Evidence based management of HBV and its liver complications using Chinese herbal medicine: Challenges ahead

Zhaoxiang Bian, MD, PhD
School of Chinese Medicine
Hong Kong Baptist University

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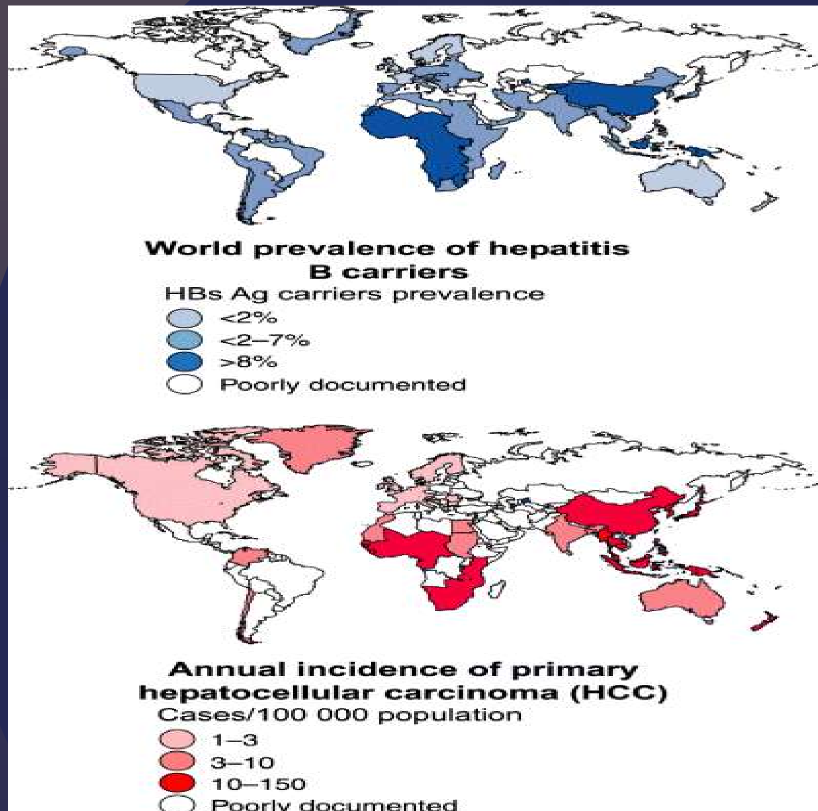
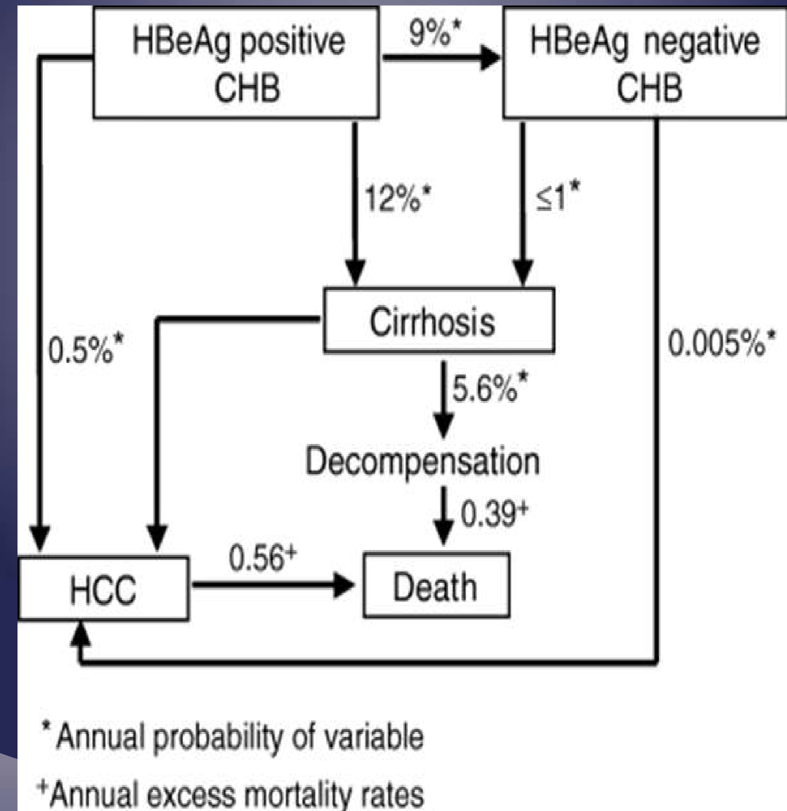
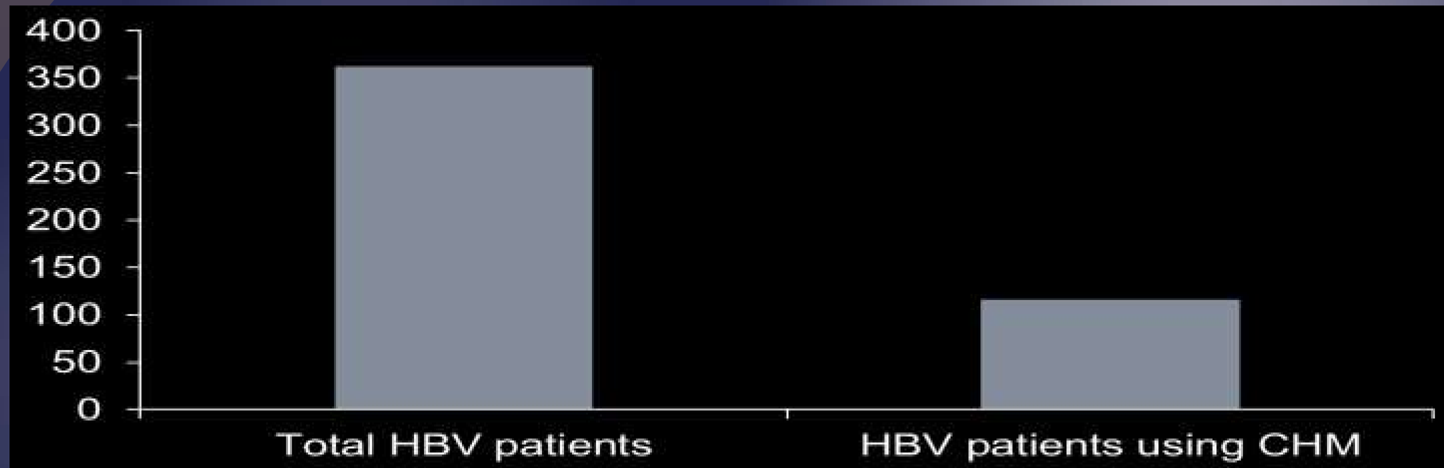
Epidemiology of HBV





Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepatitis, 2004, 11(2): 97-107

TCM usage among HBV patients



- One hundred and sixteen (32%) patients reported they had ever used traditional Chinese medicine, and 58 (50%) of them were actively using traditional Chinese medicine at the time of the study.

Wong VW, et al. A hospital clinic-based survey on traditional Chinese medicine usage among chronic hepatitis B patients. Complement Ther Med. 2005 Sep;13(3):175-82.

How to manage HBV and its complications based on current best evidence?

Evidence-based Medicine and RCT

- EBM: Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of patient (1996)
- Evidence from randomized controlled trial (RCT) and systematic review based on RCTs is regarded as best evidence.

1996

Evidence Pyramid

- Meta-analysis
- Systematic Review
- Randomized Controlled Trial
- Cohort Studies
- Case Control Studies
- Case Series/Case Reports
- Animal Research

Chinese medicinal herbs for chronic hepatitis B.

- **Selection criteria:** Randomised or quasi-randomised trials with at least three months follow-up. Trials of Chinese medicinal herbs (single or compound) compared with placebo, no intervention, general non-specific treatment or interferon treatment were included. Trials of Chinese medicinal herbs plus interferon versus interferon alone were also included. Trials could be double-blind, single-blind, or unblinded.
- Data collection and analysis: Data were extracted independently by two reviewers. The methodological quality of trials was evaluated using the Jadad-scale plus allocation concealment. Intention-to-treat analyses were performed.
- **Main results: Nine randomised trials, including 936 patients, met the inclusion criteria. Methodological quality was considered adequate in only one trial**. There was a significant funnel plot asymmetry (regression coefficient=3.37, standard error 1.40, P=0.047). Ten different medicinal herbs were tested in the nine trials. Compared to non-specific treatment or placebo, Fuzheng Jiedu Tang (compound of herbs) showed significantly positive effects on clearance of serum HBsAg, HBeAg, and HBV DNA; Polyporus umbellatus polysaccharide on serum HBeAg and HBV DNA; Phyllanthus amarus on serum HBeAg. Phyllanthus compound and kurorinone showed no significant effect on clearance of serum HBeAg and HBV DNA and on alanine aminotransferase normalisation compared to interferon treatment. There were no significant effects of the other examined herbs.
- Authors' conclusions: Some Chinese medicinal herbs may work in chronic hepatitis B. However, the evidence is too weak to recommend any single herb. Rigorously designed, randomised, double-blind, placebo-controlled trials are required

Liu, Jian Ping. McIntosh, Heather. Lin, Hui. EBM Reviews - Cochrane Database of Systematic Reviews. Cochrane Hepato-Biliary Group Cochrane Database of Systematic Reviews. 1, 2009.

Chinese medicinal herbs for asymptomatic carriers of hepatitis B virus infection

- **Search strategy**: The trials registers of The Cochrane Hepato-Biliary Group, The Cochrane Library, and The Cochrane Complementary Medicine Field were searched in combination with MEDLINE, EMBASE, and handsearches of Chinese journals and conference proceedings (October 2000).

- **Selection criteria:** Randomised or quasi-randomised trials (minimum follow-up three months) in asymptomatic carriers of hepatitis B virus. Chinese medicinal herbs (single herb or compound of herbs) compared with placebo, no intervention, general non-specific treatment, or interferon treatment. Trials of Chinese medicinal herbs plus interferon versus interferon alone were also included.

- **Data collection and analysis**: Data were extracted independently by two authors. Analysis was performed by intention-to-treat where possible. Pre-specified subgroup analyses were: ethnic origin, age at time of infection, and single herb or compound of herbs.

- **Main results**: **Three randomised clinical trials (307 patients) that followed patients for three months or more after the end of treatment were included**. The methodological quality was poor. The herbal compound 'Jianpi Wenshen recipe' had significant effects on viral markers compared to interferon: relative risk 2.40 (95% CI 1.01 to 5.72) for clearance of serum HBsAg, 2.03 (95% CI 0.98 to 4.20) for clearance of HBeAg, and 2.54 (95% CI 1.13 to 5.70) for seroconversion of HBeAg to anti-HBe. Phyllanthus amarus and Astragalus membranaceus showed no significant antiviral effect compared with placebo. Analysis of pooling eight randomised clinical trials with less than three months follow-up did not show a significant benefit of Chinese medicinal herbs on viral markers. Data on long-term clinical outcomes and quality of life were lacking.

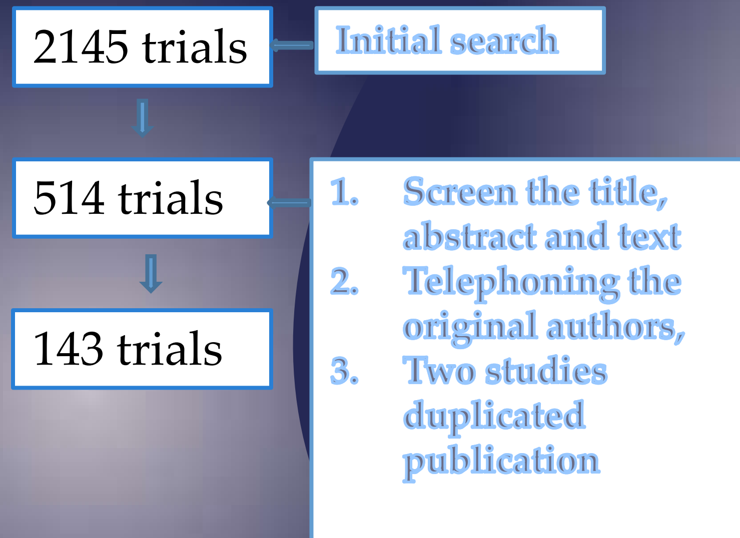
- **Authors' conclusions:** Based on one low quality trial, the medicinal herb 'Jianpi Wenshen recipe' may have an antiviral activity in asymptomatic carriers of hepatitis B virus. However, rigorous randomised, double-blind, placebo-controlled trials are needed before herbs should be used for this condition.

