological Nursing

Psychological counseling is important. It is easy to produce fear and pessimism of the patients since the development of severe hepatitis B is progressive, self-conscious symptom is getting worse, and due to visit to different hospitals, the patients usually understand of the disease. Moreover, the patients may appear emotionally unstable, showing a sensitive, lonely, more consideration, a strong sense of self-esteem and other diverse psychology since hepatitis B patients need to be isolated. When Checking, treatment and nursing, the medical staff should actively talk to the patient sand understand the psychological dynamic of patients to give correct guidance, try to achieve a consensus with patients at specific issues, so that the patients will feel valued and respected, and easy to cooperate with. The treatment effect of severe hepatitis B is relatively poor accompany with relatively high cost of treatment, the patients are prone to be pessimistic and negative, some patients even lose confidence and not willing to receive treatment. This is mainly due to Psychological stress, loss of self-value and lower self-confidence. At this time, the patients should have detailed explanation and induction, and based on their knowledge, the medical staffs should point out that although severe hepatitis B is difficult to treat, most of the symptoms can be controlled by the treatment and the coordination of the patients. In addition of comfort and encouragement, medical staffs should also create a clean and comfortable environment for the patients and stimulate the initiative of the

patients by telling them most of the previous cases were cured to transfer bad mood, establish the courage and confidence to overcome the disease.

4.3.4.3 Observation and Nursing of Complications

Patients with severe hepatitis B are in a critical condition with rapid progress, poor prognosis, multiple complications, and high mortality rate. Besides correct and timely treatment and rescue, the effective comprehensive nursing is vital in the prevention and treatment of complications. When the patient is getting worse, it is easy to induce disorder of fluid and electrolyte by vomiting and loss of appetite, coupling with restriction of protein and salt intake and application of large dose of diuretics. In addition, special attention should be paid to the other common complications such as large amount of ascites, hepatic encephalopathy, bleeding, secondary infection and liver kidney syndrome.

Care of Bleeding

Check the mucous membrane and the skin of petechiae every day, especially ecchymosis on venipuncture position, bleeding of gingival and nasal, color and traits of urinary and fecal discharge. Measure the amount and color of bleeding especially in massive hemorrhage of gastrointestinal tract. Patients with gastrointestinal bleeding should be fasted and kept at lateral position to avoid asphyxia caused by blood clots blocking the airway. Record the amount of bleeding, discharge and entry of liquid of 24 h and measure the color, frequency, quantity and nature of the stool, monitoring vital signs of the patients, and prepare for first aid.

Nursing of Hepatorenal Syndrome

Hepatorenal syndrome is one of the main reasons for death in patients with severe hepatitis B, especially in patients with ascites. It is easy to induce functional renal failure due to insufficient replenish of albumin when large amount of ascites was discharged. Closely observation of the amount of urine should be conducted in these patients, and be feedback to the doctors timely. At the same time, the amount of liquid intake and discharge should be record every 24 h, and pay attention to keep the effective circulating blood volume. Close attention should be paid to the patients who discharged a large amount of ascites at the daytime.

Secondary Infection Care

Patients with severe hepatitis B usually have decreased immune defensive function due to the dysfunction of immune system during the course of the disease, especially nonspecific cellular immune function and hypergammaglobulinemia, and are easy to be infected by a variety of infections, especially pulmonary infection and abdominal infection. Therefore, it is very important to keep the mouth and skin clean. For patients with ascites, abdominal pain and diarrhea could be the signs of spontaneous bacterial peritonitis. Help the patients with sputum and ensure of healthy drinking water and food are also very important.

The Care of Hepatic Encephalopathy

More vegetable protein and less animal protein are recommended for patients with severe hepatitis B. high calorie diet can prevent the production of ammonia and other harmful substances that inducing hepatic encephalopathy. Oral administration of lactulose is helpful to keep the smooth stool, reduce the absorption of intestinal ammonia, reduce the absorption of intestinal toxins and prevent hepatic encephalopathy.

Intervention should be given timely when the patients have the early manifestations of hepatic encephalopathy including is listlessness, indifferent, no desire, unresponsive or manic spirit, disorientation and memory loss. Intention care, more chat with patient, observe the change in behavior and consciousness will help to find early changes of the disease. For patients with hepatic encephalopathy, make their head to one side, keep respiratory tract unobstructed and give continuous low flow oxygen. Strengthen the protection and prevent falling bed for restless patients; indwelling catheter and accurately recording fluid input and output during the 24 h for patients with coma.

Care of Disorders of Water and Electrolyte

Whether the patients with fatigue, apathy, weakness, abdominal distension, convulsions and other electrolyte disorders should be observed. The diet should be adjusted based on the results of the blood electrolyte, and control the quantity of fluid input to prevent the occurrence of low dilution hyponatremia.

The Care of Ascites

Measure the abdominal circumference daily; record the fluid input and output accurately; sterile protection of the puncture wound of the ascites to prevent infection. Recommend the patient with low salt diet with the intake of salt less than 2 g/day. Control daily drinking water volume based on the severity of the disease and the amount of ascites; drinking water volume should not more than 800 mL in patients with a large number of ascites.

Reasonable Dietary Guidance

The patients should have light, low-fat, multi vitamin, proper amount of protein, easily digestible liquid and semi liquid diet to get an adequate calorie supplement. Alcohol and tobacco are prohibited. Patients with ascites, edema or cerebral edema should have low salt or no salt diet. To reduce the source of ammonia in the intestinal tract, the intake of proteins is prohibited in the patients with the precursor and early stage of hepatic encephalopathy. Diet containing preservatives should be avoided, preventing aggravating liver damage; hard, avoid fried and spicy food to prevent inducing of esophageal bleeding. Control the amount of intake each time, recommend to take little amount of diet but take it frequently according to the condition of the disease.

Strengthening the Life Care

Good life care is one of the best ways to reduce the complications. Oral cavity is the invasive pathway of secondary infection and other pathogens in patients with severe hepatitis B. Oral care is an important part of the rescue. For critically ill patients, clean the mouth three to four times per day, for self-care patients, enjoin postprandial gargle and brush teeth twice per day to keep the mouth with no smell and no mucosa ulcer. The changes of oral mucosa should be observed in patients using corticosteroids or long term using of antibiotics. Pay attention to skin and oral care for patients with coma, prevent the occurrence of mycotic stomatitis by observing the changes in oral mucosa. The process of protein metabolism may produce a large amount of ammonia, it can be excreted through the liver at normal condition, When liver dysfunction, ammonia can't get detoxification in the liver and lead to ammonia poisoning caused by elevated blood ammonia. Maintain smooth stool and an acidic environment in the intestine could reduce the absorption of ammonia. Patients with severe hepatitis B are encouraged to defecate at least once time per day. Develop a good habit of defecation, assess the cause of constipation. Patients with constipation are allowed to do cleaning enema or retention enema with acidic liquid.

Skin Care

Keep sheets dry and flat, for patients with coma, use air cushion bed to promote blood circulation and prevent pressure sores. Patients with skin itching should avoid alkaline soap when taking a bath to prevent the scratches by themselves. Warm water wash and coated with anti-itch medicine is recommended. Some of the patients with severe hepatitis B are complicated with skin itching caused by bile salt deposition that stimulate peripheral nerve. To avoid skin infections caused by scratched skin, nursing staff should help the patients to trim nails and take bath. For Patients with high serum bilirubin, skin itching caused by cholestasis can be relieved by daily warm water bath, frequently change underwear, keep the skin clean and wash with Sophora flavescens decoction or erasure with calamine lotion. Trim nails and prevent scratching are helpful to avoid skin infection.

4.3.4.4 Nursing Guidance for Post Discharge

Patients with severe hepatitis B can be discharged with continue treatment once the clinical indicators and clinical symptoms have been improved, but guidance after discharge cannot be ignored. First of all, most patients are on the basis of chronic hepatitis B, antiviral therapy must be the main treatment strategies. The anti-virus treatment should be kept a long-term, must be regularly reviewed and mustn't be stopped without permission. The treatment plan should be adjusted according to the response of the patients. Therefore, emphases the necessity and importance of regular review in detail when discharges, help the patients to make a review schedule and remind patients of the review are very important to prevent the recurrence. Explain to the patients the relationship between compliance and efficacy of the treatment, bad compliance would affect the efficacy greatly and lead to deterioration of the disease. For severe hepatitis patients on the basis of autoimmune liver disease and alcoholic liver disease should continually treat the original disease and

quit drinking after discharge. In addition, guide rational use of drugs, avoid drugs damage to liver function; pay attention to work and rest, avoid heavy manual labor within 6 months after the disease; reduce the frequency of access to public places; reduce the chances of infection; maintain a good mental state, take a pleasant, optimistic, positive attitude to life; maintain smooth stool and relieve constipation; pay attention to urine volume and the severity of ascites. Rational use of diuretics, maintain the balance of water and electrolytes. If the patients with the symptoms of abdominal discomfort, vomiting, black stool or other symptoms should be promptly send to the hospital.

In general, severe hepatitis B is a very serious disease with high mortality, active and reasonable medical care is very important to prevent the progression of the disease. Find the signs of complications as early as possible, carry out the correct nursing care and effective discharge guidance, change the traditional passive nursing to active mode, follow the principle of "early prevention, early discovery, early nursing", can obtain the better preventive effect than routine nursing.

4.4 Immunotherapy and Cellular Therapy for Acute Exacerbation of Chronic Hepatitis B and Severe Hepatitis B (Liver Failure)

Wen-Tao Wang and Xi-Ping Zhao

Severe hepatitis (SH) is the clinical syndrome with a series of manifestations including jaundice, coagulopathy, elevated alanine aminotransferase (ALT) levels, encephalopathy, liver decompensation and increased MELD (model for end-stage liver disease) score [37, 38]. According to the pathological features and progressing rate of diseases, SH can be classified into four categories: acute liver failure (ALF), subacute liver failure (SALF), acute-on-chronic liver failure (ACLF) and chronic liver failure (CLF) [39]. Despite the traditional therapy based on supportive care, the majority of patients with SH still have a very poor prognosis if liver transplantation isn't available [40]. Nowadays, orthotopic liver transplantation has been considered to be the most effective method. However, liver transplantation hardly becomes the routine treatment due to the shortage of donor, exorbitant price and long-term immunosuppressive therapy. In addition, the long-term survival rate is still unsatisfactory although liver transplantation has significantly improved the short-term survival rate [41]. Over the past decades, immunotherapy and cellular therapy has attracted more and more attention, which provides an alternative strategy for the treatment of SH. Here, we review available data regarding the application of immunotherapy and cellular therapy, and discuss the prospectives and hurdles of novel strategies in the treatment of SH. In this chapter, we will focus on the clinical application of immunotherapy and cellular therapy in the treatment of acute exacerbation of chronic hepatitis B (AECHB), considering that hepatitis B (HBV) infection is one of the most common causes of SH and the majority of SH patients manifest AECHB [37, 39]. As described in previous chapters, acute

exacerbation of chronic hepatitis B (AECHB) is characterized by the imbalanced cytokine profile, uncontrolled activation of immune cells and progressive loss of viable hepatocyte. Therefore, some strategies which have already been demonstrated to be effective in ALF, SALF and advanced liver cirrhosis may also be suitable for AECHB although this conclusion remains to be validated in the future clinical practice.

4.4.1 Effect of Cytokine on Promoting Hepatocyte Regeneration

Inhibiting the apoptosis/necrosis or promoting the proliferation of hepatocytes is a very key step to the treatment of AECHB due to the drastic reduction of viable hepatocyte. Many cytokines have been demonstrated to have protective functions of hepatocytes. Some has been applied to the treatment of AECHB, such as glucagon-insulin, hepatocyte growth factor and prostaglandin E1, while others remain to be further studied.

4.4.1.1 Glucagon-Insulin

The glucagon-insulin therapy has been applied to clinical practice in SH for a very long time because of low price and favorable curative effects [42]. The conventional usage is that glucagon 1 mg and insulin 10 U is added to 10% glucose 500 mL at one time per day for 3 weeks. It can effectively prevent the further damage of liver and protect the remnant liver tissue. During the infusion period, the side-effects like vomiting, heart palpitations and hypoglycemia should be closely observed. However, some studies also showed that insulin-glucagon infusion wasn't enough to improve the prognosis of SH patients especially in severe biopsy-proven hepatitis, indicating that the therapeutic effect of glucagon-insulin infusion is limited [43].

4.4.1.2 Hepatocyte Growth Factor (HGF)

HGF was first purified from the plasma of SH patients as a potent mitogen of hepatocyte [44]. HGF shows the special protective effects in the treatment of SH. It can stimulate the proliferation of various types of cells including hepatocytes through HGF/c-Met pathways [45]. In vitro and in vivo studies also found that HGF exerted protective and anti-apoptotic functions through preventing Fas-triggered death of hepatocytes [46, 47]. A recent study demonstrated that HGF ameliorated the immune-mediated damage during viral hepatitis by modulating DCs activation and T cell priming, but viral clearance wasn't compromised [48]. In addition, HGF induced the retention of ductal structures, avoided ductal proliferation and damage, and modulated the hepatic inflammatory response through down-regulating the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which may reduce the extent of liver fibrosis after SH [49]. Ido and his colleagues reported that repeated intravenous administration of rh-HGF at a dose of 0.6 mg/m^2 was well tolerated in SH patients [50]. The efficacy and safety of rh-HGF at an increased dose needs to be further investigated. Some potential adverse effects of rh-HGF should be carefully considered. Repeated intravenous administration of rh-HGF may increase urinary excretion of albumin and lead to a drop in blood pressure [51].

HGF may induce carcinogenesis due to stimulating the cell proliferation, so the long-dated safety should also be followed up ~~after the cure of SH~~ [52].

4.4.1.3 Prostaglandin E1 (PGE1)

PGE1 is well known as a vasodilator and exerts a broad range of protective effects on liver tissue in SH [53]. The mechanisms of promoting liver regeneration may include the following [54]: (1) improving the microcirculation through inhibiting platelet aggregation; (2) stabilizing the cell and lysosomal membrane; (3) inhibiting the cytokine release from LSECs, such as TNF-α and IL-6. In an animal model of acute liver damage, PGE1 markedly improved survival rate after massive hepatectomy in rats by enhancing heat shock protein and alleviating endoplasmic reticulum stress [53]. Co-administration of PGE1 and somatostatin obviously attenuated liver damage of rats, which down-regulated the production of inflammatory factor TNF-α and IL-6 and inhibited hepatocyte apoptosis via down-regulation of Bax and caspase-3 and up-regulation of Bcl-2 [55]. In a randomized control trial, combined therapy of lipo-PGE1 and glucagon-insulin alleviated liver damage, which was indicated by the trends of relatively lower alanine aminotransferase (ALT) levels [54]. The recommended dose is 10–20 μg lipo-PGE1 every 12 h for 1 week.

4.4.1.4 Hepatic Stimulator Substance (HSS)

HSS is a hepatotrophic protein that was first extracted from the liver cytosol of regenerating adult rat and normal weanling rats [56]. HSS has been shown to protect the mice liver from acute failure induced by chemical poisons or drugs, such as D-galactosamine, ethanol, cadmium, thioacetamide, acetaminophen or CCl4 through stabilizing biomembranes and cellular enzymatic systems [57]. Although recombinant HSS protein has been supplied, directly administrating recombinant HSS protein is limited due to short half-life and wide distribution in other organs and tissues. Li et al. constructed HSS encapsulated by sterically stable liposomes, which showed a longer half-life and markedly improved the therapeutic effect on FHF in rats [58]. Another study from China used a naked plasmid encoding human HSS, they found it effectively protected the mice liver against failure via suppressing the mitochondrial permeability transition [59]. Therefore, it is desirable to investigate the efficacy of HSS from various forms in future studies.

4.4.1.5 Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF not only enhanced hepatocyte proliferating capacity but also ameliorated the histologically evident liver injury in adult male Wistar rats [60]. Recent studies have demonstrated that G-CSF subcutaneously plus standard therapy could improve survival of SH patients, reduce Child–Turcotte–Pugh scores and prevent the development of complications when compared with placebo plus standard therapy [61, 62]. The subcutaneously injected dose was 5 μg/kg for 6 consecutive days or daily doses for the first 5 days and subsequently every 3rd day. G-CSF therapy was well tolerated in these studies. Moreover, G-CSF also induces the migration of bone marrow-derived stem cells to the injured liver, which has been demonstrated to play an important role in the cellular therapy for liver disease [63].

4.4.1.6 Other Cytokines

Epidermal growth factor (EGF) is expressed in the adult normal liver at physiological levels but is markedly up-regulated after liver injury [64]. It has been proven that EGF administration via peritoneum or vein can accelerate the proliferation of hepatocytes in mice [65]. However, various tumors such as lung cancer may also express the EGF receptor [66], and the side-effects of long-term application have to be seriously weighed. Hepassocin exerted a specific mitogenic function on primary hepatocytes in vitro via mitogen-activated protein kinase (MAPK)-dependent signaling pathway and obviously improved the survival in rats with FHL after administration [67]. Endothelial growth factor (VEGF) stimulated liver regeneration in rats with partial hepatectomy [68]. Another cytokine, platelet-derived growth factor (PDEF), were reported to up-regulate the expression of pleiotrophin, which was a potent mitogen for hepatocytes [69]. These cytokines may be applied to clinical practice when the safety is well addressed.

