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Literature Review

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HSV Serologic Testing Options

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This episode discusses three articles about herpes simplex virus (HSV) serologic diagnostic testing options and outlines the 2021 STI Treatment Guidelines recommendations on when to use HSV serology.

Topics:

- STDs
- STIs
- HSV
- Herpes
- HSV-1
- HSV-2

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[00:00] Introduction
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and

prevention of STDs.

[00:20] Background
The topic of patients wanting HSV [herpes simplex virus] serologic testing came up in clinic the other day, and I thought I'd review some recent articles published on HSV serologic testing. There is still a lot of stigma associated with herpes simplex virus infection, even though quite a few people worldwide are seropositive. Now in the U.S., 12% of persons aged 14 to 49 years are estimated to be infected with HSV-2, but most of these people have mild symptoms or are asymptomatic and are undiagnosed. We often see patients who come into the clinic and they're interested in knowing their HSV status. Now it's easy when a genital, skin, or oral lesion is present—in that case you can do an HSV PCR [polymerase chain reaction] or NAAT [nucleic acid amplification test] testing, and that can be performed on the lesion. But most of the time people don't have lesions but still want to know their status, and serologic testing for HSV *can* be a little confusing. The availability of the Western blot, which is the gold standard test, is limited. So in the clinical setting, commercially available type-specific EIA [enzyme immunoassays] tests are usually used as the initial test to detect HSV-1 or HSV-2. Now several concerns have been raised regarding the ability of the HSV EIA test to accurately identify persons who have or don't have HSV. So let's go through what's been published on this topic.

[01:42] Paper #1

Prince HE, Batterman HJ, Marlowe EM. Characterization of serum samples with discordant results in 2 herpes simplex virus type 2 IgG assays. Sex Transm Dis. 2022 May 1;49(5):353-359. **[PubMed Abstract]**

Chronic HSV infection can be identified based on assays that detect antibodies that react to type-specific HSV proteins. Now, "type-specific" means that the proteins differentiate between HSV-1 and HSV-2 infection. There are EIA tests, which stand for enzyme immunoassays, and CIA tests, which stand for chemiluminescence immunoassays. These tests provide results as an "index value." And an index value of greater than 1.1 or equal to 1.1 is considered positive. While these assays are important tools for diagnosis, they're not always accurate, and many have a false-positive and/or false-negative result. What we find is that the test characteristics may depend on how high the index values are. So, for example, more inaccurate results are at lower index values, such as in the range of 1.1 to 3 or 3.5, and this leads us to the first article to review. And this article was published in *Sexually Transmitted Diseases* in May 2022 by Dr. Prince and colleagues. It is titled "Characterization of serum samples with discordant results in 2 herpes simplex virus type 2 IgG assays."

1. The authors looked at the relationship between two types of HSV-2 IgG tests. One was called the DiaSorin HSV-2 IgG test and is a chemiluminescent immunoassay, or CIA for short, and the HerpeSelect HSV-2 IgG assay, which is an enzyme immunoassay, or EIA for short, on serum samples that were tested from January to February of 2021.
2. There were around 2,300 DiaSorin-positive samples and 411 of these (or 18%) were found to be HerpeSelect-negative. The majority of these samples with HerpeSelect-negative results, or 84%, had DiaSorin index values of 1.1 to 3.0, so a lower-end index value.
3. They then evaluated in more detail 120 DiaSorin-positive samples, 60 of which were HerpeSelect-positive and then another 60 which were discordant results (or HerpeSelect-negative) and they evaluated these samples with further testing. The further testing which was called a composite reference assay included a BioKit HSV-2 IgG assay and a HSV-2 IgG inhibition assay that was developed for the DiaSorin instrument.
4. Samples were then categorized as DiaSorin-true positive or -false positive based on a composite reference assay. A true positive or false positive was defined as an agreement among at least two of the three composite reference assays: so, the HerpeSelect, the BioKit, as well as the HSV-2 IgG inhibition assay test results.
5. In the composite reference study of 120 samples, the authors found that 59 out of the 60 samples discordant for DiaSorin and HerpeSelect were identified as actually DiaSorin-false positives, and 58 of

the 60 samples, which had concordant results for DiaSorin and HerpeSelect were identified as DiaSorin-true positives based on the additional assays that were done.

