Acute Exacerbation of Chronic Hepatitis B

Volume 2. Diagnosis and Management

Qin Ning
Editor

華中科技大學出版社
Huazhong University of Science and Technology Press

Springer

Acute Exacerbation of Chronic Hepatitis B

Qin Ning
Editor

Acute Exacerbation of Chronic Hepatitis B

Volume 2. Diagnosis and Management

華中科技大學出版社
Huazhong University of Science and Technology Press

Springer

Editor
Qin Ning
Department of Infectious Disease
Tongji Hospital
Wuhan, China

ISBN 978-94-024-1601-5 ISBN 978-94-024-1603-9 (eBook)
https://doi.org/10.1007/978-94-024-1603-9

Library of Congress Control Number: 2019930050

This Springer imprint is published by the registered company Springer Nature B.V.
The registered company address is: Van Godewijckstraat 30, 3311 GX Dordrecht, The Netherlands

My dedications go to the intelligent, committed ones Wei Che and Wen Yu who served in the editorial process. A special thanks to Dr. Dong Xu, who helped to collect manuscripts in a timely fashion from all parts of the world.

My dedications to all my teachers and my mentors Dr. Yongsui Dong and Dr. Gary Levy.

I would like to dedicate this book to my family for their love, patience, and support. To my parents Dihua and Jinping who have stood by me through thick and thin. To my children Jianing (Jenny) and Fengning (Fred), adorable individuals who know that knowledge is no substitute for wisdom. To my husband Xiaoping for that I know you are always with me near and far, and for your constant support of my professional endeavors. To my sisters Qiao, Yuan, and Huan for your understandings and encouragements.

To all my students and my secretary Ms. Jinshang Hu, you are part of my life and family.

Foreword

Acute-on-chronic liver failure (ACLF) secondary to hepatitis B virus infection is now recognized as an important worldwide life-threatening disease with a high mortality. The work described in this book by experts in the field provides important information to the reader on its pathogenesis, clinical manifestations and current and future management strategies.

The work provides important new advances in the science of HBV replication and the host response. With major advances in our understanding of the virology and immunology of HBV infection, this book gives reason for cautious optimism that we will soon be able to provide exciting new therapies for this disorder.

To date, with the exception of liver replacement therapy (transplantation), there are few therapeutic options for patients who develop ACLF secondary to HBV. However, advances in diagnosis as well as management strategies including introduction of antiviral agents and inhibitors of pro-inflammatory cytokines offer the hope of better short- and long-term outcomes.

The advances in the basic science of ACLF and the development of small animal models outlined in this book give hope that new therapeutic approaches will lead to the control or eradication of HBV and amelioration of inflammatory disease lessening the need for liver transplantation.

The work described in this book strongly supports that clinical research in ACLF should build on the findings of basic science research and be directed to carefully controlled studies with well-characterized cohorts of patients so that we can evaluate the potential of new therapeutic approaches. The use of exciting new approaches detailed here will not only provide important new therapeutics but also insights into the mechanism of disease. The findings described in this book strongly support that we are approaching an exciting new era for therapy for patients with ACLF.

Toronto, ON

Gary Levy

Preface

It is now recognized that as a consequence of chronic HBV infection, many patients with or without established cirrhosis will develop acute decompensation and multi-organ failure, a syndrome known as acute-on-chronic liver failure (ACLF). Once patients develop ACLF, they are at high risk of death. A number of triggers including reactivation of HBV, coinfection of hepatitis A or E virus, onset of bacterial infection, gastrointestinal bleeding and development of renal dysfunction can precipitate the development of ACLF in patients who have been previously stable. ACLF is prevalent in Asia where many patients have incubative chronic hepatitis B virus (HBV) infection.

