Diagnosis and Treatment Regimes for Syphilis  By Dr John Bannister

Syphilis: Serological Testing

Introduction

In an ideal world a practitioner would have assessed a patient’s medical history with regards to syphilis prior to testing.

Is the patient at increased risk of syphilis? For example is he an MSM? Does the patient have a history of syphilis? If there is a history of syphilis is there a clear history of the correct treatment?

The ideal is, however, unlikely. A GP has relentless time pressure: it is quite understandable that “syphilis screening” is requested without such a history being taken. In addition antenatal screening and immigration medicals involve mandatory testing for syphilis whether or not the GP has considered the possibility of the patient having syphilis.

Although there are a multitude of syphilis tests across NZ, the vast majority of diagnoses will be made on just three tests;

- the Treponemal Enzyme Immunosorbent Assay (abbreviated to EIA),
- the Rapid Plasma Reagin test (abbreviated to RPR)
- the Treponemal Pallidum Particle Agglutination test (abbreviated to TPPA) (See notes below).

Note 1: All District Health Board (DHB) laboratories confirmed that these are the three usual serological tests used. The author telephoned senior serological staff at the following DHBs; Northland DHB, Auckland DHB, MidCentral DHB (includes Palmeeston North, Gisborne, Wanganui and Masterton) Capital Coast DHB, Canterbury DHB (includes Westland) Otago DHD (includes Nelson–Marlborough DHB and Southland DHB)

Note 2: All private laboratories confirmed that these are the three usual serological tests used for diagnosing syphilis in the community. The author telephoned senior serological staff at the following private laboratories; Northland Pathology, Lab Tests (Auckland), Medlab (Wanganui, Masterton, Palmeeston North and Gisborne) Aotea Pathology (Wellington area) and Southern Community laboratories (covers all of the South Island except Canterbury and Westland. It covers Hawkes Bay as well).
When you test for syphilis or receive an abnormal syphilis test result ensure that other sexually transmitted infections (STIs), including HIV, have been tested for. One could consider that HIV and syphilis need to be tested for in tandem.

- Tests for syphilis should be done in conjunction with tests for other sexually transmitted infections.

**Treponemal Tests**

The first test performed is the Treponemal EIA assay. There are just a few facts to remember about the Treponemal EIA to help one interpret syphilis test results;

1. The test detects the presence of antibodies in a patient’s serum produced in response to treponemal antigens. It detects both IgM and IgG antibodies and as such it may become positive very early in the disease – IgM antibodies to syphilis can be detected as early as two weeks and IgG antibodies as early as four weeks (1) – but it could take up to three months to do so. Therefore a patient with genital ulceration due to syphilis may initially have a negative treponemal EIA. In this instance the treponemal EIA needs to be repeated in two to three weeks and the patient cautioned to avoid sexual intercourse in the interim.

2. The EIA is a very sensitive and specific test (1). However, even very specific tests are prone to false positive results when a disease, such as syphilis, is of low prevalence. On the other hand, a positive EIA result in a man who has sex with men and has a lot of sexual partners is less likely to be a false positive result.

3. Once an EIA test is reactive due to syphilis it is likely to remain reactive throughout most of a person’s life, even if the patient has been successfully treated (See figure 1).

A word on terminology: the presence of antibodies in the serum is described at being “reactive” as opposed to the test being described as “positive”. For ease of writing and reading these terms will be used interchangeably.
Northland is the one exception to this rule. If syphilis screening is requested in Northland the first test performed is the Rapid Plasma Reagin test (RPR). This does have implications for interpretation of the result. See text under non treponemal tests.

![Figure 1: Influence of time and treatment on the Treponemal serological tests (Reproduced with permission from Atlas of Sexually Transmitted Disease and AIDS (reference 6). Permission granted Elsevier Ltd.)(B)](image)

If an EIA test is reactive then two other tests are automatically performed:
- the Rapid Plasma Reagin test (RPR)
- the Treponemal Pallidum Particle Agglutination test (TPPA).

The TPPA test also detects IgM and IgG antibodies to treponemal species. The TPPA test is a more specific and sensitive test and is used to confirm the initial reactive EIA result. In 2006 Lab Plus (the Auckland Hospital laboratory) examined its data from a total of 2433 Treponemal tests. There were 84 reactive EIA tests. Of the 84 reactive tests, 15 were actually false reactive tests when the serum was tested by the TPPA method. There were, however, no false negative EIA results (2). The TPPA, in a similar vein to the EIA, quickly becomes positive if an infection is present. The TPPA, like the EIA, will usually remain positive throughout a person’s life, whether the disease has been successfully treated or not treated.
This feature of treponemal serology makes it very useful for patients and doctors to have documentation of complete treatment for syphilis.

Once a person has had syphilis, the treponemal tests (treponemal EIA and TPPA tests) are likely to remain reactive for life. This is true whether the patient has had treatment or not.

**Non-Treponemal Tests**

The RPR test is *not* testing for treponemal antibodies per se but is a measure of disease activity.

When the host's cells are infected by *T. pallidum* phospholipids are released into the bloodstream. In addition phospholipids are released directly from the *T. pallidum* bacteria. The host makes antibodies to the phospholipids (3, 4). The amount of antibody is measured with the RPR test and is expressed as the RPR titre eg.1:64. The more active the disease the more phospholipids are released and the higher the RPR titre becomes. Similarly, if the disease is successfully treated the RPR will reduce. For this reason the RPR is used to monitor the response of the patient to treatment.

Note though, that even without treatment after one to two years the patients own immune system is likely to reduce the disease activity and so reduce the RPR to very low levels e.g. to 1:2, or even become negative (see figure2).

Successful treatment is defined as a fourfold reduction in the RPR (1, 5). For example, if a patient has an RPR of 1:64 and is treated for syphilis then his RPR would have to drop to 1:16 before he/she can be considered to be cured. Cell damage and the subsequent release of phospholipids can occur in a variety of conditions other than syphilis and so the RPR is described as a *nonspecific* or *non–Treponemal test* whereas the EIA and TPPA are described as *specific* or *Treponemal tests.*
Other potential causes of positive RPR results are pregnancy, connective tissue diseases, some acute infectious diseases, injecting drug use and it can be an effect of aging (6).

The RPR test will often become negative in successfully treated disease (see figure 2). It is important to remember that the RPR can also become negative or of very low titre in disease that has not been treated but is longstanding.

There is one other complicating feature (!) albeit very rare, that should be mentioned. Due to the technique of the RPR test very high levels of antibody can in fact interfere with the procedure and cause a false negative result (7). This is called the prozone phenomenon. This is another example of how serological tests for syphilis require a history to help interpret them.

Doctors working in the Northland district need to remember that it is the RPR (and the potential causes of it being a false negative or a false positive result) which is used for screening. A positive RPR will, however, result in the reflex testing of the EIA and TPPA to aid interpretation of the result.

A patient can be re-infected with syphilis. In this situation the RPR will start to increase. An increase by four fold e.g. from 1:2 to 1:8 is highly likely to indicate re-infection. An increase of two fold is problematic. A detailed sexual history assessing any new risks of re-infection and repeat treponemal serology in two to four weeks should clarify the situation.
Figure 2. Influence of time and treatment on the Non-treponemal (RPR) test results. (Reproduced with permission from Atlas of Sexually Transmitted Disease and AIDS (reference 6). Permission granted by Elsevier Ltd.)

References


2. Unpublished data courtesy of Paul Austin, Section Leader Virology and Immunology, Lab Plus, Auckland City Hospital, New Zealand


