



Cochrane
Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis (Review)

Mantzoukis K, Rodríguez-Perálvarez M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS

Mantzoukis K, Rodríguez-Perálvarez M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS.

Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis.

Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD011645.

DOI: 10.1002/14651858.CD011645.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	12
Figure 1.	13
Figure 2.	15
Figure 3.	16
Figure 4.	20
ADDITIONAL SUMMARY OF FINDINGS	21
DISCUSSION	24
AUTHORS' CONCLUSIONS	25
ACKNOWLEDGEMENTS	25
REFERENCES	26
CHARACTERISTICS OF STUDIES	30
DATA AND ANALYSES	41
ADDITIONAL TABLES	42
CONTRIBUTIONS OF AUTHORS	43
DECLARATIONS OF INTEREST	43
SOURCES OF SUPPORT	43
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	44
NOTES	44

[Intervention Review]

Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis

Konstantinos Mantzoukis¹, Manuel Rodríguez-Perálvarez², Elena Buzzetti³, Douglas Thorburn³, Brian R Davidson⁴, Emmanuel Tsochatzis³, Kurinchi Selvan Gurusamy⁴

¹Sheila Sherlock Liver Centre, Royal Free Hospital and the UCL Institute of Liver and Digestive Health, Royal Free Hospital and University College Medical School, London, UK. ²Hepatology and Liver Transplantation, Reina Sofia University Hospital, IMIBIC, CIBERehd, Córdoba, Spain. ³Sheila Sherlock Liver Centre, Royal Free Hospital and the UCL Institute of Liver and Digestive Health, London, UK. ⁴Department of Surgery, Royal Free Campus, UCL Medical School, London, UK

Contact address: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Pond Street, London, NW3 2QG, UK. k.gurusamy@ucl.ac.uk.

Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: New, published in Issue 3, 2017.

Citation: Mantzoukis K, Rodríguez-Perálvarez M, Buzzetti E, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD011645. DOI: 10.1002/14651858.CD011645.pub2.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Infection with hepatitis B virus (HBV) can be symptomatic or asymptomatic. Apart from chronic HBV infection, the complications related to acute HBV infection are severe acute viral hepatitis and fulminant hepatitis characterised by liver failure. The optimal pharmacological treatment of acute HBV infection remains controversial.

Objectives

To assess the benefits and harms of pharmacological interventions in the treatment of acute HBV infection through a network meta-analysis and to generate rankings of the available treatments according to their safety and efficacy. As it was not possible to assess whether the potential effect modifiers were similar across different comparisons, we did not perform the network meta-analysis, and instead, assessed the benefits and harms of different interventions using standard Cochrane methodological procedures.

Search methods

We searched CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, WHO International Clinical Trials Registry Platform, and randomised clinical trials (RCTs) registers to August 2016 to identify RCTs on pharmacological interventions for acute HBV infection.

Selection criteria

RCTs, irrespective of language, blinding, or publication status in participants with acute HBV infection. We excluded trials if participants had previously undergone liver transplantation and had other coexisting viral diseases such as hepatitis C virus and HIV. We considered any of the various pharmacological interventions compared with each other or with placebo, or no intervention.

Data collection and analysis

We calculated the odds ratio (OR) and rate ratio with 95% confidence intervals (CI) using both fixed-effect and random-effects models based on available-participant analysis with Review Manager 5. We assessed risk of bias, controlled risk of random errors with Trial Sequential Analysis, and assessed the quality of the evidence using GRADE.

Pharmacological interventions for acute hepatitis B infection: an attempted network meta-analysis (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Main results

Seven trials (597 participants) met our review inclusion criteria. All trials provided information for one or more outcomes; however, five participants were excluded from analysis by study authors. All the trials were at high risk of bias. Overall, all the evidence was low or very low quality evidence because of risk of bias (downgraded one level for risk of bias), small sample size (downgraded one level for imprecision), and wide CIs (downgraded one more level for imprecision in some comparisons). Of the seven trials, six were two-armed trials, while one trial was a three-armed trial. The comparisons included hepatitis B immunoglobulin (HBIG) versus placebo (one trial; 55 participants); interferon versus placebo (two trials; 200 participants); lamivudine versus placebo or no intervention (four trials; 316 participants); lamivudine versus entecavir (one trial; 90 participants); and entecavir versus no intervention (one trial; 131 participants). One trial included only people with acute HBV with hepatic encephalopathy (i.e. people with fulminant liver failure); one trial included only people with severe acute HBV, but it did not state whether any of the people also had fulminant HBV infection; three trials excluded fulminant HBV infection; and two trials did not report the severity of acute HBV infection. The mean or median follow-up period in the trials ranged from three to 12 months in the trials that provided this information.

There was no evidence of any differences in short-term mortality (less than one year) in any of the comparisons: HBIG versus placebo (OR 1.13, 95% CI 0.36 to 3.54; participants = 55; 1 trial), lamivudine versus placebo or no intervention (OR 1.29, 95% CI 0.33 to 4.99; participants = 250; 2 trials); lamivudine versus entecavir (OR 1.23, 95% CI 0.13 to 11.65; participants = 90; 1 trial), or entecavir versus no intervention (OR 1.05, 95% CI 0.12 to 9.47; participants = 131; 1 trial). The proportion of people who progressed to chronic HBV infection was higher in the lamivudine group than the placebo or no intervention group (OR 1.99, 95% CI 1.05 to 3.77; participants = 285; 3 trials) and in the lamivudine group versus entecavir group (OR 3.64, 95% CI 1.31 to 10.13; participants = 90; 1 trial). There was no evidence of a difference in the proportion of people who progressed to chronic HBV infection between the entecavir and the no intervention groups (OR 0.58, 95% CI 0.23 to 1.49; participants = 131; 1 trial). None of the trials reported progression to fulminant HBV infection. Three trials with 371 participants reported serious adverse events. There were no serious adverse events in any of the groups (no intervention: 0/183 (0%), interferon: 0/67 (0%), lamivudine: 0/100 (0%), and entecavir: 0/21 (0%)). The proportion of people with adverse events was higher in the interferon group than the placebo group (OR 348.16, 95% CI 45.39 to 2670.26; participants = 200; 2 trials). There was no evidence of a difference in the proportion of people with adverse events between the lamivudine group and the placebo or no intervention group (OR 1.42, 95% CI 0.34 to 5.94; participants = 35; 1 trial) or number of adverse events between the lamivudine group and the placebo or no intervention group (rate ratio 1.72, 95% CI 1.01 to 2.91; participants = 35; 1 trial). One trial with 100 participants reported quality of life at one week. The scale used to report the health-related quality of life was not stated and lacked information on whether higher score meant better or worse, making it difficult to interpret the results. None of the trials reported quality of life beyond one week or other clinical outcomes such as mortality beyond one year, liver transplantation, cirrhosis, decompensated cirrhosis, or hepatocellular carcinoma.

Two trials received funding from pharmaceutical companies; three trials were funded by parties without any vested interest in the results or did not receive any special funding; the source of funding was not available in the remaining two trials.

Authors' conclusions

Low or very low quality evidence suggests that progression to chronic HBV infection was higher in people receiving lamivudine compared with placebo, no intervention, or entecavir. Low quality evidence suggests that interferon may increase the adverse events after treatment for acute HBV infection. Based on a very low quality evidence, there is currently no evidence of benefit of any intervention in acute HBV infection. There is significant uncertainty in the results and further RCTs are required.

PLAIN LANGUAGE SUMMARY

Medical treatment of acute hepatitis B virus infection

Background

Hepatitis B virus (HBV) is a virus that affects the liver. It is usually transmitted by injectable drug abuse, transfusion of infected blood, unhygienic tattooing practices, coming into contact with blood infected with HBV, or by unprotected sex. Acute HBV infection is the period that covers the period immediately after HBV infection. Most people are asymptomatic. About 5% to 40% of people with acute HBV develop symptoms such as jaundice (yellowish discolouration of the eyes and skin), tummy pain, tiredness, nausea, and vomiting. While most people clear the virus after acute HBV infection, the virus remains in others (chronic HBV infection) and causes major health problems (excessive tiredness and eventually may end with liver failure leading to vomiting blood, confusion, and death).

Occasionally, people with acute HBV may develop immediate liver failure (fulminant HBV infection). The best way to treat acute HBV is not clear. We sought to resolve this issue by performing this review. We included all randomised clinical trials (RCTs) (clinical studies where people are randomly put into one of two or more treatment groups) published to August 2016. We included only trials in which participants with acute HBV infection had not undergone liver transplantation previously and did not have liver disease due to other viral infections. Apart from using standard Cochrane methods which allow comparison of only two treatments at a time (direct comparison), we planned to use an advanced method which allows comparison of the many different treatments individually which are compared in the trials (network meta-analysis). However, because of the nature of the information available, we could not determine whether the network meta-analysis results were reliable. So, we used standard Cochrane methodology.

Study characteristics

We identified seven RCTs. Trial authors included 592 (out of 597 randomised) participants in analyses. The trials included people with acute HBV infection of varying severity. The main interventions included hepatitis B immunoglobulin (a vaccine), interferon (protein secreted in response to viral infection), and lamivudine and entecavir (medicines) which are considered to have antiviral effects and were compared with placebo or no intervention. The trials' average follow-up period ranged from three months to one year in the six trials that reported this information.

Two trials received funding from pharmaceutical companies; three trials were funded by parties without any vested interest in the results or did not receive any special funding; two trials did not report the funding source.

Quality of evidence

The overall quality of evidence was low or very low, and all the trials were at high risk of bias (the likely possibility of making wrong conclusions overestimating benefits or underestimating harms because of the way the studies were conducted is high).

Key results

There was no evidence of differences in death at less than one year between any of the treated and untreated groups. The percentage of people who progressed to chronic HBV infection was higher in lamivudine versus placebo or no intervention and lamivudine versus entecavir groups. There was no evidence of difference in the proportion of people who progressed to chronic HBV infection between entecavir and no intervention. None of the trials reported progression to fulminant HBV infection. There were no serious adverse events in any of the treatment groups in the trials that reported this information. The percentage of people who developed adverse events was higher in the interferon group (100%) than in the placebo (dummy treatment) group (27%) in the trials that reported this information. There was no evidence of differences in the percentage of people who developed adverse events or the total number of adverse events in the comparison between lamivudine versus no treatment. One trial reported quality of life at one week; however, the information provided was insufficient to determine whether there was any difference between the interferon and placebo groups. None of the trials reported quality of life beyond one week or other important outcomes such as death beyond one year, severe progressive liver damage, liver failure, requirement for liver transplantation, or liver cancer. There is currently no evidence of benefit of any treatment in acute HBV infection. There is significant uncertainty in the results and high-quality RCTs are required.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lamivudine versus no intervention for acute hepatitis B virus infection					
Patient or population: people with acute HBV infection Settings: secondary or tertiary care Intervention: lamivudine Control: no intervention					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Lamivudine			
Short-term mortality (< 1 year)	33 per 1000	43 per 1000 (11 to 147)	OR 1.29 (0.33 to 4.99)	250 (2 trials)	⊕○○○ Very low ^{1,2,3}
Progression to chronic HBV infection (6 to 12 months)	413 per 1000	584 per 1000 (425 to 726)	OR 1.99 (1.05 to 3.77)	285 (3 trials)	⊕○○○ Very low ^{1,2,3}
Progression to fulminant HBV infection	None of the trials reported this information.				
Serious adverse events (6 to 12 months)	There were no serious adverse events in either group.			250 (2 trials)	⊕○○○ Very low ^{1,2,3}
Adverse events (proportion) (12 months)	647 per 1000	722 per 1000 (384 to 916)	OR 1.42 (0.34 to 5.94)	35 (1 trial)	⊕○○○ Very low ^{1,2,3}
Adverse events (number of events) (12 months)	1235 per 1000	2124 per 1000 (1247 to 3594)	Rate ratio 1.72 (1.01 to 2.91)	35 (1 trial)	⊕○○○ very low ^{1,2,3}
Health-related quality of life (1 week)	None of the trials reported this information.				

