ABC of Sexually Transmitted Diseases

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SYPHILIS: DIAGNOSIS AND MANAGEMENT

History
Physical examination
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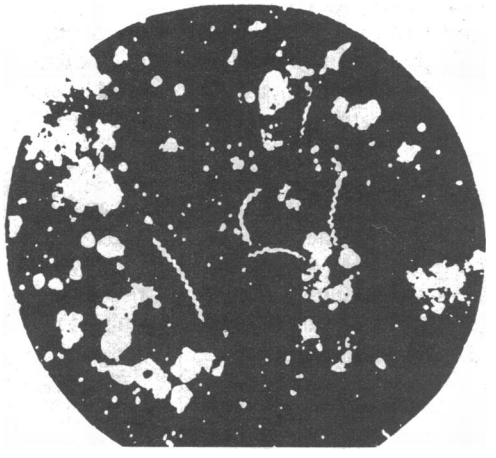
Dark ground microscopy
Serology
Lumbar puncture
Chest radiograph and screening

Establishing a diagnosis of syphilis, whatever the stage of the disease, can be difficult and it is wise for all suspected cases to be referred for specialised tests and management in a department of genitourinary medicine. The diagnosis can be confirmed by the history, physical examination, and one or all of four tests—dark ground microscopy, serology, examination of cerebrospinal fluid, and radiology. Which of these tests appear as positive will depend on the clinical stage of the patient's syphilis.

Dark ground microscopy



Dark ground microscopy can be used to establish the diagnosis from the lesions of primary and secondary syphilis or occasionally from material obtained by puncture of inguinal nodes (after recent topical application of antiseptic or antibiotic or when lesions are healed or concealed). The presence of oral commensal treponemes makes microscopy unreliable for mouth lesions. Three separate specimens from the lesion(s) should be examined by dark ground microscopy initially and, if necessary, on three consecutive days. This is done by cleaning the lesion with a gauze swab soaked in normal saline and squeezing it to encourage a serum exudate. The serum is then scraped off the lesion and placed on the three slides. After a cover slip has been placed on the material microscopy can be performed. Considerable experience is required to recognise *Treponema pallidum*. It is bluish white, closely coiled (8-24), and 6-20 μm long. There are three characteristic movements of the treponeme: watch spring, corkscrew, and angular. Dark ground microscopy is a vital test since in primary syphilis it may be the only positive means of establishing the diagnosis. Serological tests for syphilis are not always positive when primary lesions occur; the tests do not give positive results until about two weeks after the appearance of the chancre, about three to five weeks after infection.

Serological tests

Non-specific tests

Venereal Disease Research Laboratory test
Rapid plasma reagin test
Wassermann reaction

Specific tests

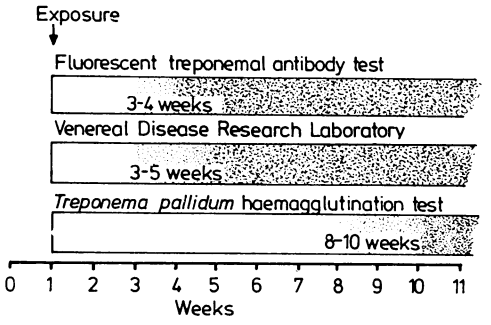
Absorbed fluorescent treponemal antibody test
Treponema pallidum haemagglutination test

Biological false positive reactions

Acute
Infections
After immunisation
Chronic
Autoimmune disease
Leprosy

The serological tests used in the diagnosis of syphilis are either non-specific or specific.

Non-specific tests—The most useful non-specific test is the Venereal Disease Research Laboratory test (VDRL), which has now largely replaced the rapid plasma reagin test and Wassermann reaction. Essentially these tests depend on the appearance of antibody (reagin) in the serum, and this may not occur until three to five weeks after the patient has contracted the infection. Thus the VDRL test will give a positive result in only about 75% of cases of primary syphilis. It is a quantitative test and this can be useful in assessing the stage and activity of the disease. The VDRL test is a flocculation test. False positive results may occur for four reasons. Firstly, technical errors may occur because of mistakes in collection, labelling, and reporting of specimens or the use of faulty materials. The moral is that the diagnosis of syphilis should never be made on the basis of only one set of tests. Secondly, some patients normally produce an excess of reagin and in such cases the specific tests will be negative. Thirdly, in other treponemal conditions similar to syphilis (yaws, bejel, and pinta), but in such instances the specific tests will also be positive. Fourthly, there may be acute or chronic biological false positive reactions.