For the past decade, with an increasing understanding of the disease mechanisms and improved general internal medications, the overall mortality has significantly decreased due to HBV infection-related ACLF (HBV-ACLF) in Chinese patients. Here we have assembled a group of hepatologists and scientists from academic hospitals and universities to explore the current understanding of the clinical, genetic, virologic and immunologic factors that contribute to ACLF. In this book of 12 chapters, we have explored the current state of knowledge of HBV infection with a specific focus on the natural history and the clinical course to define important host and viral factors to the development of ACLF, sharing our profound experience and clinical procedures in early diagnosis and treatment of HBV-ACLF patients and its complications. All together about 2649 references have been cited, of which 754 were since 2012. At the beginning of the book, there is a complete table of contents, which together with the general index makes it possible for the reader to find specific topics easily. In each chapter, there is an abstract for the reader to gain a quick information of the chapter. We have also used 55 coloured figures to make the illustrations even more visual.

We enlisted the helpful advice of friends, colleagues and senior experts to supplement or confirm our own interpretations. The contacts arising from these discussions have been immensely benignant to me. Here my special thanks to Prof. Gary Levy, Prof. Didier Samuel, Prof. Gyongyi Szabo, Prof. Lanjuan Li, Prof. Zhimeng Lu, Prof. Shiv Kumar Sarin, Prof. Stephen Locarnini, Prof. Xinhua Weng, Prof. Yuquan Wei and Prof. Hui Zhuang.

Finally I should express my gratitude to the employees at HUST Press and Springer Publishing House (Mr. James Hu) for their professional help in completing this book, especially to Ms. Lian-Di Wang, senior editor, and Mr. Wei Che, projector manager, who gave their kind support at all times.

Wuhan, China Qin Ning

Acknowledgements

We would like to thank the consultants, Editorial Committee and other staff members who have contributed to the compilation of the book "Acute Exacerbation of Chronic Hepatitis B (Chinese Version)".

Consultant (In Alphabetic Order)	
Yu-Mei Wen	Fudan University Shanghai Medical College
Ling-Xia Zhang	302 Military Hospital of China
Editorial Board Member (In Alphabetic Order)	
Cheng-Wei Chen	85TH Hospital of People's Liberation Army
Hong-Song Chen	Peking University People's Hospital
Xin-Wen Chen	Wuhan Institute of Virology, Chinese Academy of Sciences
Jun Cheng	Beijing Ditan Hospital Capital Medical University
Zhong-Ping Duan	Beijing Youan Hospital Capital Medical University
Xue-Gong Fan	Xiangya Hospital Central South University
Jin-Lin Hou	Nanfang Hospital
Ji-Dong Jia	Beijing Friendship Hospital Capital Medical University
Xiao-Hui Miao	Shanghai Changzheng Hospital
Ji-Fang Sheng	The First Affiliated Hospital Zhejiang University
Guang-Feng Shi	Huashan Hospital
De-Ming Tan	XiangYa Hospital Central South University
De-Ying Tian	Tongji Medical College Huazhong University of Science & Technology
Mo-Bin Wan	Changhai Hospital
Gui-Qiang Wang	Peking University First Hospital
Lai Wei	Peking University People's Hospital
Qing Xie	Shanghai Jiao Tong University School of Medicine
Sheng-Long Ye	Zhongshan Hospital
Xin-Xin Zhang	Shanghai Jiao Tong University School of Medicine

Other Staff Member (In Alphabetic Order)			
Min Chen	Ming-Quan Chen	Yu-Ping Ding	Jing Dong
Hong Du	Ning-Ling Ge	Xin-Wu Guo	Xiao-Feng Hang
Xiao-Meng Hu	Man Xie	Jing-Lan Jin	Chen Li
Ling-Bo Liang	Feng Liu	Yu Shi	Zhan-Hui Wang
Chun-Chen Wu	Hang-Di Xu	Xiang-Sheng Xu	Xu-Wen Xu
Qiao Yang	Yi-Jun Zeng	Lin Zhang	Wei Zhang
Heng-Hui Zhang	Li Zhou	Guang-De Zhou	
Rong-Rong Zhou	Peng Zhu	Yue-Ke Zhu	Yan Zhuang

Contents

Contributors

Chief Editor

Qin Ning Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Associate Editor

Zhi Chen The First Affiliated Hospital, Zhejiang University, Zhejiang, China

Yu-Ming Wang Southwest Hospital, Army Medical University, Chongqing, China

Guan-Xin Shen Tongji Medical College, Huazhong University of Science and Technology, Hubei, China

Advisory Board (In Alphabetic Order)

