Overview of HSV 1/2 Antibody Testing

Laboratory Alliance of Central New York performs serological testing for antibodies to herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) at the Operations Center in Liverpool. Qualitative HSV screening is accomplished using the Diamedix Immunosimplicity® Is-HSV 1&2 IgG and Is-HSV-1&2 IgM enzyme immunoassays. Specimens determined to be positive for HSV 1&2 IgG screening will be reflexively typed using the BioRad BioPlex 2200 HSV1 IgG and HSV2 IgG assays.

Clinical Significance:

Herpes simplex virus (HSV) is a common human pathogen, with more than 90% of the world’s adult population demonstrating anti-HSV antibodies. HSV is characterized into two distinct serotypes, HSV-1 and HSV-2. HSV-1 is typically associated with ulcerative lesions of the mouth and eyes. HSV-2 is primarily associated with genital and neonatal infections; however, there has been a recent upsurge in HSV-1 primary genital infections. Vertical transmission of HSV can result in devastating disseminated infection in the neonate with a mortality rate exceeding 70%. The majority of infants with congenital HSV (70%) are born to asymptomatic mothers, prompting some to advocate for HSV screening in all pregnant women. Rates of vertical transmission are much higher in primary genital infection than in recurrent infection.

Although viral culture remains the gold standard for diagnosis, it is slow and relatively insensitive. Serological testing is a rapid and sensitive adjunct to viral isolation. It can be used to confirm clinical diagnoses in patients with recurrent lesions, atypical lesions or with healing lesions and negative HSV cultures. It is also useful for demonstrating recent seroconversion, documenting symptomatic past infections and identifying at-risk immunocompromised patients. Perhaps most importantly, serological testing aids in the identification of asymptomatic carriers. In primary HSV infections, IgM antibodies usually become detectable one week after the onset of symptoms and fall to undetectable levels after two months. Detection of anti-HSV IgG typically becomes possible two weeks after the onset of infection, and IgG antibodies persist at various levels for life.

Distinction between HSV-1 and HSV-2 infection is often clinically significant. HSV-1 is the principal serotype in most herpes encephalitis cases, whereas HSV-2 shows more association with herpes meningitis. Genital HSV-2 infections tend to recur much more frequently than HSV-1 genital infections. The two serotypes also differ in their
susceptibility to antiviral therapy. Women are more susceptible to HSV-2 infection than men, and genital HSV-2 infection imparts a three-fold risk of sexually acquired HIV. Studies indicate that probably all HSV-2 seropositive people intermittently shed virus. Unfortunately, only 10-25% of people with HSV-2 antibodies are aware that they have genital herpes.

Type-specific IgG testing is directed against the unique glycoprotein G of HSV-1 and HSV-2. The manufacturer reports sensitivity of 98% and specificity of 90% for HSV-1 antibodies in sexually active individuals and 96% sensitivity and 99% specificity for expectant mothers. For HSV-2 antibodies, sensitivity is 91% and specificity 98% in sexually active individuals and sensitivity 97% and specificity 100% in expectant mothers. Screening for HSV antibodies with the type-specific assays is not recommended, as a significant percentage of people (5-10%) do not produce antibodies against the HSV glycoprotein G. A small percentage of glycoprotein G-deficient HSV isolates have also been reported. The following diagram depicts the HSV antibody screening algorithm utilized by Laboratory Alliance:
The results of the Diamedix® assays are reported as antibody indices and cannot be correlated to end-point titers. The magnitude of the measured result, above the cutoff, is not indicative of the total amount of antibody present and should not be interpreted quantitatively.

The results of the BioPlex® assays are reported as Positive, Negative or Equivocal.

The following limitations should be noted:

1) The presence of HSV 1 and/or 2 IgM cannot distinguish between primary or reactivation infection.
2) Negative results do not rule out a diagnosis of HSV infection. Time to seroconversion varies, and rare reports of seroreversion exist.
3) The continued presence of antibody cannot be used to determine the success or failure of therapy.
4) Due to cross-reactivity, rare false-positive results can occur with HSV IgM testing. This is most commonly seen in patients with rheumatologic disease and/or infection with similar viruses (EBV, VZV, CMV).
5) Results from immunosuppressed patients, cord blood and neonates should be interpreted with caution.
6) HSV serology is not intended to be used as sole criterion for the diagnosis of current infection in pregnant women with genital lesions.

*See table below for virological and serological interpretation of genital lesions.

<table>
<thead>
<tr>
<th></th>
<th>HSV-2 by culture, DFA or PCR</th>
<th>HSV-1 IgG</th>
<th>HSV-2 IgG</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;New&quot; lesions</td>
<td></td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>No lesions</td>
<td>N/A</td>
<td>-</td>
<td>-</td>
<td>Susceptible to HSV-1 and HSV-2 infection</td>
</tr>
<tr>
<td>Recurrent lesions</td>
<td></td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Possible HSV-2 infection; consider other causes of genital lesions
Options for HSV testing are as follows:

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Sunquest Order Code</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV 1/2 IgG / IgM ABS</td>
<td>HSVGMR</td>
<td>HSV 1/2 IgG and HSV 1/2 IgM antibody screens performed. If the HSV 1/2 IgG antibody screen is POSITIVE, reflexive testing for IgG antibodies to HSV 1 Glyco G and HSV 2 Glyco G will be performed.</td>
</tr>
<tr>
<td>HSV 1/2 IgG w/ Reflex</td>
<td>HSVGRE</td>
<td>HSV 1/2 IgG antibody screen is performed. If screen is POSITIVE, reflexive testing for IgG antibodies to HSV 1 Glyco G and HSV 2 Glyco G will be performed.</td>
</tr>
<tr>
<td>HSV 1/2 IgM AB</td>
<td>HSV12M</td>
<td>HSV 1/2 IgM antibody screen only</td>
</tr>
<tr>
<td>HSV1 Glyco G IgG</td>
<td>HSV1GP</td>
<td>HSV1 Glycoprotein G IgG antibody only</td>
</tr>
<tr>
<td>HSV2 Glyco G IgG</td>
<td>HSV2GP</td>
<td>HSV2 Glycoprotein G IgG antibody only</td>
</tr>
</tbody>
</table>

Test Code: See table above

Method: Enzyme Immunoassay, Multiplex Bead Immunoassay

Specimen Requirements: Serum; 1.0 mL (0.5 mL minimum). Collection in gold or SST preferred.

Unacceptable Conditions: Severely lipemic, contaminated, heat in-activated, or hemolyzed samples.

Stability: Ambient 8 hours; Refrigerated 7 days; Freeze (-20°C) for longer storage.

Storage and Transport: Refrigerated

Schedule of Testing: HSV 1/2 IgG and IgM antibody screens – Monday and Thursday
HSV1 Glyco G and HSV2 Glyco G Antibodies – Monday through Friday

CPT Code: HSVGMR – 86694 x2; add 86695 and 86696 if reflexed
HSVGRE – 86694; add 86695 and 86696 if reflexed
HSV12M – 86694
HSV1GP – 86695
HSV2GP – 86696

Billing Code: HSVGRE – 2010205
HSV12M – 2010206
HSV1GP – 2010207
HSV2GP – 2010208

Rev 2/6/13, cmh
For More Information:
For questions or concerns regarding this testing, please contact Ms. Cheryl Haskins, Chemistry Manager, at 410-7014 or cherylhaskins@lacny.com.