	Stage of disease			
	Primary %	Secondary %	Latent %	Late %
Venereal Disease Research Laboratory test	75	100	75	75
Treponema pallidum haemagglutination test	60	100	97	100
Fluorescent treponemal antibody test	90	100	97	100

Tests positive	Diagnosis
None	Syphilis not present or very early primary syphilis
All	Untreated or recently treated syphilis
VDRL and FTA	Primary syphilis
TPHA and FTA	Treated syphilis or untreated latent or late
FTA only	Early primary syphilis-untreated or recently treated
TPHA only	Treated syphilis
VDRL only	False positive reaction

Biological false positive reactions—The acute type of reaction is transient, lasting a few weeks to six months. Such reactions occur after infections (such as glandular fever, measles, chicken pox, mumps, herpes simplex and zoster, viral pneumonia) or after immunisation against typhoid and yellow fever. The chronic false positive reaction can last for many years or even a lifetime. It is seen particularly in autoimmune diseases (disseminated lupus erythematosis, haemolytic anaemia, thyroiditis) and rheumatoid arthritis. Sometimes the VDRL test is positive years before the patient develops one of these conditions. Specific tests for syphilis will be negative.

Specific tests—The two specific tests most often used to establish a diagnosis of treponemal disease are the absorbed fluorescent treponemal antibody test and the *treponema pallidum* haemagglutination test. The fluorescent treponemal antibody test is the first serological test (either specific or non-specific) to become positive; this usually occurs three to four weeks after infection. Thus this test is positive in 85-90% of cases of primary syphilis. In early untreated primary disease it may be the only positive serological test. It must not be forgotten, however, that all serological tests may be negative despite the presence of a primary lesion. The *Treponema pallidum* haemagglutination test is the last of the serological tests to become positive. Thus it will always be positive in the secondary stages of disease but only so in 60% of patients presenting with primary syphilis. As already emphasised, these specific tests can distinguish only between treponemal and non-treponemal disease but not between the different treponemal conditions. Occasionally a clinical distinction can be made, for example, between syphilis and yaws.

The findings of positive serological tests for syphilis should not necessarily be interpreted as showing that the patient has active or untreated latent disease. Thus, for example, in patients who have received adequate treatment the VDRL test may still be positive (particularly if treated late on in the infection). Responses to the fluorescent treponemal antibody and *Treponema pallidum* haemagglutination tests often remain positive for life despite adequate treatment.

Syphilis has been controlled in the United Kingdom largely because of the policy of screening patients attending antenatal clinics, departments of genitourinary medicine, and blood transfusion centres and by selective use in neurological and psychiatric assessment of certain patients. Currently the best combination of tests for screening of treponemal disease is the VDRL test and the *Treponema pallidum* haemagglutination test.

Cerebrospinal fluid and radiology

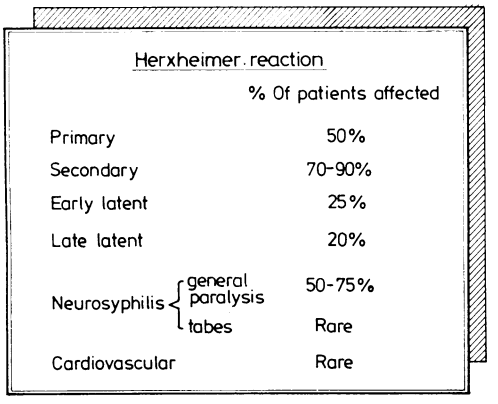
Investigations on cerebrospinal fluid

- Cell count
- Total protein
- IgG estimation (or Lange colloidal gold curve)
- Venereal Disease Research Laboratory *Treponema pallidum* haemagglutination and fluorescent treponemal antibody tests

Abnormalities of the cerebrospinal fluid may be found at any stage of syphilis and may occur early (primary and secondary stages) without symptoms. Many clinicians therefore examine the cerebrospinal fluid a year after treatment of early disease before discharging the patients as cured. Lumbar puncture may also be necessary to exclude neurosyphilis or as part of the investigation of any patient with suspected latent disease. The following tests can be performed on cerebrospinal fluid: cell count, total protein, IgG estimation, or Lange colloidal gold curve (no longer used widely), and the three serological tests. The findings vary according to the type of neurosyphilis. A cell count above $0{\cdot}005 \times 10^9$ lymphocytes per litre and protein above 40 g/l would be considered abnormal. The VDRL test on the fluid is unreliable in diagnosing neurosyphilis since it is negative in up to half of all patients with active neurosyphilis. A positive fluorescent treponemal antibody and/or *Treponema pallidum* haemagglutination test result can result from a transudate of IgG specific for *Treponema pallidum* in patients whose disease has been adequately treated. It therefore does not indicate active disease of the nervous system; negative tests, however, virtually rule out neurosyphilis.