Didier Samuel Department of Hepatology and Gastroenterology, Université Paris-Sud, Villejuif, France

Gary Levy Multi Organ Transplant Program, Transplant Institute, University of Toronto, Toronto, ON, Canada

Gyongyi Szabo University of Massachusetts Medical School, Worcester, MA, USA

Hui Zhuang Peking University Health Science Center, Beijing, China

Lan-Juan Li The First Affiliated Hospital, Zhejiang University, Zhejiang, China

Shiv Kumar Sarin Department of Hepatology, Institute of Liver and Biliary Sciences (ILBS), New Delhi, India

Stephen Locarnini Victorian Infectious Diseases Reference Laboratory, Melbourne Health, Melbourne, VIC, Australia

Xin-Hua Weng Huashan Hospital, Fudan University, Shanghai, China

Yu-Quan Wei National Key Laboratory of Biotherapy, Sichuan University, Sichuan, China

Zhi-Meng Lu Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Editorial Board Members (In Alphabetic Order)

Jun-Ying Qi Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Ke Li The Fifth Medical Center of PLA General Hospital, Beijing, China

Lan-Juan Li The First Affiliated Hospital, Zhejiang University, Zhejiang, China

Mei-Fang Han Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Qin Ning Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Tao Chen Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Xi-Ping Zhao Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Xiao-Guang Dou Shengjing Hospital of China Medical University, Liaoning, China

Xiao-Jing Wang Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Xiong Ma Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Xue-Fan Bai Tangdu Hospital, Air Force Medical University, Shanxi, China

Yi-Min Mao Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Ying-Ren Zhao The First Affiliated Hospital of Xi'an Jiaotong University, Shanxi, China

Yong-Wen He Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Hubei, China

Yu-Ming Wang Southwest Hospital, Army Medical University, Chongqing, China

Yuan-Cheng Huang Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Zhi Chen The First Affiliated Hospital, Zhejiang University, Zhejiang, China

Zhi-Liang Gao The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

Zhi-Shui Chen Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Editors

Chief Editor	Qin Ning		
Associate Editors	Zhi Chen	Yu-Ming Wang	Guan-Xin Shen

Qin Ning

Zhi Chen

Yu-Ming Wang

Guan-Xin Shen

Didier Samuel

Gary Levy

Gyongyi Szabo

Hui Zhuang

Lan-Juan Li

Shiv Kumar Sarin

Stephen Locarnini

Xin-Hua Weng

Yu-Quan Wei

Introduction

This book assembles recent achievements in both basic research and clinical management in the field of hepatology, virology, and immunology. It provides up-to-date information for clinicians who can apply the relevant knowledge to their daily clinical practice and for researchers who are interested in clinically orientated studies. The updated and detailed technology and state-of-the-art treatment strategies provided in this book serve as references for clinicians and resident physicians in the daily management of ACLF. The rationality and strategies for basic research as well as patient management in this book can also be a valuable reference for other fatal and end-stage liver diseases than HBV-induced ACLF.

This Volume 2 has six chapters and focuses on its diagnosis and management.

1 Clinical Manifestations and Laboratory Tests of AECHB and Severe Hepatitis (Liver Failure)

Liang Peng, Zhi-Liang Gao, Yu-Ming Wang, Deng-Ming He, Jin-Ming Zhao, Xue-Fan Bai, and Xiao-Jing Wang

Abstract

This chapter describes the clinical symptoms and signs of AECHB and HBV ACLF, classification, grading of HBV ACLF and their features, diagnostic principles and standards in liver pathology, biochemistry, and virology of HBV ACLF.

1. Liver failure is defined as serious damage to the liver cause by a variety of etiologies, leading to liver function disorder or even decompensation, and clinical syndromes with coagulopathy, jaundice, hepatic encephalopathy, and ascites.
2. Severe hepatitis B can be indicated pathologically by apparent hepatocellular necrosis, including extensive multifocal, confluent, bridging, sub-massive or massive necrosis.
3. Laboratory tests during the course of severe exacerbation of chronic hepatitis B can reflect pathological changes and liver function in a timely manner, providing objective and informative reference data for evaluation of disease severity and

