



The Voice of Transplantation in the UK

# Guidelines for Hepatitis B & Solid Organ Transplantation



First Edition

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Compiled by a Working Party of  
The British Transplantation Society



British Transplantation Society Guidelines



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# **1 INTRODUCTION**

## **1.1 The Need for Guidelines**

Hepatitis B is a common infectious disease that can result in progressive liver damage requiring liver transplantation. Due to the high prevalence of hepatitis B infection worldwide many patients who are transplanted with other solid organs will have either had hepatitis B in the past or have active disease. The availability of a potent vaccine also means that new infections can be prevented. It is, therefore, important that all members of the transplant multidisciplinary team are aware of this infection and that steps are put in place to manage it in the pre-, peri- and post-transplant period. This is the first British Transplantation Society (BTS) guideline on the management of hepatitis B in the transplant setting.

## **1.2 Process of Writing and Methodology**

The British Transplantation Society formed a guideline development group to produce these in May 2016, which was chaired by Dr Stuart McPherson. The guideline was produced in line with BTS Clinical Practice Guideline and the recommendations of NHS Evidence [1]. A literature search was conducted by the writing team using PubMed<sup>®</sup> to identify the relevant evidence. Search terms included combinations of hepatitis B, HBV, transplant, transplantation, immunosuppression, treatment, tenofovir, entecavir, lamivudine, HBIG, hepatitis delta, antiviral therapy, hepatitis B recurrence and co-infection, and others.

The first draft of the guideline was written between May and December 2016 by the writing team, which included Dr Ahmed Elsharkawy, Dr Andrew Bathgate (with contribution from Dr Laura Kitto), Dr William Gelson (with contribution from Dr Nicola Owen), Dr Manoj Vallapil, Professor David Mutimer, Professor Derek Manas, Dr Deepak Joshi (with contributions from Dr B Wang and Dr Kosh Agarwal), Dr Douglas Macdonald (with contribution from Dr Victoria Snowdon), and Dr Steven Masson. A consensus meeting of the guideline development group was held in January 2017 to agree the recommendations. The preliminary draft guideline was reviewed by members of the guideline development group and revised by Dr Ahmed Elsharkawy and Dr Stuart McPherson.

The final guidelines were edited by Dr Peter Andrews, Chair of the BTS Standards Committee, and opened for public consultation through the website of the British Transplantation Society in January 2018. The final guidelines were published in March 2018.

It is anticipated that these guidelines will next be revised in 2021.

### **1.3 Guideline Development Group**

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### **1.4 Declarations of Interest**

Dr Peter Andrews – none declared

Dr Andrew Bathgate – speaker Abbvie, Gilead

Dr Ahmed Elsharkawy – speaker, consultancy, research grant or travel support from Abbvie, Astellas, BMS, Chiesi, Gilead and MSD

Dr William Gelson – none declared

Dr Deepak Joshi – none relevant

Dr Douglas Macdonald – none declared

Professor Derek Manas – none declared

Dr Steven Masson – speaker, consultancy or travel support from Abbvie, Astellas, Gilead and Janssen-Cilag

Dr Stuart McPherson – speaker, consultancy or travel support from Abbvie, BMS, Gilead, MSD, Novartis and Roche

Professor David Mutimer – speaker, consultant to Biotest, BMS and Gilead

Dr Manoj Valappil – none declared

## 1.5 Grading of Recommendations

These guidelines represent consensus opinion from experts in the field of transplantation in the United Kingdom. They represent a snapshot of the evidence available at the time of writing. It is recognised that recommendations are made even when the evidence is weak. It is felt that this is helpful to clinicians in daily practice and is similar to the approach adopted by KDIGO [2].

In these guidelines, the GRADE system has been used to rate the strength of evidence and the strength of recommendations. This approach is consistent with that adopted by KDIGO, and also with guidelines from the European Best Practice Committee, and from the Renal Association [2,3]. Explicit recommendations are made on the basis of the trade-offs between the benefits on the one hand, and risks, burden, and costs on the other.

For each recommendation the quality of evidence has been graded as:

- A (high)
- B (moderate)
- C (low)
- D (very low)

**Grade A** evidence means high quality evidence that comes from consistent results from well performed randomised controlled trials, or overwhelming evidence of another sort (such as well-executed observational studies with very strong effects).

**Grade B** evidence means moderate quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength.

**Grade C** evidence means low quality evidence from observational evidence, or from controlled trials with several very serious limitations.

**Grade D** evidence is based only on case studies or expert opinion.

For each recommendation, the strength of recommendation has been indicated as one of:

- Level 1 (we recommend)
- Level 2 (we suggest)
- Not graded (where there is not enough evidence to allow formal grading)

A **Level 1** recommendation is a strong recommendation to do (or not do) something where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients.

A **Level 2** recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain

## 1.6 Abbreviations

ACLF	acute on chronic liver failure
AHB	acute hepatitis B
ALF	acute liver failure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BTS	British Transplantation Society
CHB	chronic hepatitis B
DNA	deoxyribonucleic acid
ELISA	enzyme linked immunosorbent assay
ETC	entecavir
G	genotype
GGT	gamma glutamyl transferase
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B envelope antigen
HBeAb	hepatitis B envelope antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HBIG	hepatitis B specific immunoglobulin
HCC	hepatocellular carcinoma
HDV	hepatitis delta virus
HIV	human immunodeficiency virus
Ig	immunoglobulin
LAM	lamivudine
NA	nucleo(t)side analogues
NAAT	nucleic acid amplification test
NHSBT	National Health Service Blood and Transplant
OLT	orthotopic liver transplant

RCT	randomised controlled trial
RNA	ribonucleic acid
SaBTO	UK Advisory Committee for the Safety of Blood, Tissues and Organs
SOT	solid organ transplant
TACE	transarterial chemoembolisation
TFV	tenofovir
UKELD	United Kingdom end stage liver disease score

## 1.7 Disclaimer

This document provides a guide to best practice, which inevitably evolves over time. All clinicians involved in this aspect of transplantation need to undertake clinical care on an individualised basis and keep up to date with changes in the practice of clinical medicine. These guidelines represent the collective opinions of a number of experts in the field and do not have the force of law. They contain information/guidance for use by practitioners as a best practice tool. It follows that the guidelines should be interpreted in the spirit rather than to the letter of their contents. The opinions presented are subject to change and should not be used in isolation to define the management for any individual patient.

The guidelines are not designed to be prescriptive, nor to define a standard of care. The British Transplantation Society cannot attest to the accuracy, completeness or currency of the opinions contained herein and do not accept any responsibility or liability for any loss or damage caused to any practitioner or any third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

## References

1. Andrews PA. BTS Clinical Practice Guideline 2015. Accessed at [http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current\\_Guidelines.aspx](http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx)
2. Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058-65.

3. Kidney Disease Improving Global Outcomes (KDIGO) Transplant Work Group: KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; 9(S3): S1-157.

## 2 EXECUTIVE SUMMARY OF RECOMMENDATIONS

### Chapter 3: HBV Biology and Disease

#### ***We recommend that:***

- All patients being worked up for solid organ transplantation must be tested for HBsAg, HBsAb (absolute titres) and HBcAb. (1B)
- All HBsAg positive patients undergoing transplant work up must have the following tests: HBeAg, HBeAb and HDV Ab serology, and HBV DNA levels. (1B)
- HDV RNA testing must be performed in potential transplant recipients where HDV serology is positive or equivocal. (1B)
- Any potential *transplant recipients* found to be HBcAb positive but HBsAg negative (past infection) must have HBV DNA and HDV serology testing to exclude occult HBV or HDV infection. (1B)
- All *donors* who are positive for HBcAb but HBsAg negative (past HBV exposure) must have HBV DNA testing to exclude the possibility of occult HBV infection. (1C)

### Chapter 4: Indications for Transplantation for HBV-Related Disease

#### **Acute Fulminant Hepatitis B**

#### ***We recommend that:***

- Individuals with fulminant liver failure associated with hepatitis B infection must be managed in a specialist liver centre. (1C)
- Liver transplantation must be considered in patients with fulminant hepatitis B in keeping with UK listing criteria defined by NHSBT. (1A)

#### ***We suggest that***

- As early antiviral treatment with nucleot(s)ide analogues (NA) may promote recovery, shorten disease duration and improve transplant free survival in severe AHB, treatment with tenofovir or entecavir should be strongly considered. (2B)

## **Decompensated Hepatitis B Cirrhosis and Hepatocellular Carcinoma**

### ***We recommend that:***

- Individuals with decompensated cirrhosis due to hepatitis B should be treated in specialist liver units as the application of antiviral therapy is complex and these patients may be candidates for liver transplantation. (1C)
- Individuals with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s). Entecavir and tenofovir are the first line antiviral agents and should be continued indefinitely. (1A)

### ***We suggest that***

- Listing for liver transplantation should be considered in patients with hepatitis B cirrhosis and a UKELD score >49 or with HCC within criteria defined in the UK NHSBT guidelines. (2A)

## **Chapter 5: HBV and Other (Non-Liver) Transplantation**

### ***We suggest that***

- Patients with advanced HBV-related liver disease requiring another organ transplant be considered for combined transplantation after careful consideration of the potential risks and benefits. (2C)

## **Chapter 6: Pre-Transplant Management of HBV in Individuals Being Considered for Transplantation**

### ***We recommend that:***

- All HBsAg positive individuals being considered for liver transplantation should be treated with either tenofovir or entecavir before transplantation, aiming for an undetectable HBV DNA level. (1B)
- Individuals undergoing non-liver solid organ transplantation who are HBsAg positive must have liver disease staging and suppression of HBV DNA by either tenofovir or entecavir before transplantation if there is a standard clinical indication. (1B)

## Chapter 7: Use of HBcAb Positive or HBsAg Positive Donors

### General Recommendations

#### *We suggest that:*

- The appropriate matching of an organ recipient with a donor positive for HBsAg or HBcAb should be discussed with a specialist in viral hepatitis. (2C)
- All potential recipients should be counselled during the assessment process about the possibility of receiving a liver from a donor with past or current HBV infection. (Not graded)

### HBcAb positive donation for liver recipients

#### *We recommend that:*

- The HBcAb positive (HBsAg negative) donor liver can be used for any potential liver recipient. (1C)
- When the liver comes from a hepatitis B core antibody positive donor and is given to an HBsAg positive recipient, the standard approach to prevent HBV reactivation should be adopted. (1B)
- When the liver comes from a HBcAb positive donor and is given to a HBV immune or non-immune recipient, prophylactic lamivudine should be given from the time of transplantation, and should be continued indefinitely. (1A)

#### *We suggest that*

- If other waiting list priorities permit, the hepatitis B core antibody positive donor liver should be allocated in the following order:
  1. the HBsAg-positive recipient
  2. the HBV-immune recipient (including both naturally immune and vaccine-induced immunity)
  3. the HBV non-immune recipient. (2C)

### HBsAg Positive Donation for Liver Recipients

#### *We recommend that:*

- HBsAg positive donor livers can be given to HBsAg positive recipients, as long as the recipient is known to be HDV negative. (1C)

- If urgency demands, the HBsAg positive liver can be given to an HBsAg negative patient. (1D)
- All recipients of a liver from an HBsAg positive donor must be treated with entecavir or tenofovir from the time of transplantation. (1B)
- Use of HBIg rarely achieves HBsAg negativity, and is not recommended. (1C)

### **HBcAb Positive and HBsAg Positive Donation for Non-Liver Solid Organ Recipients**

***We recommend that:***

- The kidneys, heart and lungs from the HBcAb positive organ donor can be used for any recipient, and the risk of de novo HBV infection is low. (1A)

***We suggest that:***

- If need demands, the non-liver solid organs of the HBsAg positive organ donor can be used for any recipient, after an individualised assessment of risk and benefit. (2C)
- When a HBcAb positive donor is used, lamivudine prophylaxis may be given for six months after transplantation, although the risk of transmission is very low. (2C)

### **Chapter 8: Management of Co-Infection (HDV, HCV, HIV) and Transplantation**

***We recommend that:***

- HBV/HDV recipients should receive combination HBIg/NA prophylaxis from time of transplantation. (1C)
- HBsAg positive donors should not be used for HBV/HDV co-infected recipients. (1C)
- A plan for the perioperative management of each of the HIV and HBV infections should be agreed by the multidisciplinary team before transplantation. (1D)
- HBIg could be used as HBV prophylaxis if/when HIV antivirals are suspended in the peri-operative period. After HIV antiviral treatment is re-established, the approach to HBV prophylaxis is no different from that used for transplantation of HBV mono-infection. (1C)

***We suggest that:***

- For HBV/HDV infected recipients HBIG withdrawal from combination HBIG/NA prophylaxis can be considered, but not within 12 months of transplantation. (2C)

**Chapter 9: Preventing Recurrence of HBV Post-Transplantation**

***We recommend that:***

- In HBsAg positive individuals deemed to be at high risk of recurrence, combination therapy with HBIG and/or a potent NA is recommended from the time of transplantation to prevent HBV reinfection post-liver transplant. (1B)

***We suggest that:***

- Early withdrawal of HBIG or even the use of HBIG-free prophylaxis can be considered in recipients who are at low risk for post-transplant HBV recurrence. (2C)
- Life-long combination therapy with HBIG and a potent NA can potentially be given to patients who were traditionally considered at high risk for HBV recurrence; namely those who are HBV DNA positive at time of transplant, HBeAg positive patients, those transplanted for hepatocellular carcinoma or those who are HIV co-infected; although most of the data supporting use in these groups come from retrospective studies in the lamivudine era. (2B)
- Recipients with evidence of past HBV infection (HBcAb positive alone) are at risk of HBV reactivation post-non-liver transplant and could be considered for a limited (6-12 months) course of prophylactic antiviral treatment; although monitoring for HBV recurrence is an equally acceptable strategy. (2B)

**Chapter 10: Treatment of HBV Recurrence or De Novo Hepatitis B after Solid Organ Transplantation**

***We recommend that***

- All patients with HBV recurrence post-liver transplant should have a careful review of adherence with NA prophylaxis. Resistance testing should be undertaken at a specialist laboratory. (1C)
- Lifelong antiviral therapy is recommended for all individuals with HBV recurrence or de novo hepatitis B post-liver transplantation. (1C)

- Entecavir or Tenofovir are recommended as first line treatment. Tenofovir should be used if the patient has previous lamivudine exposure. (1B)

## **Chapter 11: Monitoring for HBV Recurrence or De Novo Infection**

### ***We recommend that***

- HBV DNA and HBsAg should be monitored every three months in the first year and thereafter every six months in HBsAg positive liver transplant recipients or individuals receiving a graft from a HBcAb positive donor, regardless of treatment or prophylaxis regimen. (1C)
- Monitoring intervals should be shortened in cases of self-reported or suspected non-adherence. (Not graded)

## **Chapter 12: HBV Vaccination and Solid Organ Transplantation**

### ***We recommend that***

- All prospective solid organ transplant recipients who are HBV naive must be vaccinated (time permitting) and the response documented. (1C)

### ***We suggest that***

- Amongst liver recipients transplanted for HBV, vaccination can be considered as a strategy to develop protective serum titres of HBsAb in some recipients, but cannot currently be recommended as routine practice. (2C)
- Amongst renal transplant recipients who are HBcAb positive, if HBsAb are <100 IU/mL, then vaccination should be considered to boost the protective titre of HBsAb and minimise the risk of reactivation. (2C)
- All prospective solid organ transplant recipients should receive a high-dose, accelerated vaccine schedule. (2C)
- In those who fail to respond to the initial HBV vaccination schedule, a second series should be administered. (2C)

## **3 HBV BIOLOGY AND DISEASE**

### **3.1 Introduction**

Hepatitis B Virus (HBV) is a hepatotropic DNA virus that belongs to the *Hepadnaviridae* family of viruses. It was first discovered as the so-called 'Australian Antigen' in 1966 [1]. It is a major human pathogen and is estimated by the World Health Organisation to infect 257 million people worldwide [2]. As a consequence it results in an estimated 600,000 deaths every year through complications of end stage liver disease and hepatocellular carcinoma (HCC) [3]. Despite significant improvements in the rates of vaccination, population growth means that the number of individuals who are chronically infected with HBV is increasing [4].

The majority of chronic HBV infection result from either vertical transmission from mother to child or horizontal transmission through unsafe medical practice. Patient age at the time of initial infection with HBV is a major determinant of whether the infection becomes chronic. Infection in infants results in chronic infection in up to 90% of cases, whereas approximately 30% of children infected before the age of five develop chronic infection [5]. Adult-to-adult transmission can also occur through sexual, nosocomial or blood borne transmission (the latter often in intravenous drug users). In adult cases only, less than 10% progress to chronic infection [6].

### **3.2 Virology and Phases of Infection**

HBV has a partly circular double stranded DNA genome [2]. It attaches to hepatocytes through an interaction between heparan sulphate glycoproteins on the viral envelope and the recently identified hepatocyte specific sodium taurocholate co-transporting polypeptide (NTCP) [7]. Following endocytosis, the partially circular DNA is transported to the nucleus through poorly understood mechanisms [8]. Here it is converted to covalently closed circular DNA (cccDNA). This forms the template for the production of virions and on-going infection.

There have been significant advances in understanding the genetic and epigenetic viral and host factors involved in further viral synthesis [9]. These have been extensively reviewed elsewhere [10,11]. This new understanding may potentially lead to the development of

newer agents, potentially curing HBV rather than simply controlling the infection by suppression of viral replication as currently [11].