4.4.2 Application of Glucocorticoid

Glucocorticoids are broad-spectrum immunosuppressive agents. According to previous researches, glucocorticoids may protect liver tissue against further damage through the following mechanism [70]: (1) effectively bringing the excessive immune responses back to normal and preventing the cytolysis of infected hepatocytes; (2) stabilizing the cell and lysosomal membrane; (3) improving the microcirculation and alleviating the hypoxia of liver tissue; (4) antagonizing the effects of endotoxin and providing a favorable condition for liver regeneration; (5) enhancing the anti-stress capability of body against harmful stimulation. Several studies have demonstrated the curative effects of glucocorticoids on patients with SH. Mathurin et al. analyzed five randomized controlled trials and found glucocorticoids significantly improved the short-term survival in patients with severe alcoholic hepatitis [71]. Wu et al. assessed the therapeutic effects of short-term low-dose glucocorticoids on patients with early-stage SALF and observed that the treatment group exhibited greater improvement of survival rate and shorter mean hospitalization [70]. However, the usage of glucocorticoids in patients with SH is still controversial. Some studies suggested that the immune function in end-stage SH was suppressed and even paralyzed [72]. If steroid therapy is applied to patients with immunosuppressive status, the effects are contrary or even disastrous. Mathurin et al. proposed the three patterns of steroid responses based on Lille score which was defined by age, albumin and bilirubin, etc. [71]. The survival influence of steroid therapy was significant on complete or partial responders (Lille score <0.45) but was negligible on null responders (Lille score ≥ 0.45). Some clinicians had reported that the immunosuppressive therapy could activate HBV infections, eventually resulting in liver failure in patients with current or past HBV infections [73, 74]. Regarding these facts, the Food and Drug Administration (FDA) had warned on HBV reactivation with immunosuppressive drugs [75]. Hence, it must be prudent to use glucocorticoids in patients with SH. Agreement has yet to be reached with

regard to the dose and duration of steroids therapy. In a Japanese study, the introduction of high-dose steroids was shown to reverse deterioration in patients with early-stage severe exacerbation of chronic hepatitis [76]. The adoptive doses of prednisolone were 60 mg/day or more for a minimum of 4 days, and then were reduced to 30 mg by 10 mg every 4 days when prothrombin time was remitted in trends, and were finally tapered off by 2.5 or 5 mg/week. Collectively, glucocorticoids are like a double-edged sword, which only produce positive effects when they are used appropriately.

4.4.3 Application of Thymosin

Tα1 is a 28-amino-acid peptide and originally isolated from thymus. Tα1 has been widely applied to clinical practice as an immune enhancer including viral and bacterial infectious diseases, immune deficiency disease, cancer, and immune adjuvant for vaccines. Tα1 can involve innate immunity through interacting with Toll-like receptors (TLRs), especially with TLR9 and TLR2 on DCs and precursor T cells, and activating the p38MAPK, NF-κB and MyD88-dependent signaling pathway [77]. Tα1 has already been shown to increase the function of regulatory T cells through activating the tryptophan catabolism pathway, which inhibits the excess production of cytokine and prevents the potential pro-inflammatory cytokine storms [78]. Besides, Tα1 exerts its immune-modulating functions on subpopulations of T cells through enhancing the effects of NK cells, Cytotoxic T cells and T helper cells with the increased secretion of cytokines such as IL-6, IL-12 and TNF-α [77, 79, 80].

Zhang et al. compared lamivudine monotherapy with lamivudine and Tα1 combination therapy among HBeAg-positive patients from eight controlled Trials, and they found the latter had higher virological response rate and ALT normalization rate [81]. Based on these evidences, Tα1 has been recommended as adjuvant treatment for chronic hepatitis B (CHB) in the Asian Pacific Association for the Study of the Liver guidelines [82]. However, a recent multicenter, randomized study found that a short-term duration of Tα1 treatment combined with peg-interferon α-2a wasn't superior to only peg-interferon α-2a in CHB patients, suggesting that 3 months might be insufficient to enhance the efficacy of peg-interferon-based antiviral therapy [83]. At present, the data about Tα1 in SH are still small, and the optimal dose and treatment timing need to be explored in future clinical trials.

4.4.4 Monoclonal Antibodies Against the Inflammatory Mediators

Some relevant researches have provided an important insight into the deleterious effects of inflammatory cytokines in connection with the severity of immune dysfunction and organ failure in SH. The inflammatory cytokine cascade amplification is a very key step in the exacerbation of diseases, so blocking the action of

inflammatory mediators may alleviate liver injury. In recent years, several antibody-based drugs against inflammatory mediators have been approved by FDA or other drug supervision institutions, which will provide a golden opportunity for the usage of these drugs in patients with SH.

4.4.4.1 TNF-α Blockage

Apart from inducing apoptotic cell death, tumor necrosis factor-α (TNF-α) is also a central pro-inflammatory cytokine of SIRS [84]. It has been demonstrated that the levels of TNF-α in serum and liver tissue were significantly elevated in SH patients [85, 86]. TNF-α monoclonal antibodies, infliximab and adalimumab, have been shown to be clinically effective in various TNF-α-related diseases including rheumatoid arthritis, ulcerative colitis and Crohn's disease [87–89]. Sharma et al. evaluated infliximab therapy in 19 patients with severe alcoholic hepatitis, and found that single-dose infliximab (5 mg/kg body weight, a single 2 h infusion) significantly improved the parameters of severity and 2-months survival [90]. However, three patients had pneumonia and two developed into a flare of pulmonary tuberculosis. Another study showed that the incidence rates of seriously infectious events were higher in etanercept (another TNF-α monoclonal antibody) group with a higher 6-month mortality rate [91]. These studies remind us that it is clearly not the case what we imagine must be the same as realistic effect. Malik compared infection and inflammation to two sides of the same coin in liver failure [92]. Future studies should be performed to explore which patients are likely at high risk of subsequent infections and suitably targeted for intensive surveillance and treatment.

Immunoglobulin new antigen receptors are a subset of antibodies comprising five constant domains and a single variable domain (vNAR). VNAR domains are regarded as recognition units and attractive candidates for antibody-based therapy. In an animal model of endotoxic shock, anti-TNF vNAR single domains obviously improved the survival of murine through regulating the TNF/IL-10 balance and attenuating IL-6 gene expression [93]. Xu et al. demonstrated that soluble TNF receptor: IgG-Fc (sTNFR:IgG-Fc) prevented the development of ALF or ACLF by blocking the TNF/TNFRp55 pathway and reducing hepatocytes apoptosis [94]. These studies may provide new concepts for TNF-α blockage in future treatment of SH.

4.4.4.2 IL-1β Blockage

IL-1β is a pro-protein produced by activated macrophages and processed to its mature form by caspase-1 [95]. It is elevated in patients with SH, suggesting that IL-1β may be associated with the development of SH [96]. Sgroi et al. found that IL-1 receptor antagonist (IL-1Ra) accelerated the proliferation of hepatocytes and modulated the inflammatory stress in the early phase after partial hepatectomy [97]. Hu et al. further confirmed that IL-1Ra could inhibit hepatocellular apoptosis by reducing the release of mitochondria cytochrome c and down-regulating the expression of caspases, thereby preventing the hepatotoxic effects of acetaminophen (APAP) [98]. A recent study combined mesenchymal stem cells (MSCs) with IL-1Ra using genetic engineering technology, which suppressed local and systemic

inflammatory responses and markedly reduced mortality rates in rats with FLF [99]. Anakinra, a monoclonal antibody against IL-1 receptor, has been on sale for the treatment of rheumatoid arthritis [100]. However, Aly et al. reported a case of anakinra-associated SALF [101]. Ishibe et al. also found that IL-1Ra might increase cytochrome P450 enzyme expression, thereby aggravating APAP-induced liver injury [102]. In consequence, there is still a long way to go before IL-1Ra is widely used for patients with SH.

4.4.4.3 IL-6 Blockage

It has been documented that IL-6 is an important mediator of inflammatory response in SH [103]. Tocilizumab is a human monoclonal antibody that binds to IL-6 receptors, inhibiting IL-6-mediated signaling pathway and its inflammatory effects. Previous clinical studies showed that tocilizumab effectively alleviated the symptoms of rheumatoid arthritis [87]. In an experimental model combining trauma and hemorrhagic shock, neutralizing IL-6 with monoclonal antibody attenuated organ injury through selectively suppressing inflammatory mediator and partially normalizing immune dysfunction [104], so IL-6 blockage is still a promising method despite lack of adequate evidence in SH. Recently, Alfreijat et al. described a case of patient with rheumatoid arthritis who developed into SH after the treatment with tocilizumab [105]. The detailed causes remain unstudied, but we should attach importance to the potential hepatotoxicity of tocilizumab in future studies of SH.

4.4.5 Other Immune Strategies

4.4.5.1 Toll like Receptors (TLRs)

TLRs are characterized by leucine-rich repeat in the ectodomain, which recognize respective pathogen-associated molecular patterns (PAMPs) [106]. The TLRs family members can be usually divided into two subpopulations according to their cellular localization. TLR1, 2, 4, 5, 6 and 11 are expressed exclusively on the cell membrane, while TLR3, 7, 8 and 9 are localized in intracellular compartments. TLR4 is a transmembrane protein mainly expressed in macrophages such as Kupffer cells, which plays an important role in activating macrophage and mediating pro-inflammatory cytokine release [107]. In an animal model of endotoxin-induced acute liver injure, E5564, a TLR4 antagonist, could mitigate the liver damage through blocking TNF-α overproduction from macrophage [108]. Ma et al. found that sesamin could prevent LPS-induced FHF in mice by suppressing the expression of TLR4 [108]. TLR9 predominantly recognizes viral DNA and synthetic oligodeoxynucleotides (ODNs). The Function of TLR9 is controversial. TLR9 activation could aggravate liver injury by promoting the activation of CD4+ NKT cells [109]. However, it was recently shown that DCs secreting IL-10 may alleviate liver ischemia-reperfusion injury via TLR9 [110]. Besides, signaling through TLR2 and TLR3 has also been demonstrated to contribute to liver failure, especially in the early phase [111]. These researches lead us to TLRs blockade strategy aiming at preventing liver injure, but the roles of TLRs in SH are in need of further confirmation.

4.4.5.2 Natural Killer Cells and Natural Killer T Cells (NK/NKT Cells)

NK and NKT cells are much more abundant in liver tissue than other tissues and peripheral blood. It has been documented that the activation of NK/NKT cells involves in the progression of SH in acetaminophen and concanavalin-A (ConA) ALF models [112, 113]. For one thing, NK/NKT cells can directly induce the apoptosis of hepatocytes via perforin/granzyme or Fas/FasL pathways [114]. For another thing, activated NK/NKT cells can release large amounts of inflammatory mediators, such as IL-5, IFN-γ and IL-4, which indirectly participate in liver damage through inducing hepatocyte apoptosis, up-regulating the expression of LSEC adhesion molecule and activating other immune effector cells [115]. The biological activity of NK/NKT cells is regulated by activator and inhibitor receptors on the cell surface. NKG2D is an activating or co-stimulatory receptor and its surface expression is increased in hepatitis B. Chen's study showed that the expression of NKG2D ligands in hepatocytes was markedly increased and (HBV) transgenic mice were more susceptible to liver injury induced by ConA [116]. These findings were further demonstrated by Vilarinho's research in which the blockade of NKG2D could inhibit HBV-mediated acute hepatitis and liver injury [117]. Blocking the activator receptors on NK/NKT cells surface may be efficacious strategies for therapeutic intervention given that the activation of NK/NKT cells has been implicated in SH.

4.4.5.3 Monocytes/Macrophages and Kupffer Cells (KCs)

Monocytes/macrophages are central cellular component to both SIRS and CARS. After the exposure to LPS or other microbial constituents, monocytes/macrophages are activated and produce large amounts of pro-inflammatory cytokines [115]. Monocytes/macrophages also possess the ability to digest, process and present antigen, which in turn trigger the adaptive immune responses. The serum endotoxin level is often elevated in patients with SH [118]. Following repeated exposure to endotoxin, monocyte function is impaired with the alterations in inflammatory cytokine secretion and HLA-DR surface expression [119]. KCs, liver-specific macrophages, reside in liver sinusoid and serve as gatekeepers. Some studies confirmed that the early devastating activation of KCs has been implicated in the pathogenetic mechanisms of SH [120]. Tsutsui elaborated the important roles of KCs in two models of liver failure [121]. KCs contributed to LPS-induced liver injury through secreting pro-inflammatory cytokines and LPS tolerance as described above. However, in ConA-induced ALF, KCs initiated pathogenic intrasinusoidal thrombosis in collaboration with LSEC. In a mouse model of ConA-induced ALF, the secretion of pro-inflammatory cytokines by KCs was significantly inhibited through the blockade of intracellular HMGB1 expression [122]. Compared with wild-type mice, KCs depleted mice manifested attenuated liver damage and lung inflammation following acetaminophen-induced ALF [123]. One point must be noted: the roles of KCs are gradually altered in SH. Immunotherapy should be targeted at restraining the massive activation of monocytes/macrophages at the initiation phase of SH, but it is also crucial for the later resolution of macrophage paralysis in CARS phase.

4.4.5.4 T Cell Immunomodulators

During the early stage of HBV-related SH, massive HBV-specific CD8+ T cells are activated and may directly eliminate HBV-infected hepatocytes, resulting in liver damage [124]. Therefore, limiting effector function of HBV-specific T cell may ultimately alleviate liver damage and prevent the occurrence and development of liver failure. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a key negative regulator, which is recruited to T cell membrane upon activation of the TCR receptor where it binds to accessory molecules B7 expressed by the antigen presenting cells (APC) [125]. CTLA-4 ligation effectively prevents further activation and expansion, thereby negatively regulating T cell function. Metushi et al. found that amodiaquine and anti-CTLA-4 resulted in a greater increase in ALT level than treatment with amodiaquine alone in PD-1 (−/−) mice, which was similar to idiosyncratic liver injury [126]. A recent study demonstrated that replication-defective adenovirus expressing CTLA-4Ig could induce immune tolerance and prolong islet allograft survival [127]. In Uchida's research, they found that CTLA-4 mediated ALF through the damage of HBV-infected hepatocytes, which could be rescued by CTLA-4 immunoglobulin (CTLA-4Ig) [128]. Abatacept, as a CTLA4-Ig, has been recommended for the treatment of refractory rheumatoid arthritis [100], which may be used for the treatment of SH in the short run. Programmed death-1 (PD-1) is another T cell receptor and exerts similar biological activity to CTLA-4 [129]. PD-1 is mainly expressed on the surface of activated T cells, rendering CD8+ T cells unresponsive or exhausted. Related research has shown that decreased PD-1 expression on HBV-specific CD8+ T cells was significantly associated with ACLF [130]. They thought that the low PD-1 expression might reverse PD-1-mediated restraint of CD8+ T cell responses. In addition, Ji et al. also found that stimulating PD-1/B7 signals with anti-B7-H1 mAb could protect mice liver tissue from ischemia-reperfusion injury through inhibiting T cell activation and KCs function [131]. CD28 has been identified as an important T cell receptor for co-stimulatory ligands, such as CD80 (B7-1) and CD86 (B7-2). Previous study found that the expression of ligands CD80, CD86 and CD28 in liver tissue was enhanced in patients FLF, suggesting that abnormal expression of CD28/B7 might participate in the immune-mediated pathogenesis through excessive antigen presentation in FLF [132]. It has been proved that anti-CD28 monoclonal antibodies induced donor-specific tolerance to allografts and prong graft survival in rat liver transplantation model through blocking co-stimulatory signals [133]. Although the related study is scarce in SH, blocking co-stimulatory signals CD28/B7 may provide an alternative method for T cell immune modulation.

4.4.6 Cell Transplantation

Over the past decades, cellular therapy has been taken to new heights built on technological advance, innovatory concepts and lots of clinical studies. Hepatocyte transplantation has been demonstrated to be basically effective and safe in patients with liver failure. Stem cells hold great promise as option for the treatment of liver

failure owing to the proliferative and differentiation potential. In particular, the advent of induced pluripotent stem cells greatly revolutionizes regenerative medicine. Here, we discuss the current status and challenge facing cellular therapy and summarize our efforts in propelling them from bench studies to bedside application.

