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Hepatitis B related dilemmas in the renal unit

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Running title: HBV Dilemmas

Editorial

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Abstract

Testing for hepatitis B in dialysis patients is routine, but newer and more sensitive detection methods means there is confusion around viral loads and occult infection. There are

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frequently difficult choices surrounding isolation and treatment. Here we describe the use of HBV serology and DNA testing in decisions around patients with end-stage renal disease. We also suggest isolation decisions based on our current understanding of the virus and its infectivity.

Keywords

Clinical nephrology

End-stage kidney disease

Haemodialysis

Hepatitis B

Infectious disease

Introduction

Advances in diagnostics and our understanding of disease processes now makes decisions around Hepatitis B infection in dialysis patients more difficult. Current guidelines can be challenging to interpret or to follow when weighing individual vs cohort risks with superimposed infrastructural limitations. Decisions must be based upon balance of risks, as often it is neither practical nor possible to provide care that can deliver dialysis whilst simultaneously absolutely guaranteeing cohort safety, but an understanding of appropriate risks can allay anxiety in such decision making. National guidelines produced by Communicable Diseases Network Australia recognise this in their acknowledgement that risks can only be minimised, but never completely eliminated. *“The health care system should have an effective infection control strategy and provide a safe working environment that minimizes*

the risk of a sharps injury or exposure to body fluids, secretions and excretions and prevents the transmission of infections from person to person within the health care setting” (1).

Implementation of this advice for preventing infectious disease transmission in renal units largely relies upon the effective application of standard precautions. Improvements in the design and space utilisation in dialysis units, as well as the use of personal protective equipment (PPE), the cleaning of all equipment between patients, careful cleaning of body fluid spills and the application of good aseptic technique when changing lines or gaining intravenous access have contributed to increasing safety.

The transmission of the hepatitis B virus (HBV) in or near dialysis units is now a very rare event in Australia. This is due to the relatively low prevalence of hepatitis B, together with the promotion of home dialysis therapies, where exposure events are far less likely, and the high prevalence of renal transplantation, negating dialysis requirements altogether.

Although hepatitis B surface antigen (HBsAg) can be found in peritoneal dialysis (PD) fluid (2), transmission from PD fluid appears a very rare event now but was formerly related to cohorts of patients receiving intermittent peritoneal dialysis together (3).

There is no doubt that in the 1970–80s, there was a lower incidence of HBV infection in those units that isolated positive patients (4). Since HBV transmission in dialysis units is now unusual, some practitioners question the necessity for a different policy for HBV-positive patients, and anecdotally opinion varies across units about the necessity to formally isolate those with any bloodborne virus (BBV) infection. Perhaps surprisingly, and despite the

potential for aerosolised or frank blood spills, and the use of sharps, procedures such as haemodialysis (HD) and haemodiafiltration (HDF) are not classed as exposure-prone procedures in Australia (1). Recent Caring for Australians with Renal Impairment (CARI) guidelines (5) as well as state of Victoria-based advice (6) however continues to advocate isolating HD patients positive for HBsAg.

In Victoria, Australia, one patient whose HBV was likely reactivated by steroid use, likely transmitted the virus to another patient attending the same dialysis unit (6) suggested by close viral phylogenetic homology (personal communication). However, a Victorian Department of Health review failed to discover the exact mode of transmission, and no breaches in infection prevention precautions were identified, although recommendations for tightening of HBV related procedures were made (6).

The isolation of HBV-viraemic HD patients is common Worldwide (7), but local circumstances including the availability of isolation facilities, care teams and the distances some patients must travel for dialysis are particular problems in Australian dialysis centres. There are also recognised psychological issues associated with isolation and stigmatisation (8) of such patients.

This article aims to highlight some of the dilemmas and difficulties with HBV and how to weigh risks given new data around the virus and its detection, and provides suggestions as to how to deal with them.

