Clinical Performance Comparison among Automated Hepatitis B Surface Antigen Assays

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Clinical Brief

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Summary

Hepatitis B surface antigen (HBsAg) testing is important for the detection of hepatitis B virus (HBV) infection. Testing can include those suspected of infection as well as those for whom screening is recommended, such as pregnant women and blood donors. Published studies suggest good performance among commercially available automated HBsAg assays but also highlight clinically relevant differences. These differences include sensitivity and the ability to detect both wild-type and mutant HBV strains. Comparative studies important to the clinical use of the HBsAg assay are reviewed and discussed.

HBV: A global problem

HBV remains a major health issue in many countries despite the availability of an effective vaccine. Prevalence can vary significantly by region.[1] While the majority of infections in adolescents and adults will resolve, chronicity is high in infants and young children infected with the virus (30%–90%).[2] Chronic HBV infection may result in progressive liver disease, including cirrhosis, liver cancer, and death. Treatments are available that can limit viral replication and minimize liver damage in chronic disease, but typically infection is lifelong.

Testing for HBV

Serologic markers specific for HBV are used to diagnose and aid staging of HBV infection as well as assess treatment response (Table 1).[3] The HBsAg assay can be used to identify new or chronic infection. Initially reactive samples are typically repeated in duplicate and then undergo neutralization testing to confirm. Some assays such as the ADVIA Centaur® HBsAgII assay from Siemens Healthineers offer the ability to fully automate testing, including both repeat testing and confirmation.[4]

In some cases, the need for repeat testing can be minimized if using an assay with an alternate cutpoint that is validated to have a high correlation to confirmed samples. The Siemens Healthineers "Hot Zone" is an example of such an additional cutpoint. Application of the Hot Zone has been shown to improve workflow and reduce testing.[5]

Detection of wild-type and mutant HBsAg

In recent years, there has been increasing evidence of the emergence of HBsAg escape mutants, especially in regions with higher HBV endemicity.[6,7] Escape mutants pose a clinical concern as they could cause infection in a vaccinated population or evade detection during HBV testing. Although wild-type virus still accounts for the vast majority of infections, the ability to recognize infection due to an HBsAg mutation is valuable.

False negatives associated with mutation may have multiple explanations, including changes in the epitope an assay is designed to detect, conformational changes that may mask the epitope, and reduced expression associated with less fit viral variants. Therefore, in addition to sensitivity, both wild-type and broad mutant detection are important factors in HBsAg assay design.

Impact of assay design on HBsAg detection

To address both wild-type and mutant detection, many manufacturers have designed assays capable of recognizing multiple epitopes within the HBsAg "a" determinant (the immunodominant region that extends outside the viral membrane). Design differences include the use of only monoclonal antibodies versus a mixture of monoclonal and polyclonal antibodies. Labeling differences for detection also vary among manufacturers. Combined, these and other variations can contribute to divergent assay performance.

The ADVIA Centaur HBsAgII assay uses an all-monoclonal design in combination with a proprietary form of acridinium ester (AE), called zwitterionic acridinium ester (ZAE), for the improved detection of HBsAg.[8] In a study using a large number of seroconversion panels to compare the ADVIA Centaur assay to an assay that uses a mixture of monoclonal and polyclonal antibodies and a different form of AE (Abbott ARCHITECT HBsAg Qualitative assay), the ADVIA Centaur assay detected seroconversion earlier in 9 out of 20 panels and at the same bleed in the remaining 11 (Table 2).[9] Patient samples known to be positive were used to compare the ADVIA Centaur and Abbott ARCHITECT assays. The two assays correlated well; however, the ADVIA Centaur assay identified two infections missed by the Abbott ARCHITECT assay. These two samples were tested again in duplicate, and final reactivity was assigned according to reactive results in the case of the our ADVIA Centaur HBsAg Confirmatory assay (Table 3).[9]

A role for sensitivity as well as specificity in HBsAg mutant detection

Concern is growing over the potential for missed infections associated with HBsAg mutants. The ability to detect mutants often requires more than the ability to recognize a virion with altered epitopes, because mutants frequently show reduced abilities to replicate. Assessment of an assay's ability to detect viral mutant proteins in the assay manufacturer's laboratory, where expression levels of recombinant mutant proteins can be artificially controlled, is often insufficient to demonstrate the assay's ability to recognize the same mutant protein in a native sample (i.e., a patient isolate).