My overall take-home from this study is that the serologic testing for HSV in the form of a DiaSorin CIA can have many false-positive results and discordance between the various tests is common. Test results using these EIA and CIA assays really need to be interpreted with caution, and patients should be counseled about the limitations of available testing. So this might be one reason that the CDC 2021 STI Treatment Guidelines recommend confirmatory testing with either a BioKit or a Western blot for specimens with HSV EIA results with low indices of 1.1 to 3.0.

[05:45] Paper #2

Agyemang E, Le QA, Warren T, et al. Performance of commercial enzyme-linked immunoassays for diagnosis of herpes simplex virus-1 and herpes simplex virus-2 infection in a clinical setting. Sex Transm Dis. 2017 Dec;44(12):763-767. **[PubMed Abstract]**

There was a study published in *Sexually Transmitted Diseases* in December of 2017 by Dr. Agyemang and colleagues that also demonstrates the poor performance of the type-specific HSV EIA tests, especially at lower index values. And it is titled “Performance of commercial enzyme-linked immunoassays for diagnosis of herpes simplex virus-1 and herpes simplex virus-2 infection in a clinical setting.”

1. So in this study, they compared the results of a commercial HSV EIA with the University of Washington Western blot in persons presenting for HSV testing at a private sexual health clinic from 2010 to 2015. The majority of EIA tests performed were HerpeSelect and Captia.
2. Eight hundred and sixty-four persons were tested for HSV by EIA and Western blot; 47% were women and the median age was 36 years.
3. Now, by Western blot analysis, the HSV-1 seroprevalence was 57% and the HSV-2 seroprevalence was 31%. It’s important to note that this was a self-selected population of individuals who were presenting for HSV testing at this private sexual health clinic, and so the seroprevalence is higher than that of the general population.
4. Seven hundred and twenty-seven persons were tested for HSV-1. The sensitivity of the HSV-1 EIA was 70%—so that’s pretty low—and the specificity was 92%. In this population, the positive predictive value was 92% and the negative predictive value was 70%. They did find the positive predictive value for HSV-1 increased with higher index value cut-off ranges.
5. Now let’s take a look at HSV-2: 780 persons were tested for HSV-2. The sensitivity of the HSV-2 EIA was higher at 92% but the specificity was pretty low at 57% when compared to the Western Blot. The positive predictive value was 51% and the negative predictive value was 94%. The authors also found the HSV-2 EIA test had a lower positive predictive value with a lower index value. They found that the risk of false-positive HSV-2 EIA results was higher among persons with HSV-1 antibody compared to those persons without the HSV-1 antibody.
6. Discordant HSV-1 EIA and Western Blot results could not be explained by new HSV acquisition or ongoing seroconversion.

Overall, the authors found that the HSV-1 EIA had low sensitivity but high specificity as opposed to the HSV-2 EIA had high sensitivity but low specificity. The positive predictive value for HSV-2 EIA improved using a higher index value cutoff but it was at the cost of reducing sensitivity. My take-home point is that providers should be aware of the usefulness as well as the limitations of these EIA tests, especially when discussing with patients.

[08:51] Paper #3

Jung S, Theel ES. Overutilization of IgM serologic assays for herpes simplex virus. J Appl Lab Med. 2020 Jan 1;5(1):241-243. **[PubMed Abstract]**

Now, some providers try to order IgM testing for HSV-1 or HSV-2 and that's with the idea that IgM testing can evaluate for a new or recent infection. The 2021 STI Treatment Guidelines do not recommend IgM testing and that's for several reasons. The IgM tests are not type-specific and they also might be positive during recurrent episodes of herpes or even during asymptomatic shedding. So this brings us to the next article to discuss in this episode. It is a letter to the editor that was published in the *Journal of Applied Laboratory Medicine* in January of 2020 by Dr. Jung and colleagues. It is titled "Overutilization of IgM serologic assays for herpes simplex virus."

