Acute Exacerbation of Chronic Hepatitis B

Volume 1. Definition, Research Technology, Virology, Genetics and Immunology

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 1. Definition, Research Technology, Virology, Genetics and Immunology

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 978-94-024-1604-6 ISBN 978-94-024-1606-0 (eBook)
https://doi.org/10.1007/978-94-024-1606-0

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

1 Introduction to Acute Exacerbation of Chronic Hepatitis B (AECHB) 1
Qin Ning, Di Wu, Wei Guo, Wei-Na Li, Xiao-Jing Wang, and Ke Ma

2 Research Methods and Techniques for Acute Exacerbation of Chronic Hepatitis B 49
Zhi Chen, Dong Xu, Tao Chen, Dao-Feng Yang, and Yi-Min Mao

3 Virological Factors Involved in AECHB 119
Hong Tang, Mei-Fang Han, and Yi-Ming Zhang

4 Host Genetic Characters of Acute Exacerbation of Chronic Hepatitis B (AECHB) 159
Yu-Ming Wang, Jun-Qi Niu, Guo-Hong Deng, and Ying-Ren Zhao

5 Immunological Features of AECHB 223
Ping Lei, Guan-Xin Shen, Fu-Sheng Wang, Qin Ning, Hong Ren, Wei-Ming Yan, and Di Wu

6 Other Precipitating Factors for AECHB 315
Bao-Hong Wang, Jing Guo, Lan-Juan Li, Tao Chen, Chun-Xia Guo, and Yong-Wen He

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 1 has six chapters and focuses on the definition, research technology, virology, genetics, and immunology.

1 Introduction to Acute Exacerbation of Chronic Hepatitis B (AECHB)

Qin Ning, Di Wu, Wei Guo, Wei-Na Li, Xiao-Jing Wang, and Ke Ma

Abstract

This chapter describes definition, natural history and recent achievement debrief:

1. Although the definition and classification of liver failure have differed, a consensus has been reached regarding the definition, classification and clinical diagnosis of liver failure.
2. Acute exacerbation of chronic hepatitis B (with the most severe form, HBV-ACLF) refers to submassive to massive necrosis in the livers of HBV-infected patients with mild or moderate inflammation, taking place over a short period of time and leading to progressive damage of liver function, metabolic disorders, and secondary multiple organ failure without an appropriate management. Clinical manifestations include progressive disturbances in blood coagulation, jaundice, hepatic encephalopathy, and ascites.
3. The natural history of severe hepatitis B is mainly influenced by host factors, including gender, age, precipitating factors, and underlying diseases, and by virological factors, including virus genotype, viral mutations, and viral replication. Severe hepatitis B can be divided into early, middle and late stages according to major clinical indicators, e.g. prothrombin activity. Antiviral treatment and artificial liver support is beneficial to clinical outcomes and prognosis.
4. Recent research on the pathologic mechanism of severe hepatitis B has focused primarily on virology, host immunology, and genetics. No sensitive, reliable early warning parameters have been found to predict the development of severe hepatitis B. Early antiviral treatment has become an important means to prevent severe hepatitis B. Immune regulation and repair of liver cell damage are expected to become effective intervention measures.

Q. Ning (✉) · D. Wu · W. Guo · W.-N. Li · X.-J. Wang · K. Ma
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/10.1007/978-94-024-1606-0_1

1.1 Definition and Nomenclature of Acute Exacerbation of Chronic Hepatitis B

Di Wu, Wei Guo and Qin Ning

1.1.1 Concepts of Acute Exacerbation of Chronic Hepatitis B

Chronic hepatitis B virus (HBV) infection and its sequelae continue to be a major global health problem. World Health Organization estimates that approximately 2 billion people worldwide have been infected with HBV, representing nearly a third of the entire world population. Up to240 million are chronically infected, among which nearly 650,000 patients die of liver failure, cirrhosis and hepatocellular carcinoma (HCC) every year [1, 2]. The interaction between HBV replication and the host immune response plays an important role in determining the outcome of HBV infection. After exposure to HBV, initiation of a broad and vigorous immune response to HBV is responsible for an acute self-limited infection, leading to acute hepatitis, while an aberrant immune response may result in fulminant hepatitis [3]. Patients who fail to amount efficient immune responses against HBV develop chronic hepatitis B [4, 5]. HBV persists in the nucleus of infected hepatocytes as a stable non-integrated covalently closed circular DNA (cccDNA) even after patients' serological recovery from acute hepatitis B [6]. Breakdown of immune balance with too vigorous immune pressure can induce reactivation or acute exacerbation of chronic hepatitis B (AECHB) in patients who have been infected with HBV [7]. The incidence of AECHB is found to be directly proportional to the prevalence of chronic HBV infection in a region, making this phenomenon common in countries or areas with high or intermediate endemicity.

