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Navigating past and current hepatitis B infection in primary care

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BACKGROUND

Chronic hepatitis B (HBV) infection affects 3.5% of the global population.[1] In high-prevalence areas, new infections occur mainly at birth or in childhood. Most HBV in the UK is among migrant populations from areas with high prevalence, such as Sub-Saharan Africa, South-East Asia, and China.[2]

Health care is increasingly reliant on immune-modulating drugs that can exacerbate a chronic infection or allow a past, 'cleared' infection to reactivate. Clinicians may not appreciate the high burden of HBV among certain minority migrant groups, who may themselves have misconceptions regarding personal risk and modes of transmission, and who experience barriers to accessing health care.[3]

The busy GP needs to know who to test for HBV, how to tell if someone has chronic or past HBV infection, and when past infection may reactivate. Consulting on HBV in primary care may include counselling on transmission risk, vaccinating against HBV, and referring for specialist care.

WHEN SHOULD I TEST FOR HBV?

GPs should consider testing all patients who are at 'increased risk' of HBV (Box 1).[4] Strategies for testing within a general practice population include identifying new registrants with a risk factor for HBV, or proactively identifying existing patients who are at risk either systematically or within a consultation. The yield from systematic testing will be dictated by the demographics of individual patient populations; practices serving migrant populations might consider this a higher priority.

HOW TO TEST FOR HEPATITIS B

During current HBV infection, part of the viral

Box 1. Patients 'at risk' of hepatitis B infection who the authors would advocate for testing[a]

- Patients from countries with intermediate (≥2%) or high (≥8%) prevalence of chronic HBV (consider in people from Africa, Asia, the Caribbean, Central and South America, Eastern and Southern Europe, and the Middle East).
- Patients with known HIV or hepatitis C infection.
- People who injects drugs (past or present).
- Prison inmates.
- Young people living in care.
- Immigration detainees.
- Contacts of HBV-infected people (sexual partners, household contacts, and children of HBV-infected mothers).
- Patients who have had sexual exposure (unprotected sexual contact in/or with partner from intermediate-/high-prevalence country (see above), sexual contact of person who injects drugs, men who have sex with men, or commercial sex workers).
- Patients who have had medical exposure (including receiving blood products in the UK before 1970, medical treatment abroad in areas of intermediate/high prevalence (see above), and recipients of a needle-stick injury if donor is HBsAg positive or has unknown HBV status).
- Women in social circumstances where an additional child or the pregnancy may be at risk.

[a]Adapted from the National Institute for Health and Care Excellence.[4] HBsAg = hepatitis B surface antigen. HBV = hepatitis B virus. HIV = human immunodeficiency virus.

Table 1. Differentiating past from current HBV infection

Serological marker	Chronic HBV infection	Past HBV infection	Never infected
HBsAg	+	–	–
Anti-HBc	+	+	–
Anti-HBs	–	+/–	–

anti-HBc = hepatitis B core antibody. anti-HBs = HBV surface antibody. HBsAg = HBV surface antigen. HBV = hepatitis B virus.

Table 2. Immunosuppressant medications and risk of reactivating past HBV infection[a]

Immunosuppressant class	Risk of reactivating HBV (where HBsAg is negative and anti-HBc is positive)	Secondary care referral?
B-cell-depleting agents (for example, rituximab)	High risk (>10%)	Yes
Anthracycline-derived chemotherapy (for example, doxorubicin, epirubicin)	High risk (>10%)	Yes
Systemic corticosteroid therapy ≥4 weeks at a dose ≥10 mg prednisolone[b]	Moderate risk (1–10%)	Yes
TNF-α inhibitors (for example, etanercept, infliximab, adalimumab)	Moderate risk (1–10%)	Yes
Cytokine and integrin inhibitors (for example, natalizumab, abatacept)		
Tyrosine kinase inhibitors (for example, imatinib)		
Systemic corticosteroid therapy ≥4 weeks at a dose <10 mg prednisolone[a]	Low risk (<1%)	No
Traditional immunosupressives, for example, azathioprine, methotrexate, 6-mercaptopurine	Low risk (<1%)	No

[a]Adapted from Perrillo et al.[5] *[b]One or other systemic corticosteroid where dose is equivalent to stated dose of prednisolone. anti-HBc = hepatitis B core antibody. HBsAg = hepatitis B surface antigen. HBV = hepatitis B virus.*

envelope called surface antigen (HBsAg) will be present in peripheral blood.