*The basis for the **assumed risk** is the mean control group risk in the control group across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HBV:** hepatitis B virus; **OR:** odds ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ The risk of bias in the trial(s) was high (downgraded by 1 level for risk of bias).
- ² The sample size was small (downgraded by 1 level for imprecision)
- ³ The confidence intervals were wide (downgraded by 1 level for imprecision).

BACKGROUND

Description of the condition

Hepatitis B virus (HBV) is a member of the *Hepadnaviridae* (hepatotropic DNA virus) family, a family of viruses that infect liver cells (Ganem 2004). Currently, 10 HBV genotypes (genotypes A to J) are recognised (Lin 2011; Tanwar 2012). The major mode of transmission of HBV is by parenteral routes, which include parenteral drug abuse, transfusion of infected blood, unhygienic tattooing practices, and occupational exposure to the blood of people infected with HBV (Wright 1993; Thompson 2009; Nelson 2011). The other major modes of transmission include sexual intercourse with infected people and perinatal transmission from mother to child (Wright 1993; Shi 2010; Deng 2012). The incubation period of HBV infection is about two to four weeks (Tillmann 2014). Infection with HBV is usually self-limiting and can be symptomatic (jaundice, abdominal pain, fatigue, nausea, and vomiting) in about 5% to 40% of people or asymptomatic (Leen 1989; Ganem 2004; Kumar 2006; Choi 2011; Sharif 2013; Tillmann 2014). Acute HBV infection is usually followed by spontaneous clearance of the virus and long-lasting protection against reinfection (Ganem 2004; Choi 2011; Tillmann 2014). Acute HBV infection can be difficult to distinguish from first exacerbation of asymptomatic chronic HBV, despite serological tests (Kumar 2006). Apart from chronic HBV infection, the complications related to acute HBV infection are severe acute HBV and fulminant hepatitis characterised by liver failure. Severe acute HBV is variably defined as the presence of at least two of the following criteria: severe jaundice (bilirubin levels higher than 10 mg/dL or 171 µmol/L), international normalised ratio (INR; an expression of the blood's ability to clot) of 1.6 or greater, hepatic encephalopathy (Bruno 2014), or the presence of elevated transaminase levels along with an elevated INR (Tillmann 2014). Fulminant hepatitis is characterised by liver failure manifest as elevated INR and hepatic encephalopathy (Tillmann 2014).

In the US, approximately 3000 people developed acute HBV infection annually between 2010 and 2014, equating to about 1 in 100,000 population with highest rates in the 30- to 39-year age group and lowest rates in children and adolescents (CDC 2014). The incidence is higher in men than women (CDC 2014).

The proportion of people with fulminant hepatitis after an attack of acute HBV can be variable, depending upon whether all people with acute HBV infection are included in the analysis (2% of people with acute HBV becoming fulminant) or whether only those people with severe acute HBV infection are included in the analysis (4% to 5% of people with severe acute HBV becoming fulminant) (Leen 1989; Souza 2013; Coppola 2014). A significant proportion of people with fulminant hepatitis B require liver transplantation or may die (varies from 18% to 48%) (Leen 1989; Garfein 2004; Tillmann 2006). Overall, approximately 1% of people with acute HBV (of all severities) died (CDC 2014).

Less than 1% to 27% of people develop chronic HBV infection (persistence of acute HBV infection for more than six months) (Ganem 2004; McMahon 2014; Tillmann 2014). The risk of chronic HBV infection can be as high as 90% if the primary, acute HBV infection occurs at birth and 25% if it occurs between early infancy and five years of age (McMahon 2014). Later in life, the risk declines. Overall, in people with chronic HBV infection, about 13.5% develop cirrhosis (Yang 2009), and about 5% develop hepatocellular carcinoma (Hoofnagle 2007; Thiele 2014). People with compensated (asymptomatic) chronic HBV-related cirrhosis may develop decompensated (symptomatic) cirrhosis (3% to 5% per year), or hepatocellular carcinoma (2% to 8% per year), or die (3% to 4% per year) (Chu 2006).

Description of the intervention

Various drugs, such as nucleoside or nucleotide analogues (L-nucleosides (lamivudine, telbivudine, clevudine), acyclic phosphonates (adefovir, tenofovir), and cyclopentanes (entecavir)), N-acetyl cysteine, ursodeoxycholic acid, interferon, and thymosin, have been used to prevent the complications of acute HBV infection and progression to chronic HBV infection (Bruno 2014; Tillmann 2014). Nucleoside analogues and nucleotide analogues are administered orally (Martindale 2011). N-acetyl cysteine is an antioxidant that can be administered orally or intravenously (Martindale 2011; Bass 2013). Ursodeoxycholic acid is a bile salt that is administered orally (Lazaridis 2001; Martindale 2011). Interferons are proteins secreted by cells in response to a wide range of inducers and that confer resistance against viruses and cancer cells (NCBI 2014a). The major types of interferon include interferon-alpha (or interferon-alfa), interferon-beta, interferon-omega, interferon-lambda, and interferon-gamma (Feld 2005; NCBI 2014a). Interferon-alpha is used in acute HBV infection (Tassopoulos 1997). Interferon is usually manufactured by recombinant technology where a sequence of human DNA is combined with the DNA of a bacteria such as *Escherichia coli* (Anonymous 1981). A variation of interferon-alpha is pegylated interferon-alpha, where the structure of interferon is modified to make it long acting (Bailon 2001). Interferon-alpha is usually administered by subcutaneous or intramuscular injections (Martindale 2011). Thymosins are a family of polypeptide hormones secreted by the thymus gland (NCBI 2014b). Thymosin-alpha (or thymalfasin) is usually manufactured by recombinant technology and is administered subcutaneously (Li 2010; Martindale 2011). It should be noted that these treatments have significant complications including severe infections, anaemia, neutropenia, thrombocytopenia, renal impairment, and neuropsychiatric disorders (homicidal and suicidal ideas) (Martindale 2011). Other complications include abdominal pain, elevation of liver enzymes, and myalgia (Martindale 2011).

How the intervention might work

Nucleoside and nucleotide analogues inhibit viral replication by inhibiting reverse transcriptase (ribonucleic acid (RNA)-directed DNA polymerase) in different ways (Martindale 2011). N-Acetyl cysteine increases the levels of glutathione, which is an antioxidant and protects the cells against oxidative stress. In addition, N-acetyl cysteine increases nitric oxide production resulting in vasodilation and improved tissue oxygen delivery and uptake, and inhibits proinflammatory factors (Bass 2013). Ursodeoxycholic acid decreases the exposure of liver cells to toxic bile salts and has anti-inflammatory properties (Bass 2013). This may decrease the damage to the liver cells. Interferon is one of the natural defence mechanisms of the body against viruses (Feld 2005; NCBI 2014a). Interferons induce interferon-stimulated genes, which creates an antiviral state within the cells (Feld 2005). Thymosins increase lymphocyte production and enhance the function of T cells (Li 2010; NCBI 2014b).

Why it is important to do this review

The current guidelines on the management of acute HBV infection by the European Association for the Study of the Liver (EASL) recommends the following treatment (EASL 2012). Entecavir or tenofovir should be used in people with acute severe HBV infection or people with fulminant hepatitis. Antiviral therapy should be continued for at least three months after the appearance of anti-HBs (antibody against HBsAg, the surface antigen of HBV) or at least 12 months after appearance of anti-HBe (antibody against HBeAg, a protein secreted by virus). However, the American Association for the Study of Liver Diseases (AASLD) guidelines recommend treatment only in people with fulminant hepatitis and in people with protracted severe acute HBV infection (AASLD 2009). Lamivudine and telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is the preferred treatment (AASLD 2009). Treatment should be continued until the clearance of HBsAg or indefinitely in people undergoing liver transplantation (AASLD 2009). Interferon-alpha is contraindicated in acute HBV infection (AASLD 2009). Thus, the optimal management of people with acute HBV infection is not known.

Network meta-analysis allows combining the direct evidence and indirect evidence and allows ranking of different treatments in terms of the different outcomes (Salanti 2011; Salanti 2012). There has been no network meta-analysis on the pharmacological interventions used for treatment of acute HBV infection. This systematic review and attempted network meta-analysis intended to provide the best level of evidence for the role of different pharmacological interventions in the treatment of people with acute HBV infection.

OBJECTIVES

To assess the comparative benefits and harms of different pharmacological interventions in the treatment of acute HBV infection through a network meta-analysis and to generate rankings of the available pharmacological interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis, and assessed the benefits and harms of different interventions using standard Cochrane methodology.

When more trials become available with adequate description of potential effect modifiers, we will attempt to conduct network meta-analysis to generate rankings of the available interventions according to their safety and efficacy. This is why we retain the planned methodology for network meta-analysis in our Appendix 1. Once data appear allowing for the conduct of network meta-analysis, this Appendix 1 will be moved back into the Methods section.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised clinical trials for this systematic review irrespective of language, publication status, or date of publication. We excluded studies of other designs because of the risk of bias in such studies. We are all aware that such exclusions make us focus much more on potential benefits and not fully assess the risks of serious adverse events as well as risks of adverse events.

Types of participants

We included participants with acute HBV infection irrespective of the presence or absence of symptoms, severity of the HBV infection, method of diagnosis of the disease, or HBV genotype. We excluded participants who had undergone liver transplantation previously. We also excluded participants who had HIV, hepatitis C virus (HCV), or hepatitis delta virus (HDV) coinfections, or acute exacerbations of chronic HBV infection. However, we included participants who did not undergo testing for viral coinfections.

Types of interventions

We included any of the following pharmacological interventions used either alone or in combination and could be compared with each other or with placebo or no intervention.

Some of the pharmacological interventions that we considered were:

- lamivudine;
- telbivudine;
- clevudine;
- adefovir;
- tenofovir;
- entecavir;
- N-acetyl cysteine;
- ursodeoxycholic acid;
- interferon-alpha;
- pegylated interferon-alpha;
- other interferons;
- thymosin.

The above list of interventions was not an exhaustive list. If we identified any other pharmacological interventions that we were not aware of (we included hepatitis B immunoglobulin (HBIG)), we considered them eligible and included them in the review if they were used primarily for the treatment of acute HBV infection.

Types of outcome measures

We assessed the benefits and harms of available pharmacological interventions aimed at treating people with acute HBV infection for the following outcomes.

Primary outcomes

- Short-term mortality (up to one year).
- Progression to chronic HBV infection or fulminant hepatitis HBV infection (in trials that included only participants without fulminant HBV infection).
- Adverse events (within three months of cessation of treatment). We defined a non-serious adverse event as any untoward medical occurrence not necessarily having a causal relationship with the treatment but resulting in a dose reduction or discontinuation of treatment (any time after commencement of treatment) (ICH-GCP 1997). We defined a serious adverse event as any event that would increase mortality; was life threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might have jeopardised the person or required intervention to prevent it. We planned to use the definition used by study authors for non-serious adverse events and serious adverse events:
 - proportion of participants with serious adverse events;
 - number of serious adverse events;
 - proportion of participants with any type of adverse event;
 - number of any type of adverse event.
- Health-related quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-item Short Form (SF-36) (EuroQol 2014; Ware 2014):
 - short-term (up to one year);

- medium-term (one to five years);
- long-term (beyond five years).