Liu JP. McIntosh H. Lin H. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane. 1, 2009.

Questions of current evidence

- Number of included trials are too limited.
- Whether it is RCT or not is not sure.
- The results cannot provide sufficient information to clinical practitioners about the usage of CHM for HBV patients the clinical practice

Chinese herbal medicine in the treatment of chronic hepatitis B and its complications



- All of them were used parallel design and conducted in China.
- The TCM preparations used in each study were different or compared with different control therapy regimens.

Findings and Conclusions

Long term effect of TCM on HBV-DNA

Eighteen studies have evaluated a long term (> 48 wks) therapy of CHM for HBV patient.

- Five studies (Hu Y 2011; Yu P 2011; Ding H 2010; Zhao WL 2010; Cai HB 2007) showed the Chinese medicines *no benefit* on the normalization of the HBV-DNA when combined use with conventional medicines.
- Seven studies (Li RX 2007; Tu YY 2008; Zhang GY 2007; Lu N 2010; Lu F 2010; Zhen GZ 2009; Zhou F 2003) showed *significant effect* in the normalization of the HBV-DNA when combined use with the conventional medicines; One studies (Liu LC 2003) showed self-made TCM formular had *significant effect* in normalization HBV-DNA than other TCM formular (40% vs 25%); Two studies (He JS 2002; Wu DQ 2009) showed self-made formulars had *significant effect than placebo* (21.7%~69% versus 3.3~10%). Three studies (Zhang GY 2007; Ding H 2010; Zhao WL 2010) showed that integrative management with Chinese medicines and lamivudine had significant effect DNA variation when comparing with that lamivudine alone (3.2% (1/31) ~11.4% (8/70) versus 25% (7/28) ~36.4% (28/77)).
- One study (Yang HZ 2006) showed *a similar effect with lamivudine*.

Findings and Conclusions

Long Term Effect on HBV-HBeAg:

- Chinese medicines Xiaoyaowan (Cai HB 2007), Dahuan Zhecongwan (Yu P 2011) and compounds Biejia Ranganpian (Lu F 2010; Lu N 2010) may have *no effect* on normalization of HBeAg (the rates were 22.2%~45.5% versus 21.9%~44.1%).
- Five CHM medicine (Yang HZ 2006,Ding H 2010, Li RX 2007, Tu YY 2008,Zhen GZ 2009) showed *a significantly effect in* normalization of HBeAg ranged from 42.5% to 53.6% in the patients treated by TCMs combined with conventional medicines than in the patients treated by *the conventional medicines alone* in which the rates were 24.4% to 30.4%. Two studies (He JS 2010; Wu DQ 2009) showed the self-made Chinese medicines had *significant effect* in normalization rates than *the placebo* (21.7% vs 3.3%, and 77% vs 40%, respectively).
- Two studies (Yang HZ 2003; Song FB 2011) showed the self-made Chinese medicines had *a similar effect* as the control Chinese medicines on normalization of HBeAg (13.3%~50% vs 0%~44.4%).

