Hepatitis B and C viral infections and kidney transplant.	University Hospitals of Leicester NHS NHS Trust **Trust Reference Number C230/2016**

1. Introduction and Who Guideline applies to

1.1. This guideline is intended to guide doctors, nurses, pharmacists working with renal transplant patients. Clinical guidelines are 'guidelines' only. The interpretation and application of clinical guidelines will remain the responsibility of the individual practitioner. If in doubt consult a senior colleague or expert.

1.2. Hepatitis B and C are highly prevalent worldwide. These viruses are transmissible mainly through blood and sexual contact, but they can also be transmitted by equipment contamination (razors, tattoo needles, medical equipment), poor infection control in healthcare facilities (haemodialysis units, etc).

1.3. Many patients will have had contact with either virus at some point. Vaccination for hepatitis B is effective and should be offered to all renal patients in predialysis and dialysis clinics. There is no vaccine against hepatitis C. Curative treatment for hepatitis C has a 95% success rate and there is a global push for eradication of the virus. In the general population, treatment for active hepatitis B infection is required under certain circumstances, for example if there is liver fibrosis/cirrhosis, but is mostly suppressive and rarely curative. In the renal population, those on immunosuppression require antiviral therapy if they have evidence of active hepatitis B infection, or if they have previously cleared infection but are at risk of reactivation due to immunosuppressive drugs.

1.4. Patients with decompensated liver disease are those with ascites, hepatic encephalopathy, abnormal prothrombin time (high INR), decreased serum albumin, hyperbilirubinaemia; patients with severe portal hypertension are also considered to have significant liver disease

1.5. The goals include:

1.5.1. Preventing de novo infection

1.5.2. Preventing hepatitis B reactivation

1.5.3. Preventing progression of liver disease and development of HCC in patients with chronic hepatitis B

1.5.4. Curative treatment in patients with chronic hepatitis C

2. Guideline Standards and Procedures

2.1. Hepatitis B (HBV)

2.1.1. All potential transplant patients should be vaccinated prior to transplant (refer to Hepatitis B Vaccination in Chronic Kidney Disease UHL Renal Guideline on UHL Connect)

2.1.2. HBV infection is associated with more frequent and rapid progression to cirrhosis and hepatocellular carcinoma in transplant recipients, thus contributing to higher mortality. Hepatitis associated with HBV reactivation can lead to liver failure, especially in patients with cirrhosis.

2.1.3. The risk of HBV transmission after transplantation from a donor with active or previous HBV infection is determined by the HBV status of the donor and the immune status of the recipient. Transplantation from Hepatitis B positive (HBV+) donors has

traditionally been avoided. However, it is now recognised that in certain circumstances the risks and benefits of transplanting such organs can be justified.

2.1.4. *Pretransplant assessment of HBV status*

2.1.4.1 All patients being worked up for solid organ transplantation must be tested for HBsAg, HBsAb and HBcAb.

2.1.4.2. All HBsAg positive patients undergoing transplant work up must have the following tests: HBeAg, HBeAb and HDV Ab serology, and HBV DNA levels.

2.1.4.3. HDV RNA testing must be performed in potential transplant recipients where HDV serology is positive or equivocal.

2.1.4.4. Any potential transplant recipients found to be HBcAb positive but HBsAg negative (past infection) must have HBV DNA and HDV PCR testing to exclude occult HBV or HDV infection.

2.1.4.5. All donors who are positive for for HBcAb but HBsAg negative (past infection) must have HBV DNA testing to exclude the possibility of occult HBV infection.

2.1.4.6. Table 1. Interpretation of serologic tests for HBV (From Huprikar et al)

Tests	Interpretation
HBsAg negative Anti-HBc negative Anti-HBs negative	No infection or immunity
HBsAg negative Anti-HBc positive Anti-HBs positive	Previous infection now resolved with natural immunity
HBsAg negative Anti-HBc negative Anti-HBs positive	Vaccine immunity
HBsAg positive Anti-HBc positive IgM Anti-HBc positive Anti-HBs negative	Acute infection
HBsAg positive Anti-HBc positive IgM Anti-HBc negative Anti-HBs negative	Chronic infection
HBsAg negative Anti-HBc positive Anti-HBs negative	Four possible interpretations: - Resolved infection and immune (most common) - No infection or immunity (false-positive anti-HBc) - Occult chronic infection - Resolving acute infection

2.1.4.7 Recipients who have an anti-HBs titre ≥10 international units (IU)/mL have immunity to HBV infection either through vaccination (HBcAb negative) or through prior infection (HBcAb positive)

2.1.4.8 Patients on dialysis should have annual testing for HBsAb and booster dose of hepatitis B vaccine offered if anti-HBs titre is <10 IU/mL.

2.1.4.9 Organs from donors who are HBcAb positive can be used if HBsAg is negative and HBV DNA is negative (evidence of past infection), as the risk of de novo HBV infection is low.

