

Review Article

Better plans and more powerful evidence are needed in the research and treatment of chronic hepatitis B in China

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Abstract: China has the first largest global pool of chronic hepatitis B (CHB) infection. With the implementation of comprehensive intervention of neonatal vaccination based on national strategy, some achievements have been made in control of hepatitis B in China. However, some problems remain unresolved in the research field as well as management of CHB. Currently, empirical therapy, poor study design, inefficient management, low compliance rate of patients, lack of public awareness and economic factor hampers the research and treatment of CHB in China. We propose that China should take more effective measures to improve the study quality, social management, the relief of economic burden for the needed patients, public awareness, evidence-based policies and medicine, supervision for clinical practice, diagnostics ability and laboratory quality, the compliance of patients, and the quality of Traditional Chinese Medicine (TCM) in the management of CHB infection in the future.

Keywords: Chronic hepatitis B, treatment, management, traditional Chinese medicine, China

Introduction

Chronic hepatitis B (CHB) is one of the major global public health problems. According to the last serosurvey in 2006, hepatitis B surface antigen (HBsAg) prevalence among general population in China is 7.18%, placing China in intermediate hepatitis B endemicity zone and the number of hepatitis B carriers is estimated to be 93 million, forming the first largest global pool of CHB infection [1]. There are about 20 million cases in patients with CHB and 0.5-1.0 million new infection, resulting in more than 0.3 million deaths due to cirrhosis or hepatocellular carcinoma (HCC) [1]. Hepatitis B virus (HBV) has been found to have A-H genotypes; most of HBV was found to be type C and type B in a Chinese population [2, 3]. The HBV genotype was found to be related to the disease progression and therapeutic effect [4-12]. Presently,

the HBV genotyping is not a routine test in China. The natural course of CHB can be divided into: i) immune tolerant phase, ii) immune clearance phase, iii) immune control phase, and iv) immune escape phase [13]. The whole natural course of CHB infection can be sustainable for several years [14]. It must be noted that not all patients with CHB go through all phases. Furthermore, the duration of time spent in different phases differs, and transition from one phase to the next may be so fast that distinct phases may not be recognizable in clinical practice [13]. There are no agents available with high enough efficacy and safety to fully eradicate CHB, which is an important reason for persistent infection with CHB. Therefore, the treatment for CHB infection is difficult. According to the Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update, active HBV replication is a key driver of

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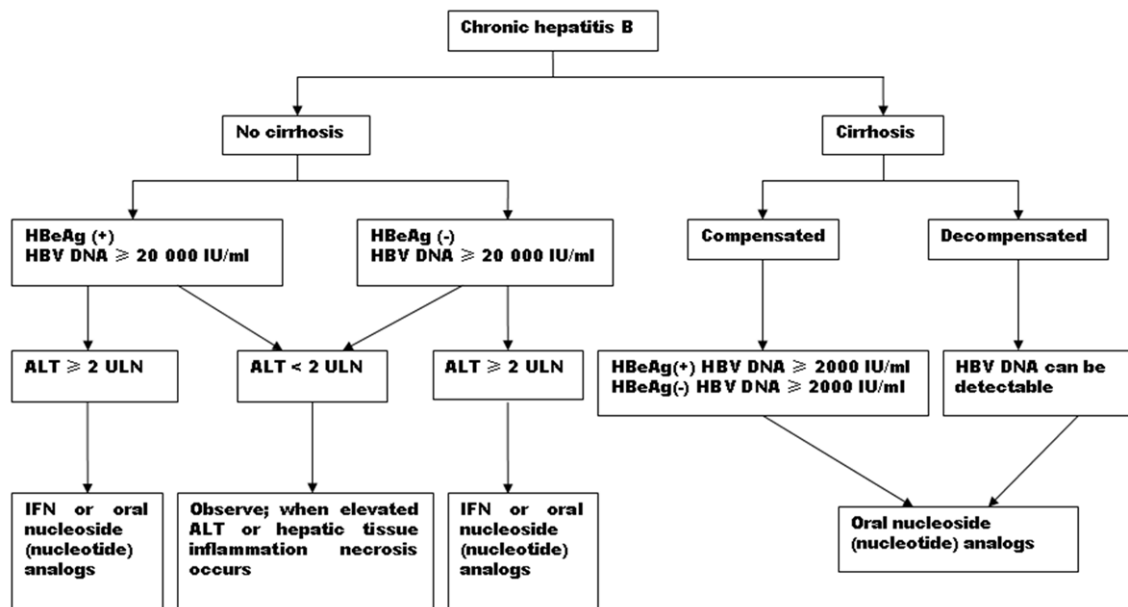