We considered short-term quality of life more important than medium-term or long-term quality of life, although medium-term or long-term quality of life are also important primary outcomes.

Secondary outcomes

- Mortality:
 - medium-term mortality (one to five years) (proportion);
 - time to death (maximal follow-up).
- Liver transplantation:
 - proportion of participants with liver transplantation (for fulminant HBV infection);
 - time to liver transplantation (maximal follow-up).
- Cirrhosis (maximal follow-up):
 - proportion of participants with cirrhosis;
 - time to cirrhosis.
- Decompensated liver disease (maximal follow-up):
 - proportion of participants with decompensated liver disease;
 - time to liver decompensation.
- Proportion of participants with hepatocellular carcinoma (maximal follow-up).

Potential surrogate outcomes (added post hoc)

We have reported seroconversion which is sometimes used as a surrogate for progression to chronic HBV infection.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OvidSP), Embase (OvidSP), and Science Citation Index Expanded (Web of Knowledge) (Royle 2003) from inception to 11 August 2016 for randomised clinical trials comparing two or more of the above interventions (including placebo or no intervention) without applying any language restrictions. We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the World Health Organization International Clinical Trials Registry Platform search portal (www.who.int/ictrp/en/), which encompasses various trial registers, including ISRCTN and ClinicalTrials.gov on 11 August 2016. Appendix 2 shows the search strategies that we used and the time spans of the searches.

Searching other resources

We searched the references of the identified trials and planned to search existing systematic reviews on acute HBV infection (we did not find any existing systematic reviews on this topic) to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Three review authors (KM, MR, and KG) independently identified the trials for inclusion by screening the titles and abstracts. We sought full-text articles for any references that at least one of the review authors identified for potential inclusion. We selected trials for inclusion based on the full-text articles. We have listed the excluded full-text references with reasons for their exclusion in the [Characteristics of excluded studies](#) table. We planned to list any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up; however, we did not find any ongoing trials on the topic. We resolved discrepancies through discussion.

Data extraction and management

Three review authors (KM, MR, and KG) independently extracted the following data.

- Outcome data (for each outcome and for each treatment arm whenever applicable):
 - number of participants randomised;
 - number of participants included for the analysis;
 - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events for count outcomes, and number of participants with events and mean follow-up period for time-to-event outcomes;
 - definition of outcomes or scale used if appropriate.
- Data on potential confounding variables:
 - participant characteristics such as age, sex, comorbidity, proportion of participants with asymptomatic or mild acute HBV infection versus severe acute HBV infection or fulminant HBV infection, and proportion of participants with different HBV genotypes;
 - details of the intervention and control (including dose, frequency, and duration);
 - risk of bias (assessment of risk of bias in included studies).
- Other data:
 - year and language of publication;
 - country in which the participants were recruited;
 - year(s) in which the trial was conducted;
 - inclusion and exclusion criteria;

- follow-up time points of the outcome.

If available, we planned to obtain the data separately for treatment-naive, non-responders, and relapsers from the report. If available, we also planned to obtain the data separately on participants with asymptomatic or mild acute HBV infection compared to severe acute HBV infection, or fulminant HBV infection, and participants with different genotypes. We sought unclear or missing information by attempting to contact the trial authors. If there was any doubt whether trials shared the same participants -- completely or partially (by identifying common authors and centres) -- we planned to attempt to contact the trial authors to clarify whether the trial report was duplicated; however, there were no such trials. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and described in the Cochrane Hepato-Biliary Module (Gluud 2016), to assess the risk of bias in included studies. Specifically, we assessed the risk of bias in included trials for the following domains using the bias risk domains with definitions below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savovic 2012a; Savovic 2012b; Lundh 2017).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, has been employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported at least short-term mortality, progression to chronic HBV infection, and treatment-related adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g.

www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.

- Unclear risk of bias: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, even though data on these outcomes were likely to have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not have been free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. inappropriate control or dose or administration of control) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (e.g. inappropriate control or dose or administration of control).

We considered a trial at low risk of bias if we assessed the trial to be at low risk of bias across all the above domains. Otherwise, we considered trials at unclear risk of bias or at high risk of bias regarding one or more of the above domains at high risk of bias.

Measures of treatment effect

For dichotomous variables (e.g. short-term and medium-term mortality, liver transplantation, progression to chronic HBV, proportion of participants with adverse events, decompensated liver disease, cirrhosis, or hepatocellular carcinoma), we calculated the odds ratio (OR) with 95% confidence intervals (CI). For continuous variables (e.g. quality of life reported on the same scale), we calculated the mean difference (MD) with 95% CI. We planned to use standardised mean difference values with 95% CI for quality of life if included trials used different scales. For count outcomes (e.g. number of adverse events), we calculated the rate ratio with 95% CI. For time-to-event data (e.g. mortality at maximal follow-

up or requirement for liver transplantation, time to liver decompensation, and time to cirrhosis), we planned to use the hazard ratio with 95% CIs. We also calculated Trial Sequential Analysis-adjusted CI to control random errors (Thorlund 2011; Wetterslev 2017).

Unit of analysis issues

The unit of analysis was people with acute HBV infection according to the intervention group to which they were randomly assigned.

Cluster randomised clinical trials

We found no cluster randomised clinical trials. However, if we found such trials, we planned to include these, provided that the effect estimate adjusted for cluster correlation was available.

Cross-over randomised clinical trials

As expected, we found no cross-over randomised clinical trials. However, if we had identified any, we planned to only include the outcomes after the period of first treatment to avoid a potentially residual effect (the carryover effect) from the treatment administered during the first period.

Trials with multiple intervention groups

We collected data for all trial intervention groups that met the inclusion criteria.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992). Otherwise, we used the data that were available to us (e.g. a trial may have reported only 'per-protocol' analysis results). As such per-protocol analyses may be biased, we planned to conduct best-worst case scenario (good outcome (e.g. no mortality) in intervention group and bad outcome (e.g. mortality) in control group) and worst-best case scenario (bad outcome (e.g. mortality) in intervention group and good outcome (e.g. no mortality) in control group) analyses as sensitivity analyses whenever possible.

For continuous outcomes, we planned to impute the standard deviation from P values according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the CIs, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study for calculation of MDs and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We assessed or planned to assess the presence of clinical heterogeneity by comparing effect estimates in participants with asymptomatic or mild acute HBV infection compared to severe acute HBV infection or fulminant HBV infection, different HBV genotypes, and the different regimens (e.g. different doses and different durations) of the pharmacological interventions. Different study designs and risk of bias may contribute to methodological heterogeneity. We used the I^2 test and Chi^2 test for heterogeneity, and overlapping of CIs to assess heterogeneity.

Assessment of reporting biases

We planned to use visual asymmetry on a funnel plot to explore reporting bias in the presence of at least 10 trials that could be included for a direct comparison (Egger 1997; Macaskill 2001). In the presence of heterogeneity that could be explained by subgroup analysis, we planned to produce a funnel plot for each subgroup in the presence of the adequate number of trials. We planned to use the linear regression approach described by Egger 1997 to determine the funnel plot asymmetry.

We also considered selective reporting as evidence of reporting bias.

Data synthesis

We performed the meta-analyses according to the recommendations of Cochrane (Higgins 2011), using the software package Review Manager 5 (RevMan 2014). We used a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In the case of a discrepancy between the two models, we reported both results; otherwise, we reported only the results from the fixed-effect model.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 3. We performed Trial Sequential Analysis to control the risks of random errors when there were at least two trials included in the meta-analysis (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). We used an alpha error as per guidance of Jakobsen 2014, power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the diversity observed in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups.

- Trials with low risk of bias compared to trials with high risk of bias.
- Asymptomatic or mild acute HBV infection compared to severe acute HBV infection or fulminant HBV infection.
- Different HBV genotypes.
- Different regimens (different doses and different durations) of pharmacological interventions.

We planned to use the Chi² test for subgroup differences to identify subgroup differences.

Sensitivity analysis

If a trial reported only per-protocol analysis results, we planned to re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible.

Presentation of results and GRADE assessments

We reported all the primary outcomes in a 'Summary of findings' table format for comparisons with at least two trials, downgrading the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias using GRADE (Guyatt 2011). One review author (KG) created the 'Summary of findings' table.

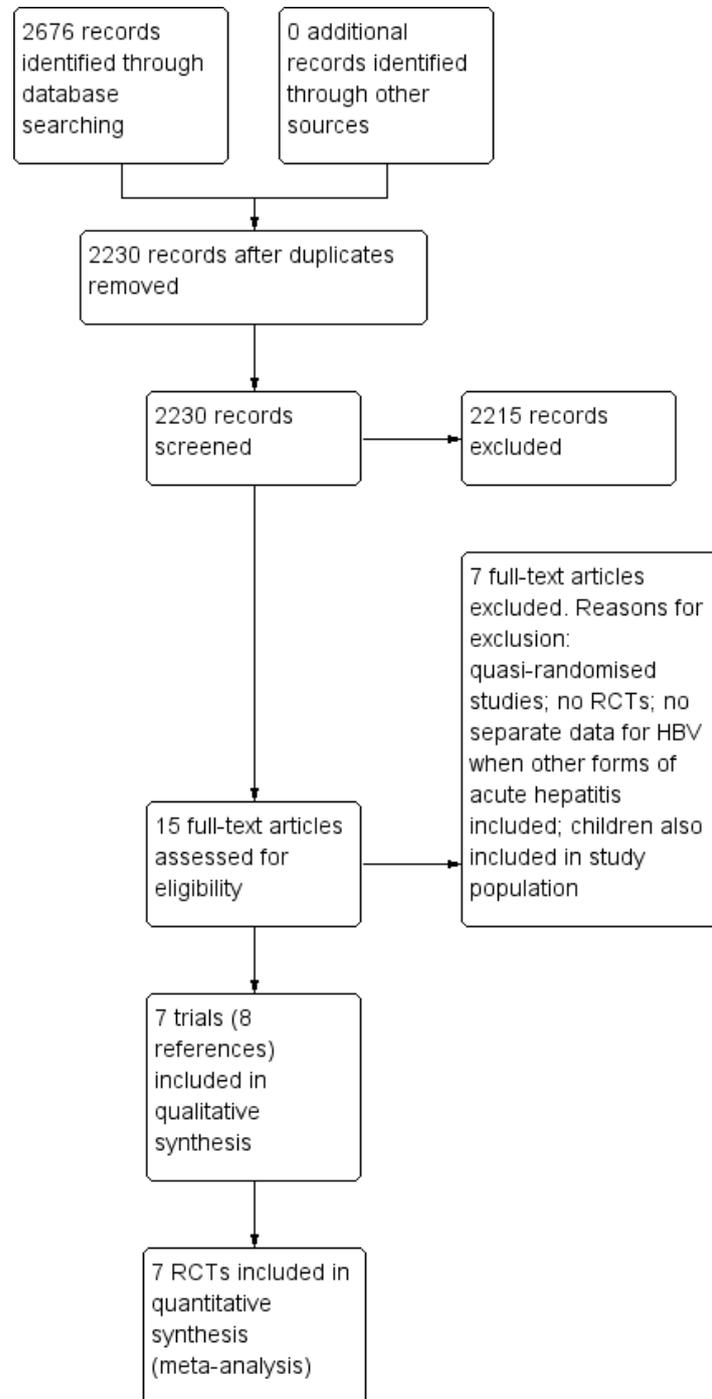
RESULTS

Description of studies

Results of the search

We identified 2676 references through electronic searches of CENTRAL (n = 238), MEDLINE (n = 1786), Embase (n = 310), Science Citation Index Expanded (n = 322), World Health Organization International Clinical Trials Registry Platform (n = 10), and ClinicalTrials.gov trials registers (n = 10). After the removal of 446 duplicates we obtained 2230 references. We then excluded 2215 clearly irrelevant references through screening titles and reading abstracts. We retrieved 15 references for further assessment. No references were identified through scanning reference lists of the identified randomised trials. We excluded seven references for the reasons listed in [Characteristics of excluded studies](#) table (Gregory 1976; Blum 1977; Botero 1991; Flisiak 2000; Sharapov 2000; Tillmann 2006; Yu 2010). In total, seven trials (eight references) met the inclusion criteria (Anonymous 1974; Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). The reference flow is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram. HBV: hepatitis B virus; RCT: randomised clinical trial.