L. Peng · Z.-L. Gao (✉)
The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
e-mail: pliang@mail.sysu.edu.cn

Y.-M. Wang · D.-M. He
Southwest Hospital, The First Hospital Affiliated To AMU, Chongqing, Sichuan, China

J.-M. Zhao
Beijing 302 Hospital, Beijing, China

X.-F. Bai
Tangdu Hospital, The Fourth Military Medical University, Shanxi, China

X.-J. Wang
Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Q. Ning (ed.), *Acute Exacerbation of Chronic Hepatitis B*,
https://doi.org/10.1007/978-94-024-1603-9_1

treatment efficacy. Among the most important laboratory tests are those for prothrombin activity, international normalized ratio, and increases in total bilirubin concentration.
4. Severe hepatitis B is associated with interactions between the virus and host factors. Detection of HBV DNA, HBV genotype, quasispecies and HBV mutation can provide important theoretical bases for the prevention, control or mitigation of the progress of severe hepatitis B.
5. Noninvasive imaging modalities can be used to visualize the entire liver and parts of it. Measuring liver volume to evaluate liver size and liver reserve capacity is regarded as important in diagnosis, surgical approach and prognostic evaluation of patients with severe exacerbation of chronic hepatitis B and liver failure.
6. Model for End-Stage Liver Disease (MELD) is the first quantitative method developed to assess whether a patient with liver failure requires a liver transplant. The predictive value of the MELD model has been improved by the MELD-Na, iMELD, and MESO models. Several other valuable prognostic models have been developed. For example, for patients with HBV-ACLF, the established TPPM scoring system was found to be more predictive than MELD score.

1.1 Clinical Manifestations of Hepatitis B Aggravation and Severe Hepatitis (Liver Failure)

Liang Peng, ZL Huang, YY Mei and Zhi-Liang Gao

1.1.1 Definitions and Clinical Classifications of Severe Hepatitis and Liver Failure

Currently, both clinical and pathophysiological diagnoses are made of severe hepatitis (liver failure) in China. According to the Guideline for the Prevention and Treatment of Viral Hepatitis (2000), severe hepatitis is classified as acute severe hepatitis, subacute severe hepatitis, and chronic severe hepatitis.

Acute severe hepatitis is initially diagnosed due to acute jaundice that rapidly progresses to liver failure within 2 weeks. Subacute severe hepatitis can be identified in patients with acute jaundice hepatitis that progresses to liver failure anywhere from 15 days to 24 weeks. Chronic severe hepatitis often develops with pre-existing chronic liver diseases. The clinical manifestations of chronic severe hepatitis are similar to those of subacute severe hepatitis in some patients, or, in some patients, appear similar to decompensated cirrhosis at disease onset. The diagnostic criteria for severe hepatitis in China remain to be fully developed and hence have not been introduced internationally.

To meet the clinical requirements and standardize the diagnosis and therapy of liver failure, the Branch of Infectious Diseases and the Branch of Hepatology of

the Chinese Medical Association invited experts in China to develop the first Guidelines for the Diagnosis and Therapy of Liver Failure in 2006. In those Guidelines, liver failure refers to severe liver damage caused by multiple factors. That damage to the liver results in either the severe impairment or decompensation of synthesis, detoxication, excretion, and biotransformation in the liver and subsequent clinical manifestations characterized by coagulation disorder, jaundice, hepatic encephalopathy, and ascites. On the basis of pathological features and disease progression, liver failure is classified as acute liver failure (ALF), subacute liver failure (SALF), acute-on-chronic liver failure (ACLF), and chronic liver failure (CLF).

ALF is characterized by the rapid appearance of clinical manifestations. Patients with ALF usually develop a clinical syndrome of liver failure characterized by high-grade hepatic encephalopathy (HE, >grade 2) within 2 weeks. Patients with SALF typically present with a clinical syndrome of liver failure anywhere from 15 days to 26 weeks. Finally, ACLF refers to the acute decompensation of the liver function in the presence of pre-existing chronic liver diseases, and CLF refers to chronic decompensation of the liver function characterized by ascites or portal hypertension, coagulation disorder, and HE due to progressive liver dysfunction in the presence of hepatic cirrhosis. The published Guidelines systemically and extensively reflect the current status of the diagnosis and therapy of liver failure. In addition, the Guidelines, for the first time, focus on liver failure rather than severe hepatitis, which broadens our horizons and highlights practicability.