Figure 1. Flowchart of the management of chronic hepatitis B in the 2005 guidelines by Chinese Society of Hepatology and Chinese Society of Infectious Diseases. ULN: upper limit of laboratory reference.

liver injury and disease progression [15]. Therefore, the primary aim of CHB treatment is to permanently suppress HBV replication, thereby reducing hepatic necroinflammation. In clinical practice, the short-term goal of treatment is to achieve 'initial response' in terms of hepatitis B e antigen (HBeAg) seroconversion and/or HBV-DNA suppression, alanine transaminase (ALT) normalization, and prevention of hepatic decompensation, and to ensure 'maintained/sustained response' to reduce hepatic necroinflammation and fibrosis during/after therapy. The ultimate long-term goal of therapy is to prevent hepatic decompensation, reduce or prevent progression to cirrhosis and/or HCC, and prolong survival [15, 16].

In recent years, China has obtained some achievements in the prevention and control of chronic hepatitis, but there are many problems to be resolved in research and treatment of CHB. As far as currently disadvantageous outcomes are concerned in China, better plans and more powerful evidence are needed in research and treatment of CHB.

Advancement and problems

Through the implementation of comprehensive intervention of neonatal vaccination based on national strategy, China has made remarkable

achievements in the control of hepatitis B, and has met World Health Organization (WHO) target in advance that the HBsAg prevalence rate of children under the age of 5 is controlled to be less than 2%. According to the latest two epidemiological surveys in 1992 and 2006, HBV carrier rate in the general population has fallen from 9.15% in 1992 to 7.18% in 2006, especially the rate in children under the age of 14 fell greatly, which the rate in 1-4 years old children is 0.96%; while in 5-14 age group is 2.42% [2, 17-19].

At present, the main drugs used in China for treating HBV are as follows: i) antiviral drugs: interferon-alpha (IFN- α) and pegylated IFN (Peg-IFN)- α 2a, lamivudine, adefovir, entecavir, and telbivudine (tenofovir has not yet been licensed by China Food and Drug Administration), ii) the drugs for the protection of liver and the reduction of jaundice: glycyrrhizic acid, polyene phosphatidyl, glutathione, and S-adenosylmethionine, iii) immune modulators including thymosin and ribonucleic acid so on, iv) traditional Chinese herbs and herbal formulas, v) combination agents. Compared with western countries, the clinicians in China have more alternatives for CHB treatment.

In recent years, some achievements have been made in treatment of hepatitis B in China, the

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effectiveness of treatment has been greatly improved. The guidelines relating to CHB have been implemented in clinical practice to some extent. Especially, the 2010 guidelines of prevention and treatment of CHB [20], which based on the update of the 2005 guideline by Chinese Society of Hepatology and Chinese Society of Infectious Diseases, plays an important role in guiding the clinical treatment of hepatitis B [21]. In fact, the fundamental function of the guideline is to provide a pathway of antiviral therapy for CHB (**Figure 1**).

In addition, “a practical guide America Institute of liver diseases in patients with chronic hepatitis B (2007)” issued by American Association for the Study of Liver Diseases [22], “Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update ” by Asian Pacific Association for the Study of the Liver, and “clinical practice guidelines: management of chronic hepatitis B virus infection” by the European Association for the study of liver diseases also provide useful references to Chinese doctors [16].

However, although “the 2010 guidelines of prevention and treatment of chronic hepatitis B” in China is based on the evidences of the studies of hepatitis B, it is believed that the 2010 guideline still has some limitations: the evidence validity of some literatures cited by guideline is not powerful in most cases; there lacks a large sample, randomized, multi-center and double blind study to support; the guideline is not based on the social-physiological-psychological perspective, only aiming to psychological individuals; there does not clarify the management details for special circumstances (such as female patients of child-bearing age, patients with concurrent HCV or HDV infection, patients undergoing immunosuppression or chemotherapy, and patients with concurrent HIV infection and so on). In addition, in the field of TCM application, the guideline does not give any standards and recommendations to clinical practice, because that is limited to the poor evidence of TCM for hepatitis B treatment.