Included studies

The seven trials included 597 participants (Anonymous 1974; Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). In these seven trials, 597 participants were randomised and data on one or more outcomes were available for 592 participants. One trial was a three-armed trial which compared lamivudine, entecavir, and no intervention (Streinu-Cercel 2016). The remaining six trials were two-armed trials (Anonymous 1974; Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014). The details of intervention, control, and the period of follow-up, and the risk of bias in the trials arranged according to intervention and control is summarised in Table 1. One trial (55 participants) compared HBIG versus placebo (Anonymous 1974). Two trials (200 participants) compared interferon versus placebo (Tassopoulos 1989; Tassopoulos 1997). Four trials (316 participants) compared lamivudine versus placebo or no intervention (Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). One trial (90 participants) compared lamivudine versus entecavir (Streinu-Cercel 2016). One trial (131 participants) compared entecavir versus no intervention (Streinu-Cercel 2016). Overall, five trials used placebo as the 'no intervention' (Anonymous 1974; Tassopoulos 1989; Tassopoulos 1997; Kumar 2007; Wiegand 2014); two trials used 'no intervention' as the 'no intervention' (Apostolescu 2001; Streinu-Cercel 2016). The mean or median follow-up period in the trials ranged from three to 12 months in the six trials that provided this information (Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016).

The mean or median age in the five trials that reported this information ranged from 32 to 41 years (Tassopoulos 1989; Tassopoulos 1997; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). The proportion of females in the trials that reported this information ranged from 14% to 54% (Tassopoulos 1989; Tassopoulos 1997; Kumar 2007; Wiegand 2014; Streinu-Cercel

2016). One trial included only participants with acute HBV and hepatic encephalopathy (i.e. participants with fulminant liver failure; Anonymous 1974); one trial included only participants with severe acute HBV, but did not state whether it included fulminant HBV infection (Streinu-Cercel 2016); three trials excluded people with fulminant HBV infection (Tassopoulos 1989; Tassopoulos 1997; Wiegand 2014); two trials did not report the severity of acute HBV infection (Apostolescu 2001; Kumar 2007). None of the trials reported the proportion of participants with different HBV genotypes.

Source of funding: two trials received financial assistance from pharmaceutical companies who would benefit from the findings of the research or one of the authors was employed by a pharmaceutical company who would benefit from the findings of the research (Tassopoulos 1989; Tassopoulos 1997); two trials did not report the source of funding (Apostolescu 2001; Kumar 2007); three trials were funded by parties without any vested interest in the results or did not receive any special funding (Anonymous 1974; Wiegand 2014; Streinu-Cercel 2016)..

Excluded studies

We excluded seven references because they were quasi-randomised studies (two references: Sharapov 2000; Yu 2010), non-randomised studies (two references: Flisiak 2000; Tillmann 2006), lack of confirmation of HBV infection in all participants (two references: Gregory 1976; Blum 1977), or because only four participants in the trial had acute HBV infection (three in intervention group and one in control group) (Botero 1991).

Risk of bias in included studies

The risk of bias in included trials is summarised in Figure 2 and Figure 3. None of the trials were at low risk of bias and were at high risk of bias in one or more domains. So, all the trials were at high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

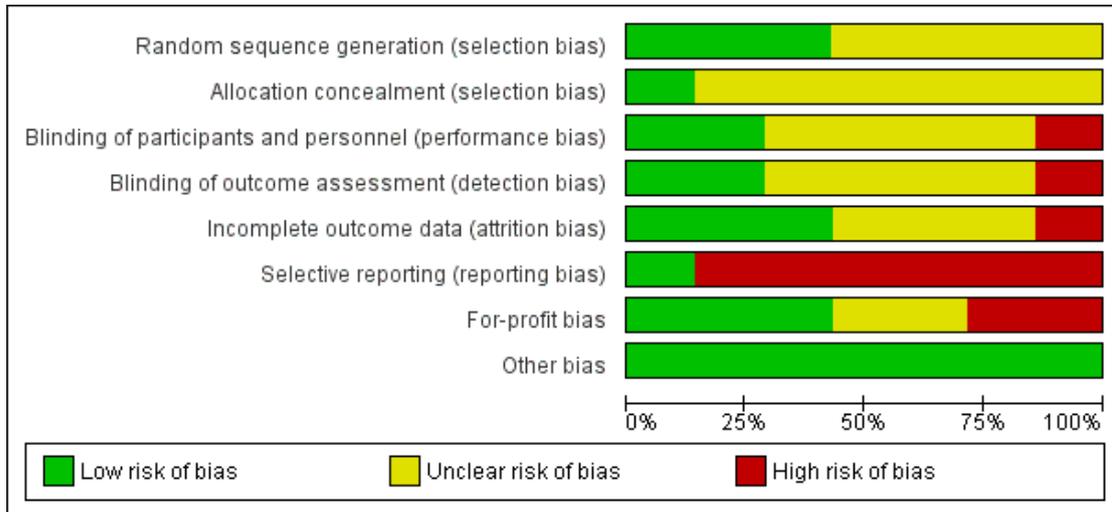


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	For-profit bias	Other bias
Anonymous 1974	+	+	?	?	?	-	+	+
Apostolescu 2001	?	?	?	?	?	-	?	+
Kumar 2007	+	?	+	+	+	+	?	+
Streinu-Cercel 2016	+	?	-	-	+	-	+	+
Tassopoulos 1989	?	?	?	?	?	-	-	+
Tassopoulos 1997	?	?	+	+	+	-	-	+
Wiegand 2014	?	?	?	?	-	-	+	+

Allocation

Three trials were at low risk of random sequence generation bias (Anonymous 1974; Kumar 2007; Streinu-Cercel 2016). The remaining trials were at unclear risk of random sequence generation bias (Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Wiegand 2014). One trial was at low risk of allocation concealment bias (Anonymous 1974). The remaining trials were at unclear risk of allocation concealment bias (Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016).

Blinding

Two trials were at low risk of bias due to lack of blinding of participants, healthcare providers, and outcome assessors (Tassopoulos 1997; Kumar 2007). One trial was at high risk of bias due to lack of blinding of participants, healthcare providers, and outcome assessors (Streinu-Cercel 2016). The remaining trials were at unclear risk of bias due to lack of blinding of participants, healthcare providers, and outcome assessors (Anonymous 1974; Tassopoulos 1989; Apostolescu 2001; Wiegand 2014).

Incomplete outcome data

Three trials were at low risk of bias due to incomplete outcome data (Tassopoulos 1997; Kumar 2007; Streinu-Cercel 2016). One trial was at high risk of bias due to incomplete outcome data (Wiegand 2014). The remaining trials were at unclear risk of bias due to incomplete outcome data (Anonymous 1974; Tassopoulos 1989; Apostolescu 2001).

Selective reporting

None of the trials had a published protocol. Two trials reported mortality, adverse events, and progression to chronic HBV, and were at low risk of reporting bias (Kumar 2007; Streinu-Cercel 2016). The remaining trials did not report these outcomes, which can be reasonably expected to be measured in trials in this field (Anonymous 1974; Tassopoulos 1989; Tassopoulos 1997; Apostolescu 2001; Wiegand 2014). So, these trials were at high risk of selecting outcome reporting.

Other potential sources of bias

Three trials were at low risk of vested interest bias (Anonymous 1974; Wiegand 2014; Streinu-Cercel 2016); two trials were at high risk of vested interest bias (Tassopoulos 1989; Tassopoulos 1997); the remaining trials were at unclear risk of vested interest bias (Apostolescu 2001; Kumar 2007). All the trials were at low risk of other bias.

Effects of interventions

See: [Summary of findings for the main comparison Lamivudine versus no intervention for acute hepatitis B virus infection](#); [Summary of findings 2 Interferon versus no intervention for acute hepatitis B virus infection](#)

Short-term mortality (up to one year)

Three trials (326 participants) reported short-term mortality (Anonymous 1974; Kumar 2007; Streinu-Cercel 2016). There was no evidence of difference in short-term mortality in any of the comparisons (Analysis 1.1).

- HBIG (19/27 (70.4%)) versus placebo (19/28 (67.9%)) (OR 1.13, 95% CI 0.36 to 3.54; participants = 55; 1 trial).
- Lamivudine (adjusted proportion: 4.3%) versus placebo or no intervention (5/150 (3.3%)) (OR 1.29, 95% CI 0.33 to 4.99; participants = 250; 2 trials).
- Lamivudine (4/69 (5.8%)) versus entecavir (1/21 (4.8%)) (OR 1.23, 95% CI 0.13 to 11.65; participants = 90; 1 trial).
- Entecavir (1/21 (4.8%)) versus no intervention (5/110 (4.5%)) (OR 1.05, 95% CI 0.12 to 9.47; participants = 131; 1 trial).

Only one comparison had more than one trial (lamivudine versus placebo or no intervention). Even in this comparison, only one trial contributed to the analysis (Streinu-Cercel 2016), as there were no events in either group in the other trial (Kumar 2007). Therefore, heterogeneity was not assessed.

Progression to chronic hepatitis B virus infection or to fulminant hepatitis B virus infection

Three trials (306 participants) reported proportion of people who continued to have HBsAg in serum (Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). The proportion of people who developed progression to chronic HBV infection was higher in the lamivudine group (adjusted proportion: 58.4%) versus the placebo or no intervention group (69/167 (41.3%)) (OR 1.99, 95% CI 1.05 to 3.77; participants = 285; 3 trials; $I^2 = 0\%$) and in the lamivudine group (53/69 (76.8%)) versus the entecavir group (10/21 (47.6%)) (OR 3.64, 95% CI 1.31 to 10.13; participants = 90; 1 trial). There was no evidence of difference in the proportion of people who progressed to chronic HBV infection between the entecavir group (10/21 (47.6%)) versus the no intervention group (67/110 (60.9%)) (OR 0.58, 95% CI 0.23 to 1.49; participants = 131; 1 trial) (Analysis 1.2).

There was no evidence of heterogeneity in the only comparison with more than one trial (lamivudine versus placebo or no intervention; $I^2 = 0\%$). None of the trials reported progression to

fulminant hepatitis. Authors also reported seroconversion which was variably defined in the different trials (see 'Seroconversion (surrogate outcome)' below). As this is an unvalidated surrogate outcome, we presented this information last and did not arrive at conclusions based on this surrogate outcome.

