Syphilis Serological Testing

**Background Information**
Syphilis testing can be divided into two categories. Treponemal assays (syphilis IgG, TP IgG) measure antibodies that directly react with the syphilis-causing organism T. pallidum, while non-treponemal assays (RPR, VDRL) measure antibodies against non-specific cardiolipin antigens released during treponemal infections.

In the traditional or classical testing algorithm for diagnosing syphilis, patient serum is initially tested with a non-treponemal test, followed by confirmation with a more specific treponemal test. This algorithm was popular because of the technical ease of performing the RPR relative to FTA or EIA testing. However, because the RPR test does not recognize treponemal-specific antibodies, a number of clinical situations could result in false-positive RPR results, including autoimmune disease, acute viral infection, recent immunizations or drug addiction. Most importantly, because RPR reactivity is a feature of active syphilis infection, the test could give false negative results in latent or late syphilis.

The CDC also recognizes another testing algorithm (the reverse algorithm) in which the patient’s blood is initially tested using a specific treponemal test and confirmed with a non-treponemal test. The algorithm below represents Cleveland Clinic’s recommended screening for syphilis serology testing.

**Clinical Indications**
A reactive syphilis IgG result indicates that a person has been exposed to T. pallidum at some point in his/her life. However, this testing may remain reactive for life in the majority of people who have had syphilis, even if they have been treated properly. Therefore, a positive result does not indicate that the person currently has untreated syphilis and the result should be confirmed with a non-treponemal test such as RPR to assess current disease activity.

If the followup non-treponemal test is reactive in the absence of a clinical history of treatment, it generally can be assumed that the patient has syphilis and should receive treatment. Most people become seronegative on non-treponemal tests following adequate treatment; however, some patients have a low RPR titer for life when they present with untreated late, latent or tertiary disease, despite being adequately treated. These patients are referred to as being “serofast.”

- VDRL (CSF) is used for diagnosis of tertiary or neurosyphilis.
- Samples tested reactive in the initial syphilis IgG screening test will be further tested by RPR. If the RPR tested positive, it will be followed with quantitative RPR with titer, then no further testing is required.

**Recommended Algorithm for Syphilis Serology Testing**

**Results Reporting**

- **Syphilis IgG**
  - Nonreactive: ≤ 0.8 A1
  - Weakly reactive: 0.9 - 5.9 A1
  - Reactive: ≥ 6.0 A1

- **RPR**
  - Nonreactive
  - Reactive

- **TP IgG**
  - Nonreactive
  - Reactive

- **Syphilis treated or latent**
  - RPR
  - RPR Titer

- **Syphilis active or recently treated**
  - RPR Titer

- **No syphilis or early syphilis**
  - Nonreactive
When the initial syphilis IgG is weakly positive (0.9-5.9) and RPR is negative, then the result will be confirmed by a second treponemal pallidum confirmation test — the TP IgG test.

Limitations of the Assay

- Infants up to 15 months with reactive syphilis IgG and/or RPR probably have a maternal antibody. Testing for IgM antibody should be performed to confirm congenital or neonatal syphilis.
- Samples with very high antibody concentrations may produce false negative results for the RPR test due to the prozone effect.

Methodology

Multiplex immunoassay (EIA) method for syphilis IgG. Flocculation method for RPR and VDRL (CSF). EIA for TP-IgG Antibody.

References


Test Overview

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Syphilis IgG with Confirmation</th>
<th>RPR with Titer</th>
<th>VDRL (CSF) (Venereal Disease Research Laboratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Range</td>
<td>Nonreactive: ≤ 0.8 AI</td>
<td>Nonreactive</td>
<td>Nonreactive</td>
</tr>
<tr>
<td></td>
<td>Weakly reactive: 0.9-5.9 AI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reactive: ≥ 6.0 AI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Preparation</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Specimen Requirements</td>
<td>1.0 mL serum</td>
<td>1.0 mL serum or EDTA plasma</td>
<td>0.5 mL CSF</td>
</tr>
<tr>
<td>Test Ordering Information</td>
<td>SYPHGX</td>
<td>RPRT</td>
<td>VDRLCF</td>
</tr>
<tr>
<td>Reflex Information</td>
<td>If Syphilis IgG is weakly reactive, RPRT and TP-IgG are ordered and billed.</td>
<td>If RPR is reactive, RPRQNT (RPR Titer) is ordered and billed.</td>
<td>If reactive, titer is performed.</td>
</tr>
<tr>
<td>Biling Code</td>
<td>84566</td>
<td>84567</td>
<td>86410</td>
</tr>
<tr>
<td>CPT Code</td>
<td>86780</td>
<td>86592</td>
<td>86592</td>
</tr>
</tbody>
</table>

Technical Information Contacts:

Robert Kreller 216.444.8679 kreller@ccf.org
Elizabeth Olson 216.445.0511 olsone@ccf.org

Scientific Information Contact:

M. Qasim Ansari, MD 216.445.2056 ansarim@ccf.org