AECHB (with the most severe form, HBV-related acute-on-chronic liver failure (ACLF))is a unique presentation with a rapid deterioration of liver function in patients with HBV-related chronic liver disease, characterized by high ALT levels, jaundice, coagulopathy, hepatic encephalopathy (HE) and ascites, which may lead to hepatic decompensation and subsequent hepatic and/or or extrahepatic organ failure. Submassive and massive necrosis of hepatocytes is a typical presentation of AECHB. According to animal studies and clinical observations, an upsurge of serum HBV DNA always precedes or coincides with the abrupt elevation of alanine aminotransferase (ALT) levels and occurrence of AECHB [8–10]. Although, there is a lack of consensus definition of AECHB, and different parameters and cut-off values have been used in different studies, this clinical entity is characterized by sudden elevation of ALT level and the abrupt increase or re-emergence of serum HBV DNA, caused by HBV flare or reactivation in a patient with chronic inactive HBV and resolved HBV infection, always due to an imbalance between virus replication and host immune responses. According to the recent Chinese guideline of prevention and treatment for chronic hepatitis acute exacerbation or flare of hepatitis B refers to elevation of serum ALT level to more than 10-times the upper limit of normal (ULN) after excluding other factors resulting in liver injury [11]. The

updated guidelines released by the Asian Pacific Association for the Study of the Liver (APASL) defines acute exacerbation or flare of hepatitis in chronic HBV-infected patient as intermittent elevations of serum aminotransferase level to more than five times the ULN and more than twice the baseline value [12].

A proportion of patients with chronic hepatitis B presents very high ALT level accompanied by jaundice and hepatic decompensation, namely severe AECHB, which may progress to HBV-ACLF [8]. HBV-ACLF, also terms as severe hepatitis B in China, is a severe clinical entity with high short-term mortality in chronic hepatitis B patient, presenting with a rapid deterioration of liver function and evolving multi-organ failure, with the highest incidences being in the Asia-Pacific and African regions [13, 14]. Both host and virus factors contribute to the mechanisms underlying the pathogenesis of severe AECHB, including excessive immune response, HBV genotype, etc. Reactivation of hepatitis B in HBV Genotype C patients may have a higher risk of progression to liver cirrhosis [15]. HBV DNA kinetics after initiating therapy can predict the severity of AECHB [16]. During AECHB, the cut-off value of 1.55×10^9 copies/mL for serum HBV DNA may identify HBeAg-positive chronic hepatitis B patients eligible for immediate antiviral therapy [17]. For patients with severe AECHB, prothrombin activities and serum bilirubin are important predictors of clinical outcome. Once hepatic encephalopathy (HE) develops in patients with AECHB, the mortality is very high, however, unlike patients with decompensated liver cirrhosis, some patients with severe AECHB can resume almost normal liver function. AECHB should be differentiated from acute hepatitis caused by HBV and other etiologies.

1.1.2 AECHB Causing Liver Function Derangements

AECHB causing Liver function derangements may be found not only in hepatitis B flare during immune clearance phase, but also as a HBV reactivation in patients with HBsAg carriers with normal ALT levels or even in patients with previously resolved HBV infection who have lost serum HBsAg, but are positive for antibody to the hepatitis B core antigen (anti-HBc), particularly when they are receiving immunosuppressive therapy, chemotherapy or organ transplantation. Several viral factors (such as HBV genotype and drug resistant mutants) and host factors (including serological and immunological status of patients, the use of immunosuppressive therapy, the existence of underlying diseases) may be associated with the occurrence of AECHB. For instance, HBeAg positive chronic hepatitis B patients are at higher risks of AECHB than those who are anti-HBe positive. Evidence showed that more than 90% of AECHB in HBeAg positive patients resulted from spontaneous viral activation during immune clearance phase, whereas only half of HBeAg negative patients developed AECHB due to spontaneous HBV reactivation, the remaining cases resulting from super infection by other hepatitis viruses [18].

The immunological mechanisms responsible for AECHB have not been completely elucidated. Disruption of host immune surveillance plays a more significant

role in breakdown of immune tolerance than HBV genomic variations [7]. During the immune tolerant phase, impaired cytotoxic T lymphocyte (CTL) function and IFN-γ production are inadequate to eradicate HBV infection, but continually induce cytolysis of hepatocytes. In the immune reactive phase, spontaneous HBeAg seroconversion usually accompany with mild transient liver function disturbances [19, 20]. However, in a proportion of patients, the immune system activation may lead to severe hepatic dysfunction and sometimes liver failure. Hepatitis B flare is related to enhanced reactivity of HBV-specific $CD4^+$ T cells. Spontaneous reactivation of HBV is associated with elevated numbers of HBV-specific $CD8^+$ T cells, which can also cause immune-mediated liver injury. By contrast, HBV reactivation in patients undergoing chemotherapy or immunosuppressive therapy is due to markedly impaired immune response. Reduction of immunosuppression in these patients lead to the renewed HBV replication and increased HBV-specific T cells, which may result in AECHB [21].