Adverse events

Three trials (371 participants) reported serious adverse events (Tassopoulos 1989; Kumar 2007; Streinu-Cercel 2016). There were no serious adverse events in any of the groups (Analysis 1.3). Three trials (235 participants) reported proportion of people with any adverse events (Tassopoulos 1989; Tassopoulos 1997; Wiegand 2014). The proportion of people with adverse events was higher in the interferon group (adjusted proportion: 99.2%) versus the placebo group (18/66 (27.3%)) (OR 348.16, 95% CI 45.39 to 2670.26; participants = 200; 2 trials; low quality evidence: downgraded by one level for risk of bias in the studies and one more level for small sample size) (Analysis 1.4). There was no evidence of heterogeneity ($I^2 = 0\%$; Chi^2 test for heterogeneity $P = 1.00$; good overlap of CIs). There was no evidence of difference in the proportion of people with adverse events between the lamivudine group (13/18 (72.2%)) versus the placebo or no intervention (11/17 (64.7%)) (OR 1.42, 95% CI 0.34 to 5.94; participants = 35; 1 trial) or the number of adverse events between the lamivudine group (38/18 (211.1 events per 100 participants)) versus the no intervention group (21/17 (123.5 events per 100 participants)) (rate ratio 1.72, 95% CI 1.01 to 2.91; participants = 35; 1 trial) (Analysis 1.5).

Health-related quality of life

One trial (100 participants) reported health-related quality of life at one week (Tassopoulos 1997). The scale used to report the health-related quality of life was not stated. Neither was information on whether higher score meant better or worse available. The mean score in the placebo group was 42.7 units. The mean score in the interferon group was 5.4 units higher. There was no information to calculate the 95% CIs or P value (Analysis 1.6). None of the trials reported quality of life beyond one week.

Mortality (beyond one year)

None of the trials reported mortality beyond one year.

Liver transplantation

None of the trials reported the proportion of people who required liver transplantation.

Cirrhosis

None of the trials reported the proportion of people who developed cirrhosis.

Decompensated liver disease

None of the trials reported the proportion of people who developed decompensated liver disease.

Hepatocellular carcinoma

None of the trials reported the proportion of people who developed hepatocellular carcinoma.

Seroconversion (surrogate outcome)

Five trials (437 participants) reported proportion of people who developed seroconversion (Tassopoulos 1997; Apostolescu 2001; Kumar 2007; Wiegand 2014; Streinu-Cercel 2016). The definition of seroconversion in the four trials that reported this information were: clearance of HBV DNA (Tassopoulos 1997), hepatitis B surface antibody at 12 months (Kumar 2007), hepatitis B surface antibody at 24 weeks (Streinu-Cercel 2016), and hepatitis B surface antibody greater than 10 U/L (Wiegand 2014). The seroconversion proportions in the different comparisons were (Analysis 1.8):

- interferon (65/67 (97.0%)) versus placebo (33/33 (100.0%)) (OR 0.39, 95% CI 0.02 to 8.38; participants = 100; 1 trial);
 - lamivudine (proportion: varied between 10.1% and 77.8%) versus placebo or no intervention (proportion varied between 22.7% and 85%) (OR varied between 0.27 and 2.63 (meta-analysis inappropriate because of variable definitions used for seroconversion and poor overlap of CI between effect estimates between trials); participants = 316; 4 trials);
 - lamivudine (7/69 (10.1%)) versus entecavir (9/21 (42.9%)) (OR 0.15, 95% CI 0.05 to 0.48; participants = 90; 1 trial);
 - entecavir (9/21 (42.9%)) versus no intervention (25/110 (22.7%)) (OR 2.55, 95% CI 0.96 to 6.74; participants = 131; 1 trial).

Of the five trials that reported the proportion of people who developed seroconversion, two trials (135 participants) reported the time taken to achieve seroconversion (Tassopoulos 1997; Wiegand 2014). Of these, only one reported the standard deviation (Tassopoulos 1997). There was no evidence of difference in the time taken to achieve seroconversion between interferon and placebo (MD -0.10 weeks, 95% CI -2.02 to 1.82; participants = 100; 1 trial) or between lamivudine and placebo or no intervention (MD 1.00 weeks, $P = 0.519$ (no details to calculate 95% CI); participants = 35; 1 trial) (Analysis 1.8; Analysis 1.9).

Subgroup analysis and sensitivity analysis

We did not perform any of the subgroup analyses because none of the trials were at low risk of bias, the trials did not report the data for different genotypes separately, and because there were too few trials to perform a meaningful subgroup analysis based on severity of hepatitis B or dosage. Only one trial reported postrandomisation dropouts but did not report the group to which the participants belonged. Therefore, we did not perform a sensitivity analysis. Since we did not impute mean or standard deviations, we did not perform a sensitivity analysis excluding trials in which mean or standard deviation were imputed.

Reporting bias

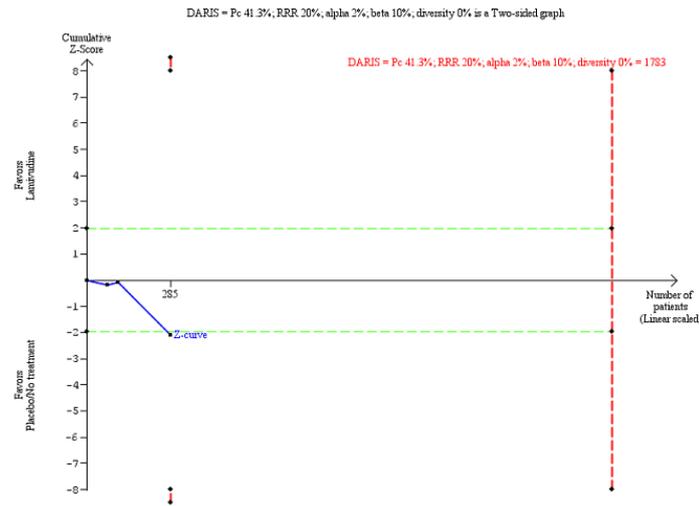
We did not explore reporting bias using funnel plot because of few trials included in the review.

Trial Sequential Analysis

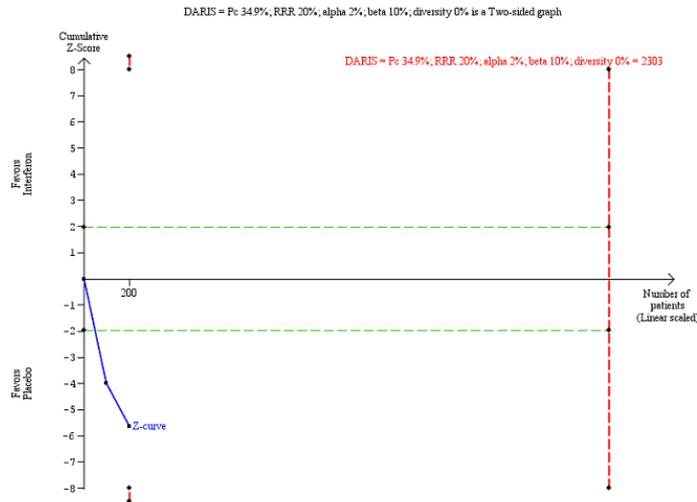
We performed Trial Sequential Analysis for comparisons with two or more trials only (progression to chronic HBV infection: lamivudine versus placebo or no intervention and adverse events (proportion): interferon versus placebo). As shown in [Figure 4](#), the accrued sample size was only a small fraction of the diversity-adjusted required information size (DARIS). The Z-curve did not cross trial sequential monitoring boundaries indicating that there was a high risk of random errors in these outcomes.

Figure 4. Trial sequential analysis of progression to chronic hepatitis B virus infection (lamivudine versus placebo or no treatment) and adverse events (proportion) (interferon versus placebo): Using the control group proportion observed in the trials ($P_c = 41.3\%$ and 34.9% respectively), alpha error of 2% , beta error of 90% , relative risk reduction (RRR) of 20% , and diversity observed in the analysis (0%), the accrued sample sizes (285 and 200 respectively) were only small proportions of the diversity-adjusted required information sizes (DARIS) (progression to chronic hepatitis B = 1783 ; adverse events (proportion) = 2303). While the Z-curve (blue lines) crossed the conventional boundary of $P = 0.05$ (dotted green lines) favouring placebo or no treatment, it did not cross any of the trial sequential monitoring boundaries (dotted red lines). There was a high risk of random errors.

Progression to chronic hepatitis B



Adverse events (proportion)



The Trial Sequential Analysis adjusted CIs were as follows.

- Progression to chronic HBV infection: lamivudine versus no intervention: 1.99 (95% CI 0.15 to 27.06).
- Adverse events (proportion): interferon versus placebo: 348.16 (95% CI 0.09 to 1,422,918.89).

Quality of evidence

The overall quality of evidence was very low for all outcomes unless indicated. The reason for downgrading was risk of bias in the trials (one level), small sample size (one level), and wide CIs (one level) ([Summary of findings for the main comparison](#)).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Interferon versus no intervention for acute hepatitis B virus infection					
Patient or population: people with acute HBV infection Settings: secondary or tertiary care Intervention: interferon Control: no intervention					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Interferon			
Short-term mortality	None of the trials reported this information.				
Progression to chronic HBV infection	None of the trials reported this information.				
Progression to fulminant HBV infection	None of the trials reported this information.				
Serious adverse events	There were no serious adverse events in either group.			100 (1 trial)	⊕○○○ Very low ^{1,2,3}
Adverse events (proportion) (4 to 6 months)	273 per 1000	992 per 1000 (945 to 999)	OR 348.16 (45.39 to 2670.26)	200 (2 trials)	⊕⊕○○ Low ^{1,2}
Adverse events (number of events)	None of the trials reported this information.				
Health-related quality of life (1 week)	The scale used to report the health-related quality of life was not stated. Neither was information on whether higher score meant better or worse available. The mean score in the placebo group was 42.7 units. The mean score in the interferon group was 5.4 units higher. There was no information to calculate the 95% confidence intervals or P value			100 (1 trial)	⊕○○○ Very low ^{1,2,3}

*The basis for the **assumed risk** is the mean control group risk in the control group across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HBV:** hepatitis B virus; **OR:** odds ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ The risk of bias in the trial(s) was high (downgraded by 1 level for risk of bias).
- ² The sample size was small (downgraded by 1 level for imprecision).
- ³ The confidence intervals were wide (downgraded by 1 level for imprecision).

DISCUSSION

Summary of main results

A total of 597 participants in seven trials were included in this review. A total of 592 participants in these seven trials contributed to one or more outcomes of this review. A total of five interventions (four active interventions and one inactive intervention) were evaluated in the seven trials included in this review. This included interferon, HBIG, lamivudine, entecavir, and inactive intervention (placebo or no intervention).

Overall, mortality at three months to one year following intervention in people with acute HBV infection was low (10/271 (3.7%)) (Kumar 2007; Streinu-Cercel 2016), except in the one trial reported in 1970s, which included only people with fulminant HBV infection (Anonymous 1974). Mortality in this trial was 69.1% (38/55) (Anonymous 1974). There was no evidence of differences in mortality between different interventions regardless of the severity of HBV infection. However, the sample size was very low to detect differences in mortality. Three trials reported the proportion of people who progressed to chronic HBV infection (defined as persistence of HBsAg after six months). None of the interventions resulted in reduction in the proportion of people who progressed to chronic HBV infection compared to placebo or no intervention. None of the trials reported progression to fulminant HBV infection either. None of the participants developed serious adverse events in the three trials that reported this information (Tassopoulos 1989; Kumar 2007; Streinu-Cercel 2016). The proportion of people who developed adverse events (such as influenza-like symptoms and vomiting), was more in the interferon group than the placebo group. However, the trial sequential monitoring boundaries were not crossed, suggesting that there may be random errors. There was no evidence of a difference in proportion of people who developed adverse events or the number of adverse events between lamivudine and placebo or no intervention. Although one trial reported quality of life at one week, the information was not sufficient to understand whether there was a difference in quality of life between the two interventions compared in this trial (interferon versus placebo) (Tassopoulos 1997). None of the trials reported the proportion of people who died during medium or long term (more than one year' follow-up); required liver transplantation; or developed cirrhosis, decompensated liver disease, or developed hepatocellular carcinoma.