4.4.6.1 Hepatocellular transplantation

Conceptually, primary adult human hepatocytes are ideal sources of cellular therapy. Hepatocyte transplantation (HT) is less invasive than orthotopic liver transplantation and multiple patients with liver failure can benefit from one donor liver [134]. What's more, hepatocytes can be cryopreserved for a long term, while donor livers must be immediately used in liver transplantation. It has been demonstrated that this procedure was basically safe for patients who undergo HT in adult and children [135, 136]. During the past 30 years, extensive studies have investigated the efficacy of hepatocyte transplantation in patients with liver failure or some metabolic liver disease [136–140]. Intraportal or intrahepatic injection is generally preferred as the method delivering hepatocytes. However, intraportal administration was reported to augment the risks of portal vein thrombosis [141]. Another concern is that intraportal injection may enhance portal venous pressure given that many patients with liver failure, especially end-stage liver cirrhosis, have distorted liver architecture and portal hypertension. In a 5-year follow-up study, MRI (Gd-BOPTA) scanning showed the existence of living hepatocytes signals in spleen even after 48 months, and histopathological analysis further demonstrated the small clusters of the surviving hepatocytes in the 2nd year, suggesting that intrasplenic infusion is feasible and effective [136]. The peritoneal cavity was also proposed as transplanting sites. However, transplanted hepatocytes normally do not survive long in the peritoneal cavity environment owing to the lack of anchorage [142]. Yokoyama et al. established a vascularized subcutaneous space with a polyethylene terephthalate mesh device coated with poly(vinyl alcohol), which effectively prolonged the survival of hepatocyte [143]. This founding provides novel insights into the procedures of hepatocyte administration. Agreement has yet to be reached with regard to the optimal doses and repeated times. In two successful reports, the used number of hepatocytes was $4.2–6.0 \times 10^{10}$ and 0.88×10^{9} per patient, respectively [136, 139]. The huge difference implied that available hepatocyte quantity in different studies limited the standardization of treatment protocols. Hepatocyte transplantation significantly improved laboratory parameters and prognostic scores in patients with liver failure, such as decreased ammonia, alanine aminotransferase and bilirubin levels, increased albumin levels, normalized prothrombin time and improved MELD scores [136, 138, 140]. Notable symptomatic improvement was only observed in a small portion of patients, and survival benefit was unsatisfactory although some patients receiving hepatocyte transplantation survived for a few years. The majority of studies regarding hepatocyte transplantation are case-reports, and the lack of control group in these clinical trials makes it difficult to assess the survival benefit. Therefore, hepatocyte transplantation is primarily applied to patients who reject liver transplantation or await liver transplantation in an effort to fight for a longer

survival time before transplantation. Similar to liver transplantation, immunosuppressive drugs are required since immune-mediated rejection can lead to allograft cell loss [144]. Unfavorably, there is still no standard regimen for immunosuppressive treatment after hepatocyte transplantation. It appears difficult to effectively expand hepatocytes *in vitro* although hepatocytes have already been proved to possess a high proliferative ability *in vivo* [145]. Moreover, the isolation and cryopreservation of hepatocytes is technically demanding. In reality, this procedure is also hampered by the shortage of honor organs and hepatocyte viability because hepatocytes are generally obtained from honor organs that are not deemed unsuitable for liver transplant. Recent researches mainly focused on efforts to seek a sustainable or available source of cells.

4.4.6.2 Stem Cell Transplantation

Bone Marrow Mononuclear Cells

Bone marrow mononuclear cells (BMMCs) are a group of unsorted bone marrow stem cells, which is harvested by BM aspiration. The procedure is low cost and simple. Some studies reported that BMMCs transplantation was well tolerated and showed some benefits in patients with decompensated liver cirrhosis. In the short term, this approach significantly improved the short-term quality of life with elevated albumin and fibrinogen level, normalized prothrombin time, decreased bilirubin levels and reduced incidence of serious complications such as hepatic encephalopathy and spontaneous bacterial peritonitis [146–148]. However, the survival benefit did not persist in the long-term clinical observations. Thus, repeated administration may be required in future clinical studies to prolong the survival benefit of BMMCs therapy. Bianca et al. described a case of graft-versus-host disease-like phenomenon after autologous BMMCs therapy, suggesting the necessities for sustained vigilance and the close follow-up of patients [149].

Hematopoietic Stem Cells (HSCs)

HSCs are identified by CD34 and CD133 markers, which can be acquired from peripheral collection through leukapheresis after G-CSF stimulation or BM aspiration. There is accumulating evidence that SH patients may benefit from HSCs transplantation. In a previous clinical study, autologous HSCs therapy caused the 2.5-fold increase of the mean proliferation rates in remnant segments after portal vein embolization compared with the control group, indicating that HSCs played a key role in liver regeneration [150]. HSCs also have a potent anti-fibrotic effect, which was proved by liver biopsy analysis in Burganova's study [151]. In a study conducted by Salama and his colleagues, 48 patients with SH underwent HSCs infusions via hepatic artery or portal vein [152]. Significant decrease in ascites and marked changes in albumin, bilirubin, INR, and ALT levels was observed in the majority of patients compared with pre-transplantation. The transplantation procedure caused serious treatment-related complications in three patients—hematemesis, hemoperitoneum and gastrointestinal hemorrhage, respectively. In another randomized controlled study, the HSCs transplanted group showed significant improvements in

hepatic function, Child-Pugh score and the quality of life in comparison with the regular treatment group [153]. The 6-month mortality rate in the control group was up to 52%—15 patients from haematemesis, 6 from hepatic coma and 5 from hepatorenal syndrome. However, the 6-month mortality rate in transplanted group was only 10%; 7 died from hematemesis, and 2 died from hepatorenal syndrome. The life span of injected cells and occurrence rate of long-term complications remains to be explored in future studies. In addition, HSCs may be not the optimal candidate for stem therapy given that only a small proportion of HSCs can finally differentiate into hepatocytes.

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are rare, non-hematopoietic progenitor cells that can be obtained from bone marrow, adipose tissue, umbilical blood, umbilical cord tissue and dental tissues, etc. [154, 155]. MSCs can engraft preferentially to the injured or inflammation sites *in vivo*, which may make peripheral vein administration feasible [156]. Another unique feature of MSCs is little or low immunogenicity due to the lack of expression of co-stimulatory molecules [155]. This phenomenon makes it possible to administer allogeneic MSCs without HLA matching for cell therapy. With the ease of harvest, culture and genetical modification, MSCs represent a promising therapeutic option to treat liver failure. Among these, bone marrow-derived MSCs are most fully characterized and considered as gold standard for MSCs clinical applications due to first discovery and extensive study. It has been reported that the majority of patients with chronic decompensated liver cirrhosis could benefit from MSCs therapy at least short-term. In a study performed by Jang et al., 11 patients received autologous BM-MSCs therapy, and 5×10^7 cells were injected twice at a 1-week interval through the hepatic artery [157]. Histological analysis revealed that the Laennec fibrosis scoring and Metavir fibrosis scoring was improved in 6 of the 11 patients, and the expressions of TGF-b1, collagen-1 and a-SMA in liver tissues were significantly decreased compared with pre-transplantation, implying the anti-fibrotic effect of MSCs therapy. In a recent clinical trial, BM-MSCs therapy was demonstrated to improve liver function through regulating the balance of Treg/Th17 cells in patients with HBV-associated liver cirrhosis [158]. Peng et al. respectively evaluated the short-term and long-term efficacy of a single BM-MSCs infusion in patients with HBV-associated liver failure [159]. Short-term benefit was favorable, and albumin, bilirubin, PT levels and MELD scores were significantly improved in the transplanted group after 2–3 weeks. However, there were no dramatic differences in long-term outcomes. This study may also explain the different results from two trials. Salama et al. assessed the efficacy of autologous BM-MSCs infusion via peripheral vein in a randomized trial [160]. The transplanted group showed significant improvements in albumin, bilirubin, INR and ALT levels within 3 months compared the regular supportive treatment group. In contrast, MSC transplantation via peripheral vein could not bring benefit to cirrhotic patients at 3 and 12 month follow-up in Mohamadnejad's study [161].

BM-MSCs only accounts for 0.001–0.01% bone marrow mononuclear cells and their quality and quantity decline with age of the donor. Thus, recent studies are

beginning to investigate the effect and safety of MSCs from other sources. For example, umbilical cord-derived MSCs (UC-MSCs) obtained by the painless and safe procedure during delivery has aroused much attention as a promising source for MSCs therapy. Several studies indicated that UC-MSCs are similar to BM-MSCs with respect to cell morphology and biology properties but more primitive, proliferative and immunosuppressive [154]. In a clinical study conducted by Wang et al., UC-MSCs were intravenously injected at a concentration of 0.5×10^6/kg body weight into patients with decompensated liver cirrhosis [162]. UC-MSCs infusions markedly improved liver function and reduced ascites. In the further research, Wang et al. demonstrated that UC-MSCs therapy not only improved liver function but also enhanced the survival rates in patients with acute-on-chronic liver Failure [163]. Hence, UC-MSCs can also be available candidates for therapeutic applications.

Some issues regarding MSCs therapy are still confusing us. Which dose, which repeated time and which injected route is optimal? Which types of patients are suitable for this therapy? Which types of patients should be forbidden for MSCs therapy? How can MSCs therapy achieve the desired effects when combined with other strategies? Animal experiments demonstrated that MSCs could reverse acute liver failure through secreting some molecules and regulating immune cells in addition to promoting liver regeneration [164]. Whether the patients with acute liver failure can benefit from MSCs therapy needs to be confirmed. Whether MSCs is required to differentiate into hepatocyte-like cells before the infusion is also controversial. For one thing, differentiated MSCs may lost several major properties such as immunosuppression and secreting hepatocyte growth factor [165]. For another thing, pure differentiation into hepatocytes from MSCs seems to be difficult *in vivo* [166]. In a phase II clinical trial, both differentiated group and undifferentiated group showed no significant difference regarding liver functions, prognostic scores and hepatogenesis by immunohistochemical analysis in patients with liver cirrhosis [167]. It was perplexing, and the results may be attributed to the release of cytokines and breakdown of scar tissue caused by undifferentiated MSCs, thereby increasing the intrinsic proliferative ability of hepatocytes. Besides, some reports indicated that MSCs possessed profibrogenic properties and might spontaneous transform into tumor during the long-term cell culture, which makes the long-term safety of MSCs therapy become uncertain [166, 168]. We believe that these questions will be well addressed in future studies.

Embryonic Stem Cells

Human embryonic stem cells (ESCs) are pluripotent cells and have the unlimited self-renewal ability *in vitro* [169]. It is well established that ESCs can differentiate into nearly all types of cells and tissues under certain conditions, including hepatocyte-like cells. Therefore, they may have therapeutic value in liver regeneration. However, some critical questions remain to be addressed before ESCs can be translated into clinical applications. First, transplantation of ESCs-derived cells may give rise to teratoma, so additional strategies are required to purify the desired cell population but eliminate tumorigenic cells. For instance, Kahan et al. isolated a population of endodermal cells with EpCAM(+) SSEA1(−) SSEA3(−) markers by

magnetic bead sorting, and the transplantation of sorted cells into immunodeficient mice could not generate teratoma [170]. It has been reported that ESCs-derived hepatocyte-like cells (ESCs-Heps) had similar karyotype, morphology and metabolic function to primary hepatocytes. *In vivo* experiment also suggested that ESCs-Heps repopulated into liver tissues and corrected metabolic liver disease after transplantation [171]. Hepatic stellate cells promoted the generation of HPCs from ESCs-derived definitive endodermal cells through creating an appropriate microenvironment [172]. In addition, it has also been demonstrated that ESCs-Heps could contribute to liver regeneration through both cell replacement and trophic factors secretion *in vivo* [173]. Thus it seems possible that differentiated ESCs progeny integrate into the liver tissue and function normally and effectively as primary hepatocytes. The immunological incompatibility can result in graft rejection and the failure of ESCs therapy. Apart from conventional immunosuppressive drugs, some studies also attempted to knock out major histocompatibility complex or other responsible gene though genetic engineering technology so as to minimize immune rejection [174]. Moreover, the usage of human ESCs has raised some ethical issues because these cells are obtained from an embryo. The results from a clinical trial recently published in Lancet were exciting [175]. Nine patients with Stargardt's macular dystrophy and nine with atrophic age-related macular degeneration respectively received the therapy of human ESCs-derived retinal pigment epithelium transplantation. During the long term follow-up, no adverse proliferation, graft rejection, or severe transplantation-related diseases occurred, and visual acuity and quality-of-life was improved in the majority of patients undergoing ESCs progeny transplantation. On the basis of previous studies, ESCs therapy in liver generation may be feasible and justified although it is too early to draw a conclusion.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) was first generated by introducing four transcription factors—*Oct3/4, Sox2, c-Myc* and *Klf4* into mouse adult fibroblasts [176]. Following this landmark findings, human somatic cells have also been documented to reprogram into iPSC through transferring four factors—*Oct4, Sox2, Nanog, Lin28 or Oct3/4, Sox2, c-Myc, Klf4* [177, 178]. These reprogrammed somatic cells resemble ESCs in morphology, telomerase activity, cell surface markers and gene expression and have the ability to generate all cells of three germ layers *in vitro*. The advent of iPSCs solves the dilemma of ethical controversy caused by ESCs and expands the sources of these pluripotent cells. On the other hand, iPSCs can be produced by autologous somatic cells, which theoretically allays some fears about immune rejection. Thus iPSCs hold great promise for regenerative medicine, including the treatment of liver failure.

To implement clinical applications, some obstacles surrounding genetic instability and pluripotent status of iPSCs remain to be overcome. Similar to ESCs, the usage of iPSCs is limited by the risk of teratoma formation. Importantly, iPSCs display many characteristic of cancer cells including unlimited proliferative properties, self-renewal activities and even bioenergetic metabolism [179]. These phenomena imply that overlapping mechanisms or similar pathways may be involved in

both oncogenesis and pluripotent cells production. The inductive process of iPSCs also increases our worries about the tumorigenicity; iPSCs may themselves be a consequence of genetic anomalies and aberrant epigenetic changes induced by reprogramming [180, 181]. Therefore, it is crucial to control the biological behavior of iPSCs and their progeny and minimize the risks of tumorigenesis *in vivo*. One safeguarding strategy is the selective ablation of undesired cells through suicide gene modifications, monoclonal antibodies, drugs or flow cytometry sorting [170, 182]. In other studies, small molecules are utilized to generate iPSCs instead of the import of exogenous genes, avoiding the risks of tumorigenesis along with gene transfer [183, 184]. Maybe the major challenge facing iPSCs application is whether iPSCs-derived hepatocyte-like cells (iPSCs-Heps) can perfectly perform the duties of primary hepatocytes *in vivo*. There were some specific differences in the expression of cytochrome P450 gene even though iPSC-Heps were compared with that from ESCs [185]. A recent study showed that human iPSC-Heps and ESCs-Heps were parallel to fetal rather than adult hepatocytes in functions and phenotype [186]. Yanagida et al. also found that iPSC-Heps exhibited a bi-potent capability to differentiate into Heps or cholangiocytic cyst-like structure *in vitro* culture system, which is extremely alike the features of HPCs [187]. These studies indicated that iPSCs-Heps were immature and had limited functional characteristics compared to adult primary hepatocytes.

Some recent studies in animal models highlighted the application value of iPSCs in liver failure. Chien et al. found that the intrahepatic delivery of miR122-modified iPSC-Heps significantly improved liver functions and mice survival time in an acute liver failure model [188]. Surprisingly, iPSC-Heps could produce albumin *in vivo* for 4 months. Chen et al. also indicated that iPSC-Heps displayed cytochrome P450 3A4 enzyme activity, urea synthesis and glycogen store *in vitro,* and iPSC-Heps transplantation reversed lethal fulminant liver failure in a severe combined immunodeficient mouse model [189]. In a study from Espejel and his colleagues, iPSCs-Heps were demonstrated to have the potential to differentiate into mature hepatocytes, possess the proliferative and repopulating ability and fulfill liver functions *in vivo* [190], thus regenerating the liver after two-thirds partial hepatectomy.

4.4.6.3 Other Cell Transplantation

Immortalized Hepatocytes

Immortalized hepatocytes can offer an unlimited supply of transplantable cells and thus may be alternative sources of hepatocytes. They can be produced through transfecting hepatocytes with lentiviral or vectors coding for antiapoptotic genes [191]. Intraperitoneal infusion of encapsulated immortalized hepatocytes obviously improved survival of mice with liver failure through providing metabolic support [191]. However, the usage of immortalized hepatocytes is still confined to animal experiments because they may become de-differentiated and participate in tumorigenesis. Several studies have explored the efficacy of conditionally immortalized hepatocytes in liver diseases [192]. For example, Kawashita et al. constructed the conditionally immortalized rat hepatocytes by stable transduction with thermolabile

mutant simian virus 40 T-antigen; interestingly, these hepatocytes proliferated at 33 °C, while they became quiescent at 37 °C for SV40 Tag was degraded [193].