The Hepatitis B Virus

Hepatitis B virus (HBV) is a partially double-stranded DNA virus which has a long-lived minichromosome called a covalently closed circular (ccc) DNA, which is recalcitrant to antiviral therapy and results in long term infection. The hallmark of chronic infection is the presence of HBsAg for greater than 6 months. The main indicator of infectivity, and therefore transmission, is HBV DNA, usually measured as HBV viral load by real time polymerase chain reaction (PCR) assay, which is now widely available. This test is exquisitely sensitive, can measure virus down to a lower limit of detection (LLOD) of 10-16 IU/ml and has high specificity.

HBV is a bloodborne DNA virus, but which can also be found in other body fluids such as semen and vaginal secretions with sexual transmission well-recognised. Body fluids, such as saliva, also contain the virus but carry a lower risk of transmission. The incubation period for HBV is 45–160 days, and exposure can lead to acute hepatitis which can be either symptomatic, associated with jaundice, or asymptomatic, but both can lead to chronic infection in ~5% of adults. The majority of chronic HBV occurs in individuals who come from countries with high rates of endemic infection, where it is acquired vertically or by early horizontal transmission. In this setting chronic infection occurs in ~90% of individuals vertically infected in the absence of vaccination or Hepatitis B Immune Globulin (HBIG).

The incidence of HBV transmission in renal units has declined dramatically over the last 40 years, but still occurs (9). HBV can remain viable outside the body on surfaces for at least seven days (10) and still be capable of causing infection (11). The HBV is a group B notifiable disease in Australia with new cases being reported within five days of laboratory diagnosis.

Haemodialysis patients are also considered immunocompromised and may be more susceptible to infection. The most common mode of transmission among patients has been found to involve the sharing of equipment between patients in dialysis units (12,13). However, it is often important to consider that there may be a considerable delay between transmission and diagnosis of infection. This delay may lead to considerable uncertainty as to the exact mode of transmission in a healthcare setting.

In HBsAg positive patients the natural history and management of chronic hepatitis B (CHB) is often divided into four phases (immune tolerance, immune clearance, inactive carrier and reactivation) with slightly different nomenclature between the American Association for the Study of Liver Disease (14) and the European Association for the Study of the Liver(15). However these phases are distinguished by HBeAg status, necroinflammatory activity (mainly defined by ALT level) and HBV viral load (16). Treatment with antiviral therapy is generally recommended in patients with an HBV viral load exceeding at least 2,000 IU/ml associated with an elevated ALT. In many jurisdictions, including Australia, subsidised treatment with antiviral therapy is limited to this group of patients. However, more recently, a fifth phase called “occult HBV infection” (OBI), where HBsAg is undetectable but HBV DNA is detectable in the plasma has now also been defined (17).

First line oral antiviral therapy for CHB consists of 3 nucleos(t)ide analogues (NAs): entecavir, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). These drugs are renally excreted and appropriate dose adjustments are required in renal impairment and dialysis. The aim of treatment is to achieve an undetectable HBV viral load and therefore to reduce

liver disease such as cirrhosis and hepatocellular carcinoma (HCC), but also to prevent transmission to other individuals (15). Patients who have elevated viral loads and meet treatment guidelines should be given antiviral therapy, but those with a low level viraemia (< 2000 IU/ml) and a normal ALT may not normally be treated due to a significantly lower risk of hepatic disease progression, despite being HBsAg positive. However, this means that such patients would require lifelong isolation during dialysis. We believe that patients with low level viraemia, who would not normally be eligible for treatment according to current guidelines despite being HBsAg positive (18), *should* be considered for treatment in this setting in order to further reduce the risk of transmission, especially in settings where HD isolation is impractical or impossible. This raises the issue of whether individuals with persistently undetectable HBV viral loads on antiviral therapy still require isolation, especially if they have become HBsAg negative. Data to support this are currently lacking, but this is the approach taken in healthcare workers (HCW) who practice exposure prone procedures (1) and may also be appropriate in the dialysis setting.

