HEPATITIS SEROLOGIC TESTS IN HEMODIALYSIS PATIENTS: INTERPRETATION AND IMPLICATION FOR DIALYSIS FACILITIES

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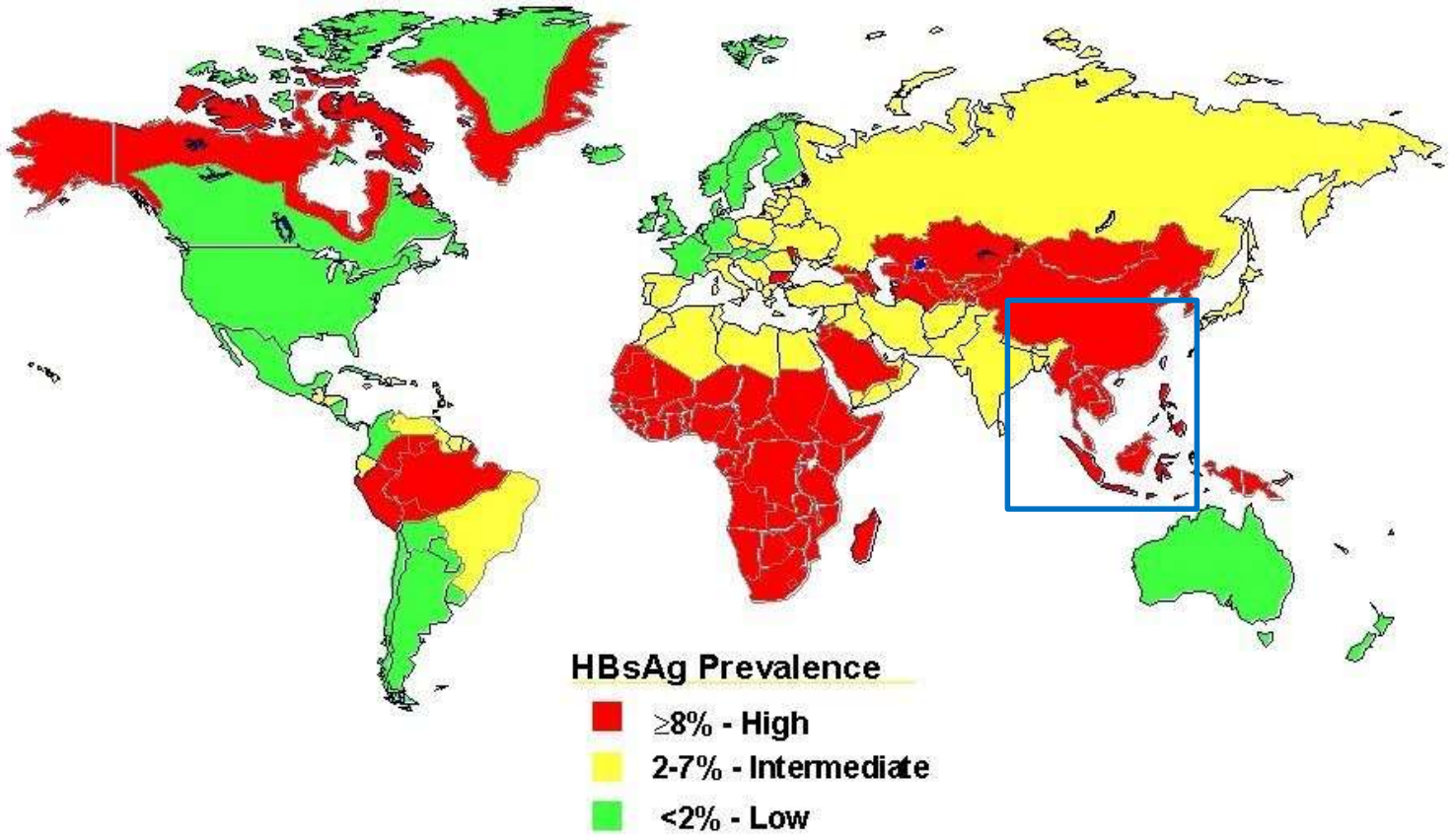
WHY DISCUSS THIS?

Because of our geographical location
Because it can cause a disease with serious implication
Because the dialysis facility is a high risk area
Because we can do something about it
Because we all advocate for safe patient care

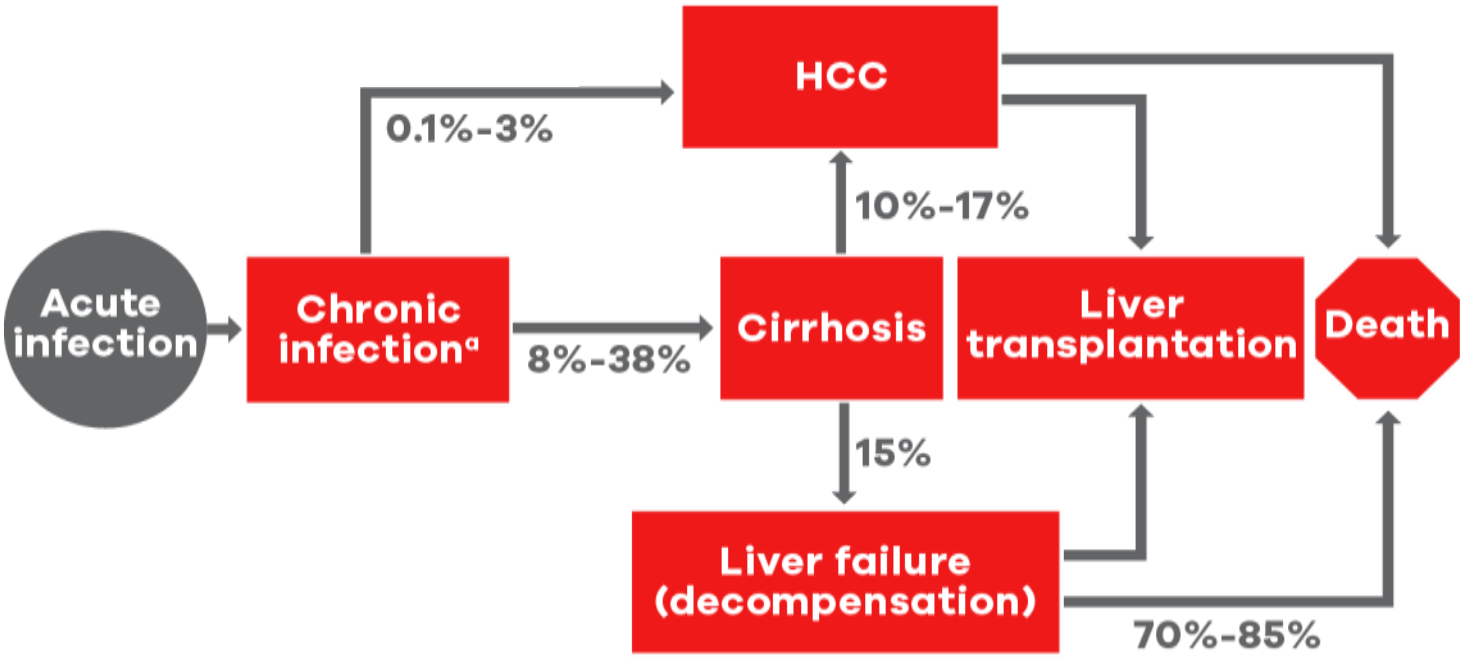
Geographic Distribution of Chronic HBV Infection