Xenogeneic Hepatocytes

Another strategy is xenotransplant of hepatocytes. Xenogeneic hepatocytes aren't limited by the availability of donor organs and can be performed repeatedly if necessary [194]. Interestingly, xenogeneic hepatocytes appear insusceptible to the infections from human hepatitis viruses [195]. The largest concern about xenogeneic hepatocytes is hyperacute and delayed xenograft rejection, thereby resulting in the failure of xenotransplant and deterioration of diseases [196]. Whether xenogeneic hepatocytes function effectively in human body environment still remains uncertain. Additionally, the origin of HIV and mad cow disease virus reminds us that potential risks transmitting unknown infectious agents from xenogeneic organ are unavoidable. In an early clinical trial, Starzl et al. undertook a liver transplantation surgery from a baboon to a 35-year-old man with HBV and HIV co-infection [197]. The patient died of lethal infectious complications, and biochemical monitoring and histopathological examination showed little evidence of hepatic rejection. At present, pigs are regarded as the preferred species for xenotransplantation due to the similarity of volume and function to human organ. In a mice model of acute liver failure, Ham et al. encapsulated and re-aggregated pig hepatocytes, which showed higher viability and greater synthesis of albumin and urea and significantly improved the survival rate of mice after intraperitoneal transplantation. Surprisingly, porcine hepatocytes stayed viable for more than 80 days after a single intrasplenic transplantation and even for more than 253 days following repeated transplantation in nonhuman primates when combined with immunosuppression to control rejection [198]. More importantly, porcine hepatocytes functioned normally and secreted albumin. Several researches utilized genetic engineering technique in an attempt to improve the survival of pig hepatocytes and overcome immune rejection in nonhuman primates, such as genetic modification with human complement regulatory protein (CRP) CD55 or α 1,3-galacto-syltransferase gene-knockout combined with transgene for the CRP CD46 [199]. In a latest study published in Science, Yang et al. successfully eradicated all porcine endogenous retroviruses with a >1000-fold reduction in a porcine cell line and avoided the transmission to human cells using CRISPR-Cas9 [200]. Hence, xenotransplant of hepatocytes may be rational as we better understand the cellular and molecular mechanisms underlying graft rejection and the safety of xenotransplant is well addressed.

Fetal Hepatocytes

Human fetal hepatocytes have been demonstrated to have higher proliferative capacity and plasticity in vitro, show greater resistance to cryopreservation, be less immunogenic and possess greater ability for repopulation *in vivo* [201, 202]. In addition to hepatocytes, HPCs and other stem cells are abundant in fetal liver tissues [201], which will be detailed in the following text. Fetal hepatocytes of 20–22 gestational ages have been functionally competent and comparable to adult hepatocyte in terms of many liver-specific functions, but they don't divide *in vitro* [202]. On the

contrary, hepatocytes of earlier gestational ages resemble hepatic precursors with high proliferative activity but low liver-specific functions. Hence, fetal hepatocytes of 20–22 gestational ages should be recommendable for cellular therapy. In a matched case-control study in patients with end-stage liver disease, intrasplenic fetal hepatocyte infusion at the doses of 5 or 10×10^8 was well-tolerated and markedly improved the model for end-stage liver disease and Child-Pugh scores, but no obvious survival benefit was observed (treatment failure in 6/9 patients compared with 14/16 patients in control group) [203]. A study with an increased hepatocyte amount and a larger scale may finally prove the clinical efficacy of fetal hepatocyte transplantation. Some obstacles remain to be overcome. Kamimura et al. evaluated the therapeutic efficacy of hepatocyte-transplantation from various differentiation stages in a mice model of lethal liver damage and found that adult hepatocyte-transplanted group (8/20, 40%) showed higher improvement of survival rate in comparison to fetal hepatocyte-transplanted group at 35 days after transplantation [204]. Fetal hepatocytes are generally regarded as immature hepatocytes. The amounts of most metabolites in glycolysis/glyconeogenesis pathway, tricarboxylic acid cycle and urea cycle are significantly lower in fetal hepatocytes, suggesting discriminative metabolic functions between fetal and adult hepatocytes [205]. Fetal hepatocytes are usually acquired from elective abortions, so their usage is limited by ethical issues. Furthermore, similar to adult hepatocyte transplantation, available fetal tissue is not infinite owing to low numbers of donors and small-size liver in fetal.

Hepatic Progenitor Cells (HPCs)

Preliminary studies in animal model showed that HPCs could salvage the damaged liver through both liver regeneration and paracrine effects [206]. HPCs-based therapies still lies in the early stages of translation. HPCs population and activity in liver tends to decline with age [207], so HPCs in current clinical trials are mainly obtained from fetal liver tissues. Khan et al. reported a case of patient with hyperbilirubinemia in biliary atresia who received HPCs transplantation via hepatic artery [208]. The total bilirubin and conjugated bilirubin was markedly decreased after cell infusions. In another study, 25 patients with end-stage liver cirrhosis were infused with fetal HPCs through hepatic artery [209]. Obvious improvement in clinical and biochemical parameters, and mean MELD score was observed during 6 months follow-up in all patients, but no hepatic encephalopathy recurred. There are some challenges facing HPCs therapy. Activated HPCs may drive a severe fibrogenic response, thereby resulting in the failure of fibrotic liver regeneration [210]. HPCs didn't regenerate significant quantities of hepatocytes during normal liver homeostasis, and HPCs activation was associated with the severity of hepatocyte loss [211, 212]. HPCs didn't substantially contribute to hepatocyte production under most liver injury insults [213]. These results call into question whether transplanted HPCs can generate sufficient number of hepatocytes *in vivo*. LPC do not substantially contribute to liver parenchymal regeneration under most liver injury insults LPC do not substantially contribute to liver parenchymal regeneration under most liver injury insults.

Induced Hepatocyte-like Cells from Other Somatic Cells

iPSCs-Heps are usually produced by sequential induction process from somatic cells to iPSCs, anterior endoderm, definitive endoderm, hepatoblasts and fully differentiated hepatocytes, respectively [214]. This approach requires lengthy culturing process and thus is of high cost. Direct conversion from other somatic cells into Heps can not only save time and materials but also bypass the pluripotent stage and lessen the risks of teratoma formation. Over the past 5 years, some studies have successfully reported the generation of Heps from other somatic cells. Huang et al. first found that mouse fibroblasts could be induced into functional Heps by introducing *Gata4, Hnf1a* and *Foxa3* and knocking out *p19Arf* [215]. Of note, induced Heps could repopulate into liver tissues, restore liver functions and rescue almost half of death in fumarylacetoacetate-hydrolase-deficient mice. Similar findings were also referred to in a study from Japan [216]. *Hnf4a* plus *Foxa1, Foxa2* or *Foxa3* could convert mouse embryonic and adult fibroblasts into Heps *in vitro*. *In vivo* experiment further suggested that induced Heps had the ability to reconstitute liver tissues. In another study, Bing Yu et al. demonstrated that *Foxa3* and liver organogenesis transcription factors are sufficient to convert mouse embryonic fibroblasts into HPCs. Recently, Kamen P. Simeonov and Hirdesh Uppal showed that human Heps was achieved through repeatedly transfecting human fibroblasts with synthetic modified mRNAs coding *Hnf1a* plus any two of *Foxa1, Foxa3,* or *Hnf4a* [217]. The human induced "Heps" had similar morphology and albumin expression with mature hepatocytes, but their functions remain to be further confirmed *in vivo*. The majority of current studies about direct conversions are from mouse because direct reprogramming of human somatic cells is actually more difficult than mouse cells. Once this technical handicap is conquered, directly induced "Heps" may provide an ideal and promising source for cellular therapy.

Prospectives and Hurdles

Undoubtedly, immunotherapy and cell-based therapy has made significant progress. Some approaches have entered into clinical trials and brought benefit to some patients with liver failure. Further studies are required to optimize their therapeutic effects. Others still lie in preclinical stage. In particular, strategies aiming at the pathological mechanism of AECHB are springing up, which provides novel insights into the treatment of AECHB. However, their clinical applications are limited by current technology, security concerns and ethical issues. Fortunately, lots of studies are conducted to investigate their therapeutic value and explore how to address current obstacles. Ultimately, these strategies may be widely translated into bedside applications from bench studies based on the integration of discoveries, technological advance, translational insights and rigorous clinical trials.

However, some barriers remain to be overcome. Everything has two sides – good or bad. Take inflammation as an example; anti-infections and damage are the two contrary sides. As we all know, infections lead to the establishment of inflammation, which, in turn, prevent the further development of infections. Inhibition of inflammatory cytokine release predisposes patients to infections, while uncontrolled inflammatory cytokine storms may bring about devastating hit on the organism.

When we take measures to treat patients through blocking inflammatory mediators or immune responses, the potential severe infections must be taken seriously. The same therapeutics displays the distinct efficacy on different patients with same diseases because of the heterogeneity of human diseases. Future medicine should concentrate on the "individualized therapy" to investigate the fine distinction underlying different efficacy. Following this, appropriate biomarkers, clinical assessment and genotype will be implemented to determine whether the given therapy can achieve the desired results and to identify which strategy apply to the treated patient. At length, what must be emphasized is the complicated signaling network inside the immune system or between immune system and other systems including coagulation system, metabolic pathways, neurohumoral system, etc. In the vast network, each signaling molecule is not independent but interconnected with one another. These extensive associations indicate the complexity of AECHB and increase the difficulty of our studies. Nevertheless, the existence of many "unknowns" compels us to unravel the mysteries and develop new strategies to address the intractable diseases.

4.5 Management of AECHB and Severe Hepatitis(Liver Failure) in Special Populations

Yanmei Li Xiong Ma

4.5.1 Severe Hepatitis B During Pregnancy

Mother to child transmission (MTCT) is the most common means of transmission in high HBV endemic areas. Furthermore, because of their young age, most mothers are HBeAg positive and highly replicative during pregnancy. Perinatal infection is the most common route of transmission (60–80%), followed by intrauterine transmission (13–44%) and postpartum transmission (5–10%). Of primary importance in preventing MTCT is HBV screening of all pregnant women and those who hope to become pregnant.

If a woman is planning pregnancy in the long-term future (>18 months) and is a candidate for antiviral treatment, interferon therapy can be considered, as this modality constitutes a defined treatment course of 48 weeks. Unfortunately, response rates with interferon are suboptimal and this therapy is associated with considerably greater adverse effects than oral antiviral agents. Additionally, candidates for interferon therapy must be willing and able to take contraceptive measures throughout therapy and for a 6-month washout period after therapy has concluded.

By contrast, women planning pregnancy in the immediate future are unlikely to be initiated on antiviral therapy due to concerns regarding fetal exposure to these drugs in early pregnancy. Nucleoside or nucleotide antiviral therapy has the potential to promote mitochondrial toxicity and is of unclear benefit in young patients

who have no clear evidence of advanced liver disease. In patients who are suspected of having more advanced fibrosis and/or cirrhosis or evidence of highly active disease, the clinical risk–benefit assessment might favour initiating therapy and continuing therapy throughout the course of pregnancy. Pregnancy itself can be associated with mild hepatitis flares, but rarely more severe flares. In the rare circumstance in which a flare occurs and if evidence of hepatic decompensation exists, initiation of antiviral therapy might be necessary to avoid untoward outcomes for both the mother and fetus.

Women who have previously received antiviral therapy for chronic HBV infection and who then present for care in early pregnancy require thoughtful evaluation to weigh the risks of antiviral discontinuation against those of exposure to nucleoside or nucleotide agents during the first trimester. The most important variable to consider is the severity of the underlying liver disease at the time antiviral therapy was initiated. Some clinicians might choose to continue therapy, and, in that case, tenofovir is often considered the long-term therapy of choice throughout pregnancy. Women presenting in the second or third trimester of pregnancy who have been taking antiviral therapy risk the possibility of rebound viral hepatitis with drug discontinuation as well as an increased risk of MTCT with high HBV DNA levels. Thus, expert opinion would favour continuation of antiviral therapy in this scenario. However, most women of childbearing age will be in the immune-tolerant phase or have early disease, in which case antiviral therapy will be deferred, except in women with high HBV viraemia, for whom initiation of antiviral therapy might be advised in the third trimester for purposes of reducing risk of MTCT. EASL recommends that in all pregnant women with high HBV DNA levels (>200,000 IU/mL) or HBsAg levels >4 $\log_{10}$ IU/mL, antiviral prophylaxis with tenofovir should start at week 24–28 of gestation and continue for up to 12 weeks after delivery. If antiviral therapy is needed, tenofovir is recommended, as it is the only third generation NA with FDA category B for pregnancy and a large registry showing no increase of birth defects. Breast feeding is not contraindicated in HBsAg-positive untreated women or on tenofovir-based treatment or prophylaxis.

Optimal management of acute liver failure (AFL) in pregnancy begins with early recognition and accurate diagnosis of the underlying etiology. Pregnancy may be a potential cause of acute exacerbation in patients with chronic HBV infection. In ideal circumstances, a coordinated multidisciplinary effort should take place that includes critical care specialists, maternal-fetal medicine physicians, hepatologists or gastroenterologists, neonatologists, and surgical transplant teams. Furthermore, there are few evidence-based recommendations for managing the pregnant woman with ALF. Therefore, management of ALF should be guided by the same principles followed for the nonpregnant patient. Avoidance of further liver-toxic agents in combination with supportive care is the typical therapy, as liver recovery for most patients with a self-limited cause resulting in ALF is the gold standard. No therapy that is considered life-saving or standard of care for ALF should be withheld simply for reasons of pregnancy status, as the risks of untreated or fulminant ALF are generally higher than the fetal risk from therapy. In addition, the risk of poor fetal

outcome for those patients with ALF in the first and second trimester (before viability) is so high that maternal survival and concerns should take precedence, and pregnancy termination should be strongly considered. A maternal-fetal medicine physician and a toxicologist can help to advise on the risks of specific therapies in pregnancy, but for most patients the maternal and fetal benefit of liver recovery outweigh most potential risks.

4.5.2 AECHB with Diabetes

Patients with HBV infection are at higher risk of developing diabetes. Several mechanisms may be involved in the association between HBV infection and the prevalence of diabetes. First, the liver is an organ that plays a key role in the regulation of glucose homeostasis by balancing the storage and output of glucose. Persistent liver damage by HBV infection may cause defective glucose homeostasis. Inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and nitric oxide, have been shown to impair the metabolic action of insulin in the liver, which results in hepatic dysfunction and, in turn, leads to insulin resistance. Secondly, several studies have found HBV infection in the pancreas. The replication of HBV in extrahepatic sites, such as the pancreas, is responsible for β-cell damage and may ultimately lead to diabetes. In addition, insulin resistance may be involved in the pathogenesis of hepatogenous diabetes. It is reported that the pre-S2 protein of HBV decreased the expression of the insulin receptor gene, leading to insulin resistance.

In a cohort of individuals with liver infection by HBV, those who developed de novo diabetes had higher risk of developing cirrhosis and hepatic complications. Diabetes might induce liver damage by promoting inflammation and fibrosis through an increase in mitochondrial oxidative stress by the action of leptin, adiponectin, interleukin-6 and TNF-α, which are produced in chronically inflamed adipose tissue. The production of these chemical mediators is stimulated by insulin resistance (IR). Some cytokines such as TGFβ1 and leptin can activate stellate cells, leading to fibrosis. Diabetes can also increase the risk of severe infection, such as spontaneous bacterial peritonitis. Cirrhotic patients with such infections may exhibit liver failure and hepatorenal syndrome, and have a high hospital mortality.

Glycaemic control is fundamental to the management of diabetes patients. The effective control of hyperglycemia may reduce complications and mortality rate in patients with diabetes and liver disease. Less stringent treatment goals might be appropriate for diabetic patients with decompensated cirrhosis. There are many obstacles to glycaemic control in cirrhotic patients because of their shorter life expectancy due to hepatic dysfunction, malnutrition, and hepatotoxicity of hypoglycaemic agents. Metformin is not recommended for patients with liver disease because of the risk of lactic acidosis and gliclazide use should be avoided in patients with severe hepatic impairment as it is metabolized in the liver. The effect of administration of meglitinides and thiazolidinediones has not been tested in patients with liver diseases. Insulin therapy may be the first-line agent to treat diabetes in patients.

However, insulin administration in cirrhotic patients should be conducted in a hospital environment with close monitoring of blood glucose due to the risk of hypoglycemia. Both hepatologist and endocrinologist working together will make possible to optimize therapeutic outcomes of these patients.

4.5.3 AECHB with Connective Tissue Diseases

Corticosteroids, anti-metabolites, TNF-α antagonists and monoclonal antibodies are often used in the treatment of connective tissue diseases. Patients infected with HBV are at risk of reactivation of the virus when they require immunosuppressive therapy. Reactivation of HBV replication can occur in patients with chronic or past HBV infection. Reactivation is best characterized as a virologic event in which there is a sudden increase in viral replication due to loss of immune control. Frequently, although not always, there is concomitant evidence inflammatory liver disease, with an elevation in serum aminotransferase levels and, in severe cases, elevation of bilirubin level.

The mechanism of CHB reactivation with conventional immunosuppressants is likely to be related to immune suppression during therapy with immune rebound on withdrawal of the immunosuppressants. During steroid therapy, there is enhancement of HBV replication through stimulation of the glucocorticoid responsive element in the HBV. In addition, high doses of steroids suppress the helper and suppressor T-cell function with increase in primary B-cell function during treatment. On withdrawal of steroid, usually after 4–10 week, there is rebound of the suppressor T-cell activity, on top of the enhanced HBV viral load.