HBV is not directly hepatotoxic [12]. Instead a complex interaction with the host immune system drives the hepatic inflammation-fibrosis-cancer axis in chronic HBV infection [2]. Indeed, the development of chronic carrier status is probably caused by the inability to mount an innate and adaptive immune response during the primary infection [5]. This complex interaction results in different, often overlapping, phases of the illness that influence patient management [13]. The phases are differentially named in various publications but rely on the patient's hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb) status, alanine aminotransferase (ALT) levels, and HBV DNA quantification.

These four phases will be discussed. It is important to stress that patients often move in between these phases and periods of observation are often needed to determine which phase predominates in an individual.

**1. HBe Antigen Positive Chronic Infection (previously called “non-inflammatory” or “immune tolerant phase”).**

This tends to occur during the first 20-30 years of life if the infection is acquired in infancy or early childhood, and is characterised by the individual being HBeAg positive and HBeAb negative with HBV DNA viral loads generally  $>10^7$  log IU/mL. The ALT level is in the normal range and liver biopsy (if performed) shows no or minimal inflammation or fibrosis. Recent data suggest that the immune system is not truly tolerant during this phase, but that there is on-going cytotoxic T cell activity [14]. Nevertheless, treatment is rarely indicated for such patients.

**2. HBe Antigen Positive Chronic Hepatitis (previously called “inflammatory” or “immune active” or “immune elimination phase”).**

The triggers to progression to this phase are poorly understood but there seems to be a shift in the balance towards attempted clearance of the virus. Patients in this phase are HBeAg positive with persistent or intermittent elevation in ALT and fluctuating HBV DNA levels that are generally lower than those with HBeAg positive chronic infection. There is immune-mediated damage to the liver with resultant inflammation and fibrosis that can progress to cirrhosis in those with prolonged, unrecognised inflammation. This phase is often asymptomatic, although it can lead to hepatic decompensation or acute liver failure (ALF) in those with underlying cirrhosis

[15]. Antiviral therapy is indicated if this phase is prolonged or there is evidence of significant liver fibrosis.

**3. HBe Antigen Negative Chronic Infection (previously called “inactive phase”).**

This phase is characterised by HBeAg negativity, HBeAb positivity with normal ALT levels and HBV DNA levels being characteristically <2000 IU/mL. HBe antigen seroconversion rates, leading to the development of HBeAg negative chronic infection, are determined by the age at the time of acquisition of HBV. HBV genotype also has a significant influence: for example, those with genotype B seroconvert more than those with genotype C [16]. The annual seroconversion rate is <2% in children younger than three years of age, whereas the equivalent rate is 12% in early adulthood [2]. Reversion to e antigen positivity can occur in up to 8% of patients but the mechanism behind this is poorly understood [17]. Individuals who undergo later HBeAg seroconversion have a much higher likelihood of developing cirrhosis and/or HCC [18]. This is especially true aged >40 years old and may reflect the lifetime exposure to subclinical hepatic inflammation. Antiviral therapy can also result in HBeAg seroconversion. Patients do not generally require therapy if established in this phase, although regular follow-up is mandatory as reactivation and the development of HBeAg negative chronic hepatitis occurs in 25%.

**4. HBe Antigen Negative Chronic Hepatitis (previously called “immune escape phase”).**

This generally occurs as a result of mutations in the basal core promoter and/or the pre-core region of the pre C/C gene [12]. These mutations lead to immune escape mutations and HBV viral replication increases, resulting in HBV DNA levels >2000 IU/mL and frequently >20,000 IU/mL, although they are generally lower than in HBeAg positive chronic hepatitis. Serum ALT levels are raised and can fluctuate significantly. Resultant liver damage can progress rapidly towards cirrhosis and HCC. This is frequently faster than in HBeAg positive chronic hepatitis [18]. Long term follow-up studies have shown that the risk of HCC is directly correlated to serum HBV DNA levels in such patients [19,20]. Antiviral therapy forms the cornerstone of management.

The different phases of infection are summarised in table 1 below.

**Table 1 Phases of Chronic Hepatitis B Infection**

	<b>HBeAg positive chronic infection</b>	<b>HBeAg positive chronic hepatitis</b>	<b>HBeAg negative chronic infection</b>	<b>HBeAg negative chronic hepatitis</b>
<b>HBeAg status</b>	Positive	Positive	Negative	Negative
<b>HBeAb status</b>	Negative	Can be positive or negative	Positive	Usually positive
<b>ALT levels</b>	Normal	High	Normal	High
<b>HBV DNA Levels</b>	Very high – classically in the millions	Usually high	<2000 IU/mL	>2000 IU/mL and frequently >20000 IU/mL
<b>Histological liver damage</b>	None	Yes, with progression to cirrhosis possible	None	Yes, with progression to cirrhosis possible

### 3.3 Serological and Virological Testing

The cornerstone for the diagnosis of HBV infection is the testing for HBV surface antigen (HBsAg) [2]. Any individuals who are HBsAg positive should be considered to have active infection and will require post-transplant treatment to control viral replication (see chapter 6). In addition, they should have HBV DNA levels measured to determine the status of the infection and help classify their current disease phase.

Testing for HBV core antibody (HBcAb) is also important as it indicates whether or not an individual has been exposed to HBV in the past. Those who have spontaneously cleared the virus from the blood will be HBsAg negative but HBcAb positive. Finally, testing for HBV surface antibody (HBsAb) is helpful to assess the veracity of the host immune response against HBV. Patients who have been vaccinated against HBV are HBcAb negative but HBsAb positive. Those who have spontaneously cleared HBV are HBsAg negative but HBcAb positive and generally HBsAb positive. The titre of HBsAb can be variable and levels

above 10 miu/mL are generally thought to be protective [21]. It is worth noting that the UK is one of very few developed countries that does not have universal vaccination against HBV, although a program is planned for implementation in late 2017 [22]. Common HBV serology profiles and their interpretation are summarised in table 2.

Although a profile of HBcAb positive with all other markers negative ('core alone') may indicate past HBV infection, this profile can also be due to passively acquired antibodies (blood transfusion), acute HBV infection (window period), or non-specific reactivity (false positive). This is particularly relevant in donors who may have received blood products. HBsAb and HBeAb antibodies may also be passively transferred from blood products.

A HB 'core alone' positive profile in the recipient must be further investigated before transplantation, including any history of blood products and risk factors for HBV, full HBV serological markers, and HBV DNA (+/- follow-up testing) to clarify the patient's HBV status.

It is important to note, however, that cccDNA remains permanently present in the hepatocytes of individuals who have cleared HBsAg from blood. Immunosuppression of these individuals with past infection can therefore result in the reactivation of HBV (see below) and the re-emergence of HBsAg [23]. In such cases, death is an unfortunate and common, but avoidable occurrence in routine clinical practice.

### **3.4 Reactivation of HBV**

HBV reactivation is defined as the reappearance of markers of active HBV replication in a patient with previously controlled HBV infection, or an increase in levels of replication compared to previous levels. The pattern of reactivation depends on baseline HBV status, underlying condition, type of immunosuppressive therapy, and host immunity. Reactivation may result from loss of immune control of HBV or lack of antiviral efficacy due to the emergence of antiviral resistant variants. Reactivation may be asymptomatic or associated with a flare of hepatitis in previously minimal or inactive disease, manifesting clinically with acute hepatitis which can progress to acute liver failure and even death if untreated. The serological and virological profile of reactivation may vary depending on the pre-existing profile in the patient (table 3).

**Table 2 HBV serological profiles and interpretation**

<b>HBV serological profile</b>	<b>Interpretation</b>
HBsAg negative HBcAb negative HBsAb negative	No evidence of current or past, controlled HBV infection. No immunity to HBV.
HBsAg negative HBcAb positive HBsAb positive	Evidence of past HBV infection and immunity.
HBsAg negative HBcAb negative HBsAb positive	Evidence of vaccine-induced immunity.
HBsAg negative HBcAb positive HBsAb negative  <i>This profile must be further investigated to clarify HBV status</i>	<p>In patients with risk factors in the past for HBV infection: past, controlled infection; resolving acute infection (window period); or occult chronic infection.</p> <p>In patients with recent history of blood/blood product transfusion: possible passively acquired anti-HB core antibody.</p> <p>In patients with no risk factors in the past for HBV infection or history of recent blood/ blood products: possible false positive result.</p>
HBsAg positive HBcAb positive IgM HBcAb positive HBsAb negative	Consistent with acute HBV infection. (Note: IgM HBcAb may be positive in HBV reactivation).
HBsAg positive HBcAb positive IgM HBcAb negative HBsAb negative HBeAg positive/negative HBeAb negative/positive	Evidence of chronic HBV, if confirmed on two samples six months apart.

**Table 3 Changes in serological and virological profiles associated with HBV reactivation**

Initial profile			Reactivation profile
HBsAg	HBcAb	HBV DNA	
Positive	Positive	Not Detected	HBV DNA detectable >100 IU/mL, confirmed on 2 separate samples
Positive	Positive	Detected	≥2 log increase in HBV DNA levels from baseline levels HBV DNA with level ≥100,000 IU/mL (if no baseline HBV DNA level available)
Negative	Positive	Not Detected	HBsAg positive/HBV DNA detectable
Negative	Positive	Detected	(Occult) HBsAg positive/increase in HBV viral load (≥2 log)

HBV reactivation can occur in patients with CHB (exacerbation of CHB) or past HBV (reactivation of past HBV). The risk of reactivation is higher in CHB (HBsAg positive) patients. Within this group, those who are HBsAg positive and hepatitis B e antigen (HBeAg) positive or have high HBV viral load are at highest risk of reactivation. However, reactivation can also occur in patients who were HBeAg negative or had undetectable serum HBV DNA prior to transplant [24,25]. Amongst patients with past HBV (HBsAg negative, HBcAb positive), reactivation is more likely to occur in those with low or undetectable HBsAb levels and may be preceded by a fall in HBsAb levels over time [26].

### 3.5 Hepatitis Delta Co-Infection

Hepatitis delta (HDV) is a hepatotropic replication deficient single stranded covalently closed circular RNA virus that hijacks the HBV replication machinery within hepatocytes to facilitate its viral replication [24]. It cannot exist in isolation. Virions are coated in HBsAg. It is estimated that around 5% of HBV infected patients worldwide are co-infected with HDV [10]. HDV infection is more prevalent in South America, Turkey, Eastern Europe and Sub-

Saharan Africa, whereas its prevalence is very low in Asia despite the large numbers of HBV-infected people in this continent [24].

A diagnosis of past or current HDV co-infection is dependent on the finding of serum HDV IgG positivity. Active HDV co-infection is confirmed by HDV RNA positivity. Indeed, HDV RNA should be performed in all cases of suspected HDV co-infection rather than relying on serology alone [2].

HDV is either acquired at the time of infection with HBV or can occur as a super-infection. HDV co-infection results in more rapid progression of liver disease to cirrhosis and HCC, especially as it is difficult to treat [25]. In cases of HDV co-infection where HBV DNA levels are above 2000 IU/mL or fluctuate above this level, it is generally recommended that HBV replication is inhibited with nucleoside analogues [26].

The management of post-liver transplant patients with HBV/HDV co-infection is slightly different to that of with HBV mono-infection (see chapter 8).

### 3.6 Recommendations

#### ***We recommend that:***

- All patients being worked up for solid organ transplantation must be tested for HBsAg, HBsAb (absolute titres) and HBcAb. (1B)
- All HBsAg positive patients undergoing transplant work up must have the following tests: HBeAg, HBeAb and HDV Ab serology, and HBV DNA levels. (1B)
- HDV RNA testing must be performed in potential transplant recipients where HDV serology is positive or equivocal. (1B)
- Any potential *transplant recipients* found to be HBcAb positive but HBsAg negative (past infection) must have HBV DNA and HDV serology testing to exclude occult HBV or HDV infection. (1B)
- All *donors* who are positive for HBcAb but HBsAg negative (past HBV exposure) must have HBV DNA testing to exclude the possibility of occult HBV infection. (1C)

## References

1. Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukaemia sera. *JAMA* 1965; 191: 541-6.
2. Fourati S, Pawlotsky J-M. Recent advances in understanding and diagnosing hepatitis B virus infection. *F1000Research* 2016; 5: 2243.
3. GBD 2013 mortality and causes of death collaborators. Global, regional and national age-specific all-cause and cause-specific mortality for 240 causes of death, 1993-2013. *Lancet* 2015; 385: 117-71.
4. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; 386: 1546-55.
5. Busca A, Kumar A. Innate immune responses in hepatitis B virus (HBV) infection. *Virology* 2014; 11: 22.
6. Bertoletti A, Tan AT, Gehring AJ. HBV-specific adaptive immunity. *Viruses* 2009; 1: 91-103.
7. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *eLife*. 2012; 1: e00049.
8. Li W, Urban S. Entry of hepatitis B and hepatitis D virus into hepatocytes: basic insights and clinical implications. *J Hepatol* 2016; 64(1 Suppl): S32-40.
9. Belloni L, Pollicino T, De Nicola F, et al.: Nuclear HBx binds the HBV minichromosome and modifies the epigenetic regulation of cccDNA function. *Proc Natl Acad Sci USA* 2009; 106: 19975-9.
10. Petersen J, Thompson AJ, Levrero M. Aiming for cure in HBV and HDV infection. *J Hepatol* 2016; 65: 835-48.
11. Zoulim F, Lebosse F, Levrero M. Current treatments for chronic hepatitis B virus infections. *Curr Opin Virol* 2016; 18: 109-16.
12. Liu B, Wen X, Huang C, et al. Unravelling the complexity of hepatitis B virus: From molecular understanding to therapeutic strategy in 50 years. *Int J Biochem Cell Biol* 2013; 45: 1987-96.
13. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. *Hepatology* 2006; 43(2S1): S173-81.
14. Bertoletti A, Kennedy PT. The immune tolerant phase of chronic HBV infection: new perspectives on an old concept. *Cell Mol Immunol* 2015; 12: 258-63.
15. Jeng WJ, Sheen IS, Liaw YF. Hepatitis B virus DNA level predicts hepatic decompensation in patients with acute exacerbation of chronic hepatitis B. *Clin Gastroenterol Hepatol* 2010; 8: 541-5.

16. Chu CJ, Hussain M, Lok AS. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. *Gastroenterology* 2002; 122: 1756-62.
17. Lok AS, Lai CL, Wu PC, et al. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987; 92: 1839-43.
18. Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. *Hepatology* 2010; 51: 435-44.
19. Chen CF, Lee WC, Yang HI, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. *Gastroenterology* 2011; 141: 1240-8.
20. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65-73.
21. Chen D-S. Hepatitis B Vaccination: the key towards elimination and eradication of hepatitis B. *J Hepatol* 2009; 50: 805-16.
22. Van Damme P, Leridan E, Hendrickx G, et al. Should Europe have a universal hepatitis B vaccination programme? *Br Med J* 2013; 347: 14-5.
23. Patullo V. Prevention of hepatitis B reactivation in the setting of immunosuppression. *Clin Mol Hepatol* 2016; 22: 219-37.
24. Berger F, Preiser W, Kachel HG, Stürmer M, Doerr HW. HBV reactivation after kidney transplantation. *J Clin Virol* 2005; 32: 162-5.
25. Grotz W, Rasenack J, Benzing T, et al. Occurrence and management of hepatitis B virus reactivation following kidney transplantation. *Clin Nephrol* 1998; 49: 385-8.
26. Kanaan N, Kabamba B, Maréchal C, Pirson Y, et al Significant rate of hepatitis B reactivation following kidney transplantation in patients with resolved infection. *J Clin Virol* 2012; 55: 233-8.
27. Sultanik P, Pol S. Hepatitis delta virus: epidemiology, natural course and treatment. *J Infect Dis Ther* 2016; 4. doi.org/10.4172/2332-0877.1000271.
28. Lampertico P, Maini M, Patpatheodoridis G. Optimal management of hepatitis B infection – EASL special conference. *J Hepatol* 2015; 63: 1238-53.
29. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-98.

## 4 INDICATIONS FOR TRANSPLANTATION FOR HBV RELATED DISEASE

### 4.1 Acute Hepatitis B

More than 95-99% of adults who acquire acute HBV (AHB) will recover spontaneously and seroconvert to HBsAb without antiviral therapy [1]. Approximately 1% of cases of AHB progress to fulminant hepatitis, which is characterised by a very high mortality rate (up to 80% [2]), often requiring liver transplantation (OLT).

Antiviral treatment is indicated in certain subgroups of patients [3]:

- Fulminant hepatitis B
- Severe AHB - based on the presence of at least two of the following criteria:
  - bilirubin >100 µmol/L
  - international normalised ratio (INR) ≥1.6
  - hepatic encephalopathy
- Protracted disease course - persistent symptoms or marked jaundice for more than four weeks after presentation
- Immunocompromised host

In patients with severe or fulminant AHB, prompt antiviral administration is warranted to shorten disease duration, promote recovery, and improve survival [4]. There have been a small number of studies supporting this strategy, mainly with lamivudine (LAM) [5]. In a case series of 17 patients with severe or fulminant AHB, LAM administered until HBsAg clearance improved survival compared to historical, untreated controls (82.4 vs. 20% survival,  $p < 0.001$ ) [5]. More recently, a randomised controlled trial (RCT) of LAM in severe AHB showed significantly lower rates of liver failure and mortality compared to placebo when LAM was started early in the disease course [6]. The evidence for LAM has not been universally positive. One RCT comparing LAM (100 mg/day) with placebo in severe AHB showed no significant difference in clinical course or outcome between groups over three month follow-up [7]. However, outcomes without antiviral therapies in severe/fulminant AHB have remained consistently poor [8-10].