In China, acute severe hepatitis, subacute severe hepatitis, and chronic severe hepatitis correspond closely to ALF, SLF, and ACLF, respectively, as illustrated in Table 1.1. In some patients, chronic severe hepatitis is similar to CLF in other

Table 1.1 Description and comparison of liver failure and severe hepatitis

Types of liver failure	Definition	Corresponding severe hepatitis
Acute liver failure	Abrupt onset of disease, development of liver failure characterized by hepatic encephalopathy of >grade 2 within 2 weeks	Chronic severe hepatitis with acute onset in patients with acute severe hepatitis, HBV carriers, and chronic hepatitis B patients with mild liver lesions
Subacute liver failure	Abrupt onset of disease and development of clinical manifestations of liver failure between 15 days and 26 weeks	Subacute onset of chronic severe hepatitis in subacute severe hepatitis patients, HBV carriers, and chronic hepatitis B patients with mild liver lesions
Acute-on-chronic liver failure	Acute decompensated liver function in the presence of chronic liver disease	Chronic severe hepatitis in the presence of chronic liver disease (characterized by chronic hepatitis and compensated hepatic cirrhosis)
Chronic liver failure	Chronic decompensated liver function in the presence of hepatic cirrhosis	Decompensated hepatic cirrhosis

HBV hepatitis B virus

Table 1.2 Laboratory test index of AECHB

Index	Mild CHB	Moderate CHB	Severe CHB	ACLF
ALT or AST	≤3 × ULN	>3 × ULN	>3 × ULN	>3 × ULN
TBil	≤2 × ULN	(2~5) × ULN	>5 × ULN	>10 × ULN or increase >1 mg/dL daily
PTA (%)	>70	70–60	60–40	<40

countries. On the basis of available Guidelines for liver failure, we define severe hepatitis B as liver failure due to hepatitis B virus infection. CLF is the most common, and ALF and SLF are rare. Acute exacerbation of chronic hepatitis B (AECHB) is a dynamic process, including mild, moderate, severe chronic hepatitis B and chronic ACLF defined in above guidelines. The reference index of abnormality in laboratory examination is shown in Table 1.2.

In addition to viral replication, other factors also contribute to the pathogenesis of hepatitis B-induced liver failure, such as concomitant infection of other hepatitis viruses (especially the hepatitis E virus), immune status, pregnancy, drug and/or alcohol consumption, concomitant bacterial infection, mental stress, and concomitant disease processes (e.g., hyperthyroidism).

1.1.2 Clinical Manifestations and Complications

The liver is the largest solid organ in humans and has complex functions. Hepatic parenchymal cells are responsible for metabolism, secretion, synthesis and bioconversion. Factors that can cause severe damage to hepatocytes (i.e., parenchymal cells, Kupffer cells) may result in disorders of metabolism, secretion, synthesis, detoxication and immunity. In turn, that damage can lead to jaundice, liver shrinkage, coagulation dysfunction, hemorrhage, secondary infection, hepatorenal syndrome, HE, and other clinical entities described in detail here.

1.1.2.1 Common Clinical Manifestations

General Condition

The physical condition of patients deteriorates, and affected individuals usually develop weakness, extreme fatigue, and a severely diminished quality of life. They frequently require assistance to perform basic personal needs, such washing their face, brushing their teeth, and using the toilet.

Gastrointestinal Manifestations

In the early stage of jaundice, in addition to developing extreme fatigue, gastrointestinal symptoms become evident, including extremely poor appetite, anorexia, intolerance of oily foods, nausea, vomiting, abdominal discomfort, and hiccups. In the jaundice stage, the gastrointestinal symptoms deteriorate further. Patients can develop refractory vomiting, hiccups, evident abdominal distension, and reduced/lack of borborygmus.

Jaundice

Clinically, patients initially note their urine color darkens, becoming a strong-tea like color. Next, a yellowish pigmentation of the ski and conjunctival membranes develops. That jaundice progressively becomes deeper, characterized by hepatocellular jaundice. In this stage, serum bilirubin increases rapidly. In fact, the daily increment in serum bilirubin may be >17 μmol/L (>1 mg/dL).