The key to prevention of HBV reactivation is the identification of patients with HBV infection prior to initiation of immunosuppressive therapy. The US Centers for Disease Control and Prevention, European Association for the Study of the Liver, and Asian–Pacific Association for the Study of the Liver recommended universal HBV screening prior to initiation of immunosuppressive therapy. Antiviral therapy is started prior to or at the same time as the initiation of immunosuppressive therapy and before any elevations in ALT or HBV DNA levels—and pre-emptive therapy, in which antiviral therapy is initiated when serum HBV DNA or ALT levels are elevated but before symptomatic manifestation of hepatitis or liver failure. Prophylactic antiviral therapy has been demonstrated to be effective in prevention of HBV reactivation and its sequelae. Entecavir is better than tenofovir because of the lack of nephrotoxicity. Lamivudine could be used in patients with undetectable serum HBV DNA before the start of immunosuppressive therapy and if the anticipated duration of use is short (for example, <12 months) to avoid resistance. Continuing preventative antiviral therapy is recommended for at least 6 months after the completion of immunosuppressive therapy and even longer for those who receive rituximab who had high serum HBV DNA levels before the start of immunosuppressive therapy. It is not necessary to delay the start of immunosuppressive therapy except in patients with high baseline serum HBV DNA levels (for example, >4 $\log_{10}$ IU/mL); for these patients, the benefit of delaying immunosuppressive

therapy until HBV DNA level is suppressed must be weighed against the risk of progression of the underlying medical condition.

Following conventional immunosuppressive therapy, and more recently with the biological therapies, such as anti-TNF-α, acute exacerbation has been mainly reported in patients with known CHB. However, with more recent very potent immunosuppressive agents like rituximab, ofatumumab, and alemtuzumab, severe (sometimes fatal) reactivation has been reported in patients with occult hepatitis B, that is, patients who are negative for HBsAg pretreatment but positive for other HBV markers, anti-HBc with or without anti-HBs. Studies showed that after elevation of ALT or HBV DNA levels has occurred, antiviral therapy is less effective in preventing progression to liver failure. Clinical signs of poor prognosis include jaundice, encephalopathy, ascites, elevated bilirubin levels or prolonged prothrombin time. A liver transplantation centre should be considered for all patients with clinical signs of liver failure, but the benefits of liver transplantation must be weighed against the prognosis of the underlying cancer or other medical condition for which immunosuppressive therapy was prescribed.

4.6 Artificial Liver Treatment for Acute Exacerbation of Chronic Hepatitis B and Severe Hepatitis (Liver Failure)

Lan-Juan Li

Liver failure is a state of severe liver dysfunction that can lead to coagulation disorders, jaundice, hepatic encephalopathy and ascites [218]. In China, the main aetiology of liver failure is acute exacerbation of chronic hepatitis B infection. The deterioration of liver functions including biotransformation, excretion, and secretion, leads to increased levels of various toxicants, such as ammonia, bile acids, mediators of oxidative stress, nitric oxide, and lactates, which in turn results in multiple organ failure. Liver failure is the leading cause of mortality among adults worldwide and has a considerable economic burden and social impact. Currently, only orthotopic liver transplantation (OLT) can reverse liver failure. Although OLT is an effective surgery to save patients with liver failure, whole-organ transplantation is hindered by the shortage of suitable donor organs. Liver support systems can prevent or reverse secondary organ failure and promote restoration of hepatic function until an appropriate liver is available for transplantation, or stimulate hepatocyte regeneration and let liver recover from injury.

Dialysis was initially developed to keep patients with acute renal failure alive until kidney transplantation. This function was incorporated into the design of the first extracorporeal liver support devices. Because of the capacity of healthy liver tissue to regenerate, early liver support devices provided short-term support to enable liver regeneration. In the 1950s, artificial kidneys were used for the first time to treat liver coma. Because of the liver's complex functions, including metabolism, synthesis, and detoxification, early approaches focused on detoxification and regulation using a cell-based platform. Those early devices included cross circulation

with both human and primates. Non-cell-based devices were also investigated during this period.

In 1970s, with the development of haemopurification technology such as membrane material, biocompatibility and adsorption capacity of adsorbents led to the development of artificial liver systems. During this period, improved methods of hepatocyte isolation, such as two-step perfusion, led to development of artificial livers based on hepatocyte culture.

In China, acute exacerbation of chronic liver disease caused by hepatitis B virus is very common; predominant liver failure cases were due to exacerbation of hepatitis B. Since 1986, Li Lanjuan's team at the First Affiliated Hospital of Zhejiang University has used their non-biological artificial liver (NBAL) (Li-NBAL 1.0; also known as the artificial liver support system [ALSS]) to detoxify patients with severe hepatitis, and maintain them until their liver has regenerated sufficiently or a donor liver is available. Plasma exchange (PE), plasma perfusion (PP), haemofiltration (HF), and haemodialysis have been systematically applied to treat patients with liver failure, alone or in combination. In 1997, a study assessed the efficacy of ALSSs. Beginning in the late-1990s, NBALs were used in an increasing number of Chinese hospitals. By 2001, more than 50 hospitals in China offered NBAL treatment. In 2002, the Artificial Liver and Liver Failure Group of the Chinese Society of Infection built guidelines for artificial liver treatment [219]. According to the pathophysiological characteristics of liver failure, Li Lanjuan's team has developed a new NBAL device, the Li-NBAL 2.0 (also known as Li-ALS), which combines PE, plasma adsorption, and filtration. In animal studies, the Li-NBAL 2.0 prolonged survival compared with PE or plasma adsorption and filtration individually [220]. A clinical trial of the Li-NBAL 2.0 is imminent.

4.6.1 Classification of Artificial Liver Systems

Generally, liver support systems are divided into non-bioartificial liver, bioartificial liver and hybrid artificial liver (Table 4.1).

4.6.1.1 Non-bioartificial Liver

NBAL devices are simple blood purification or detoxification systems that remove water-soluble and albumin-bound toxins from plasma.

Table 4.1 Types of artificial liver

Type	Functions	Example
Non-bioartificial liver (NBAL)	Removing toxins. In addition, plasma exchange can supplement biological substances	Li-NBAL, plasma diafiltration, Prometheus system, MARS, *etc*.
Bioartificial liver (BAL)	Hepatic-specific transformation and synthesis	Li-BAL, RFB, BLSS, and ELAD, *etc*.
Hybrid artificial liver (HAL)	The combination functions of NBAL and BAL	Li-HAL, AMC, HepatAssist, and MELS, *etc*.

Examples of these systems include Li-NBAL, the molecular adsorbent recirculating system (MARS), single-pass albumin dialysis (SPAD), the fractionated plasma separation and adsorption system (Prometheus), and selective plasma filtration system therapy (SEPET). In clinical practice, NBAL support therapy effectively eliminates water-soluble and -insoluble toxins and presents no serious safety concerns.

Li-NBAL 1.0

Based on advances in blood purification technologies and further understanding of the pathophysiology of liver failure, Li Lanjuan created Li-NBAL 1.0. Following the principle of individualised treatment, an appropriate method is selected according to the specific circumstances of each patient. Based on the patient's condition and symptoms, PE is performed alone or together with haemoperfusion (HP), HF, PP, plasma bilirubin absorption (PBA), and continuous haemofiltration (CHDF) (Table 4.2). For example, in patients with hepatic encephalopathy, Li Lanjuan performed PE in combination with HP. In patients with hepatorenal syndrome (HRS), PE and HF or CHDF were applied. In patients with a disturbed water or electrolyte balance, Li Lanjuan used PE and HF. More than three methods were used in some patients.

In 2004, Li Lanjuan et al. analysed 400 patients with severe viral hepatitis treated using the Li-NBAL 1.0 [22]. These patients were treated at the First Hospital of College of Medicine, Zhejiang University from 1995 to 2003. The control group also comprised 400 severe viral hepatitis patients, who were treated at the same hospital from 1986 to 1994. The artificial liver therapy was carried out two or three times in weeks 1 and 2, and then once a week until the patient's condition stabilised. Almost 90% of the patients have improved symptoms after each treatment. The liver function tests improved significantly in all patients after treatment. The serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), the serum total bilirubin (TBIL), and total bile acid (TBA) levels declined significantly ($P < 0.001$), and the prothrombin time decreased sharply. The survival rate of chronic severe hepatitis treated with Li-NBAL 1.0 therapy was 43.4% (157/362), compared to

Table 4.2 Individualised treatment using the Li-NBAL 1.0

Patient's characteristics	Method(s)
Early stage liver failure	PE
Middle stage liver failure	PE + HF, PE+ plasma perfusion
Cholestasis	Bilirubin adsorption or PE+ bilirubin adsorption
Liver failure patients with renal failure	PE + HD, PE + HF, or PE + CHDF
Liver failure patients with hepatic encephalopathy	PE + HP, PE + HF or PE + CHDF
Liver failure patients with water and electrolyte disturbance	PE + HF, or PE + CHDF
Drug and poison-induced liver failure	PE + HF, or PE + HP

PE plasma exchange, *HF* haemofiltration, *HP* haemoperfusion, *HD* haemodialysis, *CHDF* continuous haemodiafiltration

control group 15.4% (55/358) with conventional medication. In patients with acute and subacute severe hepatitis treated with the Li-NBAL 1.0, the survival rate was 78.9% (30/38), compared to 11.9% (5/42) for those treated with conventional medication (Fig. 4.1). This difference in survival rate was significant ($P < 0.001$).

Li-NBAL 2.0

Trials of coupled plasma filtration adsorption (CPFA) suggested it to have potential for systemic inflammatory response syndrome (SIRS), sepsis shock, and multiple organ dysfunction syndrome (MODS) [221–223]. However, Livigni *et al.* [224] conducted a multicentre, randomised, unblinded trial to compare the therapeutic effects of CPFA and standard care on critically ill patients with septic shock. CPFA did not reduce the mortality in patients with septic shock and did not affect other important clinical outcomes. However, the subgroup analysis showed that CPFA can reduce the mortality rate after large volume plasma treatment. Maggi *et al.* [225] reported that following liver transplantation, one patient developed early allograft dysfunction, and another hyperbilirubinemia associated with chronic rejection. After three cycles of CPFA, the bilirubin level rapidly declined in both cases. Each cycle of treatment reduced the bilirubin level by 40%.

One round of PE requires 2000–2500 mL of fresh frozen plasma. However, the supply of fresh frozen plasma is limited. Bilirubin adsorption combined with HF can clear a certain proportion of toxins, but also affects blood coagulation in liver failure patients at high risk of bleeding. Li Lanjuan found that CPFA was effective

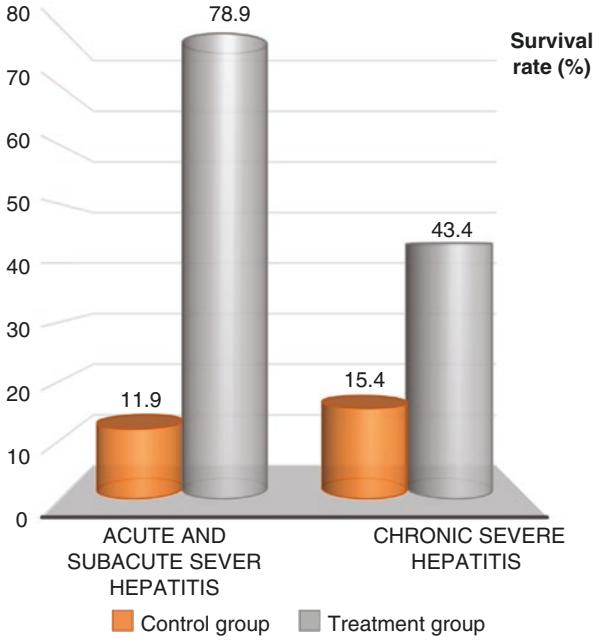

Fig. 4.1 Prognosis of severe hepatitis patients who underwent Li-NBAL 1.0 therapy

for clearing inflammatory mediators in patients with liver failure, but did not correct coagulopathy. Thus, Li Lanjuan developed a new NBAL system that coupled low-volume PE with plasma filtration adsorption, the Li-NBAL 2.0 [220].

After low-volume PE (500–1000 mL), plasma adsorption continues in parallel with plasma filtration. The technique can not only supply coagulation factors, but also removes small molecular substances and re-establishes the hydro-electrolyte acid-based equilibrium. Li Lanjuan's team used this system to treat liver failure patients. It improved the efficiency of artificial liver while plasma exchange successively combined with coupled plasma filtration adsorption. One round of treatment required 500–1000 mL of plasma, considerably less than for PE alone. The total bilirubin level was reduced by about 50%. Additionally, the treatment was well tolerated, and did not significantly influence blood cell count and coagulation function. Further studies should determine if the cure rate is increased with Li-NBAL 2.0 treatment compared with conventional PE. The Li-NBAL 2.0 treatment method and a pipeline connection diagram are shown in Fig. 4.2.

Albumin Dialysis Systems

Currently, three albumin dialysis-based devices are available: The MARS®, the Prometheus® and the SPAD®.

MARS was introduced in 1993 (Gambro Lundia, Lund, Sweden) [227]. During MARS therapy, blood from the patient is pumped through a high-flux albumin-coated haemodialyser. Toxins (both albumin-bound and soluble) are infused into the

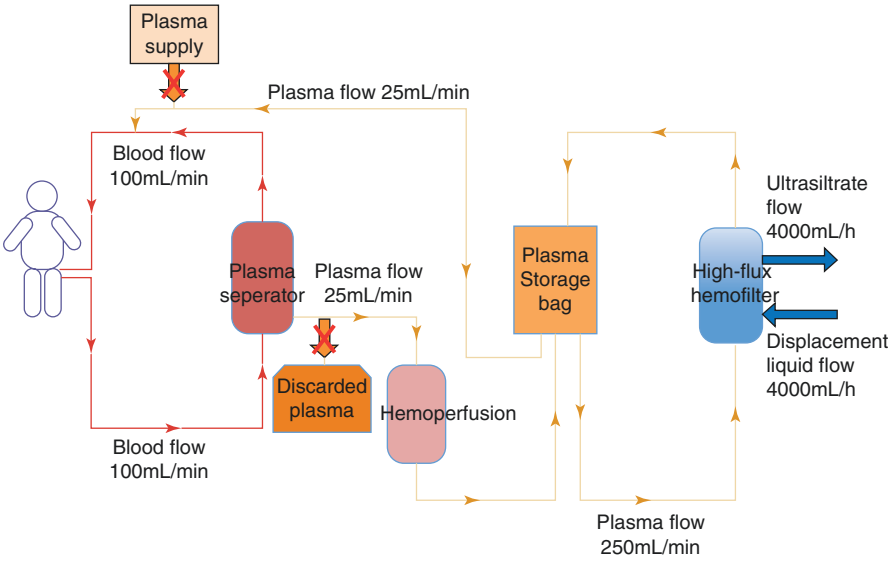

Fig. 4.2 Schematic showing the Li-NBAL 2.0 treatment method. Reproduced with permission from Lanjuan Li, editor. Artificial liver. Hangzhou: Zhejiang University Press; 2012. ISBN: 9787308106481 (in Chinese) [226]

human albumin-enriched dialysate. The exogenous albumin dialysate is then regenerated in a closed loop by dialysis against a conventional dialysate, and adsorbed by charcoal and anion exchange resin columns (Fig. 4.3). MARS can remove protein-bound toxins and water-soluble toxins, reduce intracranial pressure, improve kidney function, and prevent brain oedema, HRS, and MODS [228, 229].

MARS can improve quality of life and has been successfully used for hepatic decompensation in hepatic encephalopathy and HRS [230–232]. However, several randomised trials and a meta-analysis showed that the survival rate of liver failure patients was not higher compared with standard medication [233, 234].

Fractionated plasma separation and adsorption (FPSA) was first integrated into a commercially available device in 1999 (Prometheus®; Fresenius Medical Care, Bad Homburg, Germany) [235]. The Prometheus unit combines the use of fractionated plasma with adsorbents with downstream high-throughput haemodialysis to remove water-soluble, low-molecular-weight substances. The Prometheus system comprises three loops: blood circulation, an albumin filtrate cycle, and a dialysis cycle. Kribben *et al*. published a preliminary report in 2012 [236], in which acute-on-chronic liver failure patients were randomly divided into an FPSA group (77 cases) and a standard medical therapy group (SMT group, 68 cases). The Prometheus group underwent 8–11 treatment sessions over 3 weeks with a minimum treatment time of 4 h. The 28-day survival rate of the FPSA group was 66%, compared to 63% in the SMT group ($p = 0.70$), while the 90-day survival rate in the FPSA group was 47%, compared to 38% in the SMT group ($p = 0.35$). There was no significant difference in the 28- and 90-day survival rates between the two groups, which was disappointing. However, a pre-defined subgroup analysis found that in patients with a model of end-stage liver disease (MELD) score > 30 (total of 48 cases, 24 per group), 28-day survival rates were 42% and 57% in the SMT group and FPSA group, and the 90-day survival rates were 9% and 48% in the SMT and FPSA groups, respectively ($p = 0.02$). Therefore, the Prometheus system improved

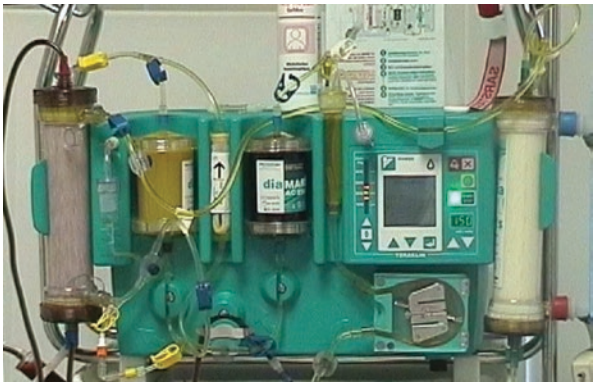

Fig. 4.3 Clinical setup of the molecular adsorbent recirculating system (MARS). Reproduced with permission from Lanjuan Li, editor. Artificial liver. Hangzhou: Zhejiang University Press; 2012. ISBN: 9787308106481 (in Chinese) [226]

survival. Randomised crossover controlled trials of Prometheus and MARS indicated that clearance, and an ultimately reduced rate of albumin-bound and water-soluble products, was higher with the Prometheus system than with MARS treatment.