Far fewer data exist for the newer nucleos(t)ide analogues (NA), tenofovir (TFV) and entecavir (ETV) in AHB. However, there is no doubt that they are superior to LAM in the

treatment of chronic HBV. On the basis of promising preliminary results, the current EASL guidelines on treatment of AHB recommend the use of ETV (0.5 mg/day) or TFV (245 mg/day) [4].

Antiviral treatment should be started early in the course of severe AHB, without waiting for the development of fulminant hepatitis [10]. Earlier initiation of NA treatment is associated with better outcomes – both in terms of virological (seroconversion of HBsAg) and clinical endpoints [6,11,12]. Delayed initiation of NAs is associated with higher mortality or requirement for OLT [6,12]. Early treatment of AHB also ensures a higher chance of rendering the patient HBV DNA negative at the time of OLT, should this be required. There are limited data regarding the required duration of antiviral treatment in AHB. However, therapy should be continued for at least three months after seroconversion to HBsAb or 12 months after anti-HBe seroconversion without HBsAg loss [4].

Liver transplantation should be considered in all patients with fulminant hepatitis. The criteria for listing for liver transplantation for acute liver failure related to hepatitis B must include hepatic encephalopathy **and**:

- Prothrombin time >100 seconds or INR >6.5
- or**
- Any three from:
  - age >40 or <10 years
  - jaundice to encephalopathy time >7 days
  - serum bilirubin >300 µmol/L
  - prothrombin time >50 seconds or INR >3.5

#### **4.1.1 Recommendations**

***We recommend that:***

- Individuals with fulminant liver failure associated with hepatitis B infection must be managed in a specialist liver centre. (1C)
- Liver transplantation must be considered in patients with fulminant hepatitis B in keeping with UK listing criteria defined by NHSBT. (1A)

***We suggest that***

- As early antiviral treatment with nucleot(s)ide analogues (NA) may promote recovery, shorten disease duration and improve transplant free survival in severe AHB, treatment with tenofovir or entecavir should be strongly considered. (2B)

**4.2 Chronic Hepatitis B**

The goal of treatment in chronic HBV (CHB) infection is to prevent disease progression to cirrhosis, hepatocellular carcinoma (HCC) and death [13]. Current treatment guidelines consider NAs or pegylated-interferon (PEG-IFN) as first-line treatment for CHB in patients with serum HBV DNA levels >2000 IU/mL in combination with elevated alanine aminotransferase (ALT) levels and/or with moderate/severe liver inflammation and/or fibrosis [4,14]. It has been well established that higher HBV DNA levels in untreated patients are associated with progression to cirrhosis, development of HCC, and liver-related mortality [15], underlying the use of HBV DNA levels as a guide to treatment. HBV-related end-stage liver disease or HCC are responsible for around 600,000 deaths per year and currently represent the cause of liver failure in 5-10% of patients requiring liver transplantation [16,17].

**4.2.1 Decompensated Cirrhosis**

Longitudinal studies of patients with untreated active CHB have shown that the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation for untreated CHB-associated cirrhotic patients is approximately 20% [4]. Untreated patients with decompensated cirrhosis have a poor prognosis, with a 14-35% 5-year survival, compared with 84% in the compensated state [4,18,19]. However, decompensated HBV cirrhosis is declining as an indication for transplantation, due to the success of HBV vaccination and the advent of potent oral antiviral agents. Prolonged and adequate suppression of HBV DNA with antiviral agents can prevent progression to decompensation [20,21] and may even enable regression of fibrosis and the reversal of cirrhosis [22].

Decompensated cirrhosis should be treated in specialised liver units as the application of antiviral therapy is complex and these patients may be candidates for OLT [4]. Existing guidelines recommend starting oral NAs for patients with decompensated cirrhosis, irrespective of serum ALT, HBV DNA and e antigen status [4,14]. Interferon is

contraindicated in cirrhosis because of the risk of potentially life-threatening complications [23,24].

Antiviral treatment has two objectives:

1. Improvement of liver function
2. Decreased risk of HBV recurrence after transplantation

Initial studies with LAM [21,25,26] and adefovir [27,28] demonstrated improved outcomes (decreased mortality and improved liver function) in patients with decompensated HBV cirrhosis. However, the emergence of LAM resistance mutations negated clinical benefit in some patients, resulting in increased Child-Turcotte-Pugh (CTP) scores [21]. Although drug resistance is much less common with adefovir, there are significant concerns regarding the slow rate of suppression of HBV replication and the potential for dose-dependent nephrotoxicity in decompensated HBV [23,29]. Therefore, TFV and ETV are currently the first-line agents, with greater potency and higher barrier to resistance [4]. ETV suppresses HBV replication more rapidly and effectively than LAM [24], is not nephrotoxic [30], and has an excellent resistance profile at 5 years in treatment-naïve patients [31].

The licensed ETV dose for patients with decompensated cirrhosis is 1 mg once daily (instead of 0.5 mg for patients with compensated liver disease). NAs should be continued indefinitely in cirrhotic patients and all patients should be monitored at least every three months for virological response with serum HBV DNA testing. Any detectable viraemia after 6-12 months of treatment should be considered as treatment failure and indicates the need for modification of therapy [4].

The NAs have a good safety profile in patients with advanced liver disease [21,32,33]. A phase 2 double-blind study compared the safety of TFV and ETV in decompensated HBV cirrhosis. Both treatments were very well tolerated and also led to an improvement in virological, biochemical and clinical parameters, although the study was not primarily designed to assess for this [21]. One serious potential side effect is mitochondrial toxicity, which can manifest as lactic acidosis, myopathy, neuropathy, or even hepatotoxicity [34]. Lactic acidosis has been reported in a German cohort of patients with advanced decompensated cirrhosis (MELD >20) treated with ETV [35], and this group of patients should be more closely monitored.

Patients with decompensated HBV cirrhosis should be considered for OLT. However, approximately one third of these patients show slow improvement on NAs over a period of three to six months, which in some cases might result in de-listing [28,36]. One study of treatment-naïve patients with decompensated HBV cirrhosis treated with ETV (0.5 mg/day) demonstrated significant improvement in Child-Turcotte-Pugh (CTP) (mean pre-treatment 8.1, mean post-treatment 6.6,  $p < 0.001$ ) and MELD scores (mean pre-treatment 11.1, mean post-treatment 8.8,  $p < 0.001$ ) after 12 months of treatment [32]. However, not all patients improved with ETV; 12 subjects showed no change in their CTP score and four subjects had progressive liver disease despite therapy. A further study of 154 patients with decompensated HBV cirrhosis treated with LAM demonstrated a biphasic pattern of survival, with most deaths occurring within the first six months of treatment [26].

It is clear that two distinct subgroups of patients exist – those who will experience prolonged survival with antiviral therapy and those who require OLT. Studies have attempted to identify prognostic indicators that could help to stratify these patient groups. In one study, 96 treatment-naïve patients with decompensated HBV cirrhosis were given TFV and followed up for 24 months. Transplant-free survival at 12 months was 95%, consistent with earlier studies [28,32]. A MELD score of  $>20$  was the most important predictor of mortality, suggesting that this cohort of patients should be assessed for early transplantation. Higher HBV DNA levels, a CTP score  $>10$ , and encephalopathy at baseline were also associated with poor outcome.

The point at which liver transplantation is of definite benefit to the patient remains uncertain. The safest option may be to list patients with a MELD  $>15$  (or UKELD equivalent approximately 55), with the possibility of removal from the list should their condition improve.

Criteria which must be satisfied for consideration of OLT in the UK include:

1. A projected one year liver disease mortality without transplantation of  $>9\%$ , predicted by a United Kingdom Model for End-Stage Liver Disease (UKELD) score of  $\geq 49$
2. A variant syndrome (e.g. diuretic resistant ascites or chronic hepatic encephalopathy) in those with a UKELD of  $<49$

It is important to know the precise HBV status of the patient prior to transplantation [37]. If HBV DNA is detectable at any level, ETV or TFV should be started as soon as possible [4]. Rendering HBV DNA undetectable before OLT decreases the risk of recurrence of HBV in the graft [38].

### **4.2.3 Hepatocellular Carcinoma**

HCC represents more than 90% of primary liver cancers [39]. Worldwide, it is the fifth most common cancer (5% of all cancer [4]), with over 500,000 new cases diagnosed annually [40]. Whilst the overall rate of cancer related death is declining, the rate of HCC-related mortality continues to increase [41], with a large proportion of these cases related to chronic viral hepatitis.

#### **4.2.3.1 Incidence and Risk Factors**

HBV is the leading risk factor for HCC globally [42,43], accounting for 50-60% of HCC [40,42]. HBV can cause HCC in the absence of cirrhosis, but the majority of HBV-related HCC (70-90%) develops in cirrhotic livers [44]. The annual incidence of HBV-related HCC in cirrhotic patients with CHB is high, ranging from 2 to 5% [45].

Several factors are known to increase the risk of HCC among individuals with HBV infection [40]:

1. Demographic – male gender, older age, Asian or African ancestry, family history of HCC
2. Viral – higher HBV DNA levels, genotype (C>B), pre-core mutations, longer duration of infection, co-infection with HCV, HIV and HDV
3. Clinical – cirrhosis
4. Environmental – alcohol, tobacco, aflatoxin exposure

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study from Taiwan followed a cohort of 3653 HBsAg-positive patients. This demonstrated that the risk of HCC increased in proportion to viral load, independent of age, sex, smoking history, alcohol consumption and HBeAg status [15]. The increased incidence of HCC in relation to levels of HBV DNA was also demonstrated in a study comparing HBeAg negative chronic infection patients (seronegative for HBeAg, HBV DNA <10,000 copies/mL and normal liver enzymes) with controls (HBsAg negative), where patients with chronic infection had an almost 5-fold greater risk of HCC [46]. It is unclear if these findings apply to Western populations who acquire HBV as adults and have different risk factors (obesity, diabetes, alcohol).

#### **4.2.3.2 Surveillance**

Effective antiviral treatment and sustained HBV DNA suppression reduces but does not eliminate the risk of HCC in individuals with CHB [39,47,48]. One recent multicenter cohort study [49] looked at 744 HBV mono-infected patients treated with ETV. The cumulative risk of HCC was low but ETV treated patients still remained at risk of HCC, especially during the first year of treatment, even though the majority (88%) achieved undetectable serum HBV DNA. Furthermore, in a large Asian study, patients with chronic HBV and cirrhosis or advanced fibrosis were given 100 mg/day of LAM or placebo for up to 5 years. 3.9% of those in the LAM group developed HCC, compared with 7.4% in the placebo group [50]. These findings have been supported by other studies in both Caucasian [48] and non-Caucasian populations [51]. HCC surveillance, with six-monthly abdominal ultrasound scans, is therefore necessary even if HBV DNA is adequately suppressed.

Surveillance should be offered to patients with CHB who remain at risk of HCC development due to baseline factors [39]. The use of serum alpha-fetoprotein (AFP) in surveillance remains controversial with many clinicians choosing to measure it six-monthly despite international guidelines no longer recommending this. Risk scores for HCC development such as REACH-B [52] apply to non-treated Asian patients without cirrhosis. A recent study has developed a risk score for Caucasian patients on therapy [53].

#### **4.2.3.3 Treatment**

The treatment of HCC related to HBV is very similar to that in other causes of HCC. In the non-cirrhotic setting, resection is the treatment of choice for a single lesion, while maintaining viral suppression with oral antiviral medication [4,54,55]. As already indicated, the majority of HCC occur in a cirrhotic liver where treatment decisions are made on the basis of size of the lesions, the number of lesions, and the serum AFP concentration. Surgical resection is the first line treatment for patients with solitary HCC and well-preserved liver function. Resection or radiofrequency ablation may be curative options for smaller lesions. However, recurrence is a significant issue, with rates of 50% at three years and 70% at five years reported [54,55]. Salvage transplantation may be an option if the listing criteria are fulfilled.

Liver transplantation for HCC is a well-established treatment option. Radiological assessment should ideally include both CT and MRI, with the size of the lesion being assessed by the widest dimensions on either scan. Extra-hepatic staging in patients being

considered for transplantation should include chest and pelvic CT. Tumor rupture, AFP >1000 iu/mL, extra-hepatic spread, and macroscopic vascular invasion are absolute contraindications to transplantation. The AFP concentration should be measured during assessment for OLT and at least every three months on the waiting list, with transplantation restricted to patients with AFP <1000 iu/mL [56].

For listing for OLT for HCC, the following criteria must be satisfied [57]:

- A single tumor  $\leq 5$  cm diameter, or
- Up to 5 separate tumors, all  $\leq 3$  cm, or
- Single tumor >5 cm and  $\leq 7$  cm diameter, where there has been no evidence of tumor progression, no extra-hepatic spread and no new nodule formation over a six month period. Loco-regional therapy +/- chemotherapy may be given during that time.

All patients listed for liver transplantation should be strongly considered for some form of loco-regional therapy such as ablation or transarterial chemoembolisation while on the waiting list [56–58].

HCC arising in a non-cirrhotic patient is less common and the Milan Criteria are not applicable to evaluate a patients' suitability for OLT [39]. In general, non-cirrhotic patients with non-resectable HCC may be considered appropriate candidates for OLT in the absence of macrovascular invasion and extra-hepatic spread [39].

It is recognised that some patients not meeting the standard listing criteria have HCC with favourable tumor biology and would benefit from transplantation. This has led to the development of expanded criteria to enable the listing of patients who have responded to initial anti-cancer therapies. At the current time, 'down-staging' is not permitted within UK guidelines. However, in view of a growing body of evidence, a recent consensus conference deemed the 'Duvoux criteria' for down-staging (which have been developed and introduced in France) appropriate for use in the UK [56,59]. Evidence to date suggests that successful down-staging achieves a 5-year survival that is comparable to that of patients who do not require down-staging [60]. At present this is to be regarded as a service development but it may in time become an additional listing criterion.

#### 4.2.4 Recommendations

##### ***We recommend that:***

- Individuals with decompensated cirrhosis due to hepatitis B should be treated in specialist liver units as the application of antiviral therapy is complex and such patients may be candidates for liver transplantation. (1C)
- Individuals with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s). Entecavir and tenofovir are the first line antiviral agents and should be continued indefinitely. (1A)

##### ***We suggest that***

- Listing for liver transplantation should be considered in patients with hepatitis B cirrhosis and a UKELD score >49 or with HCC within criteria defined in the UK NHSBT guidelines. (2A)

#### References

1. Tassopoulos N, Papaevangelou G, Sjogren M, et al. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987; 92: 1844-50.
2. Lee W, Squires R, Nyberg S. Acute liver failure: summary of a workshop. *Hepatology*. 2008; 47: 1401-15.
3. Jindal A, Kumar M, Sarin SK. Management of acute hepatitis B and reactivation of hepatitis B. *Liver Int* 2013; 33 (S1):164-75.
4. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-98.
5. Tillmann HL, Hadem J, Leifeld L, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006; 13: 256-63.
6. Yu J-W, Sun L-J, Zhao Y-H, Kang P, Li S-C. The study of efficacy of lamivudine in patients with severe acute hepatitis B. *Dig Dis Sci* 2010; 55: 775-83.
7. Baxa DM, Thekdi AD, Golembieski A, et al. Evaluation of anti-HBV drug resistant mutations among patients with acute symptomatic hepatitis B in the United States. *J Hepatol* 2013; 58: 212-6.

8. De Socio GV, Mercuri A, Di Candilo F, Baldelli F. Entecavir to treat severe acute hepatitis B. *Scand J Infect Dis* 2009; 41: 703-4.
9. Garfein R, Bower W, Loney C, et al. Factors associated with fulminant liver failure during an outbreak among injection drug users with acute hepatitis B. *Hepatology* 2004; 40: 865-73.
10. 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 Int* 2012; 32: 544-53.
11. Kumar M, Satapathy S, Monga R, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology* 2007; 45: 97-101.
12. Yu JW, Sun LJ, Yan BZ, Kang P, Zhao YH. Lamivudine treatment is associated with improved survival in fulminant hepatitis B. *Liver Int* 2011; 31: 499-506.
13. Dienstag J. Hepatitis B Virus Infection. *N Engl J Med* 2008; 359: 1486-500.
14. Lok ASF, McMahon BJ. Chronic hepatitis B: Update 2009. *Hepatology* 2009; 50: 661-2.
15. Cj C, Hi Y, Su J, Al E. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65-73.
16. Ganem D, Prince AM. Hepatitis B virus Infection - natural history and clinical consequences. *N Engl J Med* 2004; 350: 1118-29.
17. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok ASF. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; 45: 1056-75.
18. Fattovich G, Olivari N, Pasino M, et al. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut* 2008; 57: 84-90.
19. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology* 2009; 49(S5): 45-55.
20. Papatheodoridis GV, Dimou E, Dimakopoulos K, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology* 2005; 42: 121-9.
21. Liaw Y, Sheen I, Lee C, Akarca U, Papatheodoridis GV, et al. Tenofovir disoproxil fumarate (TFV), emtricitabine/TFV, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology* 2011; 53: 62-72.
22. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; 52: 886-93.

23. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. *Am J Kidney Dis* 2005; 45: 804-17.
24. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; 354: 1001-10.
25. Yao FY, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. *J Hepatol* 2000; 33: 301-7.
26. Fontana RJ, Hann H-WL, Perrillo RP, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. *Gastroenterology* 2002; 123: 719-27.
27. Schiff ER, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology* 2003; 38: 1419-27.
28. Schiff E, Lai C, Hadziyannis S, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine resistant hepatitis B: final long-term results. *Liver Transplant* 2007; 13: 349-60.
29. Hadziyannis S, Tassopoulos N, Heathcote E, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *Gastroenterology* 2006; 131: 1741-51.
30. Leung N, Peng CY, Hann HW, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: a randomized international study of entecavir versus adefovir. *Hepatology* 2009; 49: 72-9.
31. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology* 2009; 49: 1503-14.
32. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; 52: 176-82.
33. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology* 2011; 54: 91-100.
34. Fontana RJ. Entecavir in decompensated HBV cirrhosis: the future is looking brighter. *J Hepatol* 2010; 52: 147-9.
35. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009; 50: 2001-6.

36. Kapoor D, Guptan RC, Wakil SM, et al. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. *Hepatology* 2000; 33: 308-12.
37. EASL clinical practice guidelines: Liver transplantation. *J Hepatol* 2016; 64: 433-85.
38. Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009; 29: 1294-305.
39. Dufour JF, Greten TF, Raymond E, et al. EASL – EORTC clinical practice guidelines : Management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908-43.
40. Mittal S, El-Serag HB. Epidemiology of HCC: consider the population. *J Clin Gastroenterol* 2013; 47: 1-10.
41. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA Cancer J Clin* 2008; 58: 71-96.
42. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; 118: 3030-44.
43. Bialecki E, Di Bisceglie A. Clinical presentation and natural course of hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2005; 17: 485-9.
44. Yang JD, Kim WR, Coelho R, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2011; 9: 64-70.
45. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; 127(5S1): S35-50.
46. Chen J De, Yang HI, Iloeje UH, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. *Gastroenterology* 2010; 138: 1747-54.
47. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; 45: 579-87.
48. Sung JJY, Tsoi KKF, Wong VWS, Li KCT, Chan HLY. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2008; 28: 1067-77.
49. Arends P, Sonneveld MJ, Zoutendijk R, et al. Entecavir treatment does not eliminate the risk of hepatocellular carcinoma in chronic hepatitis B: limited role for risk scores in Caucasians. *Gut* 2015; 64: 1289-95.

50. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003; 124: 327-34.
51. Cho JY, Paik YH, Sohn W, et al. Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. *Gut* 2014; 63: 1943-50.
52. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; 12: 568-74.
53. Papatheodoridis GV, Dalekos GN, Sypsa V, et al. PAGE-B: risk score for hepatocellular carcinoma (HCC) development in caucasian chronic hepatitis B (CHB) patients receiving entecavir (ETV) or tenofovir (TFV). *J Hepatol* 2014; 60: S361-522.
54. Liver Cancer Study Group of Japan. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: A retrospective and nationwide survey in Japan. *Hepatology* 2000; 32: 1224-9.
55. Liver Cancer Study Group of Japan. Predictive factors for long-term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. *Cancer* 1994; 74: 2772-80.
56. NHS Blood and Transplant Liver Advisory Group. Liver transplantation for hepatocellular carcinoma in the UK - report from a national consensus meeting (Birmingham Jan 2014).
57. NHS Blood and Transplant Liver Advisory Group. Liver transplantation: selection criteria and recipient registration. [odt.nhs.uk/pdf/liver\\_selection\\_policy.pdf](http://odt.nhs.uk/pdf/liver_selection_policy.pdf)
58. Llovet JM, Mas X, Aponte JJ, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. *Gut* 2002; 50: 123-8.
59. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including  $\alpha$ -fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; 143: 986-94.
60. Clavien P, Lesurtel M, Bossuyt P, Gores G, Langer BP. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; 13: 1-21.

## **5 HEPATITIS B AND OTHER (NON-LIVER) TRANSPLANTATION**

### **5.1 Introduction**

Hepatitis B virus (HBV) infection is a major risk factor for hepatic dysfunction in solid organ transplant (SOT) recipients. Immunosuppressive therapy used in the SOT setting can modify the natural history of HBV infection leading to progressive liver damage, including fulminant hepatitis, and resulting in significant morbidity and mortality. HBV infection can adversely impact post-transplant care as it may limit the use of further immunosuppressive agents. Diagnostic tests for the diagnosis and monitoring of HBV infection are widely available. There is mounting evidence that outcome of SOT recipients with chronic HBV (CHB) or past HBV infection can be improved with the use of nucleos(t)ide analogues antiviral drugs to prevent reactivation of HBV [1].

### **5.2 Impact of Transplantation on HBV**

Both the adaptive and innate immune responses are important for the control of HBV infection. Reactivation of HBV is well described in association with the use of immunosuppressive agents such as B-cell depleting agents (e.g. rituximab), anthracycline derivatives, TNF- $\alpha$  inhibitors, cytokine inhibitors and tyrosine kinase inhibitors [2]. The immunosuppressive therapy used in SOT can modify the natural history of HBV infection. Although specific cellular immunologic mechanisms are not fully understood, it is thought to be due to the disruption of the host immune response and possibly with enhanced replication of HBV mediated by some drugs.

In in vitro models, the effect of immunosuppressive agents on HBV replication varies with the class of agent. Ciclosporin has been shown to inhibit HBV replication by binding to mitochondrial cyclophilin and also by inhibiting the cellular entry of HBV by blocking sodium taurocholate co-transporting polypeptide (NTCP), a membrane transporter [3,4]. Although earlier studies reported mycophenolate to be an inhibitor of HBV replication, more recent studies have shown that the effect of mycophenolate may vary depending on the context of replication and that it may enhance HBV replication [5,6,7]. In a hydrodynamic injection mouse model, dexamethasone, ciclosporin and cyclophosphamide were shown to enhance HBV replication, whilst replication was terminated in mice treated with mycophenolate [8].

Rapamycin (an mTOR inhibitor) has been shown to enhance HBV production by inducing cellular autophagy [9]. The use of steroids can induce reactivation of HBV secondary to the stimulatory effect on the glucocorticoid-responsive enhancer region of the HBV genome [8,10,11].

In another in vitro study using HBV DNA-transfected hepatoma cells, prednisolone and azathioprine increased intracellular viral DNA and RNA levels by approximately two-fold and four-fold respectively, but treatment with ciclosporin did not alter the levels of viral RNA or DNA. However, a combination of all three immunosuppressive agents increased the level of intracellular viral DNA eightfold, indicating an additive effect [12]. This study demonstrates that the effect of individual drugs on HBV replication in vitro may not reflect the net effect when used in combination with other drugs. It must also be noted that in vitro studies do not take into account the suppressive effect of the drugs on the immune response against HBV in vivo, which is probably more crucial in controlling the replication. Overall, although some immunosuppressive drugs exhibit anti-HBV properties in vitro, when used in combination with other drugs in the SOT setting, they usually have a net immunosuppressive effect, thus promoting HBV replication.

### **5.3 Impact of HBV Infection on Transplant Outcome**

HBV infection is associated with more frequent and rapid progression to cirrhosis and hepatocellular carcinoma in SOT recipients, thus contributing to higher mortality. Hepatitis associated with HBV reactivation can lead to liver failure, especially in patients with cirrhosis. Before the introduction of antiviral prophylaxis, the rates of HBV reactivation after renal transplantation ranged from 50 to 94% [13,14,15]. A 10-year follow-up study during this era, found that survival in HBsAg positive renal transplant patients was inferior to uninfected patients ( $55 \pm 6\%$  vs.  $80 \pm 3\%$  respectively) [16]. In that study, HBsAg positivity was found to be an independent risk factor for survival following multivariate analysis. A meta-analysis of observational studies also found HBsAg positivity to be a risk factor for death in renal transplant recipients [17]. HBV may also cause de novo membranous glomerulonephritis, potentially impacting on renal function after transplantation.

With the advent of effective antiviral therapy, post-transplant patient and graft survival rates have improved dramatically. Recent studies in kidney and heart transplant recipients with CHB without cirrhosis have reported excellent outcomes with antiviral therapy alone [18,19].

In a recent study from Canada, HBV reactivation occurred in 4.1% of non-liver SOT patients with evidence of past HBV infection, with a median time to HBV reactivation of 4.7 years. The overall five-year survival was 82% in this cohort. HBV reactivation at five-years post-transplant was slightly higher in subjects without pre-transplant HBsAb when compared to those with pre-transplant HBsAb antibodies (5.1% vs 2.6% respectively) [20].

#### **5.4 Prevalence of HBV Infection in SOT**

The prevalence of chronic HBV infection (HBsAg positive, HBcAb positive) or past HBV infection (HBsAg negative, HBcAb positive) amongst SOT recipients varies according to geographical regions of the world, following a similar pattern to HBV prevalence in the general population. The prevalence of CHB has fallen worldwide since the introduction of HBV vaccination, systematic screening of blood products, and the institution of infection prevention and control measures, especially in those with end stage renal disease and in renal transplant recipients. However, the prevalence of HBV continues to be high in endemic regions (see chapter 3).

The prevalence of CHB in dialysis units in developing countries varies, with limited reports suggesting a wide variation ranging from 2% to 20%, whereas lower rates (0-10%) have been reported in dialysis patients from industrialised nations. An HBV prevalence of 12-20% has been reported in thoracic organ transplant recipients from Paris [21].

The prevalence of past HBV infection in the SOT setting is not well reported, but will be generally higher than that of CHB. The prevalence of HBV in different SOT settings in the UK is not known. All patients likely to require SOT must be screened for HBV infection at the earliest opportunity, ideally before the administration of blood products or immunosuppression.

#### **5.5 Risk of HBV Infection in the SOT Recipient**

The overall risk of HBV reactivation/de novo infection in a SOT recipient without antiviral treatment/prophylaxis is dependent upon the donor and recipient HBV status (Table 4). Reactivation of HBV in SOT recipients with high level HBs antibodies appears to be lower than those without HBs antibodies. However, HBV variants harbouring antibody escape mutations have been described in the setting of SOT, albeit rarely [22]. Thus, although high

**Table 4 Risk of reactivation of HBV according to donor and recipient serology**

<b>Donor</b>	<b>Recipient</b>	<b>Anti-HBS status</b>	<b>Risk of HBV infection/ reactivation in non-liver SOT without antiviral prophylaxis/treatment</b>
HBsAg negative anti-HBc negative	HBsAg negative anti-HBc negative	NA	No risk
HBsAg negative anti-HBc negative	HBsAg negative anti-HBc positive	anti-HBs positive anti-HBS negative	Low Moderate
HBsAg negative anti-HBc negative	HBsAg positive anti-HBc positive	NA	Very high
HBsAg negative anti-HBc positive	HBsAg negative anti-HBc negative	anti-HBs positive anti-HBs negative	Low Low
HBsAg negative anti-HBc positive	HBsAg negative anti-HBc positive	anti-HBs positive anti-HBs negative	Low - moderate Moderate - high
HBsAg negative anti-HBc positive	HBsAg positive anti-HBc positive	NA	Very high
HBsAg positive anti-HBc positive	HBsAg negative anti-HBc negative	anti-HBs positive anti-HBs negative	High Very high
HBsAg positive anti-HBc positive	HBsAg negative anti-HBc positive	anti-HBs positive anti-HBs negative	High Very high
HBsAg positive anti-HBc positive	HBsAg positive anti-HBc positive	NA	Highest

antibody titres may indicate protection against reactivation, breakthrough infection may occur. There can be variability in the quantitative HBsAb results obtained by different assays used in hospital laboratories where SOT patients are followed up. Hence post-transplant anti-HBsAb monitoring is not routinely recommended to predict the risk of reactivation.

## **5.6 Management of SOT Recipient with CHB or Past HBV**

CHBV and past HBV are not contraindications for solid organ transplantation. Although most of the existing data come from kidney transplantation, with the advent of effective antiviral therapy, other SOT can be safely carried out in patients with CHB or past HBV infection. Such patients must be referred to a specialist in viral hepatitis for full evaluation of the recipient including assessment of HBV status, targeted antiviral therapy or prophylaxis, and post-transplant follow-up. Specific management is covered elsewhere in this guideline.

## **5.7 Non-Liver SOT Recipients with Advanced Liver Disease**

Patients with advanced liver disease requiring transplantation of non-liver organs can experience hepatic decompensation following transplantation and need careful assessment by a multidisciplinary team including a liver specialist. Combined transplantation may be considered where appropriate [23].

## **5.8 Recommendations**

### ***We suggest that***

- Patients with advanced HBV-related liver disease requiring another organ transplant be considered for combined transplantation after careful consideration of the potential risks and benefits. (2C)

## **References**

1. Potthoff A, Tillmann HL, Bara C, et al. Improved outcome of chronic hepatitis B after heart transplantation by long-term antiviral therapy. *J Vir Hepatitis* 2006; 13: 734-41.

2. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute Technical review on prevention and treatment of hepatitis B virus. *Gastroenterology* 2015; 148: 221-4.
3. Xia WL, Shen Y, Zheng SS. Inhibitory effect of cyclosporine A on hepatitis B virus replication in vitro and its possible mechanisms. *Hepatobil Pancreat Dis Int* 2005; 4: 18-22.
4. Watashi K, Sluder A, Daito T, et al. Cyclosporin A and its analogues inhibit hepatitis B virus entry into cultured hepatocytes through targeting a membrane transporter, Sodium taurocholate co-transporting polypeptide (NTCP). *Hepatology* 2014; 59: 1726-37.
5. Gong ZJ, De Meyer S, Clarysse C, et al.: Mycophenolic acid, an immunosuppressive agent, inhibits HBV replication in vitro. *J Viral Hepat* 1999, 6: 229-36.
6. Hoppe-Seyler K, Sauer P, Lohrey C, Hoppe-Seyler F. The inhibitors of nucleotide biosynthesis leflunomide, FK778, and mycophenolic acid activate hepatitis B virus replication in vitro. *Hepatology* 2012; 56: 9-16.
7. Pan Q, van Vuuren AJ, van der Laan LJ, Peppelenbosch MP, Janssen HL. Antiviral or proviral action of mycophenolic acid in hepatitis B infection? *Hepatology* 2012; 56: 1586-7.
8. Wang J, Wang B, Huang S, et al. Immunosuppressive drugs modulate the replication of hepatitis B virus (HBV) in a hydrodynamic injection mouse model. *PLoS ONE* 2014; 9: e85832.
9. Huang W, Zhao F, Huang Y, Li X. Rapamycin enhances HBV production by inducing cellular autophagy. *Hepat Mon* 2014; 14: e20719.
10. Tur-Kaspa R, Burk RD, Shaul Y, et al. Hepatitis B virus DNA contains a glucocorticoid-responsive element. *Proc Natl Acad Sci USA* 1986, 83:1627-31.
11. Tur-Kaspa R, Shaul Y, Moore DD, et al. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. *Virology* 1988; 167: 630-3.
12. McMillan JS, Shaw T, Angus PW, Locarnini SA. Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro. *Hepatology* 1995; 22: 36-43.
13. Marcellin P, Giostra E, Martinot-Peignoux M, et al. Redevelopment of hepatitis B surface antigen after renal transplantation. *Gastroenterology* 1991; 100: 1432-4.
14. Dusheiko G, Song E, Bowyer S, Whitcutt M, et al. Natural history of hepatitis B virus infection in renal transplant recipients - a fifteen year follow-up. *Hepatology* 1983; 3: 330-6.

15. Park SK, Yang WS, Lee YS, et al. Outcome of renal transplantation in hepatitis B surface antigen-positive patients after introduction of lamivudine. *Nephrol Dial Transplant* 2001; 16: 2222-8.
16. Mathurin P, Mouquet C, Poynard T, et al. Impact of hepatitis B and C virus on kidney transplantation outcome. *Hepatology* 1999; 29: 257-63.
17. Fabrizi F, Martin P, Dixit V, Kanwal F, Dulai G. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005; 5: 2913-21.
18. Harmanci O, Ilin S, Ocal S, et al. The effect of hepatitis B virus on graft and overall survival in kidney transplant patients. *Exp Clin Transplant* 2015; 13 S3: 36-40.
19. Chen YC, Chuang MK, Chou NK, et al. Twenty-four year single center experience of hepatitis B virus infection in heart transplantation. *Transplant Proc* 2012; 44: 910-2.
20. Gonzalez A, Forouton F, Humar A, Husain S. Hepatitis B reactivation among non-liver solid organ transplant recipients [abstract]. *Am J Transplant* 2016; 16 (S3).
21. Lunel F, Cadranet JF, Rosenheim M, Dorent R, et al. Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. *Gastroenterology* 2000; 119: 1064-74.
22. Shields PL, Owsianka A, Carman WF, et al Selection of hepatitis B surface "escape" mutants during passive immune prophylaxis following liver transplantation: potential impact of genetic changes on polymerase protein function. *Gut* 1999; 45: 306-9.
23. Baccaro ME, Pépin MN, Guevara M, et al Combined liver-kidney transplantation in patients with cirrhosis and chronic kidney disease. *Nephrol Dial Transplant* 2010; 25: 2356-63.

## **6 PRE-TRANSPLANT MANAGEMENT OF HBV IN INDIVIDUALS BEING CONSIDERED FOR TRANSPLANTATION**

### **6.1 Liver Transplantation**

Since the implementation of oral antiviral agents and effective vaccination programmes, liver transplantation for decompensated hepatitis B (HBV) cirrhosis has become less common [1]. HCC complicating HBV remains a prevalent indication for liver transplantation (OLT) [2]. Patients presenting with decompensated cirrhosis from HBV may regain liver function with effective viral suppression, thus avoiding the need for transplantation [3,4]. The risk of recurrent HBV after OLT is low with effective viral suppression before transplantation [5].

