Spirochetes

- Human pathogens belong to following 3 genera:
  1. Treponema
  2. Leptospira
  3. Borrelia
- Others (saprophytes) are found in water, sewage and in mouth & genital tracts of humans.

**Treponema**: Main treponemes are:

- **T. pallidum** - Syphilis: Venereal (sexual) disease
- **T. pertenue** - Yaws Non venereal
- **T. carateum** - Pinta disease

All three species are morphologically identical

**Treponema pallidum**

The organisms are actively motile, Slender spirals rotating steadily around their endoflagella even after attaching to cells by their tapered ends. They are so thin that they are not readily seen unless immunofluorescent stain or dark-field illumination is employed.

Pathogenic *T. pallidum* as Nichol’s strain has never been cultured continuously on artificial media, in fertile eggs, or in tissue culture. Nonpathogenic treponemes (Reiter’s strain) can be cultured anaerobically in vitro.

*T. pallidum* may remain motile for 3–6 days at 25°C. In whole blood or plasma stored at 4°C, organisms remain viable for at least 24 hours, which is of potential importance in blood transfusions. Drying kills the spirochete rapidly, as does elevation of the temperature to 42°C. Most
pathogenic bacteria have transposable elements, but *T pallidum* does not, which suggests that the genome is highly conserved and may explain its continued susceptibility to penicillin.

**Antigenic Structure**

*T pallidum* subspecies *pallidum* has hyaluronidase that breaks down the hyaluronic acid in the ground substance of tissue and presumably enhances the invasiveness of the organism.

Humans with syphilis develop antibodies capable of staining *T pallidum* by indirect immunofluorescence, immobilizing and killing live motile *T pallidum* and fixing complement in the presence of a suspension of *T pallidum* or related spirochetes.

The spirochetes also cause the development of a distinct antibody-like substance, reagin, which gives positive CF and flocculation tests with aqueous suspensions of cardiolipin extracted from normal mammalian tissues. Both reagin and antitreponemal antibody can be used for the serologic diagnosis of syphilis.

**Pathogenesis, Pathology, & Clinical Findings of Syphilis**

**Acquired Syphilis**

Natural infection with *T pallidum* is limited to the human host. Human infection is usually transmitted by sexual contact, and the infectious lesion is on the skin or mucous membranes of genitalia. *T pallidum* can probably penetrate intact mucous membranes, or they may enter through a break in the epidermis.

**Primary Syphilis** begin when Spirochetes multiply locally at the site of entry, and some spread to nearby lymph nodes and then reach the bloodstream. In 2–10 weeks after infection, a papule develops at the site of infection and breaks down to form an ulcer with a clean, hard base ("hard chancre") which is painless, avascular, circumscribed, indurated & ulcerated lesion; covered with a thick glairy exudate rich in spirochetes and heals spontaneously in 10-40 days
Secondary Syphilis 2–10 weeks later the "secondary" lesions appear. These consist of a red maculopapular rash anywhere on the body, including the hands and feet, and moist, pale papules (condylomas) in the anogenital region, axillas, and mouth. There may also be syphilitic meningitis, chorioretinitis, hepatitis, nephritis (immune complex type), or periostitis. The secondary lesions also subside spontaneously. Both primary and secondary lesions are rich in spirochetes and highly infectious. Contagious lesions may recur within 3–5 years after infection, but thereafter the individual is not infectious.

Tertiary Syphilis In about 30% of cases, early syphilitic infection progresses spontaneously to complete cure without treatment. In another 30%, the untreated infection remains latent (principally evident by positive serologic tests). In the remainder, the disease progresses to the "tertiary stage," characterized by the development of: granulomatous lesions (gummas) in skin, bones, and liver; also there may be Quaternary Syphilis with degenerative changes in the central nervous system (meningovascular syphilis, or paresis); or cardiovascular lesions (aortitis, aortic aneurysm, aortic valve insufficiency).

In all late syphilitic lesions, treponemes are very rare, and the exaggerated tissue response must be attributed to hypersensitivity to the organisms.