MARS and Prometheus require special training and expertise, and a specific circuit involving sorbent columns, while SPAD, initially described in clinical use by Seige *et al*. in 1999, also uses the bound-solute dialysis principle, albeit according to a more simple and less expansive design, in which effective albumin dialysis can be performed by using a conventional continuous venovenous haemodialyser, but with a dialysate being enriched with albumin [237]. A retrospective analysis of MARS and SPAD involving 163 albumin dialysis treatments (126 with MARS and 37 with SPAD, in a total of 57 patients) [238] showed that MARS caused a significant decrease in bilirubin, liver enzymes, creatinine, and urea levels, while SPAD caused a significant decrease in bilirubin and gamma-GT levels, and an increase in the lactate level. There was no differences in the need for blood transfusion or mortality rates between the two treatment modalities. However, prospective assessment is necessary to further clarify the role of SPAD in the treatment of acute and acute-on-chronic liver failure.

A meta-analysis reported that albumin dialysis reduced serum total bilirubin levels by 8 mg/dL compared to standard drug therapy, but not serum ammonia or bile acid level. Albumin dialysis improved hepatic encephalopathy compared to standard drug therapy standard medical therapy (risk ratio, 1.55), but had no effect on survival (risk ratio, 0.95) [233]. Albumin dialysis techniques require multiple treatment courses or even continuous treatment to improve spontaneous recovery or bridge towards liver transplantation. The performance of these systems thus requires improvement. In the case of acute liver failure (ALF) and acute on chronic liver failure (ACLF), we need to establish a large randomized trial to determine the adaptive evidence, timing, and effect of liver support therapy [239]. Meanwhile, these devices can be used early in ALF and ACLF patients, as well as other ways of managing these patients.

Almost all studies of MARS reported improvement of jaundice as well as hepatic encephalopathy. In the randomised controlled trial by Hassanien, patients who received MARS showed a faster and more significant reduction in hepatic encephalopathy. HRS frequently occurs in patients with acute exacerbation of chronic hepatitis, and is related to a negative short-term outcome. In a randomised clinical trial, the 30-day survival rate of patients with type I HRS receiving MARS treatment was significantly better than that of controls (mortality rate of 100% in the control group at day 7 and 62.5% in the MARS group at day 7, and 75% at day 30). In the RELIEF trial [240], up to 10 6–8-h sessions of MARS therapy did not prolong the survival of patients with ACLF, compared with traditional therapy. Another randomised controlled trial (HELIOS) investigated the effectiveness of the Prometheus device in ACLF patients. The effect of HELIOS on 28-day survival was similar to that seen in the MARS-RELIEF trial [236]. Therefore, these devices should be used only as a bridge towards liver transplantation, rather than as a solution for liver failure.

4.6.1.2 Bioartificial Liver

Bio-artificial livers (BALs) are cell-based dialysis devices for achieving blood purification and hepatic synthetic function using bioreactors containing viable animal or human hepatocytes. The patient's blood or plasma is perfused into the bioreactor, which performs the synthetic (proteins and coagulation factors), regulatory (hormones), immunological, and biotransformation functions of the failing liver.

It was showed that intravenous injection of D-galactosamine could build acute liver failure porcine models successfully [239]. Li-BAL [241] is constructed from non-woven polyester fabric with fresh isolated porcine hepatocytes or a conical fluidised bed with microencapsulated porcine hepatocytes. Li-BAL improves blood biochemical parameters and prolongs the survival of pigs with liver failure, suggesting that it could be effective against clinical liver failure.

Over the last 50 years, the extracorporeal liver assist device (ELAD) [242], bioartificial liver support system (BLSS) [243], and radial flow bioreactor (RFB) [244] were developed. However, clinical experience with BAL in patients with liver failure is limited. Most BALs use porcine hepatocytes, while C3A cells are typically used in ELAD. Almost all clinical trials of BAL showed no survival advantage compared with the control group, although some efficacy in terms of neurological or biochemical parameters was reported by most of these studies.

4.6.1.3 Hybrid Artificial Livers

Hybrid artificial livers (HALs) combine the advantages of NBAL and BAL devices, and use NBAL to remove toxins and perfuse the blood with foreign liver cell to temporarily perform complex liver functions such as synthesis, detoxification, and biotransformation.

NBALs can provide only a detoxification function, which is not sufficient to keep patients alive. In the last two decades, improvements in liver cell isolation and culture technology, further understanding of the interaction between liver cells - matrix, the availability of new biological materials, and the progress of tissue engineering have resulted in the development of a new generation of extracorporeal liver assist devices—biological and combined biological artificial livers—that have not only a detoxification function, but also synthesis and biotransformation functions. These systems have been evaluated in phase II/III clinical trials.

Porcine hepatocytes are typically used in these HAL systems, while NBAL systems also incorporate PE, plasma adsorption, and SPAD+continuous venovenous hemodiafiltration (CVVHDF). Such systems constitute a novel approach to treating liver failure. HALs in the research stage include Li-HAL [245, 246], HepatAssist [247], a modular extracorporeal liver support (MELS) system [248], and Academic Medical Center (AMC) system [249]. All of these systems were safe in phase I clinical trials.

However, only HepatAssist has been assessed in randomised controlled clinical trials, and the results were not encouraging so far [247].

4.6.2 Indications and Contraindications for Artificial Liver Treatment

4.6.2.1 Indications [241, 250]

Early- or middle-stage liver failure has various causes, and is defined by an international normalized ratio (INR) of 1.5–2.6 and a platelet count of $>50 \times 10^9$/L. NBALs can also be used for patients with end-stage liver failure, but there are more complications and higher risks in such patients. For patients without liver failure, such systems can also be used for early intervention. NBALs are also suitable for patients with end-stage liver failure awaiting liver transplantation, including those with rejection after liver transplantation, and those in a non-functional period after liver transplantation. The contraindications are serious active haemorrhage or disseminated intravascular coagulation, severe allergy to the blood preparations or drugs (e.g. heparin and protamine) used, circulatory function failure or cardiocerebral infarction in an unstable period, and patients in the third trimester of pregnancy.

4.6.2.2 Contraindications [241, 250]

The absolute contraindications for artificial liver use are out-of-control pulmonary infection, sepsis, abdominal infection, intracranial infection, and active tuberculosis; incurable extrahepatic malignant tumour; serious organic pathologic lesion/s in vital organs (e.g. heart, brain, lung, or kidney), severe heart failure, intracranial haemorrhage, brain death, renal insufficiency with renal replacement therapy for >1 month; human immunodeficiency virus (HIV) infection; severe alcoholism or drug abuse; and psychological diseases that are difficult to control.

4.6.3 Complications of Artificial Liver Therapy [241]

NBALs are used clinically to treat patients with severe hepatitis B infection. This is an effective but invasive approach that can lead to complications, of which the most common are described below.

Bleeding. Patients with liver failure have coagulation dysfunction, and anticoagulant drugs are required during artificial liver support therapy. Therefore, it is likely that bleeding complications will occur. Common bleeding complications include: (1) Bleeding at the intubation sites, subcutaneous haemorrhage, and subcutaneous haematoma. In the most severe cases, death may result. This may result from accidental vessel injury during intubation, indwelling catheter rupture, slippage of a tie connecting catheters to the skin, etc. Once bleeding is observed, the wound should be immediately bandaged, and haemostatic drugs used when necessary. (2) Digestive tract haemorrhage. The associated clinical symptoms are haematemesis, haematochezia, melena, and pale skin. In severe cases, irritability, a fine and fast pulse, and reduced blood pressure may also be observed. Emergency gastroscopy can detect diffuse haemorrhage from the gastric mucosa. Thus, routine prophylactic antacid therapy should be given prior to surgery. During the operation,

little to no heparin should be used in patients with obvious haemorrhage or a positive faecal occult blood test. Alternatively, *in vitro* heparinisation can be applied in these patients. If serious digestive tract bleeding occurs, the amount of bleeding should be accurately estimated. In addition, expansion, antacids, haemostasis, or other treatments should be carried out in a timely manner. (3) Skin mucosal bleeding. The associated clinical symptoms include nosebleeds, skin ecchymosis, and petechiae. (4) Intracranial haemorrhage. This is the most serious bleeding complication, and a cerebral herniation may result in death. Thus, it should be treated immediately by cerebral surgeons.

Coagulation. During artificial liver therapy, insufficient anticoagulant may lead to coagulation in HP. A clinical feature of this condition is rapidly increased transmembrane pressure (TMP), which may cause mechanical cellular damage that results in a marked reduction in the number of blood cells (especially platelets). When TMP exceeds a certain threshold, the artificial liver therapy should be stopped. The operation site should be flushed with saline, and it may be necessary to increase the heparin dose or replace the HP device. Furthermore, patients treated with an ALSS often receive deep vein catheterisation, which could alter blood flow at the intubation site. Local deep venous thrombosis may occur; thus, the leg circumference must be measured daily in patients receiving femoral vein catheterisation. If the circumference increases or the lower limbs swell and become painful, lower limb deep venous ultrasonography should be carried out in a timely manner to detect thrombosis. If thrombosis is observed, the affected leg should be raised, and vascular surgical consultation should take place.

Allergic reactions. Fresh frozen plasma, albumin, and protamine used in artificial liver support therapy can cause an allergic reaction in some patients. The allergic reaction induced by fresh frozen plasma usually occurs in the late stage of a blood transfusion, or at the end of an operation. The associated clinical symptoms include a skin reaction (urticaria); gastrointestinal symptoms such as nausea, vomiting, and abdominal pain; respiratory symptoms like dyspnoea and bronchospasm; and cardiovascular symptoms such as bradycardia-tachycardia and hypotension. An allergic reaction can be treated using anti-allergic drugs. Moreover, transfusion should cease if the symptoms are severe, and appropriate rescue approaches should be applied.

Hypotension. During artificial liver support treatment, hypotension may occur, and possible causes include reduced effective blood volume, bleeding, cardiac problems, plasma allergy, blood perfusion syndrome, and hypoglycaemia. Therefore, changes to the blood pressure and heart rate should be closely monitored during surgery. If low blood pressure or significant clinical symptoms (pale and sweating) are observed, then it is necessary to immediately evaluate the factors causing hypotension. If it is caused by non-cardiac factors, then an appropriate amount of physiological saline can be used to supplement the blood volume. However, if the blood pressure does not increase, hypertensors should be used. Furthermore, if arrhythmia occurs, it should be treated properly.

Infection. Some patients receiving artificial liver support therapy acquire an infection. Typically, the infection is related to artificial liver therapy catheters.

Patients who are fitted with temporary catheters (subclavian, internal jugular vein, or femoral vein catheters) may get a fever. If the infection site cannot be identified, a blood culture should be performed, and the catheters removed. The tip of the catheter can be cut and used for culturing. Prior to obtaining the blood culture results, a traditional antimicrobial therapy can be applied. It is worth noting that patients with liver failure are less tolerant to infection. In addition, a hospital infection is primarily caused by drug-resistant bacteria, and thus may lead to serious consequences.

Disequilibrium syndrome. This syndrome is defined as a set of systemic and neurologic symptoms that occur during or shortly after artificial liver support therapy. These symptoms may last for up to 24 h, and disappear gradually. Mild symptoms include a headache, restlessness, nausea, and vomiting. Serious symptoms include slurred speech, seizure, coma, and even death. Disequilibrium syndrome may need to be diagnosed differentially and distinguished from hepatic encephalopathy, hypertension encephalopathy, and hypoglycaemia.

4.6.4 Prospects of Artificial Liver

Despite recent advances, the extant artificial liver devices are far from ideal. An appropriate ALS system should perform metabolic and synthetic liver functions, as well as promote regeneration of, and prevent pathophysiological alterations in, the injured liver.

4.6.4.1 Prospects of Non-bioartificial Liver

In the future, with the continued development of tissue engineering, other biological methods will be incorporated into NBALs and used in the treatment of liver failure.

New methods of albumin dialysis, such as SPAD combined with cytokine adsorption, have been developed for treatment of fulminant liver failure [251]. Other methods, such as microglobulin-selective adsorption and cytokine adsorption, and combinations thereof in conjunction with current NBAL treatments, show promise.

Direct HP using a β2-microglobulin-selective adsorbent column eliminates inflammatory cytokines and is effective for treatment of acute respiratory distress syndrome. After treatment, inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and soluble intercellular adhesion molecule 1 (sICAM-1) were significantly reduced. However, the IL-2 level had returned to within the normal range by the next treatment [252].

Immobilised polymyxin-B fibre columns reduce plasma cytokine levels in patients with abdominal sepsis. Plasma concentrations (pg/mL) of IL-6, IL-10, and tumour necrosis factor-alpha (TNF-α) were significantly lower after HF with a polymyxin B-immobilized (PMX) fibre column. Survivors had higher IL-6, and lower IL-10 and TNF-α, levels in pre-treatment plasma compared with deceased patients. The treatment resulted in lower dose of norepinephrine requirement and an increased PaO_2/FiO_2 ratio [253]. In another study, the serum levels of some

cytokines were significantly decreased immediately after direct hemoperfusion with a PMX fibre column (PMX-DHP) ($P < 0.02$); the reductions in VEGF and IL-12 levels were of the greatest magnitude. Improved pulmonary oxygenation after PMX-DHP was correlated with the eluted VEGF. Removal of VEGF by PMX-DHP may promote a rapid improvement in oxygenation by inhibiting pulmonary vascular permeability [254].

4.6.4.2 Prospects of Bio-Artificial Livers/Hybrid Artificial Livers

In the past 30 years, in vitro BAL/HAL support system has shown the hope of curing liver failure. However, these systems are not ready for routine clinical use. BAL/HAL systems have defects in several aspects, including cell origin, bioreactor design, convenience and efficacy evaluation. In order to make the technique useful in clinical practice, highly differentiated human liver cell lines and bioreactors capable of providing a similar environment in vivo are needed.

Several cell types have been used in clinical trials of BAL/HAL, including primary porcine hepatocytes, primary human hepatocytes, and the liver cell line C3A. However, no BAL has received regulatory approval for treating liver failure. To overcome the disadvantages of the three above-mentioned cell types, genetically engineered liver cell lines and immortalised human hepatocytes have been successfully used in animal models of liver failure, and may find utility as sources of metabolically active hepatocytes for BAL.

Aside from genetically engineered liver cells and immortalised human hepatocytes, stem cells (*e.g.* human ES cells, LPC, and iPS cells) with self-renewal capacity and the potential to differentiate into hepatocytes also show promise for BAL. Importantly, large numbers of mature hepatocyte-like cells can be harvested from human adult liver stem cells for BAL. However, a number of problems need to be solved before these cells can be used as substitutes for those presently utilised in BAL/HAL, including optimisation of differentiation protocols.

As biological components of BA/HAL support system in vitro, the appropriate hepatocyte source should have the following characteristics: (1) almost complete function of mature human hepatocytes, (2) infinite life and proliferation capacity in vitro, (3) no potential risk of tumor formation, zoonotic disease transmission or immunogenicity. Unfortunately, no such cell source has been found. Highly differentiated human liver cell lines are considered suitable for use in BALS/HALS.

The ideal BAL bioreactor should provide a similar environment in vivo, which can maintain the vitality and function of a large number of hepatocytes in the external environment. However, this high level of simulation has not been achieved, and oxygenation and bile secretion are two major problems to be solved.

Modified bioreactors mimicking the liver architecture should also be developed to provide a stable long-term culture microenvironment that enhances the functionality of hepatocytes from human liver donors and stem cells. Given the rapid advances in sources of hepatocytes, next-generation BAL/HALs using novel and effective liver cells may be just around the corner. Future research should not only focus on further

understanding the proliferation and differentiation of liver cells, but also the formation of liver microstructures such as hepatic microvessels and bile ducts.

4.7 Live Transplantation for Acute Exacerbation on Chronic Hepatitis B and Severe Hepatitis (Liver Failure)

Zhi-Shui Chen Lai Wei

4.7.1 Operation Opportunity and Preoperative Preparation

In the early years of liver transplantation, the procedure was a desperate attempt to save a dying patient. Liver transplantation has been performed in the recent decades with great improvements not only technically but also conceptually [255]. However, as the shortage of the grafts for liver transplant (LT) has been severer over years, all forms of effective therapy should be explored before liver transplantation. At present, liver transplantation has been widely accepted as the standard treatment for patients with ESLD (end-stage liver disease) and hepatocellular malignant diseases [256]. In order to evaluate a patient's candidacy for transplantation, physicians have to consider the severity of liver disease and the potential benefit of liver transplantation accurately [257]. ESLD is critical to determining the appropriate timing for referral to a liver transplant center and is a key factor in prioritization for transplantation [258]. Thus, it is critical to establish a reasonable criterion to judge the best time point to accept the liver transplantation. An accurate assessment of the hepatic reserve capacity is the important point. There are several assessments to assess the stage of the liver function.