2.1.5. *Recipients who don't require any surveillance or treatment*

2.1.5.1. Patients with no documented prior hepatitis B infection or immunity should ideally receive organs from HBV negative donors and won't require any antiviral treatment

2.1.6. *Recipients who have immunity to Hepatitis B through vaccination*

2.1.6.1 Patients with vaccine induced immunity towards Hepatitis B (HBsAg negative, HBcAb negative, HBsAb >10), can receive organs from donors who are HBsAg negative and HBcAb positive (donors with prior infection), as risk of transmission is very low; they can also receive organs from donors who are HBsAg positive (donors with chronic infection) although will require antiviral treatment.

2.1.7. *Recipients who have previous (cleared) Hepatitis B infection with natural immunity*

2.1.7.1. In the pre-transplant assessment, patients with cleared Hepatitis B infection (HBsAg negative, HBcAb positive, with/without positive anti-HBs antibodies, HBV DNA negative) require liver ultrasound and fibroscan, and discussion with Hepatology if abnormal

2.1.7.2. They can receive organs from donors who are HBsAg negative and HBcAb positive (donors with previous infection), as risk of transmission is very low; they can also receive organs from donors who are HBsAg positive (donors with chronic infection) but would require long-term treatment with antivirals.

2.1.7.3. The preferred antiviral regimens are entecavir and tenofovir, although the latter can have renal side effects and entecavir is usually preferred; lamivudine is not recommended any more because of drug resistance. Choice of treatment should be discussed with and overseen by viral hepatitis clinic.

2.1.7.4. Pegylated interferon alfa and adefovir are not recommended, and the former can induce transplant rejection

2.1.7.5. For monitoring, HBsAg, HBV DNA and LFT should be checked every 3 months for the first year.

2.1.8. *Recipients with chronic HBV infection*

2.1.8.1. In the pre-transplant assessment, patients with chronic infection (HBsAg positive) will require assessment from the viral hepatitis clinic run by Infectious Diseases/Hepatology

2.1.8.2. These patients can receive a kidney from a donor with prior infection or active infection

2.1.8.3. Patients with chronic infection are likely to be on treatment already. This needs to continue indefinitely, unless the immunosuppressants are completely removed (rejection/nephrectomy, graft tolerance, etc) and they do not require treatment for other reasons such as the presence of liver fibrosis

2.1.8.4. Monitoring in this population is undertaken by HBV DNA and ALT and fibroscan

2.1.8.5. Reactivation or flare can be caused by: poor adherence, incorrect dosing, drug resistance (rare with entecavir or tenofovir)

2.1.9. ***Summary (adapted from Chan et al)***

Donor HBV status	**Recipient HBV status**	**Kidney transplant**	**Antiviral therapy needed**	**Comments**
Chronic infection *HBsAg positive*	No evidence of prior infection or immunity	No, exceptional circumstances	Yes	Might need HBIG post transplant[1]
	Vaccine immunity	Yes	Yes	Might need HBIG + Permanent antiviral therapy[1,2]
	Natural immunity	Yes	Yes	Might need permanent therapy to prevent reactivation[1,2]
	Chronic infection	Yes	Yes	Permanent treatment whilst taking immunosuppressants or for other reasons such as liver fibrosis[1,2]
Prior infection *HBsAg negative HBcAb positive*	No evidence of prior infection or immunity	Yes	No, unless donor has detectable viral load	
	Vaccine immunity	Yes	No, unless donor has detectable viral load	
	Natural immunity	Yes	Yes	Might need permanent therapy to prevent reactivation[1,2]
	Chronic infection	Yes	Yes	Permanent treatment whilst taking immunosuppressants or for other reasons such as liver fibrosis[1,2]
No evidence of prior infection *HBsAg negative, HBcAb*	No evidence of prior infection or immunity	Yes	No	
	Vaccine immunity	Yes	No	

negative, HBsAb negative	Natural immunity	Yes	Yes	Might need permanent therapy to prevent reactivation[1,2]
	Chronic infection	Yes	Yes	Permanent treatment whilst taking immunosuppressants or for other reasons such as liver fibrosis[1,2]

[1] Please discuss with Virology and/or Infectious diseases
[2] Please see section 2.1.7.3 for preferred antivirals

2.1.10. *Other considerations*

2.1.10.1. The use of a donor kidney from a donor with HBcAb positivity, for any individual recipient, should be jointly decided between the consultant transplant surgeon, the consultant nephrologist and the patient. If needed advice may be sought from virology, and nephrology pharmacists

2.1.10.2. Kidneys from donors with previous infection (HBcAb positive and HBsAg negative) have a low risk of viral transmission. If the donor has active hepatitis B infection (a positive HBsAg or positive HBV DNA), the discussion should consider a variety of factors which determine the patient's risk of staying on dialysis and their need for a transplant e.g.: age, co-morbidity, dialysis access and complications, transplant number, level of sensitization and length of wait. Transplant recipients with previous/chronic HBV infection who have abnormal LFT should have HBsAg and HBV DNA testing to identify: HBV reactivation, HBV flare, potential drug resistance or any other aetiology. These patients should be discussed with Infectious diseases/Hepatology.