Congenital Syphilis

A pregnant syphilitic woman can transmit T pallidum to the fetus through the placenta beginning in the 10th to 15th weeks of gestation. Some of the infected fetuses die, and miscarriages result; others are stillborn at term. Others are born live but develop the signs of congenital syphilis in childhood: interstitial keratitis, Hutchinson's teeth, saddle nose, periostitis, and a variety of central nervous system anomalies.

Adequate treatment of the mother during pregnancy prevents congenital syphilis. The reagin titer in the blood of the child rises with active infection but falls with time if antibody was passively transmitted from the mother. In congenital infection, the child makes IgM antitreponemal antibody.
Diagnostic Laboratory Tests

Specimens include tissue fluid expressed from early surface lesions for demonstration of spirochetes; blood serum for serologic tests.

Dark-Field Examination The exudate is examined under oil immersion with dark-field illumination for typical motile spirochetes. Treponemes disappear from lesions within a few hours after the beginning of antibiotic treatment.

Immunofluorescence Tissue fluid or exudate is fixed, stained with a fluorescein-labeled antitreponeme serum, and examined by means of immunofluorescence microscopy for typical fluorescent spirochetes.

Serologic Tests for Syphilis

These tests use either nontreponemal or treponemal antigens.

1. Nontreponemal tests—The nontreponemal tests are universally used as screening tests for syphilis. The tests are widely available and have low cost. In addition to their function as screening tests they can be used to follow the efficacy of therapy, false-positive results can occur with many other diseases. Reagin is a mixture of IgM and IgG antibodies reactive with the cardiolipin-cholesterol-lecithin complex. The nontreponemal tests can give quantitative results using serial twofold dilutions. Quantitative results are valuable in establishing a diagnosis and in evaluating the effect of treatment. Positive nontreponemal tests develop after 2–3 weeks of untreated syphilis and are positive in high titer in secondary syphilis.

Tests include: Venereal Disease Research Laboratory (VDRL) test, rapid plasma reagin card tests (RPR), and automated reagin test (ART)

The (VDRL) test is standardized for use on cerebrospinal fluid (CSF) and becomes positive in neurosyphilis. Reagin antibodies generally do not reach the CSF from the bloodstream but are probably formed in the
central nervous system in response to syphilitic infection. The serologic
diagnosis of neurosyphilis is complex.

2. Treponemal antibody tests—The treponemal tests measure antibodies
against T pallidum antigens. The tests are confirmatory for positive result
from a nontreponemal test. The treponemal tests are less useful as
screening tests because once positive following initial syphilitic infection
the tests remain positive for life independent of therapy for syphilis. The
treponemal antibody tests tend to be more costly than the nontreponemal
test, which is important when large groups of people (eg, blood donors)
are being screened. The following tests are included:

a. T pallidum hemagglutination (TPHA) based on the same principles
as the TP-PA but use sheep erythrocytes rather than gelatin particles and
may be more prone to nonspecific agglutination.

b. T pallidum immobilization (TPI) test applied when live motile
treponema stop moving by adding patient serum with antibodies and
complement. This test is dangerous because of the use of live treponema.

c. Treponemal antibody tests using the EIA for T pallidum (enzyme
immunoassay format) are available.

d. Fluorescent treponemal antibody absorbed (FTA-ABS) test is the
treponemal antibody test employed for many years. The test uses indirect
immunofluorescence to detect reactive antibodies. This is highly sensitive
and specific that become positive at early syphilis and remain positive
even after infection.

The presence of IgM FTA in the blood of newborns is a good evidence of
in utero infection (congenital syphilis). A negative FTA-ABS on CSF
tends to exclude neurosyphilis, but a positive FTA-ABS on CSF can
occur by transfer of antibodies from serum and is not helpful in the
diagnosis of neurosyphilis.

Immunity

A person with active or latent syphilis appears to be resistant to
superinfection with T pallidum. However, if early syphilis is treated
adequately the individual again becomes fully susceptible. The various immune responses usually fail to eradicate the infection or arrest its progression.