Source: CDC. Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services, CDC

Hepatitis B Complications

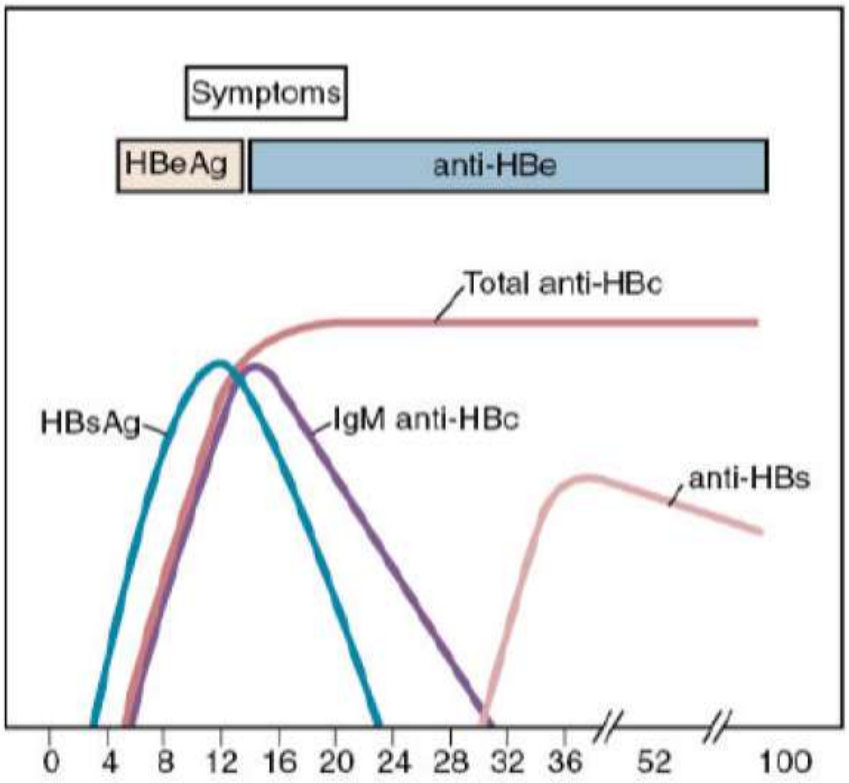
- Fulminant hepatitis
- Hospitalization
- Cirrhosis
- Hepatocellular carcinoma
- Death



Serology and course of HBV infection

Acute infection - with recovery

Acute – progression to chronic infection



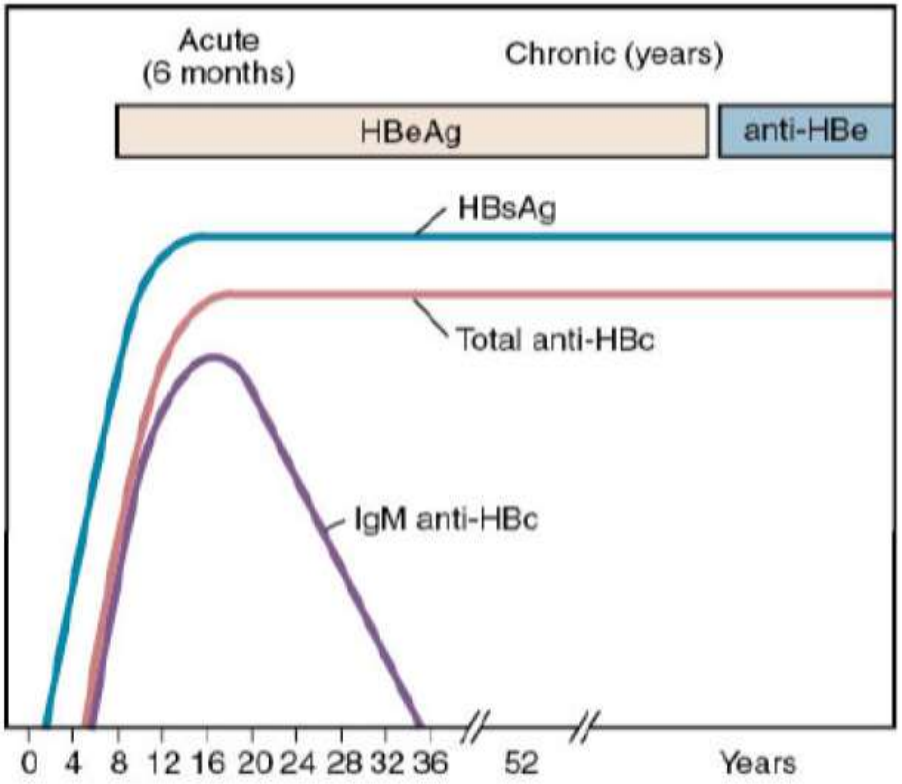


Figure 146-8 Typical course of hepatitis B. Left, Typical course of acute hepatitis B. **Right,** Chronic hepatitis B. HBc, hepatitis B core; HBe, hepatitis B early; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

HBV Serology: #101

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

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HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

"Low level" chronic infection = OBI

What is occult HBV infection (OBI)?