The final diagnostic procedure in the assessment of a patient with latent disease or cardiovascular disease is a chest radiograph (posteroanterior, left oblique) to show the arch of the aorta and screening to detect aortic dilatation. More specialised tests such as catheterisation may subsequently be indicated.

Treatment and prognosis



Changes in cerebrospinal fluid in neurosyphilis

	Stage of disease				
	Asymptomatic	Meningovascular		Parenchymatous	
		Early	Late	General paralysis of the insane	Tabes dorsalis
Cell count	±	+++	++	++	+
Protein	+	++	++	++	+
FTA	+	+	+	+	+/−
VDRL	−	+	±	++	+/−
TPHA	+	+	+	+	+/−
Pressure	Normal	++	±	Normal	Normal

Penicillin remains the cornerstone of the treatment of all types of syphilis. In primary and secondary syphilis aqueous procaine penicillin should be given for 10 days. Successful treatment depends on obtaining a minimum serum concentration of 30 IU/l and maintaining this over a long period. If there is any anxiety about patients returning or if they cannot attend daily a long acting preparation (benzathine) can be used. Erythromycin or tetracycline can be substituted in patients allergic to penicillin. Since the cure rate is lower with these, many physicians will repeat treatment after three months.

The Jarisch-Herxheimer reaction is common in primary and secondary syphilis and patients must be warned that fever and flu-like symptoms may occur 3-12 hours after the first injection; occasionally the chancre or skin lesions enlarge or become more widespread. Aspirin is recommended.

Other stages or manifestations of syphilis are also treated with procaine penicillin. Steroids, to eliminate the Herxheimer reaction, are used only in patients with neurosyphilis or cardiovascular syphilis who may develop focal lesions (cerebrovascular or coronary artery occlusion) and mania, confusion, and psychosis.

The prognosis of treated syphilis depends on the stage of the disease and degree of tissue damage in the cardiovascular and neurological systems. Thus adequate treatment of primary, secondary, and latent stages and asymptomatic neurosyphilis will result in cure and halt progression of the disease. The prognosis in symptomatic cardiovascular and neurosyphilis is variable. In general the inflammatory process is arrested by adequate treatment but the tissue damage may be too great to prevent an improvement in symptoms.

Contact tracing must be carried out on all sexual contacts that a patient with early infectious syphilis has had in the preceding three to six months. In late syphilis, when the patient is no longer infectious, serological testing is probably only practicable in the patient's regular partner. If late syphilis is diagnosed in a mother it may be necessary to test her children. Syphilis during pregnancy will be discussed in next week's article. Syphilis is a complex disease and its diagnosis, management, and follow up should not be undertaken by the non-specialist.

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Treatment of syphilis

Stage	Standard treatment	Alternatives	Prognosis
Primary and secondary	Aqueous procaine penicillin 600 000 Units/day 10 days	If penicillin allergy: Erythromycin 500 mg four times a day 15 days; Oxytetracycline 500 mg four times a day 15 days	Excellent. Relapse exceptionally first year
Latent: early (≤2 years duration)	Aqueous procaine penicillin 600 000 Units/day 10 days	If patient unable to attend daily: Benzathine 2·4 MU once only	
late (>2 years)	Aqueous procaine penicillin 600 000 Units/day 15 days	If penicillin allergy: Erythromycin 500 mg four times a day 30 days; Oxytetracycline 500 mg four times a day 30 days. If patient unable to attend daily: Benzathine 2·4 MU one a week for 3 weeks	Excellent
Neurosyphilis and cardiovascular syphilis	Aqueous procaine penicillin 600 000 Units/day 20 days + prednisone 5mg four times daily for one day before penicillin, and then same dose for two days after	If penicillin allergy: Erythromycin 500 mg four times a day 30 days; Oxytetracycline 500 mg four times a day 30 days. Benzathine not recommeded	Depends on type of neurosyphilis and extent of cardiovascular disease
Gummatous	Aqueous procaine penicillin 600 000 Units/day 15 days	If penicillin allergy: Erythromycin / tetracycline 500 mg four times a day 15 days	