Findings and Conclusions

Short term effect of TCM on HBV-DNA

- *Fifteen studies* with short term therapy presented *benefit* for normalization of HBV-DNA (Liz ZW 2011; Lan SB 2006; Yin XL 2010; Zhang JH 2005; Li J 2003; Xi RH 2010; Li MH 2010; Huang GR 2005; Zhou Q 2008; Wang YQ 2003; Lin SN 2004; Lin SN 2004; Wang J 2006; Du B 2002; Xu SF 2005),
- and some *have no benefit* for normalization of HBV-DNA (Zhang HO 2010; Ou S 2010; Zhang HF 2010; Shen MR 2010; Zhou DQ 1999; Wang XS 2005; Xu XT 2007; Chen ZT 1997; Yang HZ 2003; Lin SH 2002; Wu QK 2000; Ye YA 2006; Song FB 2011; Wang FY 2006; Zhou DQ 1998).

Short term effect of TCM on HBV-HBeAg

- Nineteen studies with short term therapy presented *benefit* on normalization of HBeAg (Li ZW 2011; Zhou DQ 1999; Ou S 2010; Zhang HO 2010; Zhang JH 2005; Xu XT 2007; Zhang ZJ 2002; Hu WD 2005; Xi RH 2010; Yang HZ 2006; Xu QM 2002; Huang GR 2005; Huang XA 1999; Lin SN 2004; Jiang W 1997; Chen ZT 1997; Wang J 2006; Li MH 2010; Xu SF 2005),
- Twenty studies showed *no benefit* (Lan SB 2006; Shen MR 2010; Yu P 2011; Wang XS 2005; Li J 2003; Yang XJ 2010; Zhu CL 2007; Yang HZ 2003; Huang ZM 1998; Lin SH 2002; Zhou Q 2008; Feng YM 2003; Su WQ 2011; Wu QK 2000; Wang YQ 2003; Huang XA 2002; Song FB 2011; Zhou DQ 1998; Wang FY 2006; Du B 2002).

Findings and Conclusions

Effect on ALT and/or AST

- Forty-three studies reported the use of Chinese Medicines can *significantly reduce* the raised ALT to normal or nearly normal with a higher effect than the control remedies, and 26 studies showed *similar effect* between Chinese medicines and control remedies.
- Forty studies reported the use of Chinese medicines can significantly reduce the raised AST level to normal or nearly normal with a higher effect than the control remedies, and 19 studies showed *similar effect* between Chinese medicines and control remedies.

Effect on liver fibrosis

- Four studies showed CHM can improve the fibrosis indexes, beside effects on normalization of HBV-DNA or/and HBeAg.

Findings and Conclusions

Quality of the evidence

Totally, the quality of the evidences is weak.

1. Only 9 studies stated the method of allocation of patients, but no detail information about how and who did it, none study mentioned allocation concealment.

2. Conflict of interest is a common risk of bias existed in the clinical studies of TCM. 39 included studies used self-prepared or self-made TCM formulations. This may be a main reason of dramatic effect appeared in some self prepared Chinese medicines, for example, study Zhou DG 1998 used self made Ruangan decoction treated 3 months, the rate of normalization of HBV-DNA was 63.3%, higher than interferon (40%).

3. Although, we identified the studies by telephoning the original authors by asking the method they used for generation of the allocation sequence, but some studies still questionable, for example, the baseline was not balanced in some studies

5. The confidence interval in the effects are wide, this decreased the quality of evidence by one to two grades.

6. The sample size of many studies is small.

Findings and Conclusions

- This review found some Chinese medicines may have effect of normalization of HBV-DNA and HBeAg, ALT and AST, and fibrosis indexes, and reducing the variation of HBV-DNA in long term therapy of chronic hepatitis B. The evidences from these studies included in the review are still weak. There is a need to conduct high quality clinical trials in the future.

Can these data help the clinical management of HBV and its complications?