Definition: Presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) of individuals testing HBsAg negative by currently available assays.

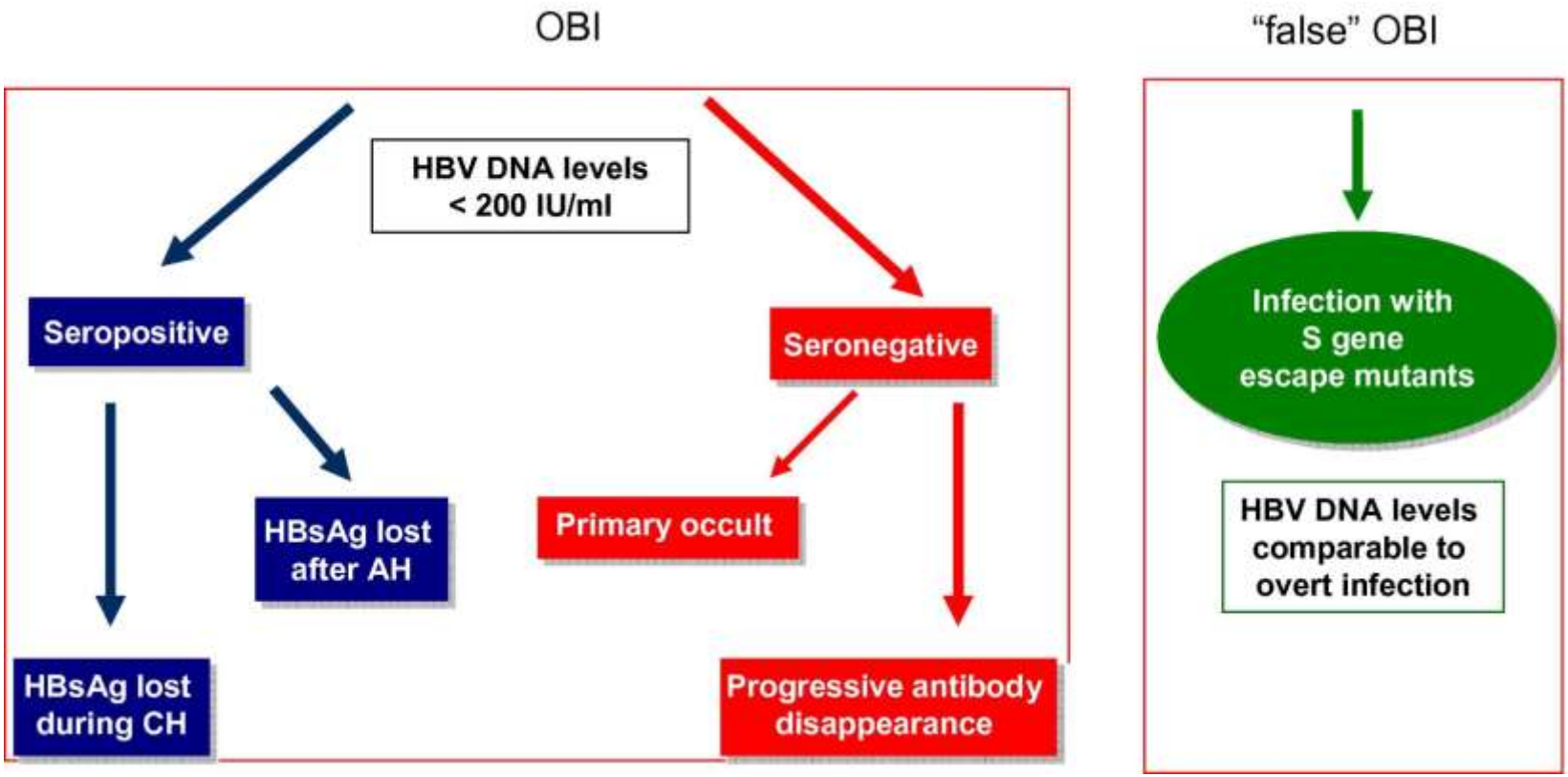
On the basis of the HBV antibody profile, OBI may be distinguished as:

1. **Seropositive-OBI** (anti-HBc and/or anti-HBs positive).
2. **Seronegative-OBI** (anti-HBc and anti-HBs negative).