4.7.1.1 Child–Turcotte–Pugh Scoring System (CTP) [259, 260]

The CTP score is calculated in the standard fashion using 5 variables, and is classified by the score as A (5–6), B (7–9), C (10–15) as the following table. The recipient of liver transplantation will have a survival benefit on condition that CTP score is more than 7 points (B and C). This score was previously used for allocation of donor organs and is still widely used to predict the risk of preoperative mortality in cirrhotic patients undergoing surgery.

Child–Turcotte–Pugh scoring system and Child–Pugh classification

	Points		
	1	2	3
Ascites	Absent	Slight	Moderate
Encephalopathy grade	0	1–2	3–4
Serum albumin level (g/dL)	>3.5	2.8–3.5	<2.8
Serum bilirubin level (mg/dL)	<2.0	2.0–3.0	>3.0
INR(International normalized ratio)	<1.7	1.7–2.2	>2.2

4.7.1.2 Model for End-Stage Liver Disease (MELD) [261]

The MELD scoring system is used to predict early mortality in patients with cirrhosis undergoing a transjugular intrahepatic portosystemic shunt, and the MELD scoring system is composed of three objective parameters, including serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine. The MELD score higher than 15 is now considered a valid indication of LT in patients with ESLD.

MELD score = $9.57 \times \log_e$ (serum creatinine [mg/dL]) + $3.78 \times \log_e$ (serum bilirubin [mg/dL]) + $11.20 \times \log_e$ (INR) + 6.43.

4.7.1.3 Pediatric End-Stage Liver Disease (PELD) Model [262]

The PELD model is implemented as an improved algorithm for allocating livers among pediatric orthotopic liver transplant (OLT) candidates. This model has been validated using an independent historical cohort of pediatric liver transplant candidates from a single institution and is currently being prospectively validated using national data. While it appears to be an accurate predictor of wait list mortality, such as predicting post-OLT survival or identifying patients who are either too sick or too well to undergo liver transplantation.

4.7.1.4 The Baveno IV Consensus Workshop Identified Four Clinical Stages of ESLD, Based on the Development of Complications, each of Which May Predict Mortality. The Risk of Clinical Decompensation and Progression from Compensated ESLD to a More Advanced Stage Is Approximately 10% per Year [263]

4.7.1.5 Preoperative Preparation [264]

Although the hepatic function is the critical factor to the survival rate and mortality, other pretransplant evaluations are necessary like the renal function, haematology, serology, radiology, cardiac assessment, respiratory assessment, neurodevelopmental assessment and dental assessment. Among above evaluations renal function is necessary to prevent the potentially nephrotoxic effect of post-transplant immunosuppression. Full blood count, platelets, coagulation indices and blood group are obtained. HLA matching is not required.

4.7.2 Liver Transplantation

Classical orthotopic liver transplant is the most common surgical option [265]. The whole transplant surgery mainly contains three parts: the donor operation, total hepatectomy and graft implantation. Living related liver transplantation and auxiliary liver transplantation are performed in some case [266].

4.7.2.1 Classical Orthotopic Liver Transplantation

The classical technique contains the suprahepatic caval anastomosis, followed by the infrahepatic caval anastomosis. According to the situation, the surgeon decide whether the vena cava is need to be preserved, then it is anastomosed either side-to-side or end -to-side with the recipient vena cava. The procedure of the caval and portal anastomosis should be completed in 45 mins. Hepatic artery anastomosis is performed at the level of the recipient's gastroduodenal artery or proximally. And the arterial flow rate should be above 150 mL/min. Depending on the anatomic situation or surgeon preference, the way to reconstruct the biliary tract contain the duct -to-duct anastomosis which is used popularly and the end to end or side to side biliojejunal anastomosis (Roux-en-Y (RY)).

4.7.2.2 Living Related Liver Transplantation

Due to the shortage of the donors, the technique of split cadaveric liver transplantation is more adapted in recent years. However some disadvantage are existing. Compared to the benefits to the recipient, there are some potential risks to the donor. Partial hepatectomy may cause the risk of donor mortality which incidence is estimated at between 1:1000 and 1:250 depending upon whether a larger right liver graft or a smaller left graft is taken [255]. To assess whether the donor is adapted to be the candidate, liver function should be tested. In additional, serology and imaging could be used to assess the size of the intended segmental graft as well as details of its vascular and biliary anatomy. In some case, the liver biopsy may be necessary to assess the steatosis and so on.

4.7.2.3 Auxiliary Liver Transplantation (ALT)

For some case, like the liver function is lost partially, and there is potential for the original liver to recover. After the removal of the partial native liver. a small amount of normal liver is needed to compensate for the loss of liver function in this situation. Then, the transplant liver grow to the native size or the native liver is recovered. and it usually is sufficient to replace the left lateral segments (II and III) with an equivalent donor graft [267]. However, the auxiliary liver transplantation in the metabolic disease requires a large auxiliary graft. Survival rate of ALT may be less than that of conventional transplantation. Dual-grafts auxiliary liver transplantation is performed in some case [268].

4.7.2.4 Anti-HBV Treatment After LTX

Up to now, the best treatment for anti-virus after liver transplantation is hepatitis B immune globulin (HBIG); combined with the common medicine. Although the hepatitis B immune globulin is not widely used, there is growing; evidence that HBIG does not affect the anti-viral effect [269]. However, the antiviral therapy which is combined entecavir with HBIG can significantly reduce the recurrence rate of hepatitis B after hepatitis B positive donor liver transplant.

4.8 Traditional Chinese Medicine (TCM) Treatment for AECHB and Severe Hepatitis (Liver Failure)

Yuan-Cheng Huang

4.8.1 Part One Overview

Severe Hepatitis B (SHB), evolved from chronic Hepatitis B or cirrhosis, characterized by Liver function failure, is a major type of severe Hepatitis B in China. The characteristics of SHB are as follows: it develops rapidly, its clinical syndromes are complicated, there are many other syndromes, it's difficult to be cured, and the patient is in a very critical condition. SHB is one of the major diseases that seriously affect Chinese physical and mental health, with a death rate that has surpassed 70 percent according to Chinese and foreign literature. Lots of clinical practices reveal that routine western medical treatment, coordinated with traditional Chinese medicine (TCM) can not only decrease the dosage and adverse reaction of western medicine, but also increase the clinical therapeutic effect. Interestingly, there is no such a disease in TCM named SHB in the first place. But because it's accompanied throughout by jaundice and often by obnubilation, and progresses fast, it tends to be classified into urgent jaundice in TCM.

4.8.2 Part Two Causes and Pathogenesis of SHB

4.8.2.1 Records of SHB in TCM Classics

Article 261 of *Cold Damage* states that a patient suffering from exogenous febrile diseases for 7 or 8 days has the symptoms of orange skin color, difficult urination, slight fullness of the abdomen, which can be cured by decoction of Yinchenhao (Artemisia capillaris). Article 238 states that a patient with Yangming disease who fevers and sweats on the body, his (her) heat and jaundice cannot give out. If the patient sweats on the head and the neck, the body doesn't sweat, the urination is difficult and is so thirsty that he (she) wants to drink water slurry, his (her) interior is attacked by stagnant heat. That's why the patient's body will be manifested by jaundice.

Synopsis of Golden Chamber states that if the Spleen color is yellow, the stagnant heat circulates….Even if the patients with jaundice often manifest Damp-heat, their long-diseased meridians tend to be blocked by blood stasis.

Symptoms of Acute Jaundice in *General Treatise on the Causes and Symptoms of Diseases* states that if the Spleen and Stomach are suffering from heat, the food qi blocks and steams. Due to the assault of heat toxin, the patient all of sudden manifests jaundice, his heart is full and breath short, and he is on the very verge of death. That's why it's called acute jaundice. Some patients have jaundice on the body, face and eyes. Some don't know they are suffering from jaundice and jaundice appears

on their bodies and faces after death. And those who have the disease and give out heat and have their hearts fluttered are suffering from acute jaundice.

Complicated Diseases in *Mr. Zhang's Panoramic View of Medicine* states that if the patient suffers from blood stasis and manifests jaundice, his defecation is definitely black and difficult, there is lump in his abdominal flank, and his pulse is sunken or intense. If his pulse is a little forceful and not so weak, by drinking Decoction of Peach Kernel for Activating Qi, jaundice will disappear when the black stool is completely excreted.

4.8.2.2 Contemporary TCM Practitioners' Perception of SHB

TCM firmly believes that there are some external and internal causes that lead to SHB. The external causes are Damp-heat and pestilence. When the patient is attacked by the exogenous Damp-heat, the dampness pathogen cannot be excreted outside from the body, the steamed dampness produces heat, so that the heat pathogen cannot disperse, its retention in return brings about dampness. When the stuffed Damp-heat pathogenic factors grow, fumigate the patient's Liver and Gall-bladder, the bile spillover causes jaundice. At the very beginning, the color of the jaundice is bright yellow, and it becomes obscure at later period. General Treatise on the Causes and Symptoms of Diseases states that sometimes jaundice is caused by the pestilence in the nature, traditionally, most of the jaundice is acute and communicable, which spreads fast.

There are some internal causes too. One is the patient has the latent heat in the interior, like the pregnant women and drunkards who are prone to bring the pathogenic factor into the body. Another example is those who all along suffer from deficiency of both qi and blood. Because the healthy qi is deficient, the pathogenic factor cannot be expelled outside from the body, the patient then suffers from deficiency of both qi and blood. Because the healthy qi is deficient, the pathogenic factor cannot be expelled outside from the body and quickly enters into blood aspect. So, the Liver and Gallbladder are stagnated, the unscrupulous discharge of bile then causes this disease.

According to TCM classics, the heat toxin is fiery and exuberant. The Damp-heat produces phlegm, the phlegm heat brings about toxin, the toxicity and fire of phlegm heat then invades the heart and is blocked in the body. The patient is sleepy or fidgety. When the body is permeated with the toxin, the triple energizer is blocked, and its function of water circulation is out of control, that's why urination decreases. More worse, the pathogenic factors have to be retained in the body so that the patient manifests fullness of ascites.

The pent-up Damp-heat turns into fire, and forces blood to circulate disorderly. The dampness tangles the spleen, deficiency of the spleen makes it fail to govern the blood. Then the phlegm dampness blocks the collaterals, the blood stasis and phlegm stagnation damage the collaterals and cause the blood to spill over.

While, the dampness turbidity and phlegm stasis are blocked in the body, the pathogenic heat invades into the pericardium, the clear orifices are beclouded, which causes the patient to fall into stupor. If the body is deficient in the healthy qi in the first place, the pathogenic heat burns inside, the nutrient yin is exhausted, which

finally develops into deficiency of both qi and yin, and deficiency of healthy qi and invagination of pathogenic factors.

4.8.3 Part Three TCM Therapy for SHB

4.8.3.1 Treatment Based on Syndrome Differentiation

When it comes to TCM therapy for SHB, TCM practitioners from different geographical places basically employ the methods of clearing away heat to discharge fire, cooling blood to bring back yin, and excreting the toxins to open the orifices. Some propose the following formula, 10–120 g of Radix Paeoniae Rubra (Red paeony root), 30–60 g of Radix Salviae Miltiorrhizae (Red-rooted salvia root), 30–50 g of Herba Artemisiae Capillariae (Oriental wormwood), 10–15 g of Fructus Gardeniae (Cape jasmine), 10–15 g of Rheum Rhabarbarum (Chinese rhubarb), 10–15 g of Radix Scutellariae (Baical skullcap root), 10 g of Fructus Forsythiae (Weeping forsythiae capsule), 20 g of Radix Curcumae (Curcuma aromatica), 15 g of Radix Gentianae Macrophyllae (Large-leaved gentian). The patient takes a dose every day. According to the principle of treatment based on syndrome differentiation, the therapeutic schedules are proposed as follow:

Firstly, Syndrome of Fiery and Exuberant Pathogenic Heat. The patient with this syndrome has the following symptoms: the body and eyes are dyed with gold-like jaundice, he runs a fever sometimes, he feels full and fidgety, his defecation is dry, his urine is little and red, his tongue body is red, his tongue coating is yellow, thick, turbid and greasy, and his pulse is surging and slippery. For this syndrome, Rhinoceros Horn Powder recorded in Sun Simiao's Golden Prescriptions for Emergencies, Coptidis Decoction for Detoxification and Cow-bezoar Bolus for Resurrection can be synthetically used with proper amount. The formula is composed of 10 g of Guangzhou Rhino horn powder, 10–12 g of Radix Paeoniae Rubra (Red paeony root), 10 g of Cortex Moutan (peony tree root bark), 15 g of Radix Rehmanniae (dried rehmannia root), 6 g of Rhizoma Coptidis (Coptis chinensis root), l0 g of Cape jasmine, 10 g of Rheum Rhabarbarum (Chinese rhubarb), 30 g of Herba Artemisiae Capillariae (Oriental wormwood), 12 g of Acorus Calamus (Sweet sedge), 10 g of Radix Curcumae (Curcuma aromatica), 15 g of Radix Salviae Miltiorrhizae (Red-rooted salvia root), 10 g of Radix Scutellariae (Baical skullcap root), 10 g of Cortex Phellodendri (Golden cypress bark) and 30 g of Radix Isatidis (Indigowoad root). The patient should decoct the formulas with water and take twice every day.

The early period of severe hepatitis is manifested as fiery and exuberant pathogenic heat, and then the static blood blocks the collaterals, which can be treated with decoction of detoxification and dissipation of blood stasis, whose formula is composed of 30 g of Paris Polyphylla, 30 g of Hedyotis Diffusa, 30 g of Herba Scutellariae Barbatae (Barbed skullcap herb), 30 g of Longhairy Antenoron Herb, 30 g of Radix Salviae Miltiorrhizae (Red-rooted salvia root), 12 g of Rhizoma Coptidis (Coptis chinensis root), 6 g of Raw rhubarb and 20 g of Fructus Aurantii Immaturus (immature bitter orange).

Secondly, Syndrome of Inner Block of Dampness and Turbidity. This syndrome coexists with the first syndrome. Dampness and turbidity are categorized into yin and cold pathogens, which should be resolved by aromatics, including Agastache rugosus (Wrinkled giant hyssop), Eupatorium Fortunei, Acorus Calamus (Sweet sedge), Radix Curcumae, Cortex Magnoliae Officinalis, Round Cardamom Fruit, etc. Mr. Lin Zongguang used the following prescription to treat severe hepatitis, that is, the decoction composed of l0 g of Rhizoma Acori Graminei, 10 g of Radix Curcumae 10 g, Radix Polygalae (Polygala root), 10 g of Rhizoma Atractylodis (rhizome of hineseatractylode), 10 g of Processed Rhizoma Pinelliae, 10 g of Pachyma Cocos, 10 g of Bile Arisaema, 6 g of Orange peel and 10 g of Fructus Aurantii (Bitter orange). Additionally, the patient should take Oriental Sweetgum twice per day.

Thirdly, Syndrome of Heat Attack Against Heart and Nutrient Qi. Clinically, the main symptoms of this syndrome are as follows: intercutaneomucous bleeding, tooth bleeding, nose bleeding, subcutaneous ecchymosis, tendency of gastrointestinal bleeding, and coma and delirium in the meantime. In this case, the patient should turn to larger dose of Decoction of Rhinoceros Horn and Rehmannia. The formula is: 3 g of Rhino horn powder, 30 g of Raw Rehmannia root, 30 g of Paeonia Lactiflora and 20 g of bark of tree peony. The Rhinoceros horn can be replaced by 15–20 g of Buffalo horn, which is decocted 1 h first. Paeonia Lactiflora can be replaced by Radix Paeoniae Rubra (Red paeony root). For the heavy bleeding patients, Sanguisorba Officinalis (Garden Burnet Root), Herba Agrimoniae, Imperata Cylindrica (Couchgrass root), Radix Notoginseng powder, etc. can be added.

Fourthly, Syndrome of Stasis and Block of Pulse Vessels and Collaterals. The situation of the patient with this syndrome is deteriorating, which affects his microcirculation and decreases his urination. The patient is inclined to suffer from Liver-Kidney syndrome. In this case, the patient should promote blood circulation to remove blood stasis. The medicinal plants can be used include: Raw Rehmannia root, Radix Salviae Miltiorrhizae, Rhizoma Chuanxiong, Peach kernel, Carthamus tinctorius, Radix Curcumae, etc. For the patients of oliguria and anuria, coloclysis with catharsis can be used as follows: 30 g of Raw rhubarb, 30 g of Sodium sulfate, 15 g of Garden burnet root, 15 g of Flos Sophorae Immaturus (Sophora flower bud), decocted with 150 to 200 mL of water and 10 mL of vinegar. Retention enema is used once or twice a day to alleviate intestinal tympanites, restore intestinal peristalsis, reduce the absorption of blood ammonia, improve the flow of Kidney blood and promote diuresis.