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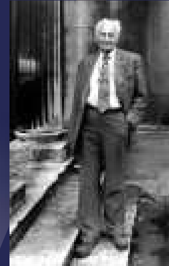
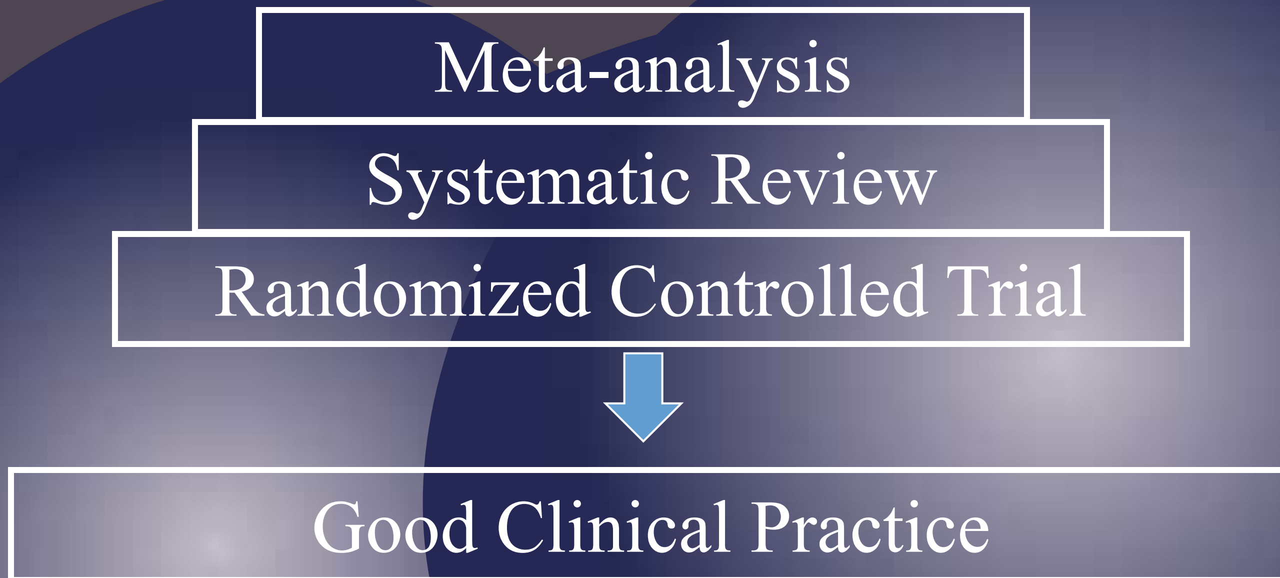


Sir Austin Bradford Hill
1948

David Sacket
1996

- From The Medical Classic of Yellow Emperor (the starting of acupuncture) to 1948, No RCT.
- After 1948, there are RCT, but not much.
- After 1996, RCT with herbal medicine starting to increase dramatically

Current fashion in medical research: RCTism



- An ideal approaches RCT-SR-Practice. A fashion now.

Challenges in Evidence based management with CHM

RCT and CHM

- Quality of RCT with CHM
- Unless it is a proprietary Chinese Medicine, the number of RCTs with same CHM is rare. Beside the proprietary Chinese medicine, some trials with the formula, originated from one form, but with modification.
- Difference between Individualization of CHM and standardization of RCT

High quality SR seek to:

Identify all relevant published and unpublished **evidence**
Select studies or reports **for inclusion**
Assess the quality of each study or report
Synthesise the findings from individual studies or reports i**n an unbiased way**
Interpret the findings and present a balanced and
impartial summary of the findings with due consideration of
any flaws in the evidence.

Future directions

RCT and CHM

- Improve the Quality of RCT with CHM,

  Design-implementation-reporting

  SPIRIT-Implementation-CONSORT for CHM

2. Syndrome-based RCT design, with modification of RCT design, to reflect the characteristics of syndrome differentiation with the syndrome/ fixed formulation as a unit for the clinical test

   Standardization of syndrome diagnosis, fixed formulation of intervention, and flexible treatment course based on the change of syndrome

SR and CHM

- Improve the Quality of SR with CHM,
  Don't synthesise the findings from the studies with different formulation, or a source formulation but with modification

2. Synthesise the data about the unit of Syndrome/fixed formulation

Future directions

Evidence should be

- Clinical usage driven
- Following rigorous stand
- Reflecting the nature of CHM: syndrome based.