After acute HBV infection antibody to core antigen (anti-HBc) develops. Whether the patient clears the infection or develops chronic infection, anti-HBc will persist. The presence or absence of HBsAg alongside anti-HBc differentiates past from current infection (Table 1). All patients with anti-HBc have a risk of reactivated infection when exposed to certain drugs. It is therefore important to test for HBsAg and anti-HBc before immunosuppressing a patient who is 'at risk' of HBV.

WHEN SHOULD I REFER TO SECONDARY CARE?

Patients with current hepatitis B infection (HBsAg positive) require specialist assessment.

Patients with past hepatitis B infection (HBsAg negative, Anti-HBc positive) do not need specialist assessment unless immunosuppression is planned (as summarised in Table 2).

Where a specialist prescribes an immunosuppressive drug, they should screen for HBV and refer those who test positive for consideration of prophylaxis to prevent reactivation. Systemic corticosteroids prescribed in primary care can also be associated with reactivation of past infection.

HOW DO I COUNSEL MY PATIENT?

The hepatitis B factsheet from NHS England is a useful prompt for doctors and patients.[6]

Patients who test positive for HBsAg can transmit HBV to sexual contacts and, less frequently, close household contacts. Patients with chronic hepatitis B should be advised to use barrier contraceptive methods. Long-term partners can be immunised; provided response to immunisation is demonstrated, barrier methods to prevent HBV transmission can be stopped.[7]

Patients with past infection do not pose a current risk of onward transmission, but may have transmitted or acquired HBV from close contacts in the past. Screening contacts is therefore indicated. Although patients with past HBV infection can be reassured that they do not have a current infection, they should be advised that HBV remains in their liver and could reactivate if given certain drugs in the future.

IMMUNISATION

Chapter 18 of Public Health England's 'Green Book' outlines who should be offered HBV vaccination.[7] A working guide is that, if an HBV test is indicated, a vaccine should be offered if that test is negative. Patients with liver disease need vaccinating because HBV acquisition could lead to liver failure. Patients receiving haemodialysis or frequent blood products should be vaccinated to prevent nosocomial transmission. Neonates born to HBV-positive mothers must be vaccinated to prevent vertical transmission.

Monovalent vaccines contain HBsAg with an adjuvant and do not pose a risk to those who are immunosuppressed. Efficacy is around 90% following a full course.[7] Engerix-B® is cheapest, followed by HBvaxPRO®. Fendrix® is more costly, but produces better antibody response for those with renal impairment.

WHICH MEDICATIONS INCREASE THE RISK OF HBV REACTIVATION?

After clearing HBV from the bloodstream and losing HBsAg positivity, HBV persists in latent form in hepatocyte nuclei. Immune surveillance continues, and memory T and B cells rapidly differentiate to stop the virus if it starts to replicate.[8] Certain drugs impair immune surveillance, and the associated risk of HBV reactivation can be quantified as low, moderate, and high (Table 2).[5]

Systemic corticosteroid therapy carries moderate (1–10% risk) of HBV reactivation when prescribed for ≥4 weeks at a dose ≥10 mg prednisolone (or equivalent).

Patients with severe SARS-CoV-2 pneumonitis treated with the IL-6 inhibitor tocilizumab are at risk of reactivating past HBV.[9] These patients will require prophylactic medication and specialist follow-up after discharge.

TREATMENTS

Tenofovir and entecavir are nucleoside analogues used to prevent reactivation of HBV in the context of immunosuppression. They are generally well tolerated. Tenofovir can cause low phosphate levels, renal impairment, and reduced bone mineral density.

CONCLUSIONS

- HBsAg (hepatitis B surface antigen) positivity indicates current infection and mandates referral to a specialist. Anti-HBc (hepatitis B core antibody) positivity (in the absence of HBsAg) indicates past infection. Referral is indicated where certain immunosuppressive treatments are planned.
- There is a risk of reactivating past HBV infection with moderate- or high-dose systemic corticosteroids administered for ≥4 weeks.
- Transmission prevention advice should be given to patients with chronic HBV infection. Contacts should be offered testing and immunisation.
- Nucleoside analogues such as entecavir and tenofovir are used to prevent reactivation of past HBV infection. Initiation and monitoring will be undertaken in secondary care.

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