“Occult” B infection

Seropositive (80%)
Anti-HBc or anti-HBs positive

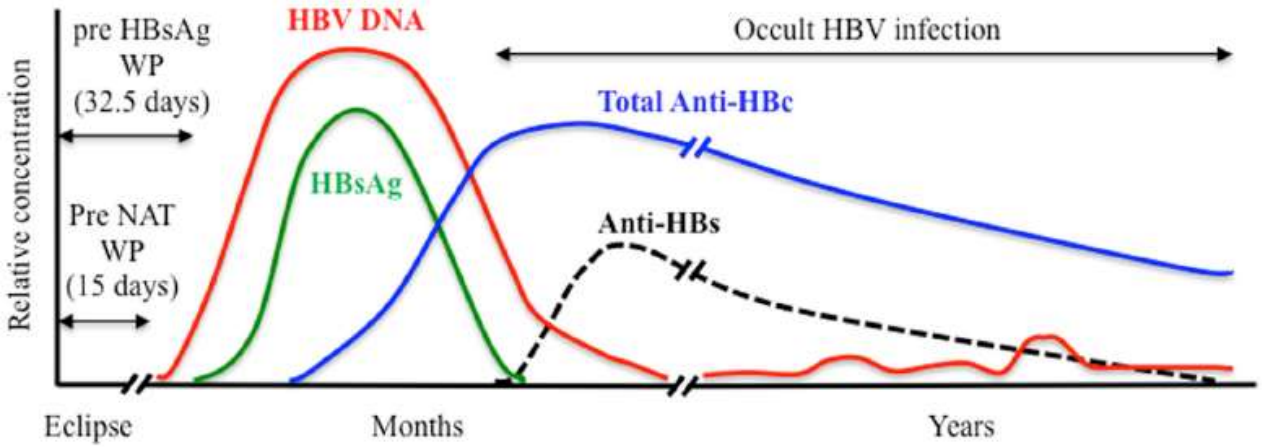
Seronegative (20%)
Anti-HBc and anti-HBs negative



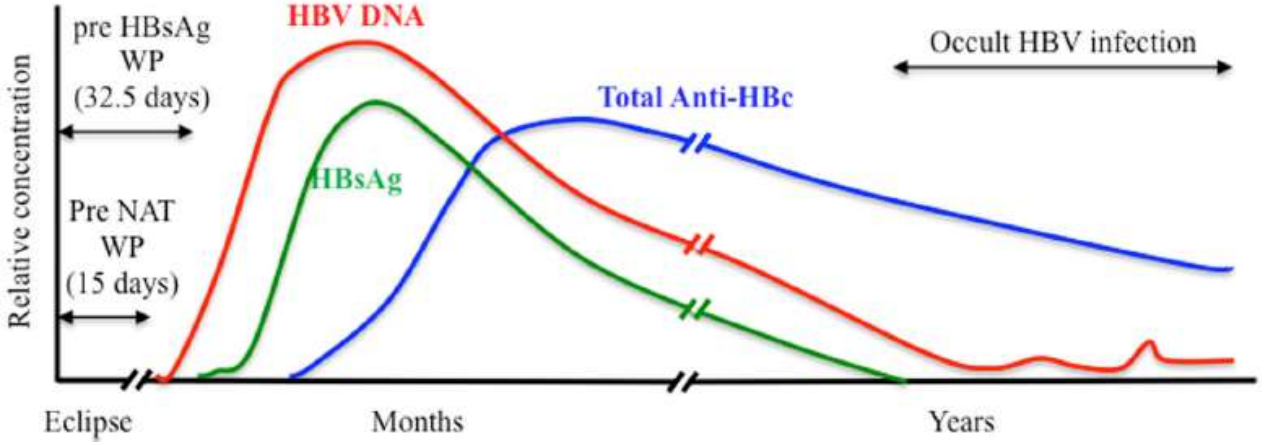
European Association for the Study of the Liver
- Expert meeting in 2008

Journal of Hepatology 49 (2008) 652–657

Recovered HBV infection



Chronic HBV infection



Front. Med. 21 February 2018

Serology in the diagnosis of HBV infection

Table 3. Diagnosis of Acute and Chronic Hepatitis B Virus (HBV) Infection

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBV DNA Detected	Interpretation Details
HBV infection	Positive	Negative	Positive	Positive	• Presence of HBsAg for >6 mo defines chronic infection • In acute infection, anti-HBc is in the form of IgM
Resolved infection	Negative	Positive	Positive	Negative	• Adults infected with HBV will resolve infection within 6 mo • HBsAg is no longer detected (termed *HBsAg loss*) • 80% of adults will develop anti-HBs (termed *anti-HBs seroconversion*)[20] • Anti-HBc is present in the form of IgG
Immunity	Negative	Positive	Negative	Negative	• Immunity gained through vaccination
Isolated core	Negative	Negative	Positive	Negative or positive	• Undetectable HBV DNA: previous infection without anti-HBs or level of anti-HBs is below the level of detection by serological test[a] • Detectable HBV DNA: occult HBV infection[a] • Period during resolution of acute infection after HBsAg loss and before appearance of anti-HBs • False-positive test result

Abbreviations: anti-HBc, HBV core antibody; anti-HBs, HBV surface antibody; HBsAg, HBV surface antigen.

[a] Individuals at risk for disease reactivation and should be identified prior to immunosuppressive therapy.

Diagnostic tests for OBI

- Ability to detect very low level of viremia (usually < 200 iu/ml)
- Ability to detect mutants or variants
- False negative vs False positive

- The preferred lower limit of detection (LLOD) for HBV DNA, standardized by the World Health Organization (WHO), is ≤5 IU/mL or ~30 copies/mL

An international collaborative study to establish the 2nd World Health Organization International Standard for hepatitis B virus DNA nucleic acid amplification technology-based assays. Vox Sang. 2008, 94, 358–362

Table 1. Prevalence rates of occult hepatitis B in patients undergoing renal replacement therapy (hemodialysis).

Authors	Year	Country	Population (n)	Prevalence
Cabrerizo[39]	1997	Spain	33	19 (58%)
Minuk[41]	2004	Canada	241	9 (3.8%)
Fabrizzi[42]	2005	Italy	585	0 (0%)
Teruel[43]	2005	Madrid	61	0 (0%)
Siagris[44]	2006	Greece	49	10 (20.4%)
Goral[45]	2006	Turkey	50	0 (0%)
Yakaryilmaz[46]	2006	Turkey	188	5 (2.7%)
Altindis[47]	2007	Turkey	153	19 (12.4%)
Jardim[48]	2008	Brazil	34	0 (0%)
Ersoy[49]	2008	Turkey	80	1 (1.25%)
Gwak[50]	2008	Korea	83	0 (0%)
Di Stefano[51]	2009	Italy	128	34 (26.6%)
Motta[52]	2010	Brazil	100	15 (15%)
Mina[53]	2010	Greece	366	3 (0.9%)
Aghakhani[54]	2010	Iran	289	9 (3.11%)
Ismail[55]	2010	Egypt	116	2 (3.8%)
Sav[56]	2010	Turkey	71	12 (16.9%)
Makarem[57]	2012	Egypt	145	6 (4.1%)
Joukar[58]	2012	Iran	514	0 (0%)
Albuquerque[59]	2012	Brazil	752	3 (1.5%)

Annals of Hepatology 2013; 12(4): 356-363

Significance of occult HBV in HD facility

- Is it transmissible?
- Is it transmissible via dialysis facility – how?
- Is Standard Precaution good enough to prevent transmission?
- Do we need to segregate or isolate them?