Screening and Vaccination

The cornerstone of HBV prevention is vaccination, which is effective in more than 93% of healthy individuals after three doses (19). The recommendation of screening and vaccination of both patients and staff is a sensible and important step to reduce risk in dialysis settings. Current guidelines suggest that screening should consist of testing for surface antigen (HBsAg), and antibodies to core and surface antigens (anti-HBc and anti-HBs respectively).

Evidence of pre-existing immunity from natural infection is anti-HBs >10 IU/ml and positive anti-HBc, or evidence of vaccination is anti-HBs >10 IU/ml and negative anti-HBc (1). If negative for all three of these markers, both patients and staff should be vaccinated (5,20) with high dose injections at 0, 1 and 6 months. Vaccination is highly effective and long lived in the normal population when given early to healthy individuals. An Italian study of medical students tested for evidence of immunity from vaccinations given by National program in early years showed ~99% efficacy with ~1% without protective immunity (HBsAb<10), and all but one of these was born outside Italy and may not have been vaccinated (21). In contrast, vaccination of patients with CKD and on dialysis is less effective and HBsAb and protective immunity is not long lived. One meta-analysis suggest that high dose HBV vaccination provides seroconversion in ~50-97% of haemodialysis patients with higher doses being more successful than lower ones(22). In the general population, the antibody responses are fairly long lived but a Chinese study showed that antibody titres decayed rapidly in HD and PD patients with geometric mean titres inadequate (<10IU/ml) after 2 years (23). Those who do not develop an adequate antibody response should be given a 4th booster and re-assessed for immunity. The development of anti-HBs levels should be tested after 4-8 weeks with the aim of developing titres of > 10 IU/ml. Testing for HBsAg before 4 weeks can be misleading as transient HBsAg detection during this time from the administration of the vaccine itself has been reported (24). If this is still unsuccessful, consideration should be given to one of the new Pre S vaccines which are highly effective in non-responders (25). Intradermal vaccination (26) is highly controversial and is not currently recommended. If immunity still cannot be

achieved, then HCW should avoid dialysing patients with HBsAg or possibly Anti-HBc regardless of anti-HBs status, and non-responding patients should be considered vulnerable and not dialysed in close proximity to HBVsAg or anti-HBc positive patients.

Although the role of post exposure antiviral therapy is currently unclear, unprotected HCW should also be aware of the post-exposure prophylactic measures that could be used in the event of an accidental exposure (e.g. HBIG)(27).

HBV vaccination (40mcg of HBVaxII IM at 0, 1, and 6 months) should be performed in the earliest possible stage of chronic kidney disease (CKD), as the likelihood of seroconversion is reduced as renal function declines (28). In Australia, patients are required to pay for these vaccinations, whereas others considered in high-risk groups (e.g. HCV positive, sex workers, men who have sex with men and haemophiliacs) receive free vaccination. Unlike immunocompetent staff, in whom once vaccinated, an anti-HBs >10 IU/L is considered adequate protection, antibody levels in patients should be repeated annually as they have been shown to wane relatively quickly and immunological memory is not as reliable (23) . Ideally patients should have Anti-HBs >100 IU/L , but even >10 IU/L appears to provide good protection, but boosters (or pre-S vaccination) should be given where the anti-HBs levels drop below 10 IU/L (25). Successful vaccination is helpful not only to prevent transmission within dialysis units, but also allows transplantation from donors who are anti-HBc positive.

Patients identified as having detectable plasma HBsAg should undergo an individual specialist assessment.