2.1.10.3. Patients with liver cirrhosis can be considered for transplantation if hepatitis B infection is well controlled and if they are not decompensated. These patients will require clearance from Hepatology during the assessment period. Patients with decompensated cirrhosis could benefit from a combined liver/kidney transplantation and this option can be explored and the patient referred to a specialist centre

2.2. **Hepatitis C (HCV)**

2.2.1. Kidney transplant patients who have active HCV have worse patient and graft survival if HCV is not eradicated

2.2.2. HCV in transplant recipients has also been associated with acute rejection, secondary infections, extrahepatic neoplasms, new onset diabetes after transplant, and kidney disease induced by HCV itself (glomerulonephritis)

2.2.3. With the development of direct acting antivirals (DAA) with interferon-free schemes, the cure rate for HCV infection is >95%

2.2.4. *Pretransplant assessment of HCV status*

2.2.4.1. ***Donor***

2.2.4.1.1. A donor with active HCV infection can transmit the infection in the deceased donor setting. Infected potential donors who are cured can be considered

for donation, when they have had natural clearance or previous treatment. Donation from a person with positive viraemia is not recommended.

2.2.4.1.2. Transplantation in this setting requires carefully consenting, as there is risk of transmission. Refer to British Transplantation Society and British Viral Hepatitis Group statement for further information.

2.2.4.2. ***Recipient***

2.2.4.2.1. Patients with a positive HCV Ab should be evaluated with blood tests (HCV RNA, liver function tests, clotting, FBC, etc) and other tests including ultrasound and fibroscan; liver biopsy is seldom required

2.2.4.2.2. Patients with cleared HCV (HCV Ab positive but HCV RNA negative) can be safely considered for transplantation

2.2.4.2.3. Patients with active hepatitis C (HCV Ab positive and HCV RNA positive) should complete treatment with DAA. Once the infection is cured and confirmed by viral hepatitis clinic, the patient can be considered for transplantation

2.2.4.2.4. Patients with liver cirrhosis related to HCV can be considered for combined liver/kidney transplantation at specialist centres

2.2.4.2.4.1. Patients with decompensated liver cirrhosis or those with severe portal hypertension should be considered for a combined transplant

2.2.5. *Antiviral treatment and monitoring*

2.2.5.1. Treatment with DAA is well tolerated with minor side effects. The choice of treatment and regime requires discussion at the viral hepatitis MDT and considers CKD/dialysis status, genotype, interactions, etc. Treatment length varies from 8 to 16 weeks. Interferon should not be considered because of the increased risk of transplant rejection

2.2.5.2. Treatment should be offered to patients who are being considered for transplantation, and it should be completed before referral to the transplant assessment clinic

2.2.5.3. Patients should have a pharmacist assessment to identify potential interactions, as DAA have effects on CYP450. Many immunosuppressants will have their trough levels affected and will require close monitoring

2.2.6. *Other considerations*

2.2.6.1. Patients with cirrhosis who become HCV RNA negative still require 6-monthly liver ultrasound for hepatocellular carcinoma surveillance

2.2.6.2. Patients with HBV and HCV co-infection, who receive treatment with DAA are still at risk of HBV reactivation

2.2.6.3. Patients should be tested for proteinuria and haematuria, if abnormal a kidney biopsy should be offered to rule out HCV-related kidney disease: membranoproliferative glomerulonephritis, cryoglobulinaemia, renal thrombotic microangiopathy, membranous nephropathy and transplant glomerulopathy

3. Education and Training

3.1. None required

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Number of patients active on UKT that have received vaccination for HBV	Proton (local electronic database)	Lead for RRT, Nephrology	Annually	
Number of patients with a kidney from a positive HBcAb donor	Transplant audit	Transplant team	Annually	

4. Supporting References (maximum of 3)

4.1. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. https://www.who.int/publications/i/item/9789240027077

4.2. British Transplantation Society. Hepatitis B and Solid Organ Transplantation Guidelines. 2018.

4.3. Huprikar S, et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. Am J Transplant. 2015 May;15(5):1162-72.

4.4. Chan TK, Lok A (2022). Kidney transplantation in adults: Hepatitis B virus infection in kidney transplant recipients. In: UpToDate, Waltham, MA

4.5. Lok A, Bonis P (2020). Hepatitis B virus reactivation associated with immunosuppressive therapy. In: UpToDate, Waltham, MA

4.6. Muche M, Baid-Agrawal S (2022). Hepatitis C infection in kidney transplant candidates and recipients. In: UpToDate, Waltham, MA

4.7. UK Position Statement on the use of Organs from Hepatitis C Viraemic Donors and Increased Infectious Risk Donors in Hepatitis C Negative Recipients. Available at: https://bts.org.uk/british-transplantation-society-statement-on-consultation-to-review-policy-on-organ-donation-copy/

5. Key Words

5.1. Kidney transplant, hepatitis B, hepatitis C

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Details of Changes made during review: **This is a new guideline**	