Significance of OBI in BBV transmission

- **Blood transfusion – YES**
- **Organ (especially Liver) Transplant – YES**
- Hemodialysis facility – UNKNOWN

** Reactivation of HBV in the context of patient receiving biologic agent or chemotherapy: high viral load (viremia) at that period of time can increase risk of transmission

Risk of HIV, HBV and HCV transmission in health care settings

Estimated risk of getting these infections from a contaminated syringe or needle.

- HBV can survive for seven days outside the human body and can cause infection if it enters the body of a person who is not infected.
- HCV can survive for up to three weeks on environmental surfaces at room temperature.
- HIV can survive in dried blood at room temperature for up to three days.

HEALTH CARE WITHOUT AVOIDABLE INFECTIONS

World Health Organization

Management of BBV Infected Patients

In addition to standard precautions

- Staff should not care for BBV positive patients and BBV negative patients at the same time including the period when HD is being discontinued on one patient and commenced on another.
- The external surface of the HD machine should be cleaned with detergent and water and disinfected using a disinfectant advised by the manufacturers after each use. Use a disinfectant with virucidial activity against BBVs. Special attention should be paid to frequently touched areas on the machine (e.g. control buttons).
- The fluid pathways of the HD machine should be disinfected after each treatment (heat and/or chemical, as per manufacturer's instructions).
- Reusable medical equipment such as blood pressure monitoring equipment, trays, stethoscopes and glucometers should be cleaned and disinfected as per manufacturers' instructions before use on another patient.

HBsAg positive patients

In addition to standard precautions

- HBsAg positive patients should be dialysed in a separate isolation room on dedicated machines with HBV immune staff dedicated for that dialysis shift.
- There is a significant risk of HBV being transmitted via environmental surfaces and therefore a dedicated machine should be used for HBV infected patients.

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April 27, 2001 / Vol. 50 / No. RR-5

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Recommendations and Reports

Management of HBsAg-Positive Patients

- Follow infection control practices for hemodialysis units for all patients.
- Dialyze HBsAg-positive patients in a separate room using separate machines, equipment, instruments, and supplies.
- Staff members caring for HBsAg-positive patients should not care for HBV-susceptible patients at the same time (e.g., during the same shift or during patient changeover).

Isolated Anti-HBc–Positive Patients.

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- If total anti-HBc is positive and IgM anti-HBc is negative, follow recommendations for vaccination.
  - If anti-HBs is <10 mIU/mL even after revaccination, test for HBV DNA.
  - If HBV DNA is negative, consider patient susceptible (i.e., the anti-HBc result is a false positive), and test monthly for HBsAg.
  - If HBV DNA is positive, consider patient as having past infection or "low-level" chronic infection (i.e., the anti-HBc result is a true positive); no further testing is necessary.
    - Isolation is not necessary because HBsAg is not detectable.
- If both total and IgM anti-HBc are positive, consider patient recently infected and test for anti-HBs in 4–6 months; no further routine testing is necessary.
  - Isolation is not necessary because HBsAg is not detectable.

CDC does not recommend isolation or having a dedicated HD machine for low level viremia (HBV DNA POS but HBsAg NEG) – also known as OBI.

Infection Control Guidelines on Nephrology Services in Hong Kong 2018

Potential risks for transmitting BBV in dialysis units

The most common causes known to be responsible for BBV transmission in dialysis units are as follows:

1.1.1 Sharing of multi-dose vials of drugs. [17,20–24,26,32,33]

1.1.2 Caring patient with contaminated hands or gloves as the healthcare workers have not properly performed hand hygiene or changed their gloves. [20,27,32,34,35]

1.1.3 Failing to clean and disinfect dialysis machines, equipment, supplies and environmental surfaces properly when they are shared between patients. [22,32,33,36,37]

1.1.4 Failing to prevent contamination of parenteral medications which are prepared on common mobile medication carts at patients' dialysis stations. [32,33]

1.1.5 Failing to identify and isolate patients who are positive for the hepatitis B virus (HBV). [1,20–22,27,28,32]

1.1.6 No dedicated haemodialysis machines, equipment, supplies or staff for the HBsAg positive patients. [20–22,27,30–32]

1.1.7 Failing to vaccinate susceptible patients against HBV. [20,21,25,32,39]

Prevention of BBV transmission in dialysis units

Based on the above experiences, the following guidelines should be strictly observed in addition to those stipulated in section 7 of this document, so as to prevent any potential risks which may arise in haemodialysis, especially for patients with hepatitis B:

1.2.1 Isolate HBsAg positive or HBV DNA positive patients in a separate room or cubicle. [32]

1.2.2 Dedicate staff for HBsAg positive or HBV DNA positive patients in the same dialysis session, if possible. [32]

1.2.3 Dedicate dialysis machines, equipment, instruments, medications and supplies for HBsAg positive or HBV DNA positive patients. [32]

1.2.4 Do not reuse dialyzers. [32]

1.2.5 Vaccinate all susceptible patients against hepatitis B. [32]

32. Centers for Disease Control and Prevention (US). Recommendations for preventing transmission of infections among chronic hemodialysis patient. MMWR. 2001;50(RR05): 1-43. Available from:

FREQUENTLY ASKED QUESTIONS (FAQS)

Q1. For patients with the following serology result: anti-HBc positive, HBsAg and anti-HBs negative, should they be classified as HBV infected and dialyzed together with HBsAg positive patients?