Conventional antiviral therapy is a key to the treatment of CHB infection. However, in China, there are a significant proportion of patients who give up the antiviral therapy due to financial difficulties, because the treatment course of antiviral drugs for CHB is long, and the drugs

are much expensive (approximately 1,500-15,000 dollars per course). Although most anti-virus drugs have been enrolled by medical insurance lists, which mainly focus on inpatients, those outpatients with CHB only receive a lower medical reimbursement, that resulting in a considerable numbers of the low-income patients were obliged to give up the therapy or to seek for an affordable complementary treatment such as Traditional Chinese Medicine (TCM).

In China, TCM is widely recognized by general population. Chinese herbs such as *Fructus Gardeniae*, *Radix Astragali*, *Radix Rehmanniae*, *Radix Paeoniae Rubra*, *Rhizoma Coptidis*, *Rhizoma Cyrtomii*, *Folium Isatidis*, and *Radix arnebiae* etc. have been reported to inhibit CHB in vitro. Furthermore, the effective components extracted from Chinese herbs such as polysaccharides, biological alkali, flavonoids, and saponins have been found having an antiviral action [23-29]. Currently, there are not only Chinese herbs, but also Chinese medicine liquids, granules, capsules, tablets, and injections have been widely used for the treatment of CHB. Clinical studies have shown that Chinese medicine might have played a role in inhibiting HBV replication and anti-fibrosis, eliminating inflammation, improving the recovery of liver function and the liver blood supply, reducing ALT and jaundice, and modulating the immune function [23-29]. However, although the numbers of clinical studies are big, the overall quality of these studies is generally very poor [30], which results in the lack of an available treatment guideline of TCM. Thus, empirical rather than evidence-based treatments of CHB are common, then curative effect is difficult to be guaranteed in the clinical area.

Before active therapy, it is essential that a professional doctor gives the patient a thorough evaluation based on serum biochemical tests, virus replication status, the severity of liver fibrosis, and CHB genotype. Besides drugs therapy for liver disease, counseling of the patient is also very important and even is crucial for successful antiviral therapy based on the guideline. Therefore, this requires qualified and professional doctors. In fact due to lack of strict standardized training and qualification system for the doctors in China, some inappropriate treatments are often rendered in clinical practice, especially in some rural and poverty areas.

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In addition, another issue lies in some for-profit hospitals at present in China, which are run by commercial companies and enterprises rather than charities; therefore constant pursuit of maximum profit is common. Meanwhile due to lack of health supervision (there are few staff whom are being engaged in health administration in China), some treatments are problematic and unnecessary.

Presently, public awareness of CHB is poor in China. Especially, as a developing country, there are still about 40 million illiterate populations and it is more difficult to increase awareness for those people than other populations. Both lack of awareness and available medical resources lead to illness delays, and even there are some patients with CHB whom have not been screened. What's more, since hepatitis B recovery relies on a long term treatment, poor awareness of the disease will lead to treatment interruption and even failure. According to the previous study, overall compliance rate of the patients with CHB is very low (only about 40%) in China [31-33]. Therefore, the public awareness of hepatitis B is needed to be addressed in future.

In the field of the research for hepatitis B, the projects have speeded up over past 30 years in China. For example, we retrieved the China National Knowledge Infrastructure (CNKI) database taken "hepatitis B" as Mesh subject, and the results showed that the number of literature increased from 465 in 1983 to 4409 in 2013, and there had an increase of nearly ten times. We also noted that the published papers were related to almost all the medical sub-disciplines. However, the clinical studies accounted for 62.5% of the total literatures and the studies in the fields of TCM was 10.3%. Although the quantity of hepatitis B research literature had a great increase, we found that the majority of the studies existed common problems such as repeat study objective, unreasonable design, poor innovation, small subject number, unclear measurement indicators, lack of follow-up and drug safety report. Especially in the field of TCM, we found that the overall quality of the studies was poorer and even some studies did not set control groups.

Prospective strategies

As a result of hepatitis B immune prevention measures of sustainable development, there

will be a reduction in new-onset patients in China, however there are a large population with CHB infection will exist for quite a long time. So the problems related to the management of CHB will continuously plague China. In order to deal with the problems, the following actions should be taken in the near future.