Hepatic Foetor

The sulfur-containing amino acids in the intestine are degraded into mercaptans that have the odor of rotting fruit. Mercaptans cannot be metabolized in the liver and are therefore excreted from the respiratory tract. This distinctive odor is specifically noted in patients with HE. The severity of hepatic foetor may, in some cases, reflect the severity of liver injury.

Coagulation Dysfunction

The occurrence of coagulation dysfunction is primarily ascribed to the reduced synthesis of coagulation factors by the liver. A majority of the both coagulation and anticoagulant factors are synthesized in the liver. In addition, some coagulation-related factors and their inhibitors are also metabolized in the liver. The outcome of coagulation dysfunction is dependent on the severity of damage to the hepatocytes. Thus, even patients in an early stage of liver failure may present with coagulation dysfunction. Prothrombin (PT) activity is often abnormal in the early stages of liver failure and may therefore serve as a sensitive indicator for the prognosis of liver failure.

Common clinical manifestations of coagulation dysfunction are mucocutaneous bleeding (i.e., spontaneous bruising, gingival bleeding, subconjunctival hemorrhage), ecchymosis at the site of injection/puncture, and purpura in more severe cases. Gastrointestinal bleeding is also common in affected individuals, whereas bleeding into/from the genitourinary tract, lung, kidney, and retroperitoneum is rare but occasionally observed in some patients. If intracranial hemorrhage develops, it is frequently life threatening. In AHF, the incidence of bleeding and severe bleeding is as high as 73 and >30%, respectively. Another cause of coagulation dysfunction is thrombocytopenia and platelet dysfunction. Of the two, thrombocytopenia is more common. Because platelets are derived from megakaryocytes in bone marrow, bone marrow fibrosis and either reduced bone marrow regeneration or invasion of lymphoma cells in the bone marrow can reduce the number of platelets. Platelets perform multiple activities, including adhesion, aggregation, release, and shrinking blood clots. Additionally, they play an important role in coagulation. Platelet dysfunction may also increase capillary permeability and fragility, which may cause either spontaneous bleeding of the skin and mucous membranes or difficult hemostasis following vascular injury.

In patients with SLF, thrombocytopenia is mainly diagnosed in the latter stage of disease in which massive hepatocyte necrosis leads to posthepatic cirrhosis, portal hypertension, and hypersplenism. In CLF patients, thrombocytopenia might be present, and hepatocyte necrosis may aggravate portal hypertension and

hypersplenism, resulting in worsening thrombocytopenia. Splenomegaly and splenic sinus hyperplasia increase the phagocytosis and destruction of platelets. Further, splenomegaly can cause enlargement of the platelet pool within the spleen. As a result, the platelets in the spleen may account for >90% of platelets in the body. The above pathological changes may finally cause a reduction in the circulating platelets. The reason for thrombocytopenia in liver disease patients without hypersplenism is still poorly understood and might be ascribed to following factors (1) the hepatitis B virus may significantly inhibit the megakaryocyte system of the bone marrow, resulting in reduced production of platelets; (2) the thrombopoietin (TPO) level is reduced. The division of megakaryocytes into platelets in the bone marrow is controlled by both megakaryocyte colony stimulating factor (Meg-CSF) and TPO. Meg-CSF primarily regulates the proliferation of megakaryocyte progenitor cells, whereas TPO stimulates the maturation of megakaryocytes and production of platelets. TPO is almost exclusively produced by hepatocytes, and only a minority of TPO is produced in the kidney and other organs. TPO is a key factor affecting the production of platelets, and the synthesis of TPO is reduced significantly in patients with either severe hepatitis or hepatic cirrhosis, which affects the production of platelets. In patients with parenchymal liver diseases, abnormalities of platelets are present in both quality and quantity. For example, when the platelet membrane glycoprotein GPI6-IX is reduced, the aggregation of platelets following ristocetin treatment and the shrinkage of blood clots are markedly compromised; and (3) patients with liver diseases usually develop immune dysfunction and are therefore susceptible to infection. Bacterial toxins and systemic inflammatory response syndrome may also cause thrombocytopenia. One published study of ICU patients found that infection was an independent risk factor of thrombocytopenia.

