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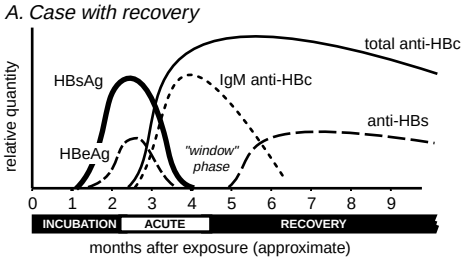
SEROLOGICAL TESTING FOR HEPATITIS B: A SHORT REVIEW

ALTHOUGH HEPATITIS B is nothing new, the plethora of available diagnostic assays for this infection can often lead to a sense of confusion when interpreting lab results. This uncertainty has implications for both clinical and public health practice.

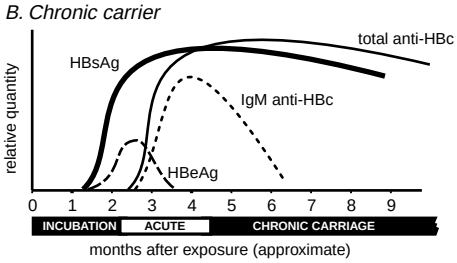
One would be hard pressed to describe hepatitis B as an emerging pathogen, unless, perhaps, one were applying for a grant. While an old standby, hepatitis B remains one of the more serious and common infections affecting Oregonians and other denizens of our planet. For the uninitiated, hepatitis B is a viral infection that can cause inflammation of the liver, i.e., hepatitis. Some fraction of those who are infected become carriers, largely depending on age at time of infection and immunologic factors. Carriers are at a greatly elevated risk of developing chonic liver disease, including chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. The virion is found in blood and sexual secretions; transmission is largely sexual or bloodborne, including vertical transmission at parturition. The incubation period of hepatitis B is quite long: 2-3 months for most, with a range of ~45-180 days.

Appearance of Serologic Markers in Typical Hepatitis B Infections

A. Case with recovery



B. Chronic carrier



The incidence of reported acute infections of hepatitis B infections in Oregon has declined over the past decade, reflecting in part changing patterns of sexual behavior and drug use, the increasing use of hepatitis B vaccine, and demographic changes. Between 135 and 200 acute cases are reported annually. What with the whole alphabet soup of viral hepatitides, though (not to mention non-viral etiologies), hepatitis testing is a common diagnostic procedure, and it is not suprising that the variety of relevant antigens and antibodies and their kinetic profiles may become a blur soon after second year medical school exams.

ANTIGENS AND ANTIBODIES

Surface antigen (HBsAg). HBV replicates in a curiously inefficient manner. Materials are cheap, however, and the strategy is effective enough. Surface (née Australia) antigen is the protein found on the outer surface of the hepatitis B virus. An excess of this protein is produced by infected cells—far more than needed to adorn the new virions. This surfeit forms particles that are serologically detectable. Surface antigen is a bad thing to have; it is a marker of replicating virus (i.e., an active and transmissible infection, either acute or chronic). With rare exception, HBsAg-positivity is the *sine qua non* of infectivity. Recombinant HBsAg is the antigen used in all hepatitis B vaccines.

Surface antibody (anti-HBs). Antibodies directed against HBsAg are produced as the host recovers from infection (or immunization), and signal protective immunity (in the absence of HBsAg). Surface antibody is a good thing; it means the patient either has recovered sucessfully from a natural infection or has responded to immunization.

E antigen (HBeAg). E antigen, a core protein that is ***e***xported from infected hepatocytes, can (roughly) be interpreted as a marker of relatively high infectivity. Anyone who is HBsAg-positive is infectious to some extent, but those who are also HBeAg-positive are considerably more so (~4 times, based on needlestick data). So HBeAg is a bad thing. Essentially all persons who are infected with HBV are HBeAg-positive for at least several weeks early in the course of infection. A proportion of carriers (~15-20%) are persistently e antigen-positive; for others, e antigen levels drift in and out of the detectable range, reflecting the intensity of viral replication. Qualitatively, then, HBeAg is a highly specific but rather insensitive measure of infectiousness; it has some quantitative implications.

E antibody (anti-HBe). Given a history of infection, e antibody is pretty much a good thing. Carriers don't make it. This is helpful in trying to identify the *rare* carrier who may test HBsAg negative.

Core antigen (HBc). The core is the part of the virus that wraps the viral DNA.[*] Not in circulation, not tested for, but important because it stimulates the following:

"Total" core antibody (anti-HBc). Core antibody forms only in the wake of natural infection, not immunization, and it forms regardless of how the infection resolves. Core antibody is not protective. Thus, total anti-HBc (usually any combination of IgG, IgA, and IgM) is a highly specific and highly sensitive marker of viral infection—past or present—but of no prognostic and of limited diagnostic value (i.e., a negative test would rule out hepatitis B, whereas a positive test is only consistent with but not itself indicative of a recent infection). Total anti-HBc testing is the best way to assessing susceptibility to infection and need for immunization (although it is rarely cost-effective to screen).