The first line antiviral therapy for patients with decompensated cirrhosis is tenofovir or entecavir monotherapy, which are preferred due to their potency and high barrier to resistance [6]. Pegylated interferon (Peg-IFN) is contraindicated for patients with decompensated cirrhosis due to the risk of further decompensation and death [7]. In cases of previous resistance to lamivudine, tenofovir is the drug of choice; in cases of resistance to adefovir, entecavir is preferred [1]. Lactic acidosis has been reported with some NAs, particularly when treated with entecavir, and patients with advanced decompensated cirrhosis may be at high risk of this complication [8]. Close follow-up of laboratory and clinical status is necessary. Tenofovir and entecavir require dosing according to renal function [6].

The aim of NA treatment is to render the serum HBV DNA undetectable at the time of transplantation, which is associated with a reduced risk of post-transplant recurrence. For patients with advanced liver disease, NA therapy is frequently associated with improvement in liver function, which can lead to delisting for liver transplantation or reduced risk in association with non-liver transplantation.

### **6.2 Non-Liver Solid Organ Transplantation**

As part of the work up for non-liver solid organ transplantation, patients should be screened for hepatitis B carriage. If a patient is found to be HBsAg positive, staging should be pursued according to well established international guidelines [6]. Pre-transplant suppression for patients with HBsAg positive disease should be given with tenofovir or entecavir to avoid

progression of liver disease with immune suppression after transplantation [1]. Interferon therapy should be avoided. HBsAg negative patients with positive HBcAb should have HBV DNA monitored on immune suppression post-transplantation and receive suppression of active viraemia [9].

### 6.3 Recommendations

#### ***We recommend that:***

- All HBsAg positive individuals being considered for liver transplantation should be treated with either tenofovir or entecavir before transplantation, aiming for an undetectable HBV DNA level. (1B)
- Individuals undergoing non-liver solid organ transplantation who are HBsAg positive must have liver disease staging and suppression of HBV DNA by either tenofovir or entecavir before transplantation if there is a standard clinical indication. (1B)

#### **References**

1. EASL Clinical Practice Guidelines. Liver transplantation. J Hepatol 2015; 64:433-85.
2. Kennedy M, Alexopoulos SP. Hepatitis B virus infection and liver transplantation. Curr Opin Organ Transplant 2010; 15: 310-5.
3. Schiff E, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. Liver Transpl 2007; 13: 349-60.
4. Kapoor D, Guptan RC, Wakil SM, et al. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. J Hepatol 2000; 33: 308-12.
5. Fung J, Cheung C, Chan SC, Yuen MF, Chok KS, Sharr W. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology 2011; 141: 1212-9.
6. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-98.
7. AASLD Guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261-83.

8. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009; 50: 2001-6.
9. Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, Burra P. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 2007; 39: 397-408.

## **7 USE OF HBCAB ANTIBODY POSITIVE OR HBSAG POSITIVE DONORS IN SOLID ORGAN TRANSPLANTATION**

### **7.1 Introduction**

A significant number of UK organ donors will have serological evidence of past HBV infection, with antibodies to the HBV core antigen (HBcAb or core antibodies). In addition, a proportion of core antibody positive donors will also have detectable antibodies (HBsAb) to the HBV surface antigen (HBsAg). It is recognised that the use of solid organs from donors with core antibodies (in the absence of HBsAg and regardless of the presence or absence of HBsAb) can transmit HBV infection to the organ recipient. The risk of transmission is very high for liver transplantation and much lower for transplantation of kidneys and thoracic organs. Transmission of infection is associated with the development of recipient HBsAg positivity, with an almost inevitable progression to chronic infection, and with high levels of HBV viral replication (typically serum HBeAg positivity with high titres of HBV DNA). This transmission has been called *de novo* HBV infection.

A much smaller number (<1%) of UK organ donors will be serum HBsAg positive. There is a smaller and emerging literature to describe recipient outcomes after the use of solid organs from donors who are HBsAg positive. There is sufficient evidence to provide confidence that nearly all solid organs from donors who are core antibody positive, whether HBsAg is negative or positive, can and should be used for transplantation.

The complete and appropriate use of these organs requires a knowledge of the HBV status of the potential recipient(s), an up-to-date understanding of the appropriate donor-recipient matching, and an understanding of the role (if any) of post-transplant anti-HBV prophylaxis.

In general, the management principles for kidney recipients and thoracic organ recipients are identical. However, the published experience of HBV in renal transplantation is significantly larger than for cardiac transplantation, and the smallest published evidence is for lung transplantation.

The following discussion will consider four settings:

1. Core antibody positive donors for liver recipients.
2. HBsAg positive donors for liver recipients.

3. Core antibody positive donors for non-liver solid organ recipients.
4. HBsAg positive donors for non-liver solid organ recipients.

## General Recommendations

### ***We suggest that:***

- The appropriate matching of an organ recipient with a donor positive for HBsAg or HBcAb should be discussed with a specialist in viral hepatitis. (2C)
- All potential recipients should be counselled during the assessment process about the possibility of receiving a liver from a donor with past or current HBV infection. (Not graded)

## 7.2 Core Antibody Positive Donation for Liver Recipients

De novo HBV infection denotes the development in the recipient of serum HBsAg positivity, and is associated with the use of core antibody positive liver donation, regardless of the HBsAb donor status. The risk of de novo infection appears dependent to a large extent on the recipient's HBV immune status. The highest risk for de novo infection is observed when the recipient is HBV-naïve, lacking markers of prior HBV exposure. In this setting and in the absence of post-transplant prophylaxis, HBsAg seroconversion will occur in more than 50% (perhaps as high as 80%) of cases.

Large published series provide data about the risk of de novo infection in HBV immune liver recipients [1,2]. Recipients with HBcAb in the absence of HBsAb have a risk of between 10% and 20% that is not significantly different from those with vaccine-induced immunity. The lowest risk is observed for recipients with both HBcAb and HBsAb, where de novo infection occurs in fewer than 10% of recipients. Prophylaxis from the time of liver transplantation can reduce the risk of de novo infection [3,4].

The ideal recipient of the core antibody positive donation is the HBsAg positive recipient. Such a recipient will receive prophylaxis to prevent graft *reinfection* by HBV, and the same prophylaxis will prevent de novo infection. An additional advantage of this donor-recipient match is that passenger donor lymphocytes will produce HBsAb in response to recipient circulating HBsAg [5]. Thus, for those patients treated by protocols that use hepatitis B immunoglobulin (HBIG) as part of the strategy to prevent graft reinfection, the use of a core

antibody positive donor is associated with a significantly reduced requirement for HBIg during the months after transplantation.

The above stated, the rate of transplantation for HBV-related indications is diminishing, so a suitable HBsAg positive recipient may be lacking. Thus, most core antibody positive donations will be used for recipients who are HBsAg negative. Indeed, factors other than recipient HBV immune status are likely to determine the choice of organ recipient.

Published series demonstrate the potential for antiviral prophylaxis to reduce the risk of de novo infection. Most series have examined the use of lamivudine, HBIg or the combination to reduce the risk of de novo infection. Based on historical comparison data, the use of prophylaxis is associated with a substantial reduction, though not a complete elimination, of de novo infection. Lamivudine is the most cost-effective approach to prophylaxis, prevents most de novo infection [6,7], and should be given indefinitely after liver transplantation. De novo infection can be observed with non-adherence to lamivudine (including the premature discontinuation by physicians), but is also occasionally observed despite adherence (as indicated by the emergence of HBV with lamivudine resistance mutations). The preferred treatment of de novo infection is with tenofovir and the stopping of lamivudine.

## **Recommendations**

### ***We recommend that:***

- The HBcAb positive (HBsAg negative) donor liver can be used for any potential liver recipient. (1C)
- When the liver comes from a hepatitis B core antibody positive donor and is given to an HBsAg positive recipient, the standard approach to prevent HBV reactivation should be adopted. (1B)
- When the liver comes from a HBcAb positive donor and is given to a HBV immune or non-immune recipient, prophylactic lamivudine should be given from the time of transplantation, and should be continued indefinitely. (1A)

### ***We suggest that***

- If other waiting list priorities permit, the hepatitis B core antibody positive donor liver should be allocated in the following order:

1. the HBsAg-positive recipient
2. the HBV-immune recipient (including both naturally immune and vaccine-induced immunity)
3. the HBV non-immune recipient. (2C)

### **7.3 HBsAg Positive Donation for Liver Recipients**

HBsAg positive liver donation may be considered for any recipient, including non-immune HBsAg negative recipients. This is possible because antiviral treatment with entecavir or tenofovir can reliably suppress HBV replication to prevent HBV-related liver disease in the recipient after liver transplantation.

When considering the use of the liver from an HBsAg positive donor, the transplant surgeon should be confident that the liver does not have significant HBV-related fibrotic damage. The donor HDV status will typically be unknown at the time of donor assessment. If known, HBV/HDV co-infected livers should not be used.

Most published experience describes the use of HBsAg positive donor livers for HBsAg positive recipients. In this setting, there will be persisting and long-term serum HBsAg positivity in the recipient [8]. The use of oral antivirals (entecavir or tenofovir) from the time of transplantation will prevent HBV-related graft damage, and should be continued indefinitely. The use of HBIg from the time of liver transplantation seldom achieves serum HBsAg negativity, so its use is not recommended. It is essential that the HDV (delta virus) status of HBsAg positive waiting list patients is documented. HBsAg positive donation is not suitable for the HBV/HDV co-infected recipient. In this case, delta virus superinfection of the HBV positive donor liver will be observed [9,10]. There is no suitable treatment for HBV/HDV infection post-transplant, and cases of rapid progression to cirrhosis have been described. HBV/HDV liver recipients must receive HBsAg negative donor livers.

The HBsAg positive liver can be used for the HBV-immune liver recipient. Most protocols require the use of antivirals in the recipient, and HBsAg clearance is usually observed during follow-up, presumably reflecting an effective persistence of the immune response to HBV despite immunosuppression. Indeed, the HBV-immune recipient may be the preferred recipient of an HBsAg positive liver donation [11].

## Recommendations

### *We recommend that:*

- HBsAg positive donor livers can be given to HBsAg positive recipients as long as the recipient is known to be HDV negative. (1C)
- If urgency demands, the HBsAg positive liver can be given to an HBsAg negative patient. (1D)
- All recipients of a liver from an HBsAg positive donor must be treated with entecavir or tenofovir from the time of transplantation. (1B)
- Use of HBIg rarely achieves HBsAg negativity, and is not recommended. (1C)

### **7.4 Core Antibody Positive Donation for Non-Liver Solid Organ Recipients**

Donation of non-liver solid organs from the core antibody positive donor is rarely associated with de novo infection of the recipient. Though serological signs of HBV infection may be documented (such as the development of HBcAb in a non-immune recipient), serum HBsAg seroconversion (de novo infection) is seldom observed. One review of core antibody positive donation to a large number of renal transplant recipients found that 45/1385 (3.2%) developed new HBV serological markers, but HBsAg seroconversion was seen in only four (0.28%) patients [12]. With such a low risk for de novo infection, it is hard to demonstrate a benefit of antiviral prophylaxis. Pre-transplant recipient HBV immunity appears to protect against de novo infection.

### **7.5 HBsAg Positive Donation for Non-Liver Recipients**

The donation of non-liver solid organs from an HBsAg positive donor to an HBsAg positive recipient can be undertaken as long as antivirals are used to suppress HBV after transplantation. In this setting, there appears to be no adverse impact on graft or patient survival.

There is a significant published literature describing the outcome of HBsAg positive kidney donation to HBV immune recipients [13-15]. In the majority of cases, antiviral prophylaxis has been given after transplantation. Chronic HBV infection appears to be an infrequent outcome, and the need for post-transplant antiviral treatment is not clearly established. If

antivirals are not used or if antivirals are stopped after a period of prophylaxis, the recipient should receive long-term monitoring for the appearance of HBsAg.

Transplantation of a non-liver solid organ from an HBsAg positive donor to a non-immune recipient will result in chronic infection of the recipient. In this setting, antivirals should be given to prevent HBV-related liver damage (see chapter 9 for more detailed discussion).

## Recommendations

### *We recommend that:*

- The kidneys, heart and lungs from the HBcAb positive organ donor can be used for any recipient, and the risk of de novo HBV infection is low. (1A)

### *We suggest that:*

- If need demands, the non-liver solid organs of the HBsAg positive organ donor can be used for any recipient, after an individualised assessment of risk and benefit. (2C)
- When a HBcAb positive donor is used, lamivudine prophylaxis may be given for six months after transplantation, although the risk of transmission is very low. (2C)

## References

1. Nery JR, Nery-Avila C, Reddy KR, et al. Use of liver grafts from donors positive for antihepatitis B core antibody in the era of prophylaxis with hepatitis B immunoglobulin and lamivudine. *Transplantation* 2003; 75: 1179-862.
2. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from antihepatitis B core positive donors: a systematic review. *J Hepatol* 2010; 52: 272-9.
3. Terrault NA, Zhou S, Combs C, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. *Hepatology* 1996; 24: 1327-33.
4. Tabor E. Infections by hepatitis B surface antigen gene mutants in Europe and North America. *J Med Virol* 2006; 78 (S1): S43-7.
5. Lo CM, Fury JT, Lau GK, et al. Development of antibody to hepatitis B surface antigen after liver transplantation for chronic hepatitis B. *Hepatology* 2003; 37: 36-43.
6. Saab S, Waterman B, Chi AC, Tong MJ. Comparison of different immunoprophylaxis regimens after liver transplantation with hepatitis B core antibody positive donors: a systematic review. *Liver Transpl* 2010; 16: 300-7.

7. Mutimer DJ. Prevention of de novo hepatitis B infections: more seems no better. *Liver Transpl* 2010; 16: 256-8.
8. Loggi E, Conti F, Cuchetti A, et al. Liver grafts from hepatitis B surface antigen positive donors: a review of the literature. *World J Gastroenterol* 2016; 22: 8010-6.
9. Franchello A, Ghisetti V, Marzano A, et al. Transplantation of HBsAg positive livers into hepatitis B positive recipients and the role of hepatitis delta co-infection. *Liver Transpl* 2005; 11: 922-8.
10. Bahde R, Holzen JP, Wolters HH, et al. Course of a HBsAg positive liver transplantation in a hepatitis B and D virus co-infected recipient. *Ann Hepatol* 2011; 10: 355-60.
11. Loggi E, Bihl F, Chisolm JV, et al. AntiHBs re-seroconversion after liver transplantation in a patient with past HBV infection receiving a HBsAg positive graft. *J Hepatol* 2009; 50: 625-30.
12. Mahboobi N, Tabatabaei SV, Blum HE, et al. Renal grafts from anti hepatitis B core positive donors. A quantitative review of the literature. *Transpl Infect Dis* 2013; 14: 445-51.
13. Pilmore HL, Gane EJ. Hepatitis B positive donors in renal transplantation: increasing the deceased donor pool. *Transplantation* 2012; 94: 205-10.
14. Simethkul V, Ingsathit A, Jirasiritham S. 10 year follow-up of kidney transplantation from hepatitis B surface antigen positive donors. *Transplant Proc* 2009; 41: 213-5.
15. Jiang H, Wu J, Zhang X, et al. Kidney transplantation from hepatitis B surface antigen positive donors into hepatitis B surface antibody recipients: a prospective non-randomised controlled study from a single centre. *Am J Transplant* 2009; 9: 1853-8.

## **8 MANAGEMENT OF CO-INFECTION (HDV, HCV, HIV) IN THE LIVER TRANSPLANT RECIPIENT**

### **8.1 Management of HBV/HDV Co-Infection**

The prevalence of HDV infection in Western Europe, including the United Kingdom, is relatively low. Up to 10% of chronic HBV infections in the UK will be complicated by HDV co-infection, and the majority of infected patients are first generation migrants from parts of the world where delta virus co-infection is endemic.

HBV/HDV infection is typically associated with an aggressive chronic hepatitis with progression to cirrhosis and liver failure. HBV replication is relatively suppressed, so the majority of co-infected patients will be HBeAg negative with relatively low levels of serum HBV DNA. The only available antiviral therapy for HBV/HDV co-infection is alpha interferon, but response rates are disappointing, and are further reduced in patients with cirrhosis. HDV/HDV infection is unresponsive to treatment with nucleoside analogues.

Before the availability of effective oral antiviral treatment as a component of post-transplant HBV prophylaxis, the early experience with hepatitis B immunoglobulin (HBIg) showed that HBIg administration, sustained indefinitely after transplantation, was particularly effective for the prevention of post-transplant serum HBsAg recurrence in HDV co-infected patients. Samuel and colleagues reported excellent results of HBIg prophylaxis against disease recurrence for HBV/HDV co-infected recipients [1]. In their series, five-year patient survival was 88% and only 10% of patients experienced HBsAg recurrence.

Much of the data describing the pathology and outcome of HBV/HDV precedes the availability of nucleoside analogues, and from a period when delta virus co-infection of the indigenous European population was much more prevalent. Subsequently, as background delta virus infection diminished, we have seen for HBV the introduction and use of nucleoside analogues, with or without routine use of HBIg, and eventually the development of strategies for HBIg withdrawal from combination nucleoside/HBIg regimens.

Remarkably, the delta virus status of the many and large cohorts of HBV patients who have been exposed to these various strategies for HBV prophylaxis have not routinely been reported. One recent study reported that HBIg withdrawal from combination HBIg/nucleoside

prophylaxis was achieved without serum HBsAg recurrence in 32/34 HBV/HDV patients [2]. Recurrent infection was associated with a shorter duration of combination prophylaxis prior to HBIg withdrawal. This failure rate and its association with short duration of HBIg exposure are consistent with the observations of Mederacke and colleagues [3]. They examined blood and liver biopsy tissue from a cohort of patients transplanted for HBV/HDV co-infection. They found that delta antigen was expressed in the liver, in the absence of peripheral blood HDV RNA detection, and for as long as 18 months after transplantation.