A1. An isolated anti-HBc positive would suggest occult hepatitis B infection or past infection. Further testing e.g. HBV DNA may be used to confirm the low level infection. If HBV DNA is positive, the patient should be regarded as HBV infected and dialyzed together with HBsAg positive patients; on the contrary, if HBV DNA is negative, the patient should be regarded as susceptible to hepatitis B and dialyzed together with HBsAg negative patients.

Patients with occult hepatitis B infection usually have low and fluctuating levels of HBV DNA viremia. They may be a source of HBV transmission in haemodialysis setting.

Q2. For patients who are anti-HBc positive, HBsAg, anti-HBs and HBV DNA negative, how often should HBsAg and HBV DNA be checked?

A2. HBsAg should be checked every 6 months for patients on haemodialysis. The frequency of HBV DNA checking should be individualized, based on consideration of multiple factors (e.g. comorbidities, transplantation, chemotherapy, immunosuppressive therapy and antiviral treatment).

The prevalence of occult hepatitis B virus (hbv) infection in a large multi-ethnic haemodialysis cohort

Luciana Sowole[1], Wendy Labbett[1], Mauli Patel[1], Aisling O'Riordan[2], Jennifer Cross[2], Andrew Davenport[2,3*] and Tanzina Haque[1]

Royal Free London NHS
NHS Foundation Trust

BMC Nephrology

Results: 15 (2%) of 793 patients had chronic HBV infection (HBsAg positive). 161 (20%) were anti-HBcAb positive but HBsAg negative suggesting past infection. 335 (54%) of the remaining 617 patients were considered immune following vaccination (anti-HBsAb > 10 IU/L). Three (2.2%) of the 138 anti-HBcAb positive, HBsAg negative patients had detectable HBV DNA (3, 5 and 9 IU/ml). Standard liver function tests were normal in these patients.

It is difficult to ascertain the exact levels of HBV DNA in blood that may lead to transmission in the haemodialysis setting. The UK Department of Health guidelines recommend that HBV infected healthcare workers can be allowed to perform exposure prone procedures if their HBV DNA level is suppressed to <1,000 copies/ml (around 250 IU/ml) [17].

Who to screen for OBI?

- Blood and organ donor
- Those undergoing biologic therapy and chemotherapy
- Those with unknown cause of liver cirrhosis
- Those to be treated for chronic HCV infection
- **All maintenance HD patients with anti-HBc POS?**

OBI in HD facility

- Transmission in HD facility has never been reported (from OBI) – OBI has been known since the early 90s
- Do we manage OBI in HD facility the same as for HBsAg POS or more like HCV POS and HIV POS?
- Is there harm in placing a patient with “OBI” diagnosis with those HBsAg POS patients?
- Added cost of screening for OBI – how frequent or just once?
- HBV DNA in OBI can fluctuate – between detectable viremia and not detectable: how to rule out OBI conclusively?

KDIGO 2018 CLINICAL PRACTICE GUIDELINE FOR THE PREVENTION, DIAGNOSIS, EVALUATION, AND TREATMENT OF HEPATITIS C IN CHRONIC KIDNEY DISEASE

1.1.2: We recommend screening all patients for HCV infection upon initiation of in-center hemodialysis or upon transfer from another dialysis facility or modality (1A).

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (1A).

The most usual strategy for diagnosis of HCV infection consists of initial screening with an inexpensive serological assay and, if the assay is positive, subsequent NAT. However, in high prevalence settings or very high risk groups, immediate NAT is an appropriate alternative.

1.2.1: We recommend screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients every 6 months (1B).

Surveillance testing for HCV infection

- Those with initial anti-HCV NEG, can be followed up with anti-HCV testing
- Those with initial anti-HCV POS but NAT NEG should be followed up with NAT testing

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HCV-Positive Patients. Patients who are anti-HCV positive (or HCV RNA positive) do not have to be isolated from other patients or dialyzed separately on dedicated machines. Furthermore, they can participate in dialyzer reuse programs. Unlike HBV, HCV is not transmitted efficiently through occupational exposures. Thus, reprocessing dialyzers from HCV-positive patients should not place staff members at increased risk for infection.

Prevention and Management of HIV Infection

Routine testing of hemodialysis patients for HIV infection for infection control purposes is not necessary or recommended. However, patients with risk factors for HIV infection should be tested so that, if infected, they can receive proper medical care and counseling regarding preventing transmission of the virus (*201*).

Infection control precautions recommended for all hemodialysis patients (see Recommended Practices at a Glance) are sufficient to prevent HIV transmission between patients. HIV-infected patients do not have to be isolated from other patients or dialyzed separately on dedicated machines. In addition, they can participate in dialyzer reuse programs. Because HIV is not transmitted efficiently through occupational exposures, reprocessing dialyzers from HIV-positive patients should not place staff members at increased risk for infection.

Chapter 3: Preventing HCV transmission in hemodialysis units

Chapter 3: Preventing HCV transmission in hemodialysis units

3.1: We recommend that hemodialysis facilities adhere to standard infection control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (see Table 1) (*1A*).

Table 1 | Infection control practices ("hygienic precautions") particularly relevant for preventing HCV transmission

- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
- Proper injectable medication preparation practices following aseptic techniques and in an appropriate clean area, and proper injectable medication administration practice
- Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
- Adequate separation of clean supplies from contaminated materials and equipment

3.1.1: We recommend regular observational audits of infection control procedures in hemodialysis units (*1C*).
3.1.2: We recommend *not* using dedicated dialysis machines for HCV-infected patients (*1D*).
3.1.3: We suggest *not* isolating HCV-infected hemodialysis patients (*2C*).
3.1.4: We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (*2D*).

3.3: Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients (*Not Graded*).