Machine isolation

Traditionally, dialysis machines used for patients with HBsAg are isolated for use only for HBV patients. This practice has been recently challenged by some nephrologists, since machine manufacturers go to great lengths to ensure that the blood path can never contaminate other parts of the machine, and this theoretically means there should never be carry-over between patients. Weak points where blood contamination may potentially occur include pressure transducers (despite anti-reflux mechanisms at the connecting nipples) or blood leaks into the dialysate from dialyser malfunction. Fluid pathways are however designed such that any contamination will not flow back to the next patient. Cleaning of all the fluid paths with heat sterilisation (>80°C for >15mins) along with a thorough machine surface clean (with aldehydes, alcohols, cationic surfactants or bleach), are generally excellent protective strategies. Most transmission events between dialysis patients have been tracked to surface contamination of shared equipment (e.g blood pressure cuffs). A full wipe down of machines and ancillary equipment is time consuming and care is needed that this is performed diligently every time to inactivate any residual virus. The purpose of isolating patients is to physically separate them and the ancillary equipment and staff caring for a viraemic patients to avoid human error e.g. reaching across to silence alarms without changing gloves. Nevertheless, some nephrologists feel that machine isolation is now unnecessary, as long as equipment and staff are not shared during sessions and careful cleaning occurs. Machine or patient isolation may be impossible or at least exceptionally difficult in some units. However, the basic infection control precautions of hand hygiene, keeping used and unused medication trolleys

separate and avoiding multidose vials and regular audits are fundamental in prevention of all BBV infection.

Thus, knowing the HBV status, especially HBV viral load, of every patient in the unit and having an audit trail of machines and dialysis spaces used is vital to adequately risk assess and to perform contact tracing if required.

Diagnostic role of HBV DNA

Hepatitis B viral load by PCR has been shown to directly correlate to clinical outcomes such as cirrhosis and hepatocellular carcinoma (HCC) as well as being a marker of infectivity. It is routinely performed in HBsAg positive patients and has become an integral part of the assessment of CHB as well as response to therapy. The assay techniques are now very reliable, standardised, sensitive and specific with very low detection limits with the lower limit of detection of currently available assays is 10-20 IU/ml (15). In the current CARI guideline on blood borne viruses in dialysis patients, there is no discussion or requirement to measure HBV DNA in the plasma (5). Yet, if measured the results can be a source of confusion (table 1)

A patient who is HBsAg negative, anti-HBc negative and anti-HBs positive indicates that the patient is immune through vaccination, and yearly anti-HBs titres indicate when a booster vaccination is required (<10 IU/ml). Such a patients does not need HBV DNA testing, unless there is suspicion of an acute hepatitis.

We strongly suggest that any patient who has anti-HBc antibodies or who has at any time has been HBsAg positive has a baseline HBV DNA test, and that this is repeated if anti-HbsAb

waned or there is any immunosuppression. A negative HBV DNA test in any dialysis patient indicates that such an individual has a very low risk of transmitting virus.

If a patient is anti-HBc positive but they are HBsAg negative and HBV DNA negative they can be considered to have low infectivity risk and managed with other patients without any isolation. However, HBsAg and HBV DNA should be periodically rechecked (3-6 monthly with a low threshold for re-testing) in order to detect reactivation. If HBV is detected consider treating to render the DNA undetectable to render HBV viral load undetectable and NA therapy can be used if necessary, to achieve this and the patient should undergo ultrasound +/- alpha fetoprotein (AFP) for HCC screening periodically (29). Reactivation is more likely if patients are immunosuppressed and notably drugs like corticosteroids, anti-CD20 agents and others are a particular risk.

Occult HBV Infection (OBI)

Occult HBV infection (OBI) is defined by the presence of an episomal (not genome integrated) replication-competent, plasmid-like intermediate of the HBV virion, the cccDNA minichromosome in the hepatocytes of infected individuals. As a consequence, virion DNA may be detectable by PCR in the plasma of persons who are HBsAg negative. Typically, an individual is anti-HBc positive and anti-HBs negative, but may occasionally be anti-HBc positive and anti-HBs positive (seropositive OBI) (15). In the more common situation DNA levels may be detected intermittently by currently approved PCR assays and usually at low levels <200 IU/ml (15). More worryingly DNA can also occasionally be detected even in those

who have *no serological* markers of past HBV infection; anti-HBc negative, HBsAg negative, anti-HBs negative (seronegative OBI) (15).