Finally, Syndrome of Obnubilation of Clear Orifices. In this case, the patient is in deep coma, his complexion is depressed and pulse slow. He makes no response to others' calling, all his reactions disappear, because his primordial qi is greatly consumed and his healthy qi is in serious deficiency and pathogenic qi severely sunken. For this kind of patients, intravenous drip of Pulse-activating Injection should be utilized for emergency. For patients whose hands and feet are cold in syncope and blood pressure declines, 15–30 g of ginseng and 10–15 g of processed aconite can be infused from the stomach. For those whose digestive tracts are bleeding, take the decoction made of 20 g of Rhizoma Bletillae, 10 g of raw rhubarb, 30 g charred Radix Rehmanniae and 60 g of Rhizoma Imperatae (Cogongrass root).

4.8.3.2 Treatment According to Symptoms

Removing the Jaundice

The thickening of the color of jaundice is an important indicator of the deterioration of the severe hepatitis. It's of great significance to stop the process and finally remove jaundice. Therefore, combination of TCM and western medicine based on the treatment based on syndrome differentiation can improve the effectiveness of eliminating jaundice and the recovery rate.

Firstly, the most popular methods of removing jaundice nowadays are diuresis and smoothing defecation. Lots of clinical research findings show that Herba Artemisiae Capillariae (Oriental wormwood), Baical Skullcap root, Radix Bupleuri, Rhizoma Polygoni Cuspidati and Chinese rhubarb do good to the removal of jaundice. So they can be utilized properly.

Secondly, because microcirculation disorder, like the stasis of blood, is an important factor for severe hepatitis, to treat intractable jaundice of qi stagnation and blood stasis, the patient can turn to Radix Paeoniae Rubra (Red paeony root), Radix Salviae Miltiorrhizae, root-bark of tree peony, raw Radix Rehmanniae, peach kernel, Radix Angelicae Sinensis, Rhizoma Sparganii, Rhizoma Curcumae, etc. The above-mentioned medicinals with nature of cooling and activating blood and removing stasis are able to reduce the gathering of red blood cells, ameliorate the microcirculation of the Liver, restore the normal metabolism of liver cells and blood supply, and promote the damage repair and regeneration of liver cells.

Finally, medicines for removing jaundice often have the side-effect of impairing yin and the Spleen and Stomach due to their bitter and cold nature. Consequently, their use should take into account of medicines with nature of invigorating the Spleen and Harmonizing the Stomach so that the patient would defecate twice to three times a day, and discharge the toxins without impairing the healthy qi. After medically stable, less amount of medicines for removing jaundice should be used and regulating and tonifying methods added.

Inducing Diuresis

Patients with severe hepatitis of ascites retrogression often have high degree of abdominal distention but smaller amount of ascites. When abdominal distention is serious, proper diuresis can be used to alleviate the condition. Please note, don not take large dose of diuretic prescriptions.

Firstly, the Use of Retained Water Dispelling Medicines.

Indications: for patients whose excess syndrome is ascites, or who don't benefit from dampness-excreting medicines, or whose ascites is not removed completely. The feeble patients should use the medicines and reinforce the tonification in the meantime.

Frequently-used Prescriptions: One, Large Chengqi Decoction, one dose once per day. Two, Powder of Euphorbia kansui, encapsulated, 0.5–1 g once per day. Additionally, Decoction of Ten Dates, Pellet for Eliminating Phlegm and Saliva, Pill for Relieving Ascites, Pill of Euphorbia Lathyris, and the like are often chosen for use.

Usage and dosage: which is decided by the patient's condition. Two, the therapeutic process ends with the disappearance of ascites, and the patient should stop taking the drug for several days when feels worn out. Three, the common side-effects include nausea, vomiting, abdominal pain, lack of appetite, debilitation, sometimes accompanied by heart-burn, dizziness, palpitation and sweat, which are often found 1–2 h after administration and would disappear 4–5 h later.

Contra-indications: the following patients should not take medicines for dispelling the retained water, those who suffer from bleeding in the digestive tract recently, like haematemesis, melena and showing positive in the stool test; who suffer from hepatic coma or the early stage of hepatic coma; the pregnant women with severe heart attack, ulcer and acute gastroenteritis; who suffer from intense heat; and who are vulnerable to extreme emaciation and ambiguous pulse manifestations.

Secondly, TCM Retention Enema.

The use of this ancient method of smoothing Fu-organs to transform the turbidity with enema mainly by raw rhubarb is a method of clearing azotemia in the body, which to some extent has the effect of colon dialysis.

Prescription One: Decoction of Five Medicinals, raw rhubarb, Flos Sophorae, Chinese Pulsatilla root, Cortex Phellodendri Chinensis 30 g respectively and Manchurian wild ginger (later decocted) 9 g. Use retention enema once per day.

Prescription Two: Retention Enema of Descending the Turbid, raw rhubarb, raw oyster, and Serissa Japonica 30 g respectively, concentratedly decocted into 120–150 mL. Use retention enema from a high position. Two to three hours later, clean the enema with 300–500 mL of clean water, once per day, with 10 days as a whole therapeutic process.

4.8.3.3 Other Therapeutic Measures

Therapy with Acupuncture and Moxibustion

The basic acupoints are Zhiyang (GV9), Yanglingquan (GB34) and Taichong (Liv3). If the patient suffers from intense heat, Dazhui (GV14) is added. From unconsciousness, Renzhong (GV26), Zhongchong (P9) and Shaochong (H9) (for bloodletting) are added. The patient who runs high fever impairs yin and stirs the Wind, so Baihui (GV20), Fengfu (GV16), Fengchi (G20), Dazhui (GV14) and Yongquan (K1) are added. If the heat enters the nutrient qi and blood and forces the blood to circulate irregularly, Quze (P3), Laogong (P8), Weizhong (B40), Xinjian and Shixuan (Extra 30) are added. If the patient nosebleeds, Shenting (GV24), Tianfu (L3), Hegu (LI4), Fengfu (GV16) and Duiduan (GV27) are added. If the patient suffers from hematochezia, then Changqiang (GV1), Cimen, Shangjuxu (ST37), Chengshan (B57) and Zusanli (ST36) are added. Every time, three to five acupoints are selected, needled once or twice a day, approximately 30 min for every acupuncture session.

Medical Application to the Navels Therapy

One, the Jaundice-removing Powder, made of even amount of rhubarb, raw alum and Fructus Gardeniae, ground. Fill the navel with ground powder and secure with proof fabric. Change the dressing once 2–3 days. This therapy aims at the patients with yang jaundice syndrome.

Two, the Yin Jaundice Powder, made of Flos Caryophyllata 10 g and Herba Artemisiae Capillariae 30 g. Fill the navel with the mixture of ground powder and ginger juice and secure with proof fabric. Apply hot with hot-water bag for 15–20 min once a day. This therapy also aims at the patients with yin jaundice syndrome.

Intravenous Injection

First, the Mind Refreshment and Tranquilization Injection, modified on the basis of Cow-bezoar Bolus for Resurrection, which affects human muscles. Every time inject with 4 mL, three times a day. The intravenous medication is 10–20 mL, added with 10% glucose 500 mL, twice a day. This therapy aims at the patients at early stage of hepatic coma.

Second, the Liver-Clearing Injection, made of Cape jasmine, Herba Artemisiae Capillariae, rhubarb, Radix Curcumae, etc. Every time inject with 20–40 mL, mix into 10% glucose 200–300 mL, once per day. This therapy aims at the patients with yang jaundice syndrome.

Third, the 50% Rhubarb Injection. Inject with 40 to 80ml every day, mixed into glucose 300 mL, drip into the veins once or twice a day. This therapy can be used at different stages of severe hepatitis.

Retention Enema

Infuse the colons with the decoction made of rhubarb 10–20 g, which is added with vinegar 20–30 mL and glucose water 300 mL so that the toxins can be excreted out of the enteric cavities.

4.8.3.4 Dietary Nursing

Dietary DOs and DONTs

First, the patient should choose food of proper proteins and calories, choose food of good quality like the lean meat, the animal livers, fish, poultry and the fresh fruits as well.

Second, the food should be soft. The patient should avoid choosing food with bones and thorns, food of coarse fiber like the celery, leek and the over-mature cabbage and the fried food in order to prevent the esophagus from being punctured, which causes hemorrhea of the digestive tract.

Third, if the patient has the bleeding tendency, blood coagulation food should be supplemented, like the pork jelly salad, beef tendons, trepang, etc. If the patient plasma protein is low and accompanied by anemia, food with iron can be chosen, like the animal liver mash, the cabbage mash, the dates mash, longan and porridge of red beans. If the patient suffers from ascites, diuretic food should be added to his diet, like the crucian carp soup, goat milk, watermelon juice, white gourd, etc.

Forth, the patient should strictly forbid himself from drinking alcohol. He cannot have drinks with alcohol, stimulant and spicy food, and cans with lead and additives either. If the upper digestive tract bleeds, he should stop having food. He should restrict sodium salt if ascites happens to him.

4.8.4 Part Four Reflections on TCM Therapy for Severe Hepatitis B

4.8.4.1 The Therapeutic Effect of TCM Therapy for Severe Hepatitis B Can Never Be Denied

Abundant research findings show that integrative medicine gains better therapeutic effect in treating SHB compared with purely western medicine. At the early stage of comprehensive treatment of western medicine, namely, using large doses of medication of clearing heat and removing toxins, inducing diuresis and eliminating jaundice, smoothing Fu-organs and promoting purgation, coordinated with drugs of promoting blood circulation and removing blood stasis, clearing stagnancy and harmonizing the Stomach, is an extremely effective measure in clearing the heat toxin, reducing the absorption of the intestinal poisonous substances, intercepting the progress of the disease as soon as possible and alleviating and controlling hepatic inflammation activity. Meanwhile, this treatment promotes the disappearance of jaundice, restoration and regeneration of the liver cells and excretion of metabolites like endotoxin, relieves all kinds of clinical symptoms and increase the survival rate by 10–15%. However, the overall therapeutic effect of the treatment is not satisfying for the patients at the moderate and advanced periods, and the mortality rate is especially high at the advanced stage.

On the basis of the comprehensive treatment of western medicine, the application of TCM plays an important role in controlling the degree of hepatic inflammation necrosis, alleviating different kinds of clinical symptoms, reducing the occurrence of complications, lengthening the survival period and improving the living standard of the patient, and decreased the death rate by 5–10%. The severe hepatitis is progressing rapidly, while its treatment with western medicine is therapeutically limited. By contrast, TCM treatment is widely recognized in clinical practices. The therapies of TCM injections, TCM colonic dialysis and acupuncture and moxibustion are comparatively effective, cheap and convenient. Currently, widespread use of Chinese medicinals and TCM therapies has already become an part and parcel in the treatment of viral hepatitis in China.

4.8.4.2 The Internal and External Treatments with Multi-route Administrations Should Be Done

Except for taking TCM decoction under the principle of treatment based on syndrome differentiation and specific prescription and medication, what should also be positively applied include acupuncture, electroacupuncture, auricular acupuncture, acupoint injection, acupoint application, therapy of nasal cavity, retention enema, etc. in order to make good use of different kinds of TCM treatments and give full play to TCM therapeutic effect. The comprehensive treatment is expected to greatly improve the therapeutic effect and reduce the death rate.

4.8.4.3 Emphasis Should Be Laid on the Principal Syndromes of Severe Hepatitis

Judging from the pathogenesis of severe hepatitis, the patients' main clinical symptoms are jaundice, hepatic encephalopathy, hemorrhage and so on. The rapid thickening of jaundice is a significant indicator of the worsening of severe hepatitis, whereas hepatic encephalopathy, massive hemorrhage of the upper alimentary tract and cerebral edema are the major causes of death for patients afflicted with severe hepatitis. Therefore, hindrance of the thickening at early stage is the key to preventing the liver cells from necrosis. Therapeutic measures such as stopping bleeding, turning the tide of hepatic coma and eliminating cerebral edema aim to help the patients survive the critical stage and make more time for hepatic restoration and regeneration.

Consequently, the key to the improvement of the therapeutic effect is to look for effective prescriptions directed at the main syndromes. The three treasures, namely, removing jaundice by clearing heat and relieving toxins on the basis of taking rhubarb and Herba Artemisiae Capillariae, dispelling the exogenous pathogens by purgation and taking the Cow-bezoar Bolus for Resurrection comply with the standard that the tip of the disease should be treated first when it's urgent. Whereas invigorating the Spleen and Kidney, promoting blood circulation and removing blood stasis, and regulating the microcirculation system comply with the standard that the root of the disease should be treated first when it's not urgent. These two standards have been widely recognized by the majority.

In the recent years, with the advance and better use of modern medical technologies, it's extremely important to strengthen the research on the main syndromes of severe hepatitis. Meanwhile, how to strengthen the research on the causes of a disease and its immune aspects, to maintain and restore the hepatic function and explore new therapies emerges as a crucial research project in traditional Chinese medicine.

4.8.4.4 The Fundamental Research on SHB Should Be Strengthened, the Rule Research on Syndromes Differentiation and Signs Classification of Chronic Severe Hepatitis Launched and the Selection and Reform of Effective Prescriptions Promoted

Currently, a consensus has been almost reached on TCM nomenclature and pathogenesis of SHB. However, views differ among different TCM doctors concerning the detailed syndromes and treatments. Perhaps because the severe hepatitis is extremely dangerous, complicated, changeable, different patients have different constitutions and complications, and different schools of TCM practitioners have different medical habits, there is still lack of a national standard in syndromes differentiation and signs classification of chronic severe hepatitis and the therapeutic evaluation, which often brings about uncertainties of the therapeutic schemes and deviation of the assessment of therapeutic effect.

Therefore, we should struggle to sum up the complicated principle of treatment based on syndrome differentiation and improve the efficacy of the simple recipes

and proved recipes in TCM, and to lay solid foundation on the clinical research in order that the recovery rate and effective repetition rate will be enhanced. The new TCM prescriptions administrated by veins like Mind-Refreshment Injection and Compound Injection of Radix Salviae Miltiorrhizae have witnessed satisfying effect in the treatment of severe hepatitis, therefore are innovations in TCM treatment means. What needs to be done urgently at present is to carry out a further selection of effective prescriptions by observing the principle of syndrome differentiation and maintaining the characteristics of TCM compound recipes as well, then gradually form a line of medical products.

4.8.4.5 The Evidence-Based Medical Research Should Be Carried out on TCM Treatment of Chronic Severe Hepatitis

TCM treatment for chronic severe hepatitis has proved to be effective, but so far is not supported by evidence-based medicine with large samples, multi-centers, randomization, contrast, blind methods and other clinical materials, which to some degree influences the evaluation of the therapeutic effect. By now there are no especially effective medicines and treatments against the complications like hepatic encephalopathy, upper gastrointestinal hemorrhage, renal failure and serious and mixed infection. TCM clinical participation is still quite limited.

Nowadays, TCM treatment for chronic severe hepatitis is mainly based on decoctions, which is in serious lack of new forms of prescriptions with clear therapeutic effect. The clinical intervention for patients who cannot take decoctions is rather limited. So, we should, by following the principle of evidence-based medicine, carry out TCM treatment for chronic severe hepatitis with large samples, multi-centers, randomization, contrast and blind methods to make sure of the effectiveness and points of action.

4.8.4.6 Research Should Be Done on the Prevention and Treatment Schemes of Chronic Severe Hepatitis with Integrative Medicine

The current medication of chronic severe hepatitis is complex and confused, based on the standardized syndrome differentiation and comprehensive treatment, making a standard and reasonable use of Chinese medicinals and different kinds of prescriptions and working out a therapeutic evaluation standard with TCM characteristics is a particularly effective way of preventing chronic severe hepatitis under the principle of treatment of undiseased in traditional Chinese medicine.

4.8.4.7 Research Should Be Carried out on Effective Chinese Medicinals and Multi-route Administration for Chronic Severe Hepatitis

Research should be done on the effective prescriptions and single medicines to explore the main components and sites of action, promote the reform of dosage forms, search for the methods, effective medicines and their functional mechanisms of colon administration and treatment, and develop and enlarge the external treatments like acupuncture and moxibustion.

4.8.4.8 Life Quality Scale for Survey Should be Mapped out

Aimed at the advantage of TCM in changing the symptoms and improving the living standard of the patients, combined with the WHO's Quality of Life Scale, quality of life scale for survey should be mapped out for the severe hepatitis patients in order to make an objective judgment of the precise therapeutic effect of TCM on enhancing the patients' quality of life.

4.8.4.9 Direction of TCM Prevention and Treatment of Chronic Severe Hepatitis Should Be Decided

The development direction of TCM prevention and treatment of chronic severe hepatitis is that identification of diseases and diagnosis are mainly based on western medicine, while the main content of treatment is the principle of treatment based on syndrome differentiation.

To improve the clinical therapeutic effect and generalization of clinical experience, we propose the uniform standard and main use of western medicine in the identification of diseases clinically. On this basis, further treatment according to different stages and types or specific prescriptions and medications should be carried out.

4.8.4.10 Integrative Medicine Should Be Used

Promoting actively the medications with multi-methods and multi-routes and protecting the Liver, Brain and Kidney and other Zang and Fu organs and making a reasonable use of artificial liver to support the liver transplantation are great ways of decreasing the death rate of the patients.

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