Except liver function derangements resulting from HBV clearance and reactivation, AECHB can occur during or after antiviral treatment, which can be caused by development of nucleoside analogs (NAs)-resistant mutants, withdrawal of NAs, IFN-induced immune stimulation. Besides, liver function derangements due to other possible causes, including the emergence of HBV genotypic variations, such as core promoter mutant and HBV DNA polymerase mutant, may also cause AECHB [22, 23].

1.1.3 Differentiating AECHB from Acute Viral Hepatitis B

Because some patients with chronic HBV infection are asymptomatic or have mild nonspecific symptoms, AECHB may often be present as the first clinical manifestation of HBV infection, thus, this condition may be mistaken as acute hepatitis B (AHB) [24, 25]. AECHB is difficult to differentiate from AHB without accurate history of chronic HBV infection or recent infection with HBV. It is estimated that more than half of patients presenting AECHB may be misdiagnosed as AHB in endemic areas. Misdiagnosis is essentially due to the facts that clinical, biochemical and serological characteristics of AECHB closely resemble those of AHB, including the abrupt onset of severe liver injury, development of advanced grades of HE, high ALT levels and elevated international normalized ratio (INR), and HBV DNA, HBsAg and HBcAb IgM seropositivity. A combination of high HBV DNA levels, low HBcAb IgM titers, evidence of preexisting HBV-related chronic liver disease could be helpful in differentiating severe AECHB and AHB [9, 10].

Differentiation between AECHB and AHB is very important and necessary because these two distinct clinical entities require different therapeutic strategies and have differential prognosis. Most patients with AHB may spontaneously resolve and only few patients who develop fulminant hepatitis B will need therapy. On the contrary, patients with AECHB often require treatment since the liver dysfunction may result in severe acute exacerbation and subsequent hepatic decompensation and organ failure.

1.1.4 The Concept and Classification of Liver Failure

Liver failure (LF) is considered a life-threatening condition with significant morbidity and mortality induced by various causes and is defined as severe hepatic dysfunction of synthesis, metabolism and detoxification, characterized by coagulopathy, jaundice, HE and ascites. LF can be classified into acute liver failure (ALF) [26], chronic liver failure (CLF) and acute-on-chronic liver failure (ACLF) [27].

ALF is a critical condition with rapid deterioration in liver function characterized by abrupt onset of jaundice, coagulation disturbance, and HE, in the absence of preexisting liver disease. The natural course of ALF proceeds with rapid hepatic dysfunction, resulting in multiple organ failure and eventually death. The overall mortality rate remains as high as 80%. Based on the time interval from onset of first hepatic symptoms (e.g. jaundice) to onset of HE, different subdivisions of ALF exist. One classification of ALF defines hyperacute as within 7 days, acute as 8–28 days, and subacute as 4–24 weeks [28].CLF usually occurs in the context of cirrhosis characterized by progressive, irreversible deterioration in liver function. Compensated cirrhosis is not usually symptomatic and clinically detectable. As patients develop more advanced liver fibrosis, pressure in the portal vein increases, potentially leading to the development of cirrhosis-related complications, including those associated with hepatic insufficiency (e.g. jaundice, hypoalbuminemia), and those associated with portal hypertension (e.g. peripheral edema, ascites, variceal bleeding or HE), which is called decompensated cirrhosis. Generally, survival in patients with decompensated cirrhosis is poor, only treatment being timely liver transplantation.

Recently, increasing attention has been given to a third form of liver failure, known as ACLF. The essential characteristics of ACLF include preexisting liver disease, precipitating factors, severe but possibly reversible liver dysfunction (different from CLF), multiple organ failure, and high short-term mortality. ACLF is a severe condition where an acute insult superimposed on an underlying chronic compensated (known or unknown) liver disease due to the precipitating events, manifested as jaundice, coagulopathy and HE, with development of subsequent extra-hepatic organ failure involving dysfunction of brain, kidney, respiratory, circulatory, coagulation, and usually accompanied by sepsis, resulting in high mortality. ACLF is particularly frequent in alcoholic liver disease and hepatitis B-related cirrhosis. The prognosis of ACLF is determined not by the severity of preexisting liver disease, but by the severity of end-stage organ failure. ACLF should be distinguished from both ALF and CLF, because ACLF of preexisting chronic liver disease leads to significantly higher short-term mortality than decompensated cirrhosis, ACLF is often due to precipitating events, Besides, in ACLF, the acute deterioration of hepatic function may be reversible [29, 30].