There are however documented cases of blood transfusion and organ donation where DNA positivity *alone* appears enough to transmit HBV. This is concerning, and all donors and blood pools are currently tested for HBV by nucleic acid testing (NAT). NAT testing has a high specificity of 99.9% and an even lower limit of detection of 2-4 IU/ml when applied to individual units. In essence therefore, the principle is that the presence of HBV DNA, regardless of viral load level, equates to infectivity.

In some people OBI is due to infection with a mutant s gene ('S-escape' mutations), s promotor or splice variant, which produces an HBsAg that is not recognised by current commercial assays, but this is very uncommon (15).

As discussed above, these OBI cases are related to the persistence of small circular chromatinised episomal HBV DNA sequences (covalently closed circular intrahepatic DNA-cccDNA) that are replication competent. These 'mini chromosomes' are transcriptionally active and produce HBV RNA, which may be able to drive viral protein production. The cccDNA may be detected in the liver but never in the serum. Since hepatocytes are long-lived cells, they may persist for some time and may cause immune responses associated with viral suppression and limited control but may not generate traditional clearing "neutralising" antibodies.

The lower limit of detection of most currently available commercial HBsAg assays is 0.05 IU/ml. Recent studies found that between 1% and 48% of samples that tested negative using these assays, test positive using more sensitive HBsAg assays with a lower limit of detection of 0.005 IU/ml. The lower limit of detection of available commercial HBV DNA assays is 10–20 IU/ml and it is reassuring to know that HBV DNA assays have similar performance across the ten different HBV genotypes and subtypes, because DNA is usually present in low concentrations and only intermittently (15).

A report from Slovenia describes three HBsAg negative, DNA negative blood donors who transmitted the virus to 9 recipients of their blood products. On the basis of these cases the infectious ‘dose’ of DNA was revised from 20 IU/ml down to 3 IU/ml of HBV DNA (HBV 1 IU/ml = 5.6 copies/ml). The NAT sensitivity required to prevent HBV transmission by transfusion would therefore need to be lowered from the current 3.4 IU/ml to a new lower limit of detection of 0.15 IU/ml (~0.84 copies/ml) to detect such cases (Wolfram Gerlich, personal communication). However, in the case of dialysis unit transmission the inoculum is likely to be small, unlike blood product transfer where often several hundred millilitres is transfused. For example in the case of a 16G hollow bore needlestick injury, the transfer volume is ~0.5 µl (30) even if present at 0.15 IU/ml, would work out at ~0.00075 IU or 0.0042 copies) probably too low to be infectious, and thus NAT sensitivity is likely to be enough to prevent transmission. Using this threshold then, we reason that risks from dialysis patients are exceptionally low (but not zero) with viral loads less than the lower limit of detection of commercial NAT assays if they are HBsAg negative.

Taken together, we recommend that all patients who are either HBsAg or anti-HBc positive should undergo regular HBV DNA testing.

Illustrative Examples

1. HBsAg neg, Anti-HBc pos, Anti-HBs neg, DNA undetectable.

This is an example of an isolated anti-HBc positive result with undetectable HBV viral load. HBV viral loads are undetectable in the vast majority of such individuals. Such an individual has acquired HBV and has at some point lost HBsAg and not acquired anti HBs or lost it. They can be safely dialysed without special precautions, but should be periodically checked for viral replication, especially if immunosuppressed.

2. HBsAg neg, Anti-HBc pos, Anti-HBs pos (titre 40 IU/ml), DNA detectable at < 20 IU/ml.

This patient has naturally acquired HBV and has resolved infection and developed immunity, but despite having circulating antibodies to the virion, has detectable DNA in the plasma. This is an example of OBI defined by detectable HBV viral load. We feel that this individual is at very low risk and probably does not need to be dialysed in isolation, but ideally patients dialysing nearby should have anti-HBs levels >100 IU/L. The patient does however require regular HBV DNA testing and follow up and, if this increases, they may also require isolation.

