

Syphilis

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1. Introduction

Syphilis is a chronic infection caused by the bacterium *Treponema pallidum* which was first described over 500 years ago. The manifestations of disease are notoriously protean¹ and, untreated, can have several different stages.

2. History

In the 1490s, a highly contagious venereal disease (which may have been the same as the modern syphilis we now see or an ancestral equivalent) spread through port cities of Southern Europe and beyond. Its disfiguring symptoms were considered more repulsive by some than leprosy or elephantiasis (lymphatic filariasis). It had never been described in prior medical literature, either contemporary or ancient.

In 1905, Fritz Schaudinn discovered the causative agent of syphilis: *Treponema pallidum*. Soon thereafter, the causative organisms for the other non-sexually transmitted human treponemal diseases were identified.

Medical historians have speculated that Spanish explorers while visiting the island of Hispaniola in 1492 may have picked up *Treponema pertunae*, the cause of non-sexually transmitted yaws, from young Taino girls who they raped. It is postulated that *Treponema pertunae*, upon finding itself in a slightly different, European, host and in a more temperate climate (upon the explorers' return to the Old World), mutated into modern *Treponema pallidum* and began it spread as a new sexually-transmitted disease: syphilis.

3. Etiology

T. pallidum is a bacterium from the order *Spirochaetales* and is one of several closely related treponemes which cause human disease. It is approximately 10 to 13 microns long but only 0.15 microns in width. This thin width makes visualization using direct light microscopy very difficult or impossible. .

T. pallidum can be seen by using darkfield microscopy which uses a condenser to cast an oblique light. On darkfield microscopy, *T. pallidum* is corkscrew-shaped with tightly wound spirals. It exhibits a characteristic rotary motion with flexing and back-and-forth movement, features considered sufficiently characteristic to be diagnostic. This undulating movement about its center (flexuose) distinguishes it from nonpathogenic treponemes.

¹ Proteus: an ocean deity able to appear in many different forms, assuming different shapes; changeable in form. In Greek mythology, Proteus is an early sea-god, one of several deities whom Homer calls the "Old Man of the Sea"

Family Spirochaetaceae (*Treponema*, *Borrelia*, *Leptospira*)

- a. *Treponema pallidum* subsp. *pallidum* (syphilis)
- b. *Treponema pallidum* subsp. *pertenue* (yaws)
- c. *Treponema pallidum* subsp. *endemicum* (bejel, endemic syphilis)
- d. *Treponema pallidum* subsp. *carateum* (pinta)

T. pallidum cannot be cultured *in vitro*. It can be cultured with difficulty *in vivo* in rabbit testes. This property makes studies of *T. pallidum* very difficult. Unlike other pathogenic bacteria, the genome lacks transposable elements and its genome is, overall, highly conserved which may explain its persistent sensitivity to penicillin. It has a paucity of genes involved in biosynthesis of nutrients or energy production and is, thus, likely a scavenger to some extent.

4. Epidemiology

Early syphilis is a reportable disease because of its high transmissibility in the early stages. In the US, there was a mini-epidemic in the late 80s to early 90s which coincided with the HIV epidemic. Case rates in the US were higher than they had been at any time since the introduction of penicillin.

Special risk groups:

- A. MSM: The CDC estimates that in 2004, approximately 64 percent of all cases of primary and secondary syphilis were in MSM.
- B. HIV: Among the 6862 cases of primary and secondary syphilis documented in 2002 by the CDC, 25 percent occurred in persons co-infected with HIV.

The risk group with the highest incidence rates was HIV-infected MSM

Transmission of *T. pallidum* can occur via sexual contact, vertical transmission, kissing/close contact with active lesions, transfusions, or accidental injection. The disease is most infectious early on during primary and secondary syphilis when patient's have chancres, mucous patches, condyloma latum and other lesions which are highly infectious.

An immunologically intact person cannot, essentially, spread disease sexually after 4 years. The USPHS, CDC and local health departments, therefore, focus their efforts on identifying and treating primary, secondary and early latent cases of syphilis.

5. Pathophysiology

T. pallidum pathophysiology research is hindered by the inability to grow the organism in culture. Knowledge of growth characteristics and metabolism are limited.

T. pallidum infection is most often initiated when the organism enters subcutaneous tissues via microscopic abrasions that occur during sexual intercourse. The organism's estimated dividing time is 30 hours and its initial incubation period prior to manifestations of primary disease is about 10-90 days with shorter incubations associated with higher initial treponeme inocula. *T. pallidum* evades the initial host immune response. The first clinical sign of infection is often a painless ulcerative lesion at the site of entry. This is

known as a syphilitic chancre. During this initial stage of infection, the organism also travels to and establishes itself in regional lymph nodes.