[†] Unlike HAV or HCV, HBV is a DNA virus—and therefore more closely related to, say, smallpox and herpes than to those other hepatitides.

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INFLUENZA ARRIVES

The first influenza cases to be confirmed in Oregon this season came from Lincoln and Deschutes county residents with onsets on 12 and 22 December, respectively. Both were type A. It is not too late to immunize your patients!

IgM core antibody (IgM anti-HBc). As with most infections, HBV stimulates an initial IgM response that soon yields to an IgG response. While the IgG (and IgA) levels will remain elevated, typically for life, circulating IgM is relatively transient, being detectable with normal assays for 3–6 months, typically (and rarely, longer). Thus, core antibody IgM is a highly sensitive and highly specific marker of a *recent* HBV infection. Unfortunately, this test is sorely underutilized by many clinicians, and—inexplicably, to our thinking—it is not offered as a part of a standard hepatitis panel by many laboratories. Because IgM testing is more expensive than total antibody screening (>$5 more/test), it may be cost-effective to *screen* patients with acute hepatitis for total, but it isn't good practice do so unless the positives are then followed up with an IgM test.

INTERPRETATION OF RESULTS

The figures (obverse) illustrate the typical comings and goings of these markers during the course of infection. Lab results at any given time can be predicted by reading a vertical cross-section. The table is a handy reference on how to interpret common hepatitis B results. When in doubt, look it up, get a consult, or just call your local health department.

Hepatitis B (both acute and chronic infections) is reportable in Oregon. Laboratories are required to report all positive tests for HBsAg and IgM anti-HBc. Local health department nurses routinely follow up each report with a case investigation, which includes an assessment of risks to family, sexual, and other contacts. These investigations typically lead to health counseling for the cases and others involved, and often to contact-targeted immunizations. Special follow-up is indicated when pregnant women are involved.

Unfortunately, many of the hepatitis B cases reported in Oregon each year cannot be easily categorized. We reviewed the first 312 hepatitis B case investigation forms completed by local health department nurses in 1998, comprising 108 reported as "acute infections" and 204 reported as "chronic carriers." Even among the supposedly acute cases, IgM anti-HBc results were indicated for only 89 (82%). For would-be carriers, the total was a pitiful 52 (25%). Thus, while a good (albeit unvalidated) guess could be made for many of these cases, based on clinical and other history, fewer than half had definitive laboratory results. A casual physician chart-review study conducted early in 1998 suggested that IgM anti-HBc results were in fact available for some of the patients who were reported without them, but for the majority the tests were apparently never done. Neither explanation is a happy one. Whatever the reason, it is a vexing problem to those who toil in the public health trenches, not only because we like to pigeonhole people, but because the implications for counseling and case investigation are quite different.

But the distinction between acute infection and chronic carriage is at least as important for the clinician. Isn't it important to know if your patient is a chronic carrier? Don't patients with chronic liver disease need specific counseling about the synergistic risks of hepatitis B infection and other liver insults—alcohol abuse, other hepatitides, &c.? Don't you need to evaluate the prospects for treating your patients who may be carriers? Isn't it important for your patient to understand, if they are a chronic carrier, that they carry a [probably] lifelong risk of infecting others via bloodborne or sexual transmission, and, if they are pre-menopausal females, via childbirth? (These are rhetorical questions. The correct answer is "yes.")

If you don't know which hepatitis tests are included on a standard panel, ask your lab. If you're evaluating a patient for hepatitis B, make sure you can distinguish between acute and chronic infections. We trust you'll agree that it's better to *know* your patient's hepatitis B status than to *guess* at it. With a core IgM test, that agonizing uncertainty can be dispelled. Pick one up today!

Interpretation of Selected Hepatitis B Serology Patterns

HBsAg	anti-HBs	anti-HBc total	anti-HBc IgM	Likely Interpretation
–	+	+	?	*Recovered after infection. (Recently? Distant past?)*
–	+	–		*Seroconverted after immunization.*
+	–	+	?	*Acute case? Chronic carrier? Currently infectious.*
+	–	+	–	*Chronic carrier. Currently infectious.*
–	+	+	+	*Recent case (usually <6 months old). Recovered.*
+	–	+	+	*Recently infected. Too early to assess long-term status.*
–	–	+	?	*Window period (see figure)? Abnormal old case or carrier?*