As a consequence of the limited literature, the efficacy of HBIg-free or HBIg withdrawal strategies for the prevention of recurrent HBV/HDV infection cannot be concluded with confidence. The low failure rate, in unselected HBV patients, of these recent and popular strategies implies that HBV/HDV relapse is rarely observed. Nevertheless, HBIg-containing protocols, in comparison with nucleoside only protocols, achieve more rapid post-transplant clearance of HBsAg from serum and may be critical for the prevention of HBV/HDV recurrence. One review has recommended that HDV-infected liver recipients should receive antiviral prophylaxis that includes the use of HBIg from time of transplantation for a period of 12 to 24 months [4].

There is no proven effective treatment for recurrent (or acquired) graft HBV/HDV infection, and rapid progression to cirrhosis is likely.

## **8.2 Management of HBV/HCV Co-Infection**

An up-to-date discussion of HCV treatment with direct acting antivirals (DAAs) is beyond the scope of this guideline. The majority of HCV-infected potential liver transplant recipients will be successfully treated with DAAs before or following liver transplantation.

HBV antiviral protocols for the management of HBV infection in the recipient, and protocols for the use of core antibody positive or HBsAg positive donations are unaffected by the presence of HCV co-infection.

## **8.3 Management of HBV/HIV Co-Infection**

The management of HBV/HIV co-infection has been transformed by the availability of tenofovir which provides potent monotherapy against HBV infection, and is also a frequent

component of combination antiretroviral therapy. Thus, the majority of co-infected patients will have undetectable HIV RNA and undetectable HBV DNA at the time of liver transplantation. Indeed, sustained and potent inhibition of HBV replication means that the majority of co-infected patients have primary liver cancer on a background of well compensated cirrhosis as the indication for liver transplantation.

Protocols for the peri-operative management of the HIV infection vary between liver transplant units, though the majority require temporary suspension of the HIV antivirals. HIV antivirals are typically reintroduced when gut and renal function have been stabilised/restored after transplantation. This approach minimises the potential for partial and inadequate treatment of the HIV during a period when gut absorption and renal clearance of the components of the HIV antiviral treatment may be unpredictable.

The use of HBIg from the time of transplantation can provide adequate HBV antiviral prophylaxis during the planned suspension of the HIV antivirals (including tenofovir). Subsequently, the management of the HBV antiviral prophylaxis can be managed according to the local protocol for HBV mono-infection. If, at any stage post-transplant, it is necessary to stop the tenofovir component of the HIV regimen, then the approach to HBV prophylaxis must also be revised. Options would include the introduction of entecavir.

## **8.4 Recommendations**

### ***We recommend that:***

- HBV/HDV recipients should receive combination HBIg/NA prophylaxis from the time of transplantation. (1C)
- HBsAg positive donors should not be used for HBV/HDV co-infected recipients. (1C)
- A plan for the peri-operative management of each of the HIV and HBV infections should be agreed by the multidisciplinary team before transplantation. (1D)
- HBIg could be used as HBV prophylaxis if/when HIV antivirals are suspended in the perioperative period. After HIV antiviral treatment is re-established, the approach to HBV prophylaxis is no different from that used for transplantation of HBV mono-infection. (1C)

***We suggest that:***

- For HBV/HDV infected recipients HBIg withdrawal from combination HBIg/NA prophylaxis can be considered, but not within 24 months of transplantation. (2C)

**References**

1. Samuel D, Zignego AL, Reynes M, et al. Long-term clinical and virological outcome after liver transplantation for cirrhosis caused by chronic delta hepatitis. *Hepatology* 1995; 21: 333-9.
2. Cholongitas E, Goullis I, Antoniadis N, et al. Nucleoside analogue prophylaxis after HBIg withdrawal against hepatitis B and D recurrence after liver transplantation. *Transpl Infect Dis* 2016; 18: 667-73.
3. Mederacke I, Filmann N, Yurdaydin C, et al. Rapid early decline in the peripheral blood but prolonged intrahepatic hepatitis delta antigen persistence after liver transplantation. *J Hepatology* 2012; 56: 115-22.
4. Roche B, Samuel D. Liver transplantation in delta virus infection. *Sem Liver Dis* 2012; 32: 245-55.

## **9 PREVENTING RECURRENCE OF HBV POST-TRANSPLANTATION**

### **9.1 Introduction**

Hepatitis B virus (HBV) recurrence after liver transplantation is defined as the reappearance of circulating hepatitis B surface antigen (HBsAg), with or without detectable HBV DNA. Without appropriate prophylactic treatment, HBV recurrence is almost universal [1]. In the era before prophylaxis, HBV recurrence resulted in poor graft and patient survival; in one report, 20% of patients suffered graft loss within six weeks due to HBV recurrence and another reported mean patient survival to be 12 months [1,2]. HBV-related liver disease was considered to be a relative, if not absolute, contraindication to transplantation [3]. However, with the introduction of post-transplant prophylactic treatment with hepatitis B immunoglobulin (HBIG) and more recently nucleos(t)ide analogues (NA), graft reinfection rates have reduced to <10% and HBV-related liver disease is now a well-accepted indication for liver transplantation [4]. All of the major international liver disease associations have guidelines for the prevention of HBV recurrence after transplantation [5-8].

In transplant recipients with serological evidence of past exposure to HBV, consideration also needs to be given to potential reactivation of hepatitis B in the immunosuppressed post-transplant state and prophylactic treatment is usually indicated [9].

The following sections present recommendations for the prevention of hepatitis B recurrence in the specific patient groups along with the rationale behind the recommendations.

### **9.2 Hepatitis B Surface Antigen Positive Recipients**

The prevention of post-transplant HBV recurrence in HBsAg positive patients begins before transplantation. The HBV DNA viral load at the time of transplantation is a key determinant in the risk of HBV recurrence with studies showing a direct linear correlation [10]. All patients on the transplant waiting list should therefore be treated with antivirals with the aim of achieving an undetectable HBV DNA level [5-7]. First line antiviral treatments are the potent nucleos(t)ide analogues (NA) such as entecavir or tenofovir (TFV), which have very low rates of resistance (<1%) as well as optimal safety profiles [11,12]. Their efficacy and safety

in patients with decompensated cirrhosis has been well documented [13-15]. In comparison, interferon is absolutely contraindicated in patients with cirrhosis due to an increased risk of infection and hepatic decompensation [6,7]. Patients on the waiting list with HBV-related hepatocellular carcinoma, with or without cirrhosis, are considered by some as high risk for recurrence and should also be treated with NAs [16]. It is important to note that this finding has not been replicated in other studies and was conducted in the era of lamivudine and adefovir.

Following transplantation, prophylactic treatment of HBV recurrence should be with a combination of HBIG and NA antivirals [5-8]. The early studies using HBIG monotherapy demonstrated good graft and patient survival with recurrence rates falling from 75% to 33% and patient 3-year survival improving from 53% to 83% [1]. However, long-term HBIG monotherapy was problematic: the need for indefinite therapy with frequent infusions to maintain high HBsAb levels resulted in high costs; there were problems with local and systemic side effects; and HBV mutants resistant to HBIG emerged [17]. The advent of effective NA therapy allowed more efficient combination treatment with synergistic effects and better tolerability.

Combination therapy with NA antivirals is therefore currently recommended, with evidence summarised in several meta-analyses and systematic reviews [17-20]. The specific HBIG regimen used in combination varies between centres but typically consists of an intravenous dose, typically 5000-10000 IU in the anhepatic phase and then immediately post-transplant (for example 5000 IU/day on alternate days for one week). This is followed by intermittent low doses either at fixed intervals or at a frequency dictated by hepatitis B surface antibody (HBsAb) levels, usually to maintain levels at  $\geq 50$ -100 IU/L [6,21]. Alternative routes of HBIG administration such as intramuscular and subcutaneous low doses are now accepted as strategies to reduce cost and side effects [22,23]. Alongside HBIG, the NA of choice is recommended as TFV or ETC, again for their potency and high genetic barrier to resistance, as well as good short- and long-term safety profiles [24]. The potential bone and renal toxicity of TFV has been well described, although the clinical significance of this is debatable [25,26]. On-treatment monitoring of renal function and bone profile is recommended.

For patients defined as being at low risk of HBV recurrence, i.e. e antigen negative and HBV DNA negative at time of transplant, early HBIG withdrawal and maintenance with NA monotherapy can be considered (Table 1). Several studies have shown this strategy to be effective and safe, with comparably low rates of recurrence of 9-14% even in the long-term (up to 91 months) [27-29]. Lamivudine and adefovir have been studied in this context,

although single-centre experience also exists for the more potent NA [30]. NA monotherapy prophylaxis was traditionally not thought to be appropriate for high-risk patients such as patients with detectable HBV DNA at the time of transplantation and those with HCC. The latter finding comes from a single centre study and some of the dogma surrounding the use of HBIG post-liver transplantation has recently been challenged by a large series of patients from Hong Kong [31]. In this study 265 consecutive patients transplanted for hepatitis B were treated with entecavir monotherapy without HBIG. The rates of HBsAg positivity were 15%, 12%, 13% and 8% at 1, 3, 5 and 8 years respectively. Perhaps more importantly, 95%, 99%, 100% and 100% of patients had undetectable HBV DNA at the same assessed time points. There was no significant difference in liver stiffness between those who were HBsAg positive and those who were HBsAg negative and there were no deaths from hepatitis B recurrence. Six patients had additional therapy with tenofovir. It would seem that the presence of HCC at the time of transplant was not a risk factor for HBsAg positivity in this study. Therefore, HBIG-free NA prophylaxis can be considered in low risk recipients.

Although HBV/HDV co-infected patients have been shown to have reduced rates of HBV recurrence [1], there are very limited treatment options for delta hepatitis and thus HBV/HDV co-infected patients are often managed as high risk [32]. In these patients, HBIG prophylaxis should continue for longer (see chapter 8) [6,8]. A similar approach in HIV/HBV co-infected patients is recommended in some guidelines; outcomes using combination prophylaxis have been reported to be very good [33]. However, more robust evidence is not available.

### **9.3 Hepatitis B Core Antibody Positive Recipients**

Hepatitis B core antibody (HBcAb) positivity, with or without HBsAb, with negative HBsAg and negative HBV DNA is indicative of past HBV infection. Although such patients have undetectable serum HBV DNA, HBV persists in the liver with replication controlled by the immune system [34,35]. When the immune system is therapeutically suppressed in the context of non-liver solid organ transplantation, there is potential for HBV reactivation. This can present as a range of clinical manifestations from asymptomatic reappearance of HBV DNA or HBsAg (so called reverse seroconversion), through acute hepatitis to liver failure and even death [36]. These patients therefore need particular consideration post-transplant. HBcAb positivity may also be suggestive of occult HBV infection, with negative HBsAg but detectable HBV DNA in serum. Following liver transplantation, patients with occult HBV infection should be managed in the same way as HBsAg positive patients.

For patients with serological evidence of past infection, the risk of HBV reactivation has been best studied in recipients of kidney transplantation and is estimated at 1-5% [37,38]. There is also a large body of work describing the risk of HBV reactivation in other immunosuppressed states such as prolonged steroid use, chemotherapy for cancer, and with other immunomodulatory agents such as rituximab [39-41]. There are no studies specifically focused on the risk post-liver transplant and therefore the management of these patients has been extrapolated from other areas [42]. In general, there is evidence for prophylactic treatment, with lamivudine being the most studied; a systematic review concluded a risk reduction of 79-100% [43]. Entecavir has also been studied with good efficacy in the setting of rituximab treatment [44]. Conversely, there is also an argument for close monitoring without prophylaxis, and only starting treatment if reactivation is confirmed (HBsAg positivity and/or detectable HBV DNA) [6,42]. Although this strategy may be more cost-effective, it requires very close follow-up of patients with regular hepatitis B serological testing. Moreover, in the context of liver transplantation, the acquisition of a hepatotropic virus infection may be clinically more significant.

#### **9.4 Hepatitis B Core Antibody Positive Donors**

The use of organs from donors with evidence of previous HBV exposure has become commonplace as a safe way of expanding the donor organ pool [45,46]. In HBV naïve recipients, however, there is a significant risk of de novo hepatitis B, especially following liver transplantation with HBcAb positive donors; the risk is estimated to be 48-58% [46,47]. This risk is reduced to 18% with recipient vaccination against HBV before transplantation, but remains significant [47]. Prophylactic antiviral treatment is therefore indicated, with lamivudine being the most widely used [48]. In one systematic review, this has been shown to reduce the risk of de novo hepatitis B from 58% to 11% in naïve recipients, and 18% to 2% in vaccinated recipients [46]. In a single centre report, no cases of de novo hepatitis B were seen in 45 patients treated with lamivudine over a median follow-up period of 32 months [49]. Combined therapy with HBIG has been used in some centres but has not been shown to confer significant additional benefit [50], and the newer NA antivirals such as entecavir and TFV are less cost-effective than lamivudine in the long-term [51].

HBcAb positive organs are also used in other non-liver transplantation such as kidney or heart. The risk of de novo hepatitis B in these patients is thought to be less, at up to 27% in kidney transplants and around 3% in heart/lung transplants [52,53]. Pre-transplant vaccination against HBV potentially offers enough protection, although some centres use

lamivudine prophylaxis for up to one year post-transplant [45].

## **9.5 Hepatitis B Surface Antigen Positive Donors**

Organs from donors chronically infected with HBV are not routinely used at present. However, single-centre case series exist of HBsAg positive donor livers used either in patients who are HBsAg positive with HBV-related liver disease or in HBcAb positive recipients [54,55]. In these cases, HBV recurrence is 100% and there is persistence of HBsAg. However, in some reports, following adequate antiviral treatment plus HBIG, there were no differences in graft or patient survival and no episodes of graft dysfunction attributable to HBV persistence [55]. There is also the precedent of using HBsAg positive kidneys in patients with HBsAb immunity, showing good graft and patient survival using a combination of HBIG and lamivudine prophylaxis [56]. In carefully selected patients with appropriate consent, the use of HBsAg positive donor organs may be a useful strategy to further expand the donor pool.

## **9.6 Recommendations**

### ***We recommend that:***

- In HBsAg positive individuals deemed to be at high risk of recurrence, combination therapy with HBIG and/or a potent NA is recommended from the time of transplantation to prevent HBV reinfection post-liver transplant. (1B)

### ***We suggest that:***

- Early withdrawal of HBIG or even the use of HBIG-free prophylaxis can be considered in recipients who are at low risk for post-transplant HBV recurrence. (2C)
- Life-long combination therapy with HBIG and a potent NA can potentially be given to patients who were traditionally considered at high risk for HBV recurrence; namely those who are HBV DNA positive at time of transplant, HBeAg positive patients, those transplanted for hepatocellular carcinoma, or those who are HIV co-infected; although most of the data supporting use in these groups come from retrospective studies in the lamivudine era. (2B)

- Recipients with evidence of past HBV infection (HBcAb positive alone) are at risk of HBV reactivation post-non-liver transplant and could be considered for prophylactic antiviral treatment; although monitoring for HBV recurrence is an equally acceptable strategy. (2B)

## References

1. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993; 329: 1842-7.
2. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. *J Hepatol* 1992; 14: 104-11.
3. Eason JD, Freeman RB Jr, Rohrer RJ, et al. Should liver transplantation be performed for patients with hepatitis B? *Transplantation* 1994; 57: 1588-93.
4. Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009; 29: 1294-1305.
5. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl* 2013; 19: 3-26.
6. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; 10: 1-98.
7. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017; 67: 370-398.
8. EASL clinical practice guidelines: liver transplantation. *J Hepatol* 2016; 64: 433-85.
9. Hwang JP, Lok AS-F. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014; 11: 209-19.
10. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and the risk of hepatitis B virus recurrence. *Liver Transpl* 2005; 11: 402-9.
11. Chang TT, Lai CL, Kew Loon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010; 51: 422-30.
12. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; 381: 468-75.
13. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; 52: 176-82.

14. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TFV), emtricitabine/TFV, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology* 2011; 53: 62-72.
15. Jan JW, Choi JY, Kim YS, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. *Hepatology* 2015; 61: 1809-20.
16. Faria LC, Gigou M, Roque-Afonso AM, et al. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. *Gastroenterology* 2008; 134: 1890-9.
17. Loomba R, Rowley AK, Wesley R, et al. Hepatitis B immunoglobulin and lamivudine improve hepatitis B-related outcomes after liver transplantation: meta-analysis. *Clin Gastro Hep* 2008; 6: 696-700.
18. Rao W, Wu X, Xiu D. Lamivudine or lamivudine combined with hepatitis B immunoglobulin in prophylaxis of hepatitis B recurrence after liver transplantation: a meta-analysis. *Transpl Int* 2009; 22: 387-94.
19. Katz LH, Paul M, Guy DG, Tur-Kaspa R. Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. *Transpl Infect Dis* 2010; 12: 292-308.
20. Cholangitas E, Goulis J, Akriviadis E, Papatheodoridis GV. Hepatitis B immunoglobulin and/or nucleos(t)ide analogues for prophylaxis against hepatitis B virus recurrence after liver transplantation: a systematic review. *Liver Transpl* 2011; 17: 1176-90.
21. Jiang L, Yan L, Li B, et al. Prophylaxis against hepatitis B recurrence post-transplantation using lamivudine and individualised low-dose hepatitis B immunoglobulin. *Am J Transplant* 2010; 10: 1861-9.
22. Gane EJ, Angus PW, Strasser S, et al. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following live transplantation. *Gastroenterology* 2007; 132: 931-7.
23. De Simone P, Romagnoli R, Tandoi F, et al. Early introduction of subcutaneous hepatitis B immunoglobulin following liver transplantation for hepatitis B virus infection: a prospective, multicentre study. *Transplantation* 2016; 100: 1507-12.
24. Cholangitas E, Papatheodoridis GV. High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. *Am J Transplant* 2013; 13: 353-62.
25. Woodward CL, Hall AM, Williams IG, et al. Tenofovir-associated renal and bone toxicity. *HIV Med* 2009; 10: 482-7.
26. Lampertico P, Chan HL, Janssen HL, Strasser SI, Schindler R, Berg T. Review article:

- long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. *Aliment Pharmacol Ther* 2016; 44: 16-34.
27. Yuefeng M, Weili F, Wenxiang T, et al. Long-term outcome of patients with lamivudine after early cessation of hepatitis B immunoglobulin for prevention of recurrent hepatitis B following liver transplantation. *Clin Transplant* 2011; 25: 517-22.
  28. Wong SN, Chu CJ, Wai CT, et al. Low risk of hepatitis B recurrence after withdrawal of long-term hepatitis B immunoglobulin in patients receiving maintenance nucleos(t)ide analogue therapy. *Liver Transpl* 2007; 13: 374-81.
  29. Buti M, Mas A, Prieto M, et al. A randomized study comparing lamivudine monotherapy after a short course of hepatitis B immune globulin (HBIG) and lamivudine with long-term lamivudine plus HBIG in the prevention of hepatitis B virus recurrence after liver transplantation. *J Hepatol* 2003; 38: 811-7.
  30. Cholongitas E, Vasiliadis T, Antoniadis N, Goulis I, Papanikolaou V, Akriviadis E. Hepatitis B prophylaxis post liver transplantation with newer nucleos(t)ide analogues after hepatitis B immunoglobulin discontinuation. *Transpl Infect Dis* 2012; 14: 479-87.
  31. Fung J, Wong T, Chok K, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: results up to 8 years. *Hepatology* 2017; 66: 1036-44.
  32. Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. *J Hepatol* 2012; 56: 1189-97.
  33. Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfecting transplant recipients. *Am J Transplant* 2010; 10: 1268-75.
  34. Fong TL, Di Bisceglie AM, Gerber MA, Waggoner JG, Hoofnagle JH. Persistence of hepatitis B virus DNA in the liver after loss of HBsAg in chronic hepatitis B. *Hepatology* 1993; 18: 1313-8.
  35. Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med* 1996; 2: 1104-8.
  36. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology* 2009; 49(5S): S156-65.
  37. Berger A, Preiser W, Kachel HG, Stürmer M, Doerr HW. HBV reactivation after kidney transplantation. *J Clin Virol* 2005; 32: 162-5.
  38. Chen GD, Gu JL, Qiu J, Chen LZ. Outcomes and risk factors for hepatitis B virus (HBV) reactivation after kidney transplantation in occult HBV carriers. *Transpl Infect Dis* 2013; 15: 300-5.
  39. Lok AS, Liang RH, Chiu EK, Wong KL, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study.

- Gastroenterology 1991; 100: 182-8.
40. Yeo W, Chan PK, Hui P, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003; 70: 553-61.
  41. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011; 22: 1170-80.
  42. Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014; 11: 209-19.
  43. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med.* 2008; 148: 519-28.
  44. Huang YH, Hsiao LT, Hong YC, et al. Randomised controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013; 31: 2765-72.
  45. Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015; 15: 1162-72.
  46. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010; 52: 272-9.
  47. Skagen CL, Jou JH, Said A. Risk of de novo hepatitis in liver recipients from hepatitis-B core antibody-positive grafts – a systematic analysis. *Clin Transplant* 2011; 25: E243-9.
  48. Perillo R. Hepatitis B virus prevention strategies for antibody to hepatitis B core antigen-positive liver donation: a survey of North American, European and Asian-Pacific transplant programs. *Liver Transpl* 2009; 15: 223-32.
  49. Vizzini G, Gruttadauria S, Volpes R, et al. Lamivudine monophylaxis for de novo HBV infection in HBsAg-negative recipients with HBcAb-positive liver grafts. *Clin Transplant* 2011; 25: E77-81.
  50. Saab S, Waterman B, Chi AC, Tong MJ. Comparison of different immunoprophylaxis regimens after liver transplantation with hepatitis B core antibody-positive donors: a systematic review. *Liver Transpl* 2010; 16: 300-7.
  51. Wright AJ, Fishman JA, Chung RT. Lamivudine compared with newer antivirals for prophylaxis of hepatitis B core antibody positive livers: a cost-effectiveness analysis. *Am J Transplant* 2014; 14: 629-34.
  52. Pilmore HL, Gane EJ. Hepatitis B-positive donors in renal transplantation: increasing the deceased donor pool. *Transplantation* 2012; 94: 205-10.
  53. Pinney SP, Cheema FH, Hammond K, Chen JM, Edwards NM, Mancini D. Acceptable

recipient outcomes with the use of hearts from donors with hepatitis-B core antibodies. *J Heart Lung Transplant* 2005; 24: 34-7.

54. Loggi E, Micco L, Ercolani G, et al. Liver transplantation from hepatitis B surface antigen positive donors: a safe way to expand the donor pool. *J Hepatol* 2012; 56: 579-85.
55. Ju W, Chen M, Guo Z, et al. Allografts positive for hepatitis B surface antigen in liver transplant for disease related to hepatitis B virus. *Exp Clin Transplant* 2013; 11: 245-249.
56. Chanchaoenthana W, Townamchai N, Pongpirul K, et al. The outcomes of kidney transplantation in hepatitis B surface antigen (HBsAg)-negative recipients receiving graft from HBsAg-positive donors: a retrospective, propensity score-matched study. *Am J Transplant* 2014; 14: 2814-20.

## **10 TREATMENT OF HBV RECURRENCE OR DE NOVO HEPATITIS B POST SOLID ORGAN TRANSPLANTATION**

### **10.1 Introduction**

Hepatitis B recurrence after liver transplantation (OLT) is defined as detectable hepatitis B surface antigen (HbsAg) and/or detectable viral load (HBV DNA) after transplantation for complications of chronic hepatitis B. It can be associated with biochemical or clinical evidence of active disease, although this is less commonly seen in the era of entecavir or tenofovir therapy.

In chronic hepatitis B (CHB) infection, spontaneous eradication of hepatitis B virus (HBV) from the host is rare. Even after hepatitis B surface antigen (HBsAg) seroconversion, it is likely that HBV persists within the host due to a stable pool of covalently-closed circular HBV DNA. Despite the removal of the liver, HBV may persist in extrahepatic sites and the circulation in sufficient quantities to re-infect the donor graft. Recurrence of hepatitis B represents a failure of preventative strategies to mitigate this risk.

De novo hepatitis B infection after OLT is defined as newly detectable HbsAg, and/or detectable HBV DNA, in those without prior CHB (HBcAb negative). De novo infection can occur due to HBV exposure in the post-OLT period in the context of absent or ineffective HBV vaccination. However, the main risk of de novo hepatitis B after OLT is in those who receive allografts from donors who are hepatitis B core antibody (HBcAb) positive. The imbalance between the high demand for transplant organs and the paucity of donors has necessitated the use of these organs. The risk of developing de novo hepatitis B in recipients depends on their hepatitis B serological status and the prophylactic measures used. A systematic review by Cholangitas et al found that if recipients were negative for both HBcAb and HBsAb the risk of recurrence was 48%, if the recipient was HBcAb positive and HbsAb negative the risk was 13%, and if the recipient was HBcAb positive and HBsAb positive, the risk was reduced to <2% [1]. Irrespective of recipient serological status, these guidelines recommend prophylaxis post-OLT where the donor is HBcAb positive, as discussed in previous chapters.

Early studies highlighted the detrimental impact of recurrent hepatitis B in transplanted grafts. Before the availability of effective antiviral and immune prophylactic agents, high rates

of hepatitis B recurrence after OLT for chronic hepatitis B (CHB)-related diseases were almost universal in those with detectable viraemia at the time of transplantation. Todo et al [2] found accelerated development of hepatitis in patients with recurrent HBV infection post-OLT. Beyond two months after transplantation, the mortality and rate of graft failure were significantly higher in the HBV-related group than in the non-HBV related group. In a retrospective analysis of 58 transplants performed for CHB, there was a median time to reinfection of 145 days (range 15 to 2615 days) and fibrosing cholestatic hepatitis was reported in three of the 16 HBV re-infected patients, all of whom died within one year post-OLT [3].

## **10.2 Review of Literature**

HBV recurrence after OLT represents a failure of prophylaxis. This may occur for a number of reasons which will determine subsequent management. These include viral resistance (and previous treatment regimens) and patient adherence. Other significant risk factors include detectable HBV DNA levels at the time of transplantation, hepatocellular carcinoma, or HIV. Immunosuppression taken by all post-transplant patients increases levels of HBV replication and progression of liver disease with HBV recurrence [2].

The therapeutic goal once recurrent or de novo hepatitis is diagnosed is control of viral replication (suppression of HBV DNA) and stabilisation of graft function, in line with management of patients with CHB who are immunocompetent. There are no data re the optimal timing to start treatment for recurrent or de novo hepatitis B but, given the risk of accelerated graft dysfunction in post-transplant patients, treatment should be started at diagnosis.

In deciding on the type of treatment, it is important to establish the individual's prior treatment and prophylaxis history. Much of the guidance post-transplant is extrapolated from studies of non-transplanted, immunocompetent CHB patients. Owing to increasing evidence of lamivudine resistance in patients post-transplantation, lamivudine is not recommended for treatment of hepatitis B recurrence or de novo hepatitis B [4-6]. However, there are no randomised controlled trials assessing the efficacy of the different nucleo(t)side inhibitors in either scenario. In a small non-randomised non-blinded study of entecavir and/or tenofovir post-transplant, both were demonstrated to be safe and effective in prophylaxis treatment, even in combination with immunosuppressive agents [7]. Subsequent widespread use for prophylaxis has reinforced this. A longitudinal five-year study of entecavir therapy in non-

transplanted patients showed it to be effective with a low resistance profile in nucleo(t)side naïve patients. However, there was a significantly higher risk of developing resistance and hence lack of viral suppression in those refractory to lamivudine [8]. In two retrospective studies from the same group, patients transplanted for CHB on lamivudine prophylaxis with HBV recurrence post-OLT, all patients subsequently treated with tenofovir showed suppression of HBV DNA, suggesting efficacy in patients with lamivudine resistance [9,10]. Therefore, entecavir is not recommended in patients previously treated with lamivudine who have subsequently developed HBV recurrence.

All patients on entecavir or tenofovir nucleo(t)side therapy who develop recurrent hepatitis B post-OLT should have a careful review of adherence. Patients on entecavir should also have viral resistance testing, irrespective of reported levels of compliance.

In a prospectively collected and retrospectively analysed study of 44 patients over 12 years who received HBcAb positive organs, five patients (12.5%) developed de novo hepatitis and four went on to be treated with entecavir with restoration of normal ALT in all, and three out of four showed complete suppression of HBV DNA and no graft failure [11]. For patients who have previously been exposed to lamivudine and not responded, tenofovir should be offered as first line therapy.

### **10.3 Recommendations**

#### ***We recommend that***

- All patients with HBV recurrence post-liver transplant should have a careful review of adherence with NA prophylaxis. Resistance testing should be undertaken at a specialist laboratory. (1C)
- Lifelong antiviral therapy is recommended for all individuals with HBV recurrence or de novo hepatitis B post-liver transplantation. (1C)
- Entecavir or tenofovir are recommended as first line treatment. Tenofovir should be used if the patient has previous lamivudine exposure. (1B)

## References

1. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010; 52: 272-9.
2. Todo S, Demetris AJ, Van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology* 1991; 13, 619-26.
3. Lerut JP, Donataccio M, Ciccarelli O, et al. Liver transplantation and HBsAg-positive postnecrotic cirrhosis: adequate immunoprophylaxis and delta virus co-infection as the significant determinants of long-term prognosis. *J Hepatol* 1999; 30: 706-14.
4. Seehofer D, Rayes N, Bechstein WO, et al. Therapy of recurrent hepatitis B infection after liver transplantation. A retrospective analysis of 200 liver transplantations based on hepatitis B associated liver diseases. *Z Gastroenterol* 2000; 38: 773-83.
5. Perrillo R, Rakela J, Dienstag J, et al. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. Lamivudine Transplant Group. *Hepatology* 1999; 29: 1581-6.
6. Fontana RJ, Hann HW, Wright T, et al. A multicenter study of lamivudine treatment in 33 patients with hepatitis B after liver transplantation. *Liver Transpl* 2001; 7: 504-10.
7. Jimenez-Perez M, Saez-Gomez AB, Mongil Poce L, et al. Efficacy and safety of entecavir and/or tenofovir for prophylaxis and treatment of hepatitis B recurrence post-liver transplant. *Transplant Proc* 2010; 42: 3167-8.
8. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology* 2009; 49: 1503-14.
9. Neff GW, O'Brien CB, Nery J, et al. Outcomes in liver transplant recipients with hepatitis B virus: resistance and recurrence patterns from a large transplant center over the last decade. *Liver Transpl* 2004; 10: 1372-8.
10. Neff GW, Nery J, Lau DT, et al. Tenofovir therapy for lamivudine resistance following liver transplantation. *Ann Pharmacother* 2004; 38: 1999-2004.
11. Han JH, Kim DG, Na GH, et al. De novo hepatitis B virus infection developing after liver transplantation using a graft positive for hepatitis B core antibody. *Ann Surg Treat Res* 2015; 89: 145-50.

# 11 MONITORING FOR HBV RECURRENCE OR DE NOVO INFECTION POST LIVER TRANSPLANTATION

## 11.1 Introduction

Definitions of HBV recurrence or de novo infection are outlined in chapter 10 of these guidelines. This chapter will address the monitoring required of post-transplant patients to detect HBV infection in a timely manner.

## 11.2 Review of Literature

To prevent graft dysfunction secondary to recurrent hepatitis B infection, monitoring of virological, serological, and clinical markers of infection post-transplantation is essential to evaluate prophylaxis efficacy. This may be compromised by non-adherence and/or virological resistance and breakthrough, although the latter is rare with nucleo(t)side analogue (NA) therapies with a very high genetic barrier to resistance.

There are no randomised trials comparing different intervals of monitoring for recurrence of HBV infection post-liver transplant. Non-transplant patients receiving immunoprophylaxis against HBV recurrence during high-risk immunosuppression are typically monitored for reactivation, but guidelines do not indicate an ideal monitoring interval [1]. Three-monthly monitoring is recommended for those at low risk of HBV recurrence taking immunosuppressive therapy without HBV prophylaxis, although there are scant data to support this strategy. Several factors have been identified that increase the risk of recurrence after OLT. These include transplantation for HCC [2], HBeAg positivity pre-OLT [3], and an HBV viral load >100,000 IU/mL at the time of transplantation [4]. With regard to recipients of livers from HBcAb positive donors, the greatest risk of de novo infection is in those recipients who are HBcAb negative [5]. However, some of these data are drawn from historical studies predating highly effective NA prophylaxis or using suboptimal HBIG regimens.

A further patient characteristic that increases the risk of recurrence is non-adherence, which is difficult to identify or quantify. Up to 10% of deaths post-OLT have been attributed to self-reported non-adherence with immunosuppression post-OLT, and it is reasonable to assume

that the rates of non-adherence are greater than those that manifest clinically and extend to other medications [6]. Male gender, lack of social support and mental illness are established risk factors for non-adherence in this context (reviewed in [7]).

We recommend monitoring for recurrence more frequently in the first year post-OLT, where failure of prophylaxis (or complications/side-effects thereof) is more likely to manifest. We recommend an interval of three months between monitoring for HBV recurrence in the first year post-OLT, akin to the recommended monitoring of patients newly established on NA therapy for active HBV infection [8], followed by monitoring every six months thereafter in the absence of evidence of recurrence/de novo infection and with good self-reported adherence. Monitoring intervals should be shortened where non-adherence is suspected or self-reported.

Although both recurrent and de novo infection are conventionally defined by the reappearance of HBsAg, we recommend that monitoring should consist of both HBV DNA quantification and HBsAg testing. Either may be present in the absence of the other in early recurrence and the combination of these tests is, therefore, likely to increase the sensitivity of detection.

### **11.3 Recommendations**

#### ***We recommend that***

- HBV DNA and HBsAg should be monitored every three months in the first year and thereafter every six months in HBsAg positive liver transplant recipients or individuals receiving a graft from a HBcAb positive donor, regardless of treatment or prophylaxis regimen. (1C)
- Monitoring intervals should be shortened in cases of self-reported or suspected non-adherence. (Not graded)

### **References**

1. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; 148: 221-44.

2. Faria LC, Gigou M, Roque-Afonso AM, et al. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. *Gastroenterology* 2008; 134: 1890-9.
3. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993; 329: 1842-7.
4. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transpl* 2005; 11: 402-9.
5. Cholongitas E., Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010; 52: 272-9.
6. Lamba S, Nagurka R, Desai KK, Chun SJ, Holland B, Koneru B. Self-reported non-adherence to immune-suppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors. *Clin Transplant* 2012; 26: 328-35.
7. Oliveira RA, Turrini RN, Poveda VdeB. Adherence to immunosuppressive therapy following liver transplantation: an integrative review. *Rev Lat Am Enfermagem* 2016; 24: e2778.
8. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-98.