Chapter 3: Preventing HCV transmission in hemodialysis units

Transducer protectors

- External transducer protectors should be fitted to the pressure lines of the extracorporeal circuit.
- Before commencing dialysis, staff should ensure that the connection between the transducer protectors and the pressure-monitoring ports is tight, as leaks can lead to wetting of the filter.
- Transducer protectors should be replaced if the filter become wet, as the pressure reading may be affected. Using a syringe to clear the flooded line may damage the filter and increase the possibility of blood passing into the dialysis machine.
- If wetting of the filter occurs after the patient has been connected, the line should be inspected carefully to see if any blood has passed through the filter. If any fluid is visible on the machine side, the machine should be taken out of service at the end of the session so that the internal filter can be changed and the housing disinfected.
- Some blood tubing sets transmit pressure to the dialysis machine without a blood-air interface, thus eliminating the need for transducer protectors.

External cleaning

- After each session, the exterior of the dialysis machine and all surfaces in the dialysis treatment station should be cleaned with a low-level disinfectant if not visibly contaminated. Pay particular attention to high-touch surfaces that are likely to come into contact with the patient (e.g., arm rests or blood pressure cuff) or staff members' hands (e.g., machine control panel).
- Disinfection of external machine surfaces should not commence until the patient has left the dialysis treatment station. A complete (unit-wide) patient-free interval between shifts might facilitate more thorough cleaning and disinfection of the unit.
- If a blood spillage has occurred, the exterior should be disinfected with a commercially available tuberculocidal germicide or a solution containing at least 500 p.p.m. hypochlorite (a 1:100 dilution of 5% household bleach) if this is not detrimental to the surface of dialysis machines. Advice on suitable disinfectants, and the concentration and contact time required, should be provided by the manufacturer.
- If blood or fluid is thought to have seeped into inaccessible parts of the dialysis machine (e.g., between modules or behind the blood pump), the machine should be taken out of service until it can be dismantled and disinfected.

Disinfection of the internal fluid pathways

- It is not necessary for the internal pathways of a single-pass dialysis machines to be disinfected between patients, even in the event of a blood leak. Some facilities may still opt to disinfect the dialysate-to-dialyzer (Hansen) connectors before the next patient.
- Machines with recirculating dialysate should always be put through an appropriate disinfection procedure between patients.

Healthcare-Associated Hepatitis B and C Outbreaks (≥ 2 cases) Reported to the Centers for Disease Control and Prevention (CDC) 2008-2017

Summary

61 outbreaks (two or more cases) of viral hepatitis related to healthcare reported to CDC during 2008-2017; of these, 58 (95%) occurred in non-hospital settings.

Hepatitis B (total 24 outbreaks including one of both HBV and HCV, 179 outbreak-associated cases, >10,935 persons notified for screening):

- 18 outbreaks occurred in long-term care facilities, with at least 133 outbreak-associated cases of HBV and approximately 1,680 at- risk persons notified for screening
  - 83% (15/18) of the outbreaks were associated with infection control breaks during assisted monitoring of blood glucose (AMBG)
- 5 outbreaks occurred in other settings, one each at: a free dental clinic in school gymnasium, an outpatient oncology clinic, a hospital surgery service, and two at pain remediation clinics (one outbreak of HBV and one with both HBV and HCV), with 46 outbreak-associated cases of HBV and > 8,500 persons at-risk persons notified for screening

Hepatitis C (38 total outbreaks including one of both HBV and HCV , >295 outbreak-associated cases, >105,632 at-risk persons notified for screening):

- 14 outbreaks occurred in outpatient facilities (including the above mentioned outbreak of both HBV and HCV), with 116 outbreak-associated cases of HCV and >74,457 persons notified for screening
- 21 outbreaks occurred in hemodialysis settings, with 102 outbreak-associated cases of HCV and 3,026 persons notified for screening
- Three outbreaks occurred because of drug diversion by HCV-infected health care providers, with at least 78 outbreak-associated cases of HCV and >26,217 persons notified for screening

Only HCV outbreaks reported from dialysis facilities in US in past 10 years, no occurrence of HBV outbreak reported.

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Transmission of hepatitis B virus in dialysis units: a systematic review of reports on outbreaks

Aim: We performed a systematic review of HBV outbreaks in dialysis units of developed and less-developed countries published between 1992 and 2014 to elucidate the most frequent mechanisms of patient-to-patient transmission of HBV in this setting.

Authors	Country	Publication year	Outbreak duration (mo)	Incident HBV, *n*	Deaths, *n*
Roll M, et al (11)	Sweden	1995	13	2	0
Tanaka S, et al (12)	Japan	1995	2	5	4
CDC (13)	U.S.	1996			
	(Texas		4	14	0
	California		3	2	0
	California		2	7	0
	California		2	11	0
	Nebraska)		4	4	0
Parry C, et al (14)	U.K.	1997	2	1	0
Hutin Y, et al (15)	U.S. (Pennsylvania)	1999	4	6	0
De Castro L, et al (16)	Brazil	2000	12	5	1
Balshaw A, et al (17)	U.K.	2000	2	1	0
Lewis-Ximenez L, et al (18)	Brazil	2001	13	21	1
Igaki N, et al (19)	Japan	2003	4	5	4
Manfredi R, et al (20)	Brazil	2003	30	29	NA
Kondili L, et al (21)	Italy	2006	17	3	0
Ramalingam S, et al (22)	U.K.	2007	2	2	0