1.1.5 The Definition of ACLF

While ALF and CLF are clearly understood and well defined, there are no universal definition and widely accepted diagnostic criteria for ACLF. ACLF is a distinct

disease entity involving two injuries, with one being preexisting injury caused by underlying chronic liver disease, and one being superimposed acute injury induced by an acute hepatic insult, subsequently resulting in rapid deterioration of liver function and hepatic failure with or without extra-hepatic organ failure.

The term of ACLF was first introduced in 1995 to describe a condition in which ongoing and chronic liver insult and acute hepatic insult were operating simultaneously [31]. Several societies of hepatology have conducted extensive studies in order to standardize the definition and diagnostic criteria for ACLF. To date, more than a dozen definitions of ACLF have been developed, however, these definitions differ from each other, causing a great deal of confusion. Although the general aspects of this clinical entity have been vaguely defined, the lack of a precise definition limits research regarding ACLF and its clinical application. The reason for the absence of universally accepted and employed definition and diagnostic criterion for ACLF is that underlying liver disease, precipitating events, and clinical manifestations are quite diverse.

A universal consensus of ACLF can not only help us understand mechanisms of pathogenesis as well as natural history, but more importantly, may allow earlier identification of patients at increased risk of deterioration and short-term mortality. Recently two representative consensus definitions have been commonly accepted and widely used. One was proposed by the Asia-Pacific Association for the Study of the Liver (APASL) in 2009, the other one was developed by the European Association for the Study of the Liver (EASL) -Chronic Liver Failure (EASL-CLIF) Consortium in 2013 [32, 33].

1.1.6 APASL Definition of ACLF

In 2009, APASL first established a consensus diagnostic criterion for ACLF through analyzing data from 200 patients, describing ACLF as “acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease”. Then APASL ACLF Research Consortium (AARC) was formed in 2012, which collated and analyzed data from a large cohort of patients in the Asia-Pacific region, subsequently released an updated and revised consensus guideline in 2014,which defines ACLF as “an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dl (85micromol/l) and coagulopathy (INR ≥1.5 or prothrombin activity<40 %) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality”. This updated consensus also proposed the term, the potential therapeutic “golden window” described as “A short period of about1 week before the onset of sepsis and development of extra-hepatic organ failure in a patient with ACLF”. During this critical period, timely intensive management and specific treatments may prevent

the onset of multi-organ failure and potentially ameliorate or reverse the liver injury and failure [32, 34].

1.1.7 EASL-AASLD and EASL-CLIF Consortium Definition of ACLF

In 2011, EASL and the American Association for the Study of Liver Disease (AASLD) formed a research consortium and proposed a definition of ACLF as follows, "acute deterioration of preexisting, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure" [35]. However, the definition has been established on a theoretical ground rather than experimental evidence.

In order to establish a definition of ACLF encompassing other unknown features of ACLF (including prevalence, precipitating factors, pathogenic mechanisms) and allowing identification of cirrhotic patients at high risk of death, in 2013, the EASL-CLIF consortium performed the prospective observational study of 1343 cirrhotic patients with acute decompensation of the disease, called EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, in eight European countries, which define ACLF based on the modified Sequential Organ Failure Assessment (SOFA), the Chronic Liver Failure-SOFA (CLIF-SOFA). According to the number of organ failures involvement, three grades of ACLF are defined, ACLF grade 1 (ACLF-1) refers to cirrhosis patients with renal failure, or a non-renal organ failure with creatinine levels of 1.5–2 mg/dl and/or grade I or II HE. ACLF-2 involved two organ failures, while ACLF-3 refers to ACLF patients with three organ failures or more [33].

Except definitions and diagnostic criteria proposed by EASL-CLIF and APASL consortium, efforts have also been made by several other working parties and consortiums, including World Gastroenterology Organization (WGO) working party, North American Consortium for the Study of End-stage Liver Disease (NACSELD), to understand and better define ACLF as well as bridge the definition gap between the West and the East. NACSELD proposed a special type of ACLF definition termed as infection-related ACLF (I-ACLF) [36–38]. Recently, according to the three kinds of underlying chronic liver disease, Jalan classified ACLF into three different types, namely, non-cirrhosis (type A ACLF), compensated cirrhosis (type B ACLF) and decompensated cirrhosis (type C ACLF). However, there is still an urgent need to validate these proposed definitions and classifications in large prospective studies [39].

1.1.8 Severe AECHB and HBV-Related ACLF

In China, rates of HBsAg prevalence in the general population are relatively high with an estimated 7.18% in 2006. In chronic hepatitis B patients, severe