1. This was a retrospective review of all PCR and serologic HSV tests that were ordered through the Mayo Clinic Laboratories from May through July of 2018.
2. They looked at the utilization and positivity rates for different assays. These different assays included an HSV-1 and an HSV-2 PCR, an HSV IgM test only, a serologic panel that included the HSV IgM and an HSV-1 and -2 IgG test, and when a provider ordered both the HSV IgM and HSV-1 and -2 PCR together.
3. During the three-month time frame, more than 22,000 HSV tests were ordered. Forty-four percent were the HSV-1 and -2 PCR, 36% were the HSV serologic panel, and 20% were HSV IgM only tests.
4. Among the HSV IgM only orders, positivity was 2.3%, so pretty low.
5. There were 171 instances when both the HSV PCR and the HSV IgM only test were ordered concurrently. Among these, 44% were negative by both assays, 50% were positive by the HSV PCR only, and 1.2% were positive for HSV IgM only; 4.7% (so 8 of the 171 instances) were positive by both HSV IgM and the HSV PCR.

So in summary, this study shows that HSV IgM serologic testing overall accounted for greater than 55% of all HSV-related testing performed at the Mayo Clinic Laboratories during the three-month study period, even though the positivity rate was very low. So, the study helps to demonstrate the lack of HSV IgM utility in diagnosing herpes infections despite it often being ordered by providers. And as a result of this study, Mayo Clinic Laboratories has actually stopped offering HSV IgM testing.

[11:39] HSV Guidelines

Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. **[HSV Guidelines]**

So when would a provider do HSV serologic testing and how should it be interpreted? HSV testing can be an important tool in some circumstances. Patients often want to know their HSV status, and patients are coming into our clinic asking for testing, so it is important to be able to have the conversation about what are the indications and limitations about our current testing, and often, a shared decision making approach is required when deciding about whether or not to order these tests.

The 2021 STI Treatment Guidelines recommend using HSV serology in the following circumstances:

1. Patients who have recurrent or atypical genital symptoms,
2. Those persons with lesions with a negative HSV PCR or culture result,
3. Someone who's had a clinical diagnosis of herpes without laboratory confirmation, *or*
4. A patient's partner has genital herpes.

While serologic screening among the general population is not recommended, it can be considered for patients who are at higher risk of infection in certain situations. If you're interested in learning more about this, I'm going to have you look at the guidelines.

The guidelines also recommend using a confirmatory test for serologic diagnosis of HSV-2 infection for persons with those low positive test results (or the index values are low), and they recommend either using a

Western blot or a BioKit test. Now realizing that confirmatory testing is not always available, the guidelines recommend discussing these limitations with patients before doing these testings in the first place.

The guidelines also recommend against testing people for HSV-1 serology, because we cannot tell the difference between oral and genital infection with the blood test and then also because of, as we demonstrated in some of the studies we discussed today, the low sensitivity of commercially available tests.

[13:30] Summary
To conclude, I'd like to summarize some key points from this session:

1. Type-specific serologic tests for HSV-1 and -2 in the form of EIA and CIA assays can be helpful in certain situations but need to be interpreted with caution.
2. The DiaSorin chemiluminescent immunoassay for HSV-2 can have many false-positive results, especially with indices less than or equal to 3.
3. The HerpeSelect and Captia HSV-1 EIA was found to have low sensitivity but high specificity and the HSV-2 EIA had high sensitivity but low specificity, and so providers need to be aware of the usefulness as well as the limitations of these EIA tests when discussing with patients before doing the testing.
4. The 2021 STI Treatment Guidelines do *not* recommend using IgM herpes serologic testing as it is not a useful test.
5. And lastly, there are some instances to use HSV-2 serologic tests but a good understanding of the test limitations is important.

[14:34] Credits
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