No dialysis facility related HBV transmission were reported from 2008-2014

Int J Artif Organs 2015; 38 (1): 1-7

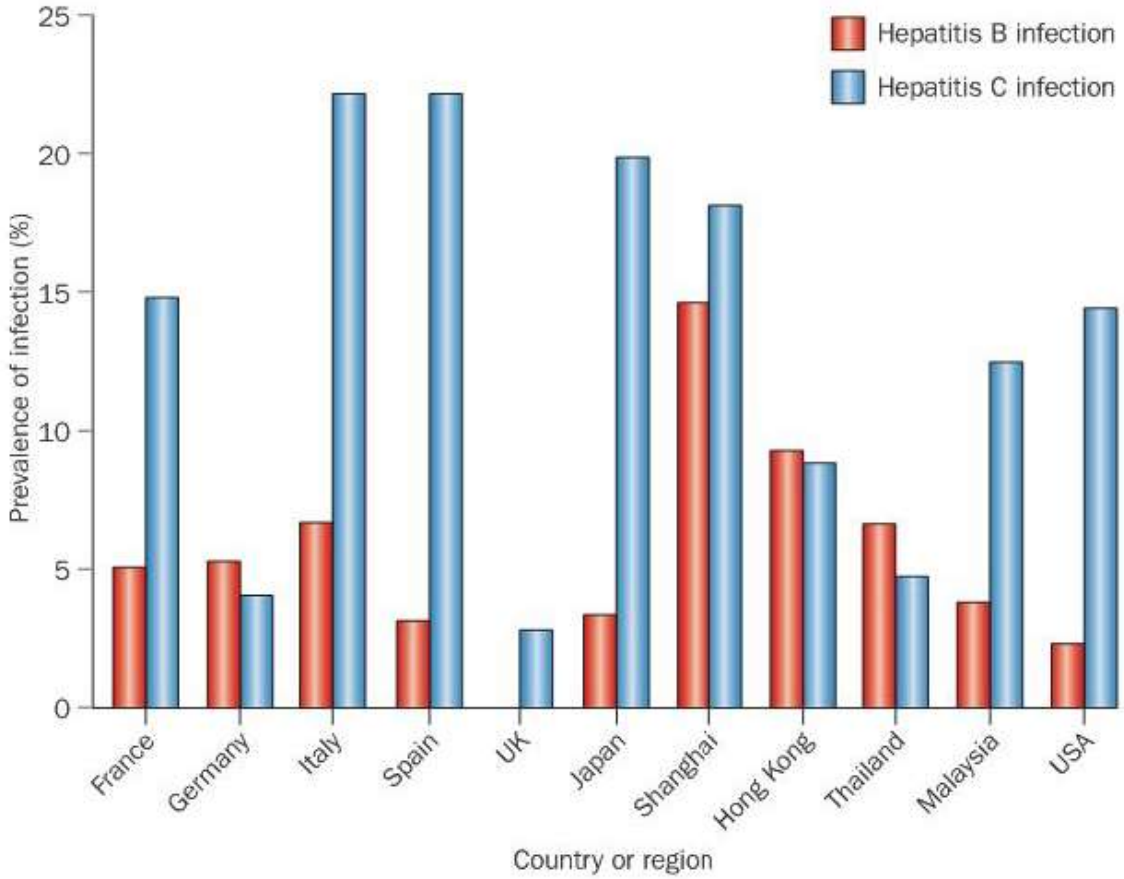
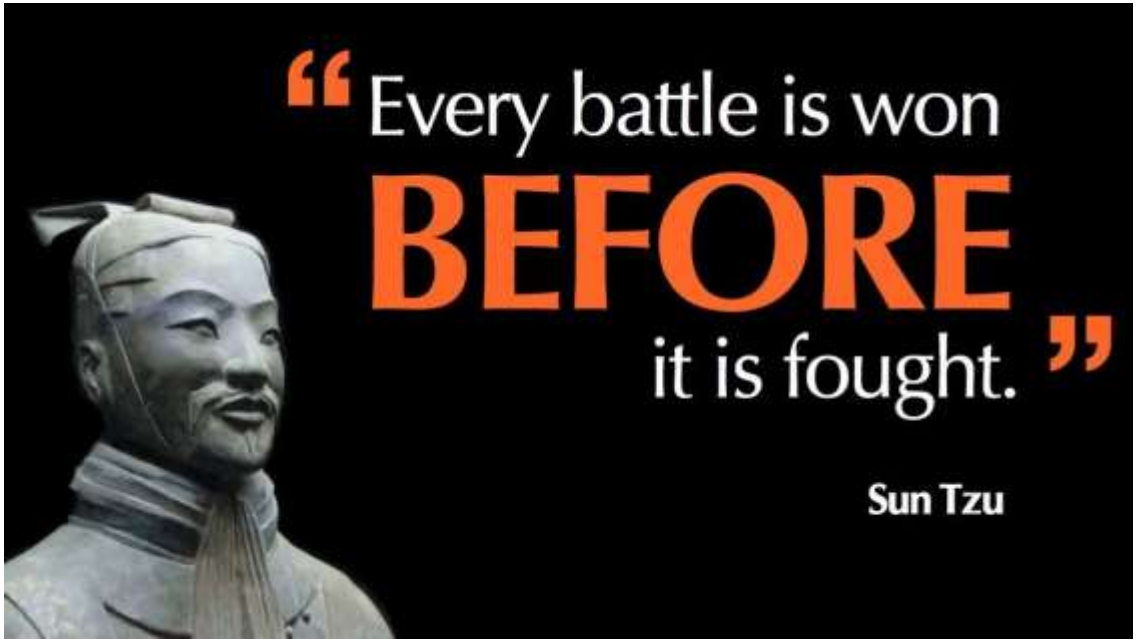


Figure 1 | Variation in hepatitis B and hepatitis C virus prevalence rates in hemodialysis units by country and region. These prevalence data were derived from previous publications (including the Dialysis Outcomes and Practice Patterns Study), which involved cross-sectional cohorts of patients treated in adult hemodialysis facilities.[76–78] The prevalence of hepatitis B infection in the UK is 0%.[76]

76. Burdick, R. A. *et al.* Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int.* **63**, 2222–2229 (2003).
77. Johnson, D. W. *et al.* Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. *Nephrol. Dial. Transplant.* **24**, 1598–1603 (2009).
78. Fissell, R. B. *et al.* Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int.* **65**, 2335–2342 (2004).



Prevent transmission and you don’t need to fight hepatitis.