## **12 HEPATITIS B VACCINATION AND SOLID ORGAN TRANSPLANTATION**

### **12.1 Rationale for Vaccination**

Immunosuppressed solid-organ recipients develop a more severe and rapidly progressive HBV infection upon acquisition of HBV [1]. It is especially important to prevent this in areas where there is a high prevalence of HBV infection amongst the organ donor pool, as donors may transmit HBV infection to recipients. HBV vaccination may provide protection against donor-derived HBV infection [2,3]. In addition, reactivation of latent HBV whilst on immune suppression has been well described in solid-organ recipients [4,5]. It is therefore important to consider the role of HBV vaccination in potential solid organ recipients.

### **12.2 Liver Transplantation**

#### **12.2.1 Donor-derived infection**

Liver donors with serological evidence of past resolved HBV infection (i.e. HBsAg negative, HBcAb positive) may transmit HBV infection to recipients. Indeed, liver grafts from HBcAb positive donors are now the main source of de novo HBV infection after liver transplantation [6]. HBV DNA may persist in the liver (or serum) in non- or low-replicative forms following recovery from HBV infection [7]. This presents a potential risk of de novo HBV in the context of immune suppression after transplantation which may increase viral replication.

Successful pre-transplant HBV vaccination can substantially reduce the risk of de novo HBV infection to around 10% [6] and, with additional HBV prophylaxis, this risk can almost be entirely eliminated. Therefore, as a potential strategy to allow optimal utilisation of these HBcAb positive grafts and allow potential recipients access to the full donor pool, it is recommended that HBV vaccination should be offered to all HBV naïve patients with chronic liver disease.

### **12.2.2 Recurrent HBV**

In the early days of liver transplantation, there was an unacceptably high rate of recurrent HBV infection amongst patients transplanted for HBV [8].

Long-term passive immunoprophylaxis with HBIg attains a significant reduction in the risk of graft re-infection with consequent improvements in both graft and patient survival [9]. However, this strategy is costly and inconvenient, leading to attempts to devise other safe prophylactic strategies. HBV vaccination has been proposed as an alternative. In one study, standard recombinant vaccine was administered to selected liver transplant recipients with no HBV recurrence detected during follow-up, allowing the stopping of life-long HBIg in those that developed protective serum titres of HBsAb [10]. Another group used a commercial vaccine combined with a novel adjuvant system to achieve an even stronger response, shown by the higher HBsAb titres achieved [11]. However, other groups have failed to replicate these results using the standard recombinant vaccine [12,13], third generation recombinant vaccine [14], or when combined with other adjuvants [15].

Overall, HBV vaccination with the subsequent development of protective serum titres of HBsAb is possible in some liver transplant recipients. This can allow the safe withdrawal of HBIg. However, published studies have included patients with a wide range of characteristics, varying risk of recurrent HBV infection, and a variety of different vaccine types and administrations. Therefore, HBV vaccination cannot currently be recommended as a routine alternative strategy for the prevention of HBV recurrence after liver transplantation. Further work is required to define the optimal patient and vaccine characteristics.

### **12.3 Renal Transplantation**

HBV infection is also an important consideration in potential renal transplant recipients. A recent meta-analysis of published studies identified a significantly higher all-cause mortality (relative risk 2.21, 95% CI 1.56-3.14) and all-cause graft loss (relative risk 1.44, 95% CI 1.26-1.63) amongst renal transplant recipients with HBV [16]. HBV is prevalent in patients with end stage renal disease, though there has been a significant reduction in the prevalence of haemodialysis patients with chronic HBV in most Western dialysis units [17].

There are relatively few published data on the risk of hepatitis B virus (HBV) reactivation in patients with past resolved HBV infection (i.e. HBsAg negative/HBcAb positive) who

subsequently undergo renal transplantation. Historically, the risk of reactivation was thought to be low or clinically insignificant [18,19]. More recent data suggest that the risk of reactivation is higher than previously thought (around 6.5%), particularly amongst those recipients without HBsAb at the time of renal transplantation [5]. In studies that reported on reactivation of HBV amongst renal transplant recipients with past resolved HBV infection, in nearly all cases of reactivation, the recipient had an HBsAb titres of <100 IU/mL [5,20].

In addition, donor-derived infection is a significant consideration, particularly in certain parts of the world such as the Asia-Pacific region where >70% of the donor pool may have been previously exposed to HBV [21]. In the UK, donor-derived infection rates are much lower, with rates of active chronic HBV infection (HBsAg positive) of <1% and past resolved HBV infection (HBsAg negative/HBcAb positive) of around 2% [21]. Transmission of HBV is universal after use of renal grafts from HBsAg positive donors and may also occur from donors who are only HBcAb positive [21]. HBV vaccination has been proposed as a strategy to minimise the risk of HBV infection in both reactivation and donor-derived infection. Whilst no prospective trials evaluating such an approach have been performed, there is some rationale for this in the published literature.

In terms of donor-derived infection, there are small case reports of HBV immune patients safely undergoing renal transplantation from HBsAg positive donors with no evidence of HBV transmission, as long as the recipients have protective titres of HBsAb (>10 IU/mL) [22,23]. The presence of this protective titre of HBsAb, irrespective of whether from previous exposure or vaccination, will also protect against de novo HBV infection in renal transplant recipients from HBcAb positive donors [21].

For these reasons, HBV vaccination is recommended in HBV seronegative patients with end-stage renal disease. In part, this is in order to increase the use of HBcAb positive kidneys amongst those who mount a protective HBsAb response (i.e. >10 IU/mL). Furthermore, in patients with resolved past resolved infection (HBcAb positive), vaccination should be considered to boost the protective titre of HBsAb and minimise the risk of reactivation.

#### **12.4 Timing of Vaccination**

Having established a rationale for the administration of HBV vaccination in potential solid-organ transplant recipients, there remains a practical issue about the optimal timing of the

administration of vaccination. In common with many vaccines, the immunological response to HBV vaccination is diminished in patients with organ failure and in patients who are immunosuppressed.

In healthy individuals, HBV vaccine is highly immunogenic. Upon administration of a series of three doses of HBV vaccine (either plasma-derived or recombinant), healthy subjects will develop HBsAb (with protective serum titres of >10 U/L) in the vast majority of cases (95-99%) [24]. In the pre-transplant period, the immunogenicity of the HBV vaccine has been shown to be less potent. In patients with end-stage cirrhosis awaiting liver transplantation, less than one third of patients seroconvert after receiving standard dosing [25]. Providing a double dose schedule increases the seroconversion rate to 37-62% [26,27]. The efficacy of HBV vaccination has been reported to vary according to the severity of chronic liver disease. In patients who are not yet at the stage of requiring liver transplantation, higher HBV vaccination efficacy of around 90% has been reported in patients with chronic hepatitis C [28]. Amongst heavy alcohol drinkers, HBV vaccination is reported to be less effective (50-75%), particularly amongst those with liver disease (18%) [29,30]. A poorer response has also been demonstrated in patients with end stage renal disease, with many studies reporting effective vaccination rates of around 60-90%, depending on the population included [31]. Furthermore, an association between the severity of renal impairment and lack of response to the HBV vaccine has been shown [32]. Ideally, therefore, vaccination should be considered early in the course of disease.

While the response to HBV vaccine may be suboptimal in the pre-transplant period, it is even more disappointing in the post-transplant period. In a retrospective cohort of patients vaccinated post-liver transplantation, the total response rate (HBsAb >10 U/L) was 40% but there was a rapid decline of titres such that at the end of the follow-up period only 17% had protective antibodies [33], presumably relating to immune suppression. In a prospective study of consecutive liver transplant recipients from the Mayo Institute, an accelerated double-dose HBV vaccination schedule achieved a seroconversion rate of 36% [34]. However, two years after transplantation, the prevalence of persistent protective antibodies had dropped to 8%. Although all patients had started the HBV vaccine schedule before OLT, the majority completed this after transplantation. Patients with higher titres of HBsAb before OLT were more likely to have persistence of antibodies at two year follow-up [34].

A similar pattern is seen in renal transplant recipients. A recent retrospective study described a considerable decrease in antibodies against hepatitis B surface antigen in the year following kidney transplantation. The loss of protective immunity was significantly more

frequent in patients with lower HBsAb titres at the time of transplantation (<100 U/L) compared with those patients with higher titres [35].

## 12.5 Vaccination Method

In healthy individuals, the usual vaccination schedule is a series of three intramuscular doses of HBV vaccine which are administered at baseline, one and six months. In healthy subjects, this is highly effective and protective HBsAb will develop in the vast majority of cases (95-99%) [24]. In the UK, currently available recombinant vaccines are HBvaxPro® (standard dose 10 µg), Engerix-B® (standard dose 20 µg) and Fendrix® (standard dose 20 µg).

In patients with end-stage liver disease, the response to standard-dose HBV vaccinations is lower [25]. These patients *may* benefit from a high-dose HBV vaccine [26,27]. In the UK, this would be with double-dose Engerix-B (i.e. 40 µg) at baseline, one and six months. Similarly, patients with end-stage renal disease, particularly those on dialysis, demonstrate a poorer response to the standard-dose regimen. In the UK, higher-dose vaccine formulations are available for use in patients with end-stage renal disease: HBvaxPro® (40 µg/mL standard dose 40 µg) and Fendrix® (40 µg/mL, standard dose 20 µg). An accelerated regimen, where four doses of the vaccine (HBvaxPro and Engerix-B 40 µg or Fendrix 20µg) given at 0, 1, 2 and 6 months is recommended for these patients. If HBV vaccination has to be given after solid-organ transplantation, the standard vaccine schedule with standard-dose vaccines at 0, 1 and 6 months is recommended.

In all these patients, HBsAb titres should be measured one to three months after the completion of the vaccination schedule. In those who fail to respond to the initial vaccination schedule (i.e. have antibody titres  $\leq 10$  IU/L), a further vaccine schedule should be administered. In a retrospective study in patients with chronic liver disease, repeated high-dose HBV vaccination (80 µg) was safe and effective in a cohort of patients who did not respond to the standard HBV vaccine schedule [36]. Therefore, the subsequent additional HBV vaccine schedule administration may involve standard- or high-dose, in 3- or 4-doses, depending on patient circumstances.

## 12.6 Recommendations

### *We recommend that*

- All prospective solid organ transplant recipients who are HBV naive must be vaccinated (time permitting) and the response documented. (1C)

### *We suggest that*

- Amongst liver recipients transplanted for HBV, vaccination can be considered as a strategy to develop protective serum titres of HBsAb in some recipients, but cannot currently be recommended as routine practice. (2C)
- Amongst renal transplant recipients who are HBcAb positive, if HBsAb are <100 IU/mL, then vaccination should be considered to boost the protective titre of HBsAb and minimise the risk of reactivation. (2C)
- All prospective solid organ transplant recipients should receive a high-dose, accelerated vaccine schedule. (2C)
- In those who fail to respond to the initial HBV vaccination schedule, a second series should be administered. (2C)

## References

1. Crespo J, Fabrega E, Casafont F, et al. Severe clinical course of de novo hepatitis B infection after liver transplantation. *Liver Transpl Surg* 1999; 5: 175-83.
2. Bárcena Marugán R, Garcia-Hoz F, Vázquez Romero M, et al. Prevention of de novo hepatitis B infection in liver allograft recipients with previous hepatitis B infection or hepatitis B vaccination. *Am J Gastroenterol* 2002; 97: 2398-401.
3. Su WJ, Ho MC, Ni YH, et al. High-titer antibody to hepatitis B surface antigen before liver transplantation can prevent de novo hepatitis B infection. *J Pediatr Gastroenterol Nutr* 2009; 48: 203-8.
4. Phillips MJ, Cameron R, Flowers MA, et al. Post-transplant recurrent hepatitis B viral liver disease. Viral-burden, steatoviral, and fibroviral hepatitis B. *Am J Pathol* 1992; 140: 1295-308.
5. Kanaan N, Kabamba B, Maréchal C, et al. Significant rate of hepatitis B reactivation following kidney transplantation in patients with resolved infection. *J Clin Virol* 2012; 55: 233-8.

6. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010; 52: 272-9.
7. Michalak TI, Pasquinelli C, Guilhot S, Chisari FV. Hepatitis B virus persistence after recovery from acute viral hepatitis. *J Clin Invest* 1994; 94: 907.
8. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993; 329: 1842-7.
9. Muller R, Samuel D, Fassati LR, Benhamou JP, Bismuth H, Alexander GJ. 'EUROHEP' consensus report on the management of liver transplantation for hepatitis B virus infection. European Concerted Action on Viral Hepatitis. *J Hepatol* 1994; 21: 1140-3.
10. Sánchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; 31: 496-50.
11. Bienzle U, Günther M, Neuhaus R, et al. Immunization with an adjuvant hepatitis B vaccine after liver transplantation for hepatitis B-related disease. *Hepatology* 2003; 38: 811-9.
12. Angelico M, Di Paolo D, Trinito M, et al. Failure of a reinforced triple course of hepatitis B vaccination in patients transplanted for HBV-related cirrhosis. *Hepatology* 2002; 35: 176-81.
13. Di Paolo D, Lenci I, Trinito MO, et al. Extended double-dosage HBV vaccination after liver transplantation is ineffective, in the absence of lamivudine and prior wash-out of human hepatitis B immunoglobulins. *Dig Liver Dis* 2006; 38: 749-54.
14. Karasu Z, Ozacar T, Akarcu U, et al. HBV vaccination in liver transplant recipients: not an effective strategy in the prophylaxis of HBV recurrence. *J Viral Hepat* 2005; 12: 212-5.
15. Rosenau J, Hooman N, Rifai K, et al. Hepatitis B virus immunisation with and adjuvant containing vaccine after liver transplantation for hepatitis B related disease: failure of humoral and cellular immune response. *Transplant Int* 2006; 19: 828-33.
16. Fabrizi F, Dixit V, Martin P, Messa P. Hepatitis B and survival after renal transplant: meta-analysis of observational studies. *J Viral Hepatitis* 2014; 21: 542-50.
17. Burdick R, Bragg-Gresham J, Woods J, et al. Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2003; 63: 2222-9.

18. Knoll A, Pietrzyk M, Loss M, Goetz WA, Jilg W. Solid-organ transplantation in HBsAg-negative patients with antibodies to HBV core antigen: low risk of HBV reactivation. *Transplantation* 2005; 79:1631-3.
19. Berger A, Preiser W, Kachel HG, Sturmer M, Doerr HW. HBV reactivation after kidney transplantation. *J Clin Virol* 2005; 32: 162-5.
20. Savas N, Colak T, Yilmaz U, Emiroglu R, Haberal M. Hepatitis B virus reactivation after renal transplantation: report of two cases. *Transpl Int* 2007; 20: 301-4.
21. Pilmore H, Gane E. Hepatitis B-positive donors in renal transplantation: increasing the deceased donor pool. *Transplantation* 2012; 94: 205-10.
22. Sumethkul V, Ingsathit A, Jirasiritham S. Ten year follow up of kidney transplantation from hepatitis B surface antigen positive donors. *Transplant Proc* 2009; 41: 213-5.
23. Berber I, Aydin C, Yigit B, Turkmen F, Titiz IM, Altaca G. The effect of HBsAg-positivity of kidney donors on long-term patients and graft outcome. *Transplant Proc* 2005; 37: 4173-5.
24. Mast E, Mahoney F, Kane M, Margolis H. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. Philadelphia: Saunders, 2004: 299-337.
25. Villeneuve E, Vincelette J, Villeneuve JP. Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. *Can J Gastroenterol* 2000; 14 Suppl B: 59B-62B.
26. Horlander JC, Boyle N, Manam R, et al. Vaccination against hepatitis B in patients with chronic liver disease awaiting liver transplantation. *Am J Med Sci* 1999; 318: 304-7.
27. Dominguez M, Barcena R, Garcia M, Lopez-Sanroman A, Nuno J. Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. *Liver Transpl* 2000; 6: 440-2.
28. Lee SD, Chan CY, Yu MI, Lu RH, Chang FY, Lo KJ. Hepatitis B vaccination in patients with chronic hepatitis C. *J Med Virol* 1999; 59: 463-8.
29. Mendenhall C, Roselle GA, Lybecker LA, et al. Hepatitis B vaccination. Response of alcoholic with and without liver injury. *Dig Dis Sci* 1998; 33: 263-9.
30. Rosman AS, Basu P, Galvin K, Lieber CS. Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* 1997; 103: 217-22.
31. Janus N, Vacher LV, Karie S, Ledneva E, Deray G. Vaccination and chronic kidney disease. *Nephrol Dial Transplant* 2008; 23: 800-7.

32. DaRoza G, Loewen A, Djurdjev O, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *Am J Kidney Dis* 2003; 42: 1184-92.
33. Loinaz, C, de Juanes JR, Gonzalez EM, et al. Hepatitis B vaccination results in 140 liver transplant recipients. *Hepatogastroenterology* 1997; 44: 235-8.
34. Arslan M, Wiesner RH, Sievers C, Egan K, Zein NN. Double-dose accelerated hepatitis B vaccine in patients with end stage liver disease. *Liver Transpl* 2001; 7: 314-20.
35. Moal V, Motte A, Vacher-Coponat H, Tamalet C, Berland Y, Colson P. Considerable decrease in antibodies against hepatitis B surface antigen following kidney transplantation. *J Clin Virol* 2015; 68: 32-6.
36. Aziz A, Aziz S, Li DS, et al. Efficacy of repeated high-dose hepatitis B vaccine (80 microg) in patients with chronic liver disease. *J Viral Hepat* 2006; 13: 217-21.