The primary chancre usually resolves spontaneously which may be related to local immune control of the infection. However, widespread dissemination of the spirochetes occurs during this period with many organ systems including the CNS seeded with organisms, this dissemination leads to the subsequent signs and symptoms of secondary and late syphilis if untreated.

Treponema pallidum elicits cellular immune responses in skin and blood at the site of the initial lesion. The host immune response involves lesional infiltration of PMNs followed by T lymphocytes. These lesional fluids are enriched for CD4+ and CD8+ T cells and dendritic cells. These dendritic cells express HIV co receptors (e.g., CCR5 and DC-SIGN), which may shed some light on the epidemiologic link between syphilis and HIV transmission.

After infection with *T. pallidum*, humoral immune responses are generated, and a variety of antibodies are generated, more on serologic testing later.

6. Natural History, Stages and Clinical Manifestations of Syphilis

Natural History

Knowledge about the natural history of syphilis is derived from various sources, some now infamous:

1. In the late 19th century, a Norwegian physician described the infection in more than 1400 patients with syphilis. Patients received no treatment.
2. Between 1917 and 1941 382 adults with syphilis underwent autopsies between. This provided pathologic data on the late manifestations of syphilis.
3. The Tuskegee study conducted between 1932 and 1962 collected data on 431 black men whose syphilis was untreated despite the introduction and availability of effective antibiotic treatment which occurred during the study.

Almost all new syphilis infections are sexually-transmitted except for rare cases occurring via vertical transmission from mother to child. Syphilis is most infectious and transmissible during its primary and secondary stages and its efficiency of transmission is estimated at approximately 30 percent. This high efficiency of transmission during these two stages explains the public health strategies used to combat syphilis.

Stages and Clinical Manifestations:

- A. Infectious Stages (shorter treatment durations):
 - a. Primary syphilis: chancre at the site of inoculation. Most chancres are painless and many individuals do not seek medical attention at this stage. The lesions often resolve spontaneously within 1-3 weeks. Many times, individuals do not realize they have a lesion, this can be especially true if the chancre is in or near the anus or inside the vagina. These lesions can be highly infectious.

- b. Secondary syphilis: Weeks to a few months later, 25 percent of individuals with untreated infection develop a systemic illness which is secondary syphilis. The symptoms of secondary syphilis can vary tremendously and include:
 - i. Rash
 - 1. Typically involves palms and soles, often maculo-papular, popular or annular. Can take on almost any form except vesicular
 - ii. Fever
 - iii. Headache
 - iv. Malaise
 - v. Anorexia
 - vi. Diffuse lymphadenopathy
 - vii. Condyloma latum
 - viii. Mucous patches
 - ix. Alopecia

These symptoms also tend to resolve spontaneously if the disease goes untreated.
- c. Early latent syphilis: Less than one year from infection with no symptoms but infection demonstrable by serologic testing and a higher likelihood of spontaneous mucocutaneous relapses; therefore a higher potential infectivity.

B. Non- or less infectious stages (longer treatment durations):

- a. Late latent syphilis or latent syphilis of unknown duration
- b. Late syphilis/tertiary syphilis: In these stages, individuals are at risk for the major complications of the infection. The clinical manifestations of late syphilis may appear at any time from 1 to 30 years after primary infection and may involve a wide variety of different tissues. Individuals with untreated syphilis have up to a 40% chance of developing tertiary syphilis
 - i. Central nervous system involvement
 - 1. meningitis/meningoencephalitis/meningovascular
 - 2. ocular
 - a. Argyll Robertson pupil²
 - 3. general paresis
 - a. **P**ersonality, **A**ffect, **R**eflexes, **E**yes, **S**ensorium, **I**ntellect, **S**peech
 - 4. tabes dorsalis
 - a. demyelination of the posterior columns
 - ii. Cardiovascular syphilis
 - 1. aortitis)
 - iii. Gummatous syphilis: granulomatous, nodular lesions which can occur in a variety of organs, most commonly skin and bones

² Argyll Robertson pupils (“AR pupils”) are bilateral small pupils that constrict when the patient focuses on a near object (they “accommodate” with near vision), but do not constrict when exposed to bright light (they do not “react” to light). They are a highly specific sign of neurosyphilis. Pupils that “accommodate but do not react” are said to show light-near dissociation.

7. Diagnosis

Diagnosis of primary syphilis is usually accomplished via Darkfield microscopy of a chancre scraping and identification of the corkscrew-shaped organisms with tightly wound spirals and the typical forward and backward motion with rotation with soft side-to-side bending and twisting. This test is specific but not sensitive. Other diagnostic tests for primary syphilis include a direct fluorescent antibody test of a specimen (DFA-TP) which is more sensitive but not widely used.

For other than primary stages of syphilis, serologic tests are used to make the diagnosis. There are two types of serologic tests used: non-treponemal tests which are sensitive but not specific, less expensive and are used for screening purposes and/or to follow response to treatment as well as treponemal antibody tests which are sensitive and specific and are used to confirm diagnoses.