1.1.2.2 Complications of Liver Failure

HE

HE is both a neuropsychiatric syndrome, a type of central nervous system dysfunction, and metabolic disturbance due to hepatocellular dysfunction and portosystemic shunting. HE is clinically characterized by mental and neurological abnormalities, such as abnormal personality and behaviors, irritability, sleep perversion, drowsiness, and complete loss of consciousness or coma. HE is one of the major causes of severe complications and death in patients with liver failure and is typically classified into one of the four following stages:

Stage 1: the prodromal stage. This stage usually manifests with mild abnormal personality changes and behaviors, such as euphoric excitement, indifference, taciturnity, being sloppily dressed, and inappropriate defecation/urination. The affected individual can usually provide correct responses to questions but they are inarticulate and have slow speech. Flapping tremor/hepatic tremor might also be present. To test for flapping tremor, patients are asked to close their eyes with their arms stretching straight, elbows flexed, palms in dorsal extension, with separated fingers. A positive response is determined when the metacarpophalangeal joint, wrist, elbow, and shoulder show irregular movements (jitter) when held in that position within

30 s. Physicians may also ask the patients to hold the their hand for 1 min. If the physician feels the hand tremor, the test suggests a positive diagnosis of flapping tremor. The condition is caused by afferent dysfunction of joint-reticular formation of the brainstem and a characteristic neurological manifestation. That said, flapping tremor has no specificity fro HE and can also be found in patients with either uremia or hypoxemia due to chronic respiratory disease/heart failure. The presence of flapping tremor in a patient with severe liver disease, however, is helpful for early diagnosis of HE. Patients with HE usually have a normal electroencephalogram. Stage 1 of HE lasts anywhere from several days to several weeks. Several patients with HE in the prodromal stage may have no evidence of clinical symptoms; therefore, misdiagnosis is possible.

Stage 2: the precoma stage. Patients with HE in this stage usually presents with confusion, sleep and behavioral disorders, and symptoms as described in the prodromal stage further deteriorate. Patients suffer from disorientation and understanding disorders as well as conceptual confusion over time, place, and person. Patients are unable to perform simple intellectual composition (e.g., building blocks, arranging matchstick into pentagon), and have decreased computing capacity (e.g., 100–7 and continuing). Slurred speech, writing disorders, and abnormal behaviors are also common. Sleep perversion and daytime sleep and night awaking may be present. Further, hallucinations, fear, and mania are also observed, and some patients can be misdiagnosed with mental diseases. Patients with liver failure in this stage usually have evident neurological signs such as tendon hyperreflexia, increased muscle tone, ankle clonus, and presence of the Babinski sign. Flapping tremor and an abnormal electroencephalogram can also be observed. Patients may also suffer from uncontrolled muscular activities and ataxia.

Stage 3: the lethargic stage. Patients with HE in the lethargic stage mainly manifest lethargy and insanity, and neurological signs continue and deteriorate. In the majority of time, patients are in a lethargic state, but can be waken up. Patients respond to questioning, but may present confusion and hallucination. Flapping tremor is also present. Muscular tension increases, and there is resistance in the passive limb movements. Pyramidal signs and abnormal waves in EEG can also be noted.

Stage 4: the coma stage. Patients have complete loss of consciousness and are unable to be awakened. In a light coma, patients are responsive to painful stimuli and uncomfortable postures, have tendon hyperreflexia, and increased muscular tension. Patients in this stage are usually unable to co-operate during an examination, and a flapping tremor may not be inducible. In a deep coma, various reflexes disappear; muscular tension reduces; pupils become dilated; and there are paroxysmal convulsions, ankle clonus, hyperventilation, and abnormalities on an electroencephalogram.

Stage of HE is an important indicator of severity of disease. It may reflect not only the severity of brain damage but also the severity of liver disease. It is important to recognize that there is no clear boundary between two neighboring stages and that there might be some overlap between two neighboring stages (therefore missing the middle stage of HE). When the disease condition either deteriorates or improves after therapy, the severity of HE may be reduced by one or two stages.