The trials reported seroconversion as a surrogate outcome for progression to chronic HBV infection. The definition used in the trials was variable, reflecting the problem with using lack of seroconversion as a surrogate marker for chronic HBV infection. In any case, the only comparison where there was evidence for difference was lamivudine versus entecavir: seroconversion was lower in people who received lamivudine compared with those who received entecavir. There was no evidence for differences in the time taken for seroconversion in the trials that reported this information.

Overall completeness and applicability of evidence

Overall, it appears that none of the interventions are beneficial for people with acute HBV infection.

Considering that lamivudine or interferon do not offer any benefit but have the potential to cause harm, it may be appropriate to test entecavir or other similar antiviral interventions such as tenofovir. We have included all the major interventions used for treating acute HBV infection that have been compared in randomised clinical trials in this review. The severity of acute HBV infection was variable across trials. In particular, only one trial clearly indicated inclusion of fulminant HBV infection (Anonymous 1974). Three trials clearly excluded fulminant HBV infection (Tassopoulos 1989; Tassopoulos 1997; Wiegand 2014). It was unclear whether any participants with fulminant HBV infection were included in the remaining trials (Apostolescu 2001; Kumar 2007; Streinu-Cercel 2016). Considering that the main interventions that are currently recommended for treatment of acute HBV infection are antiviral drugs (Tillmann 2012) (and there was no comparison of antiviral interventions versus no intervention in people with fulminant HBV infection), the findings of this review are applicable only to people with acute HBV without fulminant liver failure. The findings are also applicable only in adults with acute HBV infection, as none of the trials appeared to include children. The findings are also applicable only in people who have not undergone liver transplantation and those who do not have other coexisting viral diseases, since we did not consider trials conducted in these populations.

Quality of the evidence

The overall quality of evidence was low to very low for all the outcomes. All the trials were at high risk of bias for at least one of the domains as shown in Figure 2 and Figure 3. The sample size was small for all the comparisons. There were also wide 95% CIs (the CIs overlapped 20% increase or decrease and minimal clinically important difference) for many of the comparisons. Moreover, when we calculated Trial Sequential analysis-adjusted CI, the inconsistency exploded. There was insufficient information to assess whether the diagnostic criteria for acute HBV and the severity of acute hepatitis HBV were similar across trials. In general, there was no evidence of statistical heterogeneity in most comparisons with the exception of the seroconversion in the comparison lamivudine versus placebo or no intervention, where there was moderate heterogeneity.

Potential biases in the review process

We followed the guidance of *Cochrane Handbook for Systematic Reviews of Interventions* with two review authors independently selecting studies and extracting data. We performed a thorough

search of literature. However, the search period included the pre-mandatory trial registration era and it is likely that some trials on interventions that were not effective or were harmful were not reported at all.

We only included randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. According to our choice of studies (i.e. only randomised clinical trials), we might have missed a large number of studies that address reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We did not search for interventions and trials registered at regulatory authorities (e.g. US Food and Drug Administration; European Medicines Agency, etc.). This may have overlooked trials and as such trials usually are unpublished, the lack of inclusion of such trials may make our comparisons look more advantageous than they really are. However, this is of academic interest only because there is no evidence of benefit of any treatment in people with acute HBV infection (i.e. there is no reason to suggest that any of the interventions should be used in routine clinical practice regardless of the adverse event profile of the intervention).

We planned to perform a network meta-analysis. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Performing a network meta-analysis in this scenario can be misleading. So we did not perform the network meta-analysis, and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

Agreements and disagreements with other studies or reviews

This is the first systematic review on the topic. Our review does not support the recommendations of EASL or the AASLD (AASLD 2009; EASL 2012). This is probably because we have based our conclusions on randomised clinical trials. Information from non-randomised studies is likely to provide biased effect estimates, since the people who receive antiviral drugs are likely to differ significantly from those who do not receive antiviral drugs.

AUTHORS' CONCLUSIONS

Implications for practice

Low or very low quality evidence suggests that progression to chronic hepatitis B virus (HBV) infection was higher in people

receiving lamivudine compared with placebo, no intervention, or entecavir. Low quality evidence suggests that interferon may increase the proportion of people who develop adverse events after treatment for acute HBV infection. Thus, there is a likelihood that reality is worse. Based on very low quality evidence, there is currently no evidence of benefit of any intervention in acute HBV infection. There is significant uncertainty in this issue and further randomised clinical trials are required.

Implications for research

Researchers should use clinical outcomes for research on this topic. The trials should include placebo as one of the treatment arms since there has been no evidence from randomised clinical trials that any of the interventions are effective in improving clinical outcomes. Considering that lamivudine or interferon do not offer any benefit but have the potential to cause harm, it may be appropriate to test entecavir or other similar antiviral interventions such as tenofovir against placebo. The participants should be followed up for at least one year and progression to chronic HBV infection should be one of the primary outcomes in such trials. In trials of people with acute fulminant failure, mortality or requirement for liver transplantation are suitable primary outcomes. The trials should be designed and reported using guidance from the SPIRIT statement (Standard Protocol Items: Recommendations for Interventional Trials; Chan 2013) and the CONSORT statement (Schulz 2010).

ACKNOWLEDGEMENTS

We thank the Cochrane Comparing of Multiple Interventions Methods Group and the Cochrane Hepato-Biliary for their support and advice. We thank the copy editors for their support.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark. Disclaimer: the views and opinions expressed in this review are those of the authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

Peer reviewers of review: Nathorn Chaiyakunapruk, Malaysia; Robert Gish, USA; Anders Boyd, France.

Contact editor: Christian Gluud, Denmark.

Sign-off editor: Christian Gluud, Denmark.

REFERENCES

References to studies included in this review

Anonymous 1974 *{published data only}*

Anonymous. Treatment of fulminant type B hepatitis with hepatitis B immune globulin a cooperative trial. *Gastroenterology* 1974;**66**:752.

Apostolescu 2001 *{published data only}*

Apostolescu CG, Rebeda I, Coltan G, Iacob SA, Caruntu FA. The efficacy of lamivudine in acute viral hepatitis with hepatitis B virus [abstract]. *Journal of Hepatology* 2001;**34**(1):144.

Kumar 2007 *{published data only}*

Kumar M, Satapathy S, Monga R, Das K, Hissar S, Pande C, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology (Baltimore, Md.)* 2007;**45**(1):97–101.

Streinu-Cercel 2016 *{published data only}*

Streinu-Cercel A, Sandulescu O, Stefan M, Streinu-Cercel A. Treatment with lamivudine and entecavir in severe acute hepatitis B. *Indian Journal of Medical Microbiology* 2016;**34**(2):166–72.

Tassopoulos 1989 *{published data only}*

Tassopoulos N, Hadziyannis S, Wright G. A randomized double-blind placebo-controlled trial of alpha-interferon in acute type II hepatitis. *Hepatology (Baltimore, Md.)* 1989;**10**(4):576.

Tassopoulos 1997 *{published data only}*

Tassopoulos NC, Koutelou MG, Polychronaki H, Paraloglou-Ioannides M, Hadziyannis SJ. Recombinant interferon-alpha therapy for acute hepatitis B: a randomized, double-blind, placebo-controlled trial. *Journal of Viral Hepatitis* 1997;**4**(6):387–94.

Wiegand 2014 *{published data only}*

* Wiegand J, Wedemeyer H, Franke A, Roessler S, Zeuzem S, Teuber G, et al. Treatment of severe, nonfulminant acute hepatitis B with lamivudine vs placebo: a prospective randomized double-blinded multicentre trial. *Journal of Viral Hepatitis* 2014;**21**(10):744–50.

Wiegand J, Wedemeyer H, Franke A, Stolzel U, Zeuzem S, Teuber G, et al. Treatment of acute hepatitis B with lamivudine vs. placebo: a prospective randomized multicenter trial. *Hepatology (Baltimore, Md.)* 2012;**56**:385A–6A.

References to studies excluded from this review

Blum 1977 *{published data only}*

Blum AL, Berthet P, Doelle W, Goebell H, Kortum K, Pelloni S, et al. Treatment of acute viral hepatitis with (+)-cyanidanol-3. *Lancet* 1977;**2**(8049):1153–5.

Botero 1991 *{published data only}*

Botero RC, Delgado C. Placebo controlled trial of intravenous s-adenosylmethionine (SAME) in patients with acute hepatitis-A, hepatitis-B, and NNB. *Hepatology (Baltimore, Md.)* 1991;**14**(4):A199–200.

Flisiak 2000 *{published data only}*

Flisiak R, Prokopowicz D. One year follow-up of patients treated with misoprostol in acute phase of viral hepatitis B. *Prostaglandins & Other Lipid Mediators* 2000;**60**(4-6):161–5.

Gregory 1976 *{published data only}*

Gregory PB, Knauer CM, Kempson RL, Miller R. Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methyl-prednisolone versus placebo. *New England Journal of Medicine* 1976;**294**(13):681–7.

Sharapov 2000 *{published data only}*

Sharapov M. Treatment with alfa-2 interferon in children with acute hepatitis B. *Gut* 2000;**47**(Suppl III):A287.

Tillmann 2006 *{published data only}*

Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *Journal of Viral Hepatitis* 2006;**13**(4):256–63.

Yu 2010 *{published data only}*

Yu JW, Sun LJ, Zhao YH, Kang P, Li SC. The study of efficacy of lamivudine in patients with severe acute hepatitis B. *Digestive Diseases & Sciences* 2010;**55**(3):775–83.

Additional references

AASLD 2009

Lok ASF, McMahon BJ. AASLD practice guidelines. Chronic hepatitis B: update 2009. www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic%20Hep%20B%20Update%2009%208%2024%202009.pdf (accessed 13 October 2014).

Anonymous 1981

Anonymous. Interferon production by genetic engineering. *British Medical Journal (Clinical Research Ed.)* 1981;**282**(6265):674–5.

Bailon 2001

Bailon P, Palleroni A, Schaffer CA, Spence CL, Fung WJ, Porter JE, et al. Rational design of a potent, long-lasting form of interferon: a 40 kDa branched polyethylene glycol-conjugated interferon alpha-2a for the treatment of hepatitis C. *Bioconjugate Chemistry* 2001;**12**(2):195–202.

Bass 2013

Bass S, Zook N. Intravenous acetylcysteine for indications other than acetaminophen overdose. *American Journal of Health-System Pharmacy* 2013;**70**(17):1496–501.

Bruno 2014

Bruno R, Carosi G, Coppola N, Gaeta GB, Puoti M, Santantonio T, et al. Recommendations for the management of acute hepatitis B: position paper of the Italian Society for the Study of Infectious and Tropical Diseases (SIMIT). *Infection* 2014;**42**(5):811–5.

CDC 2014

Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis - United States, 2014. www.cdc.gov/hepatitis/statistics/2014surveillance/pdfs/2014hepsurveillancerept.pdf (accessed on 12 February 2017).

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;**3**(2): 161–76.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;**8**(10):e76654.

Chan 2013

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**(3):200–7.

Choi 2011

Choi HJ, Ko SY, Choe WH, Seo YS, Kim JH, Byun KS, et al. Clinical features of acute viral hepatitis B in Korea: a multi-center study. *Korean Journal of Hepatology* 2011;**17**(4):307–12.

Chu 2006

Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. *Seminars in Liver Disease* 2006;**26**(2):142–52.

Coppola 2014

Coppola N, Sagnelli C, Pisaturo M, Minichini C, Messina V, Alessio L, et al. Clinical and virological characteristics associated with severe acute hepatitis B. *Clinical Microbiology and Infection* 2014;**20**(12):O991–7.