We believe that there is no reason why low-level detectable HBV viral load, HBsAg neg patients should not be transplanted BUT they should receive lifelong antiviral therapy post-transplant with first line nucleos(t)ides such as entecavir and tenofovir.

3. HBsAg neg., Anti-HBc pos, Anti-HBs neg, HBV DNA 14,000 IU/ml and normal LFTs.

This is also a case of OBI with an isolated anti-HBc profile but a significantly elevated HBV viral load. Such individuals need isolation and expert advice on treatment which may be considered for infectivity reasons despite normal liver function tests, although such an elevated viral load may also increase the risk of liver-related endpoints such as HCC as well.

4. HBsAg-neg, Anti-HBc pos, Anti-HBs pos (titre 70) HBV DNA detectable but <20 IU/ml.

This is another case of seropositive OBI. This individual should be isolated if easy to do so, but if not, ensure patients nearby and staff have detectable anti-HBs, ideally > 100 IU/L. DNA should be routinely reviewed 3-6 monthly.

Conclusion

The HBV virus in the dialysis patients may not be straightforward, as the field is dynamic and changing rapidly. Vaccination is the cornerstone of prevention for both patients and HCWs, and more patients/staff should be receiving the newer pre-s vaccines. In Australia, more work needs to be done to obtain vaccination for those who cannot afford to pay for it. HBV DNA assessment is critical to determining infectivity. Patients who meet treatment criteria should be referred for specialist care and offered antiviral therapy. Patients who do not meet treatment criteria but have significant HBV viral loads should be considered for therapy to minimise the risk of transmission. Patients with HBsAg or HBV DNA >200 IU/ml should be

isolated, and the infectivity risk assessed by experts in viral hepatitis. Those who are HBsAg-neg and HBV DNA <20 IU/ml can be dialysed with others (preferably who are anti-HBs-positive with a titre of at least >10 IU/L) but should be expertly reviewed regularly. Patients with HBV DNA <200 IU/ml are likely of low infectivity but should only be dialysing near another patient who ideally has an anti HBs titre >10 but preferably > 100 IU/ml.

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COI declaration

SGH declares no conflicts of interest.

SL provides consultant services to all the major pharmaceutical companies involved in hepatitis B drug development. He is a named inventor on 14 patents and two copyright agreements. Seven of these patents have been licensed to Evivar Pty Ltd, a listed start-up company jointly developed by Melbourne Health (RMH) and the Australian Technology Fund (ATF) (see www.evivar.com). Stephen is a scientific consultant and member of the Board of Management of Evivar Pty Ltd.

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Table 1: HBV Serology and DNA results with suggested management.

USS= ultrasound liver , AFP= Alphafetoprotein blood testing yearly

Table 1	HBsAg	Anti-HBcAb	Anti-HBsAb	HBV DNA	Isolate	Action	Needs virologist review
Not immune	negative	negative	negative	Only indicated for acute hepatitis	Isolate from any potentially positive patient	Vaccinate	No
Immune through vaccination	negative	negative	>10IU/ml	not indicated	no isolation	Repeat HBsAb yearly and booster if <10.	No
Active HBV	positive	positive	negative	indicated for monitoring	Isolate	Treatment indicated; USS +/-AFP	Yes
Chronic hepatitis B	positive or negative	positive	Positive or negative	>200 IU/ml	isolate	Consider treatment; USS+/- AFP	Yes
Seropositive OBI	negative	positive	usually negative (occ positive)	<20 IU/ml or negative	no isolation	Monitor HBV DNA 3-6 monthly	Yes
Seropositive OBI	negative	positive	usually negative (occ positive)	20-200 IU/ml	isolate if possible but low infectivity	Monitor HBV DNA 3-6 monthly	Yes
Seronegative OBI	negative	negative	negative	detected	Isolate	Recheck results; carefully look for seroconversion monitor viraemia	Yes