- A. Non-treponemal
 - a. Tests
 - i. Venereal Disease Research Laboratory (VDRL) test
 - ii. Rapid Plasma Reagin (RPR) test
 - b. Properties
 - i. Easy and cheap, used for screening
 - ii. Reported as a titer
 - iii. Used to follow treatment
 - iv. Sensitive but not specific
- B. Treponemal
 - a. Tests
 - i. Fluorescent treponemal antibody absorption (FTA-ABS) test
 - ii. Microhemagglutination test for antibodies to *Treponema pallidum* (MHA-TP)
 - iii. *Treponema pallidum* particle agglutination assay (TPPA)
 - b. Properties
 - i. Sensitive and specific
 - ii. Reported as positive or negative

Both types of tests can suffer from false positives and false negatives but the non-treponemal tests are more likely to face these issues.

- A. Acute false positives non-treponemal test: Pneumococcal pneumonia, TB, HIV, Measles Infectious mononucleosis, Viral hepatitis, Pregnancy...
- B. Chronic false positive non-treponemal test: Chronic liver disease, Malignancy, Injection drug use, Connective tissue disease...
- C. False positive treponemal test: Lyme borreliosis, Malaria, Infectious mononucleosis, Leptospirosis, Systemic lupus erythematosus...

Syphilis serology in HIV

Patients with HIV tend to have more false positive non-treponemal tests. Those who do have syphilis tend to have higher non-treponemal titers than non-HIV infected. In late HIV disease, there can be a loss of reactivity to serologic testing. In general, patient with HIV and syphilis typically have a slower decline of titers on treatment.

Screening

Individuals with certain risk factors should be routinely screened for syphilis. This is done through a two step process. The initial step involves a non-treponemal test which, if positive, is followed by a confirmatory treponemal test. Risk factors include MSM who engage in high risk behaviors, people with HIV, persons found to have other STDs, commercial sex workers, persons who exchange sex for drugs and persons in adult correctional facilities.

8. Treatment

Prolonged antibiotics are necessary since *T. pallidum* divides slowly with one doubling *in vivo* per day. Long-acting preparations of antibiotics are often used. *T. pallidum* has (luckily) remained highly sensitive to penicillin.

- A. Early syphilis (primary, secondary, early latent)
 - a. Benzathine penicillin G 2.4 million units intramuscularly x 1
- B. Late latent syphilis or latent syphilis of unknown duration
 - a. Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks
- C. Neurosyphilis
 - a. See below

Other antibiotics which can be used for the treatment of syphilis include Doxycycline, Azithromycin and Ceftriaxone.

Jarisch-Herxheimer reaction: An acute febrile reaction during first 24 hrs of therapy which often involves headache and myalgias and is thought to be due to the release of antigens from treponemes which are being lysed. It is most common among patients with early syphilis. Antipyretics can be used for symptomatic treatment.

Patients treated for syphilis need to have their response monitored. This usually involves monitoring changes in the titer of reagin antibodies using the same testing method as used at initial diagnosis (e.g., RPR or VDRL). Patients with primary and secondary syphilis should expect a fourfold decline in their titers by six months and an eightfold decline by 12 months. Slower rates of decline among patients with early latent syphilis can be expected with a fourfold decline by 12 months being typical. If the expected change in titer does not occur, the patient should be test for HIV

9. Neurosyphilis

Patients with latent syphilis and any of the following should have their CSF examined to rule out neurosyphilis:

- A. Ophthalmic signs or symptoms
- B. Evidence of active tertiary syphilis
- C. Treatment failure (including failure of nontreponemal tests to fall appropriately)
- D. HIV infection with late latent syphilis or syphilis of unknown duration

The CSF analysis should include a cell count, protein concentration and a CSF-VDRL titer. Patients with neurosyphilis typically have a moderate mononuclear pleocytosis,

elevated protein concentration, and positive CSF-VDRL. These tests are very specific but not sensitive for neurosyphilis.

Treatment of neurosyphilis involves Penicillin G 3 to 4 million units IV every four hours or 24 million units continuous IV infusion for 10 to 14 days. Patients should have a repeat neurological examination and lumbar puncture three to six months after treatment and every six months thereafter for 1-2 years. CSF WBC count should normalize and CSF VDRL should become non-reactive by 2 years after treatment. Failure to respond or a worsening of CSF WBC should prompt re-treatment.

10. Syphilis in pregnancy

There can be many sequelae of congenital infection including:

- A. Perinatal death
- B. Premature delivery
- C. Low birth weight
- D. Congenital anomalies
- E. Active congenital syphilis in the neonate

All pregnant women are screened for syphilis as part of routine prenatal care.