Del Re 2013

Del Re AC, Spielmans GI, Flückiger C, Wampold BE. Efficacy of new generation antidepressants: differences seem illusory. *PLoS One* 2013;**8**(6):e63509.

DeMets 1987

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987;**6**(3):341–50.

Deng 2012

Deng M, Zhou X, Gao S, Yang SG, Wang B, Chen HZ, et al. The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis. *Virology Journal* 2012;**9**:185.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932–44.

Dias 2012a

Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment, September 2011 (last updated April 2012). www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf (accessed 27 March 2014).

Dias 2012b

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 1: introduction to evidence synthesis for decision making, April 2011 (last updated April 2012). www.nicedsu.org.uk/TSD1%20Introduction.final.08.05.12.pdf (accessed 27 March 2014).

Dias 2014a

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pair wise and network meta-analysis of randomised controlled trials, August 2011 (last updated April 2014). www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf (accessed 8 October 2014).

Dias 2014b

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials, May 2011 (last updated April 2014). www.nicedsu.org.uk/TSD4%20Inconsistency.final.15April2014.pdf (accessed 8 October 2014).

EASL 2012

European Association for Study of Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *Journal of Hepatology* 2012;**57**(1):167–85.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34.

EuroQol 2014

EuroQol. About EQ-5D. www.euroqol.org/about-eq-5d.html (accessed 8 October 2014).

Feld 2005

Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* 2005;**436**(7053):967–72.

Ganem 2004

Ganem D, Prince AM. Hepatitis B virus infection - natural history and clinical consequences. *New England Journal of Medicine* 2004;**350**(11):1118–29.

Garfein 2004

Garfein RS, Bower WA, Loney CM, Hutin YJ, Xia GL, Jawanda J, et al. Factors associated with fulminant liver failure during an outbreak among injection drug users with acute hepatitis B. *Hepatology (Baltimore, Md.)* 2004;**40**(4): 865–73.

Gluud 2016

Gluud C, Nikolova D, Klingenberg SL. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2016, Issue 10. Art. No.: LIVER.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2012

Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98–110.

Hoofnagle 2007

Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok ASF. Management of hepatitis B: summary of a clinical research workshop. *Hepatology (Baltimore, Md.)* 2007;**45**(4):1056–75.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. *International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines*. Vol. 1, Pennsylvania: Barnett International/PAREXEL, 1997.

Jakobsen 2014

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**(1):120.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982–9.

Kumar 2006

Kumar M, Jain S, Sharma BC, Sarin SK. Differentiating acute hepatitis B from the first episode of symptomatic exacerbation of chronic hepatitis B. *Digestive Diseases and Sciences* 2006;**51**(3):594–9.

Lazaridis 2001

Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *Journal of Hepatology* 2001;**35**(1):134–46.

Leen 1989

Leen CL, Davison SM, Flegg PJ, Mandal BK. Seven years experience of acute hepatitis B in a regional department of infectious diseases and tropical medicine. *Journal of Infection* 1989;**18**(3):257–63.

Li 2010

Li J, Liu CH, Wang FS. Thymosin alpha 1: biological activities, applications and genetic engineering production. *Peptides* 2010;**31**(11):2151–8.

Lin 2011

Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: recent advances. *Journal of Gastroenterology and Hepatology* 2011;**26**(Suppl 1):123–30.

Lu 2006

Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006;**101**(474):447–59.

Lundh 2017

Lundh A, Sismondo S, Lexchin J, Busuico OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.MR000033.pub3]

Macaskill 2001

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Statistics in Medicine* 2001;**20**(4):641–54.

Martindale 2011

Sweetman S, editor. Martindale: the complete drug reference (online version), 37th edition, 2011. www.pharmpress.com/product/MC`MART/martindale-the-complete-drug-reference (accessed 23 September 2014).

McMahon 2014

McMahon BJ. Chronic hepatitis B virus infection. *Medical Clinics of North America* 2014;**98**(1):39–54.

Mills 2012

Mills EJ, Ioannidis JP, Thorlund K, Schünemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246–53.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**(9128):609–13.

NCBI 2014a

NCBI. Interferons, 2014. www.ncbi.nlm.nih.gov/mesh/68007372 (accessed 11 October 2014).

NCBI 2014b

NCBI. Thymosins, 2014. www.ncbi.nlm.nih.gov/mesh/68013947 (accessed 15 October 2014).

Nelson 2011

Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011;**378**(9791):571–83.

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837–41.

OpenBUGS 3.2.3 [Computer program]

Members of OpenBUGS Project Management Group. OpenBUGS. Version 3.2.3. Members of OpenBUGS Project Management Group, 2014.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Research Ed.)* 2014;**349**:g5630.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, Cochrane. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, Cochrane, 2014.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591–603.

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163–71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80–97.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1–82.

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429–38.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical Research Ed.)* 2010;**340**:c332.

Severini 1993

Severini TA. Bayesian interval estimates which are also confidence intervals. *Journal of the Royal Statistical Society. Series B (Methodological)* 1993;**55**(2):533–40.

Sharif 2013

Sharif O, Krishnan PV, Thekdi AD, Gordon SC. Acute hepatitis B in an urban tertiary care hospital in the United States: a cohort evaluation. *Journal of Clinical Gastroenterology* 2013;**47**(9):e87–90.

Shi 2010

Shi Z, Li X, Ma L, Yang Y. Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission-a meta-analysis. *International Journal of Infectious Diseases* 2010;**14**(7):e622–34.

Souza 2013

Souza LA, Mattos AA, Fiorini M, Ribeiro P, Tovo CV. Clinical outcome of a patient cohort with acute hepatitis B. *Clinics* 2013;**68**(5):718–20.

Stata/SE 14.2 [Computer program]

StataCorp LP. Stata/SE 14.2 for Windows[64-bit x86-64]. Version 14. College Station: StataCorp LP, 2017.

Tanwar 2012

Tanwar S, Dusheiko G. Is there any value to hepatitis B virus genotype analysis?. *Current Gastroenterology Reports* 2012;**14**(1):37–46.

Thiele 2014

Thiele M, Gluud LL, Fialla AD, Dahl EK, Krag A. Large variations in risk of hepatocellular carcinoma and mortality in treatment naive hepatitis B patients: systematic review with meta-analyses. *PLoS One* 2014;**9**(9):e107177.

Thompson 2009

Thompson ND, Perz JF, Moorman AC, Holmberg SD. Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998-2008. *Annals of Internal Medicine* 2009;**150**(1):33–9.

Thorlund 2011

Thorlund K, Engström J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/tsa/files/tsa_manual.pdf 2011 (accessed 24 November 2016).

Thorlund 2012

Thorlund K, Mills EJ. Sample size and power considerations in network meta-analysis. *Systematic Reviews* 2012;**1**:41.

Tillmann 2012

Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat?. *Liver International* 2012;**32**(4):544–53.

Tillmann 2014

Tillmann HL, Patel K. Therapy of acute and fulminant hepatitis B. *Intervirology* 2014;**57**(3-4):181–8.

TSA 2011 [Computer program]

Copenhagen Trial Unit. TSA - Trial Sequential Analysis. Version 0.9 Beta. Copenhagen: Copenhagen Trial Unit, 2011.

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of

- Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818–27.
- van Valkenhoef 2012**
van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012;**3**(4):285–99.
- Ware 2014**
Ware JE. SF-36® health survey update, 2014. www.sf-36.org/tools/sf36.shtml (accessed on 8 October 2014).
- Wetterslev 2008**
Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64–75.
- Wetterslev 2017**
Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential
Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.
- Wood 2008**
Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601–5.
- Wright 1993**
Wright TL, Lau JY. Clinical aspects of hepatitis B virus infection. *Lancet* 1993;**342**(8883):1340–4.
- Yang 2009**
Yang YF, Zhao W, Zhong YD, Xia HM, Shen L, Zhang N. Interferon therapy in chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma: a meta-analysis. *Journal of Viral Hepatitis* 2009;**16**(4):265–71.
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anonymous 1974

Methods	Randomised clinical trial.
Participants	Country: US. Number randomised: 55. Postrandomisation dropouts: not stated. Revised sample size: 55. Mean age: not stated. Females: not stated. Inclusion criteria <ul style="list-style-type: none"> • Acute illness clinically compatible with viral hepatitis. • Progression within 6 weeks of onset of first symptoms from stage II to stage IV encephalopathy. • Prothrombin time \leq 20%. • Positive test for hepatitis B antigen.
Interventions	Participants were randomly assigned to 2 groups. Group 1: HBIG 8 mL for 6 months and then 32 mL (n = 27). Group 2: placebo (n = 28).
Outcomes	Mortality.
Notes	Follow-up period: not stated.

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Accession were stratified by a centralised computer program for stage of encephalopathy..."
Allocation concealment (selection bias)	Low risk	Quote: "Accession were stratified by a centralised computer program for stage of encephalopathy..."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the placebo was indistinguishable from the HBIG treatment, but they did not say whether participants or clinicians (or both) were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the placebo was indistinguishable from the HBIG treatment, but they did not say whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.

Anonymous 1974 (Continued)

Selective reporting (reporting bias)	High risk	Comment: neither adverse events nor progression to chronic HBV
For-profit bias	Low risk	Comment: study funded by the National Heart and Lung Institute
Other bias	Low risk	Comment: no risk of other bias.

Apostolescu 2001

Methods	Randomised clinical trial.
Participants	Country: Romania. Number randomised: 31. Postrandomisation dropouts: not stated. Revised sample size: 31. Mean age: not stated. Females: not stated. Inclusion criteria <ul style="list-style-type: none"> Acute viral hepatitis with HBV.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine 100 mg once daily for 3 months (n = 15). Group 2: no intervention (n = 16).
Outcomes	Seroconversion.
Notes	Follow-up period: minimum 3 months.

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although authors stated double blind, further details (e.g. whether placebo used) not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although authors stated double blind, further details (e.g. whether placebo used) not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.

Apostolescu 2001 (Continued)

Selective reporting (reporting bias)	High risk	Comment: mortality, adverse events, and progression to chronic HBV not reported
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no risk of other bias.

Kumar 2007

Methods	Randomised clinical trial.
Participants	<p>Country: India. Number randomised: 71. Postrandomisation dropouts: 0 (0%). Revised sample size: 71. Mean age: 37 years. Females: 19 (26.8%). Inclusion criteria</p> <ul style="list-style-type: none"> • Acute HBV: recent onset of acute illness including prodromal symptoms, jaundice, and other typical symptoms. • Laboratory test results that supported the diagnosis of acute hepatitis (serum alanine transaminase and serum bilirubin levels > 2.5 times the upper limit and a positive immunoglobulin M anti-HBc test. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Coinfection. • History of hepatotoxic drug intake. • Alcohol use > 20 g/day. • Evidence of past chronic liver disease at presentation or during follow-up. • Serum bilirubin < 5 mg/dL at presentation.
Interventions	<p>Participants were randomly assigned to 2 groups. Group 1: lamivudine 100 mg once daily for 3 months (n = 31). Group 2: placebo (n = 40).</p>
Outcomes	Mortality, adverse events, progression to chronic HBV infection, and seroconversion
Notes	Follow-up period: minimum 12 months

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done with a random number table."
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.

Kumar 2007 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: investigators and participants blinded to randomisation arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: investigators and participants blinded to randomisation arm
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality, adverse events, and progression to chronic HBV reported
For-profit bias	Unclear risk	Comment: source of funding not reported.
Other bias	Low risk	Comment: was no risk of other bias.