Enforces scientific evidence-based policies and supervision for clinicians and hospitals

Past experiences have proved that the government plays the most powerful and important role in the management of public health, there is no any organization that can replace it. Whereas, it is crucial that how the government enacts and implements the scientific strategy for the management of CHB. And yet the majority of government staff did not have a medical background. Therefore the government should counsel the expert opinions from the organizations of the management of CHB, such as the Chinese Foundation for Hepatitis Prevention and Control is the most important non-profit organization working in the management of CHB. In the past, the organization has made some great contributions. In the future, the government should closely collaborate with the professional organizations including the Chinese Society of Hepatology, Chinese Society for Infectious Diseases and Chinese Foundation for Hepatitis Prevention and Control and so on to put forward more feasible and more scientific programmes for CHB. Especially, the national programmes and strategies for the management of CHB must be performed under the guideline of credible professional organizations based on the scientific evidence and data.

It is also urgent to carry out a national policy of the qualification access for hospitals and physicians for the diagnosis and treatment of CHB, especially for CHB antiviral therapy. Meanwhile, the public health administration should enhance supervision for profit-driven hospitals, and inappropriate treatment of CHB should be prohibited rigorously. It is very important that the treatment should be based on a clear and standard path as soon as possible; what's more, the internal and external quality control standards on CHB treatment should be set.

Reduces the cost for treatment of chronic hepatitis B

Based on the fact that many patients cannot afford the high cost on the treatment of CHB,

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the government should increase fund on it. In addition, new medical insurance policy should allow outpatients to enjoy the same benefits as inpatients. It is vital to reinforce that prevention is more privileged than treatment. Thereby, focusing on only treating end-stage hepatitis B patients is inappropriate. It is proposed that a national policy should be established on free screening, vaccination and basic treatment for poverty populations. Especially, the program of hepatitis B immunoglobulin (HBIG) combined with hepatitis B vaccine immunization should be widely implemented in newborn infants within 24 hours of birth among those mothers with HBV [34-36]. In order to offer cheaper antiviral treatment for patients with hepatitis B, it is recommended to develop domestic drugs and new medicines in replacement of imported ones.

Improves the diagnostic ability and laboratory quality

Some useful diagnostic methods, kits and tools such as fluorescent quantitative PCR kit, chemiluminescence quantitative kit, HBV genotyping, immunological and biochemical analyses, and non-invasive methods for evaluating severity of hepatic fibrosis such as liver stiffness measurement (LSM) [37-39] should be widely used in clinical practice. In order to treat patients with CHB, assessment of hepatic fibrosis is of paramount importance, LSM could be used as a more practical alternative to liver biopsy in patients with chronic hepatitis B. In China, the primary health care is still vulnerable, there are a significant proportion of patients with chronic diseases whom do not know their infectious conditions due to poor medical resources. So both improving laboratory quality and increasing access to diagnostic tools are essential in China. It is necessary to implement a national policy of free HBV serum screening for early discovery of HBV in the future.

Raises public awareness of CHB

It must be pointed out that the improvement of the awareness of hepatitis B of the government staff is more urgent than that of the public in China. CHB awareness courses should be conducted for the staff from health administration offices, especially those in the primary health sectors. Health education on CHB should be held more regularly for the public through con-

ventional talks or education services through the media. However, for illiterates, it should carry on the special educational activities to improve their cognition ability about the disease.

Increases the compliance rate of patients with CHB

Before the treatment, doctors should make an effective communication with each patient and understand their financial and mental status, and make a full assessment. It is understood that patients' compliance to treatment will be improved if an agreement has been reached between doctors and patients. In the long term treatment of CHB, the government, organizations, communities, families, and doctors should actively participate in patients' follow-ups, and ensure patients comply with their treatments. Adopting the comprehensive intervention models such as a doctor-community-family-patient model may significantly increase the compliance rate.