Thus, it is important to use a wide range of patient samples harboring known HBsAg mutant forms to assess detection. Table 4 provides an example of such a study in a comparison of five commercially available immunoassays and shows that not all assays have equivalent mutant detection capability.[10] Another study conducted by a Brazilian blood bank used the ADVIA Centaur HBsAgII assay to test 1027 donor samples presumed negative for HBsAg according to initial assessment using the Abbott ARCHITECT HBsAg assay. Three of the Abbott ARCHITECT-negative samples were reactive with the ADVIA Centaur assay, and further characterization confirmed the presence of three separate HBsAg mutants (including a double mutation; Table 5).[11]

While the authors did not investigate whether the Abbott ARCHITECT false negatives were associated with the altered epitopes or assay sensitivity, the low viral load suggests assay sensitivity could have been a factor.

Conclusion

Commercially available automated HBsAg assays demonstrate good performance but differences in their ability to detect HBsAg. Variations in the ability to recognize native HBsAg mutants are likely associated with aspects of assay design such as choice of antibodies and detection labels. The ability to detect low levels of HBsAg is an important feature for both wild-type and mutant detection.

Table 1. Hepatitis B assays and the status with which they are associated. Adapted from Mast, et al.[2,12]

	Assay	Associated with
Antigen	HBsAg	Current acute or chronic infection
	HBeAg	High level of HBV replication
Antibody	Anti-HBc IgM	Acute or recent infection
	Anti-HBc Total	Viral exposure: acute, chronic, or resolved infection
	Anti-HBs	Immunity
	Anti-HBe	Lower/absent viral activity: chronic or resolved infection

Table 2. Comparison of mutant detection by the ADVIA Centaur HBsAgII assay and the Abbott ARCHITECT HBsAg assay using 20 seroconversion panels.[9]

Detection results	Number of panels
ADVIA Centaur detected seroconversion earlier[a]	9
Abbott ARCHITECT detected seroconversion earlier	0
ADVIA Centaur and Abbott ARCHITECT detected seroconversion equivalently	11

[a]*All panels detected 1 bleed earlier. Results of specific panels are presented in the original poster and are available upon request.*

Table 3. The ADVIA Centaur HBsAgII assay detected two samples known to be HBsAg positive that were missed by the Abbott ARCHITECT HBsAg assay. Confirmatory testing (i.e., antibody neutralization) for each assay was performed on all repeat-reactive and discordant results with the ADVIA Centaur HBsAg Confirmatory assay.[9]

Assay	Positive (n)	Negative (n)	Confirmed negative (n)	False negatives (n)	Sensitivity
Siemens Healthineers ADVIA Centaur HBsAgII	403	0	0	0	100%
Abbott ARCHITECT HBsAg	401	2	0	2	99.5%

Table 4. Variable detection of HBsAg mutants by five assays in 71 native (patient) samples.[10]

Assay	N	%
Siemens Healthineers ADVIA Centaur HBsAgII	71	100.0
Abbott ARCHITECT HBsAg Qualitative II	71	100.0
DiaSorin LIAISON XL HBsAg Quantitative	70	98.6
Roche ELECSYS/COBAS HBsAgII Qualitative	69	97.2
Roche ELECSYS/COBAS HBsAgII Quantitative	51	71.8

Table 5. Variable detection of HBsAg "a" determinant mutations in blood donor samples.[11]

ADVIA Centaur HBsAgII	Abbott ARCHITECT HBsAg	HBV DNA (copies/mL)	Determinant mutation type
Reactive	Nonreactive	3,800	Double
Reactive	Nonreactive	4,200	Single
Reactive	Nonreactive	3,600	Single

The outcomes achieved by the Siemens Healthineers customers described herein were achieved in each customer's unique setting. Since there is no "typical" laboratory and many variables exist (e.g., laboratory size, case mix, level of IT adoption), there can be no guarantee that others will achieve the same results.

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Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

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