Streinu-Cercel 2016

Methods	Randomised clinical trial.
Participants	<p>Country: Romania. Number randomised: 200. Postrandomisation dropouts: 0 (0%). Revised sample size: 200. Mean age: 36 years. Females: 107 (53.5%).</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ● People with severe acute HBV infection. ● Previous negative screening for HBsAg within previous 6 months. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ● Viral infections such as Epstein-Barr virus, cytomegalovirus, or HIV. ● Other causes of hepatitis including viral and non-viral causes. ● Prior exposure to study drugs. ● Other chronic liver diseases. ● Obstructive or haemolytic malignant jaundice. ● Systemic causes of prolonged prothrombin time. ● Intravenous drug use. ● History of drug hypersensitivity. ● Alcohol or substance abuse or prior therapy that would make the subject unsuitable for treatment.
Interventions	<p>Participants were randomly assigned to 3 groups.</p> <p>Group 1: lamivudine 100 mg once daily oral until seroconversion, development of serious adverse events, or for maximum of 24 weeks (n = 69).</p> <p>Group 2: entecavir 0.5 mg once daily oral until seroconversion, development of serious adverse events, or for maximum of 24 weeks (n = 21)</p> <p>Group 3: no intervention (n = 105).</p>

Outcomes	Mortality, progression to chronic HBV infection, and seroconversion	
Notes	Follow-up period: minimum 11 months.	
<i>Risk of bias</i>		
		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated list of random numbers was used."
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This was a prospective, open-label study conducted in Romania... Given the different formulation and appearance of the administered drugs (lamivudine comes as oval-shaped, white tablets and entecavir as triangular, blue tablets) and the individualised nature of the usual care administered in the control group, masking could not be performed and patients and physicians were aware of the allocated groups."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "This was a prospective, open-label study conducted in Romania... Given the different formulation and appearance of the administered drugs (lamivudine comes as oval-shaped, white tablets and entecavir as triangular, blue tablets) and the individualised nature of the usual care administered in the control group, masking could not be performed and patients and physicians were aware of the allocated groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: intention-to-treat analysis performed including all randomised participants
Selective reporting (reporting bias)	High risk	Comment: mortality and adverse events reported; however, progression to chronic HBV not reported
For-profit bias	Low risk	Quote: "Financial support and sponsorship: nil."
Other bias	Low risk	Comment: no risk of other bias.

Tassopoulos 1989

Methods	Randomised clinical trial.
Participants	Country: Greece. Number randomised: 100. Postrandomisation dropouts: not stated. Revised sample size: 100. Mean age: 33 years. Females: 39 (39%). Inclusion criteria <ul style="list-style-type: none"> • Acute benign hepatitis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: interferon-alpha 3 MU or 10 MU 3 times weekly for 3 weeks (n = 67). Group 2: placebo (n = 33).
Outcomes	Adverse events.
Notes	Follow-up period: minimum 5 months.

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, it was not clear whether placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, it was not clear whether placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor progression to chronic HBV reported
For-profit bias	High risk	Comment: 1 of the coauthors was an employee of a pharmaceutical company
Other bias	Low risk	Comment: no risk of other bias.

Tassopoulos 1997

Methods	Randomised clinical trial.
Participants	<p>Country: Greece. Number randomised: 100. Postrandomisation dropouts: 0 (0%). Revised sample size: 100. Mean age: 32 years. Females: 39 (39%).</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Symptoms and signs compatible with the occurrence of acute HBV for < 1 month. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Aged > 65 years. • Fulminant course. • Therapy with steroids. • Immunosuppressive drugs or parenteral antiviral drugs. • Pregnancy. • HIV positive. • Serious medical illness. • History of chronic liver disease. • Alcoholism or metabolic liver disease. • Exposure within the past 2 months to hepatotoxic drugs. • Parenteral drug use.
Interventions	<p>Participants were randomly assigned to 2 groups. Group 1: recombinant interferon alpha2b 3 MU or 10 MU 3 times weekly subcutaneously for 3 weeks (n = 67). Group 2: placebo (n = 33).</p>
Outcomes	Adverse events, quality of life, seroconversion, and time to seroconversion
Notes	Follow-up period: minimum 5 months.

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "patients were randomly assigned to one of the three treatment options using the randomization sequences prepared by Schering-Plough Corporation, the sponsor of the study." Comment: further details of random sequence generation not available</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "patients were randomly assigned to one of the three treatment options using the randomization sequences prepared by Schering-Plough Corporation, the sponsor of the study." Comment: further details of allocation concealment not available</p>

Tassopoulos 1997 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “neither the patients nor the investigators knew which drug the patients received.” Comment: placebo used to achieve blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “neither the patients nor the investigators knew which drug the patients received.” Comment: placebo used to achieve blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included for the analysis of most outcomes
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor progression to chronic HBV reported
For-profit bias	High risk	Comment: trial funded by a party with vested interest in the results (funded by Schering-Plough)
Other bias	Low risk	Comment: no risk of other bias.

Wiegand 2014

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 40. Postrandomisation dropouts: 5 (12.5%). Revised sample size: 35. Mean age: 41 years. Females: 5 (14.3%). Inclusion criteria <ul style="list-style-type: none"> ● Severe non-fulminant acute HBV infection. ● Aged \geq 18 years. Exclusion criteria <ul style="list-style-type: none"> ● Other liver diseases. ● Ongoing drug abuse. ● Organ transplantation. ● Any immunosuppressive therapy or chemotherapy. ● Renal impairment. ● Pregnancy or lactation. ● Predicted low compliance.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine 100 mg once daily for 4 weeks after disappearance of HBsAg in serum or maximum of 24 weeks (n = 18). Group 2: placebo (n = 17).
Outcomes	Adverse events, seroconversion, and time to seroconversion.

Wiegand 2014 (Continued)

Notes	Follow-up period: not stated. Reasons for postrandomisation dropouts: violated inclusion criteria, withdrawn consent, or worsening of disease to treatment
-------	---

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, it was not clear whether placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, it was not clear whether placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor progression to chronic HBV reported
For-profit bias	Low risk	Quote: "the study was not supported by any manufacturer of lamivudine."
Other bias	Low risk	Comment: no risk of other bias.

anti-HBc: antibody to hepatitis B core antigen; HBIG: hepatitis B immunoglobulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Blum 1977	Hepatitis B virus infection not confirmed in all participants
Botero 1991	Not participants with hepatitis B virus infection.
Flisiak 2000	Not a randomised clinical trial.

(Continued)

Gregory 1976	Hepatitis B virus infection not confirmed in all participants
Sharapov 2000	Quasi-randomised study (allocation based on alphabet of participant's name)
Tillmann 2006	Not a randomised clinical trial.
Yu 2010	Quasi-randomised study (allocation based on admission order)

DATA AND ANALYSES

Comparison 1. Pharmacological treatments for acute hepatitis B virus infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Hepatitis B immunoglobulin (HBIG) versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Lamivudine versus placebo or no intervention	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Lamivudine versus entecavir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Entecavir versus no intervention	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Chronic hepatitis B virus infection	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Lamivudine versus placebo or no intervention	3	285	Odds Ratio (M-H, Fixed, 95% CI)	1.99 [1.05, 3.77]
2.2 Lamivudine versus entecavir	1	90	Odds Ratio (M-H, Fixed, 95% CI)	3.64 [1.31, 10.13]
2.3 Entecavir versus no intervention	1	131	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.23, 1.49]
3 Serious adverse events			Other data	No numeric data
3.1 Interferon versus placebo			Other data	No numeric data
3.2 Lamivudine versus placebo or no intervention			Other data	No numeric data
3.3 Lamivudine versus entecavir			Other data	No numeric data
3.4 Entecavir versus no intervention			Other data	No numeric data
4 Adverse events proportion	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Interferon versus placebo	2	200	Odds Ratio (M-H, Fixed, 95% CI)	348.16 [45.39, 2670.26]
4.2 Lamivudine versus placebo or no intervention	1	35	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.34, 5.94]
5 Adverse events number	1		Rate Ratio (Fixed, 95% CI)	Totals not selected
5.1 Lamivudine versus placebo or no intervention	1		Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Health-related quality of life			Other data	No numeric data
6.1 Interferon versus placebo			Other data	No numeric data
7 Seroconversion	5		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Interferon versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Lamivudine versus placebo or no intervention	4		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Lamivudine versus entecavir	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

7.4 Entecavir versus no intervention	1	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Time to seroconversion	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Interferon versus placebo	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Time to seroconversion [weeks]		Other data	No numeric data
9.1 Lamivudine versus placebo or no intervention		Other data	No numeric data

ADDITIONAL TABLES

Table 1. Characteristics of included studies arranged according to comparison

Study name	Intervention	Control	Follow-up period (months)	Sequence generation	Allocation concealment	Blinding of participants and health-care providers	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Source of funding	Other bias	Overall risk of bias
Anonymous 1974	Hepatitis B Immunoglobulin	Placebo	Not stated	Low	Low	Unclear	Unclear	Unclear	High	Low	Low	High
Tasopoulou 1989	Interferon	Placebo	Min 5	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low	High
Tasopoulou 1997	Interferon	Placebo	Min 5	Unclear	Unclear	Low	Low	Low	High	High	Low	High
Apostolescu 2001	Lamivudine	No intervention	Min 3	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low	High
Kumar 2007	Lamivudine	Placebo	Min 12	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear
Wiegang 2014	Lamivudine	Placebo	Not stated	Unclear	Unclear	Unclear	Unclear	High	High	Low	Low	High

Table 1. Characteristics of included studies arranged according to comparison (Continued)

Streinu- Cercel 2016	Lamivu- dine	Control 1: ente- cavir Control 2: no inter- vention	Min 11	Low	Unclear	High	High	Low	High	Low	Low	High
----------------------------	-----------------	---	--------	-----	---------	------	------	-----	------	-----	-----	------

Min: minimum.

CONTRIBUTIONS OF AUTHORS

KM, MRP, and KG extracted data and provided them in a format that could be analysed.

KG wrote the review.

EB helped KM with data extraction and completing the 'Characteristics of included studies' table.

DT, ET, and BD critically commented on the review.

All review authors agreed on this version before publication.

DECLARATIONS OF INTEREST

This report is independent research funded by the National Institute for Health Research (NIHR Cochrane Programme Grants, 13/89/03 - evidence-based diagnosis and management of upper digestive, hepato-biliary, and pancreatic disorders). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health.

KM: no financial disclosures.

MRP: acted as advisory for Astellas and has received educational grants from Astellas and Novartis.

EB: no financial disclosures.

DT: funded by Astellas for his attendance at the International Liver Transplantation Society meeting in 2014; received GBP 25,000 from Boston Scientific to fund a clinical research fellow in 2013.

BD: no financial disclosures.

ET: no financial disclosures.

KG: no financial disclosures.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

External sources

- National Institute for Health Research, UK.
- Andrew Burroughs Fellowship, Other.

Dr Elena Buzzetti was supported by the Andrew Burroughs Fellowship from AIGO (Associazione Italiana Gastroenterologi Ospedalieri) and M.I.M.I (Montecatini Interactive Medicine International).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- It was not possible to assess whether the potential effect modifiers were similar across different comparisons as this information was missing in many trials. Therefore, we did not perform the network meta-analysis, and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. The methodology that we plan to use if we conduct a network meta-analysis in future is available in Appendix 1.
- We performed Trial Sequential Analysis in addition to conventional methods of assessing the risk of random errors using P values.
- We have reported seroconversion which is sometimes used as a surrogate for progression to chronic hepatitis B virus infection.

NOTES

Considerable overlap is evident in the 'Methods' sections of this review and those of several other reviews written by the same group of authors.