Promotes the research quality of CHB based on EBM

Presently in China, majority clinicians and researchers are lack of the general knowledge on the study design and evidence-based medicine, therefore, scientific research training programs should be conducted among them. To ensure study quality, the clinicians and researchers should refer to the relevant standards of trials and studies including the Consolidated Standards of Reporting Trials Statement (CONSORT) [40, 41], the Consolidated criteria for Reporting Qualitative Research (COREQ) [42, 43], the Standards for Reporting of Diagnostic Accuracy (STARD) [44], the Reporting of Observational Studies in Epidemiology (STROBE) [45]. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [46], the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [47], the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [48], the Strengthening the Reporting of Genetic Association studies (STREGA) [45] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [49]. Meanwhile, the clinical practice should depend on evidence-based medicine (EBM) rather than empiric treatment. Therefore,

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a systematic and comprehensive evaluation including the effectiveness, measures, safety, health economics, and ethics should be applied before the treatment of CHB. As far as the current treatment of CHB is concerned, it is urgent to train the doctors to master and practice evidence-based medicine in clinical setting.

However, we believe that Chinese periodicals and journals should play important roles in the EBM popularization and the improvement of study quality. Currently, most of Chinese medical periodicals and journals adopt the summary or the abstract of four-section style including objective, method, result and conclusion for clinical trials. It is believed that this type of abstract is too simple to identify key research ideas; hence its style should be changed. In order to help the researchers improve study designs, it is recommended that Chinese medical periodicals and journals should follow an updated abstract format complying with CONSORT Statement including objectives, design, setting, participants, interventions, results, conclusions, and trial registration (where applicable, reports registry number for clinical trials) to scholars for clinical trials reports. Undoubtedly, the quality control and guides of professional periodicals and journals for clinical trials will be helpful to enhance the research quality of hepatitis B.

Improves the quality of the clinical research and treatment of TCM

In the fields of the TCM, in order to reverse the confused situation in the treatment and research of TCM, several aspects should be strictly followed in the future: i) research design is rigorous and scientific; ii) outcome measurements and effect standard is objective; iii) treatment must be based on EMB; iv) it is urgent to perform an effective components analysis and effect elevation on Chinese medications used commonly in the treatment of CHB such as *Artemisia Capillaris*, Giant Knotweed Rhizome, Chinese Thorowax Root, *Radix Salviae Miltiorrhizae*, *Radix Curcumae*, *Radix Astragali*, Baical Skullcap Root, and *Radix Isatidis* etc; v) it needs a useful animal model for the study of hepatitis antiviral TCM drug; vi) TCM should closely combine with modern scientific tools such as animal trial, molecular diagnostics, microstructural observation, extra-cellular matrix metabolism and histological

observation so as to find their efficient component and clarify related mechanisms; vii) it is necessary to evaluate the safety of TCM especially for the liver damage of some herbs; viii) it must pay more attention to the quality control of TCM to ensure the clinical medication of high reliability and good effect.

Strengthens the partnership among the different organizations

At present, hepatitis B research projects are supported by many different agencies and organizations, there lacks a communication platform for the researchers. Therefore, there need to establish a specialized agency to coordinate hepatitis B research plans to avoid repeat studies and resource wastage. In the future, high quality of large sample prospective studies should be encouraged and preferred, because they can provide more convincing evidence for the clinical treatment of CHB.

Clarifies some important unresolved issues in the management of CHB

There are some important issues that are completely unsolved in the management of CHB in China as follows: i) the significance of CHB genotyping in Chinese populations, ii) the treatment strategy for multi-drug resistance, iii) the anti-virus treatment for children and pregnant and special patients with CHB infection such as combine with HIV, cancer and auto-immune diseases, iv) the reliable TCM therapy and combination therapy, v) the withdrawal time of antiviral drug, and vi) application of evidence non-steroidal anti-inflammatory drugs. These issues are needed to be further clarified in the future.

Despite some advances in the management of CHB infection, the current situation is still not optimistic in China. It is time for China to act quickly to reverse unreasonable behaviors in research and treatment of hepatitis B, and to establish a novel system to effectively manage hepatitis B.

Conclusion

In the future, it should take comprehensive measures to improve the disadvantageous outcome in the research and treatment of CHB. The key points should be focused on the improvement of study quality, social manage-

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ment, the relief of financial burden, public awareness, evidence-based policies and medicine, supervision for clinical practice, diagnostic ability and laboratory quality, the compliance rate of patients, and the development of evidence-based TCM in the treatment of CHB infection in China.

In brief, more effective management strategies, more scientific research plans and more rigorous therapies conforming to evidence-based medicine should be carried out in the research and treatment of CHB infection in China.

Disclosure of conflict of interest

None.

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