**Treatment**

- Penicillin is the drug of choice
- 2nd line- Erythromycin, Tetra/ Doxycycline
- Neurosyphilis - Ceftriaxone

**Borrelia**

are arthropod transmitted Spirochetes and they cause Relapsing fever – two types:

a. Epidemic – is caused by *B. recurrentis* and is transmitted by human lice.

This is a more severe form of the disease than the endemic form.

b. Endemic – is caused by many *Borrelia species* and is transmitted by ticks

Both types of relapsing fever follow the same clinical pattern.

**Borreliae** are irregular spirals, highly flexible and move both by rotation and by twisting. Borreliae stain readily with bacteriologic dyes as well as with blood stains such as Giemsa's stain or Wright's stain. The organism can be cultured in fluid media containing blood, serum, or tissue, but it rapidly loses its pathogenicity. Can be grown in chick embryos. At 4°C, the organisms survive for several months in infected blood or in culture.

**Pathogenesis & Clinical Findings**

12-15 days after infection there is an abrupt onset of fever, headache, and myalgia for 4-10 days. Then when Antibodies are formed and the number of organisms decrease → This leads to an afebrile period for a few days to several weeks → The fever then relapses because the organism has
undergone antigenic variation. Then antibodies are no longer effective and the organism numbers increase.

Several relapses may occur with each one being less severe than the previous one.

**Laboratory diagnosis**

Blood specimens are obtained during the rise in fever, for smears and animal inoculation.

1- Smears: Thin or thick blood smears stained with Wright's or Giemsa's stain reveal large, loosely coiled spirochetes among the red cells.

2- Animal Inoculation: White mice or young rats are inoculated intraperitoneally with blood. Stained films of tail blood are examined for spirochetes 2–4 days later.

3- Serology: Spirochetes grown in culture can serve as antigens for CF tests, but the preparation of satisfactory antigens is difficult.

**Borrelia vincenti**

Normal mouth commensal but may give rise to ulcerative gingivostomatitis or oropharyngitis (Vincent’s angina) during malnutrition or viral infections in association with fusiform bacilli – fusospirochetosis. Usually diagnosed by gram staining of exudates and treated with Penicillin.

**Borrelia burgdorferi**

Lyme disease – caused by *Borrelia burgdorferi* and transmitted by ticks. This is a systemic illness that may begin with the appearance of a red skin lesion called erythema chronicum migrans (ECM) because the lesion expands in a circular manner. The patient may also have a fever, headache, nausea, vomiting, myalgia, and fatigue. If untreated, the patient may develop arthritis (acute or chronic), and cardiac or neurologic complications weeks or months later due to immune complexes.
Diagnosis

In some symptomatic patients, the diagnosis of early Lyme disease can be established clinically by observing the unique skin lesion. When this skin lesion is not present it is necessary to perform diagnostic laboratory tests. There is, however, no one test that is both sensitive and specific. Blood, CSF or joint fluid can be obtained, but culture usually is not recommended but used to detect *B burgdorferi* DNA by the polymerase chain reaction.

Leptospira

Pathogenic *Leptospira interrogans* must be differentiated from the free-living nonpathogenic species(*Leptospira biflexa*)causes Weil’s disease or leptospirosis which is a zoonosis of worldwide distribution.

*Leptospirae* are tightly coiled, thin, flexible spirochetes, with very fine spirals, one end is often bent, forming a hook. Grow best under aerobic conditions at 28–30°C in semisolid medium. They are actively motile, which is best seen using a dark-field microscope. Leptospirae can survive for weeks in water, particularly at alkaline pH.

Leptospirosis is acquired by contact with the urine of an infected animal or ingestion of contaminated food or water. It is more a disease of animals other than man. Infection can vary from asymptomatic to fulminant.

In most cases the incubation is 2-20 days followed by fever, chills, severe headache, myalgia, malaise, nausea and vomiting. The CNS, liver, and kidneys are most commonly infected. Jaundice occurs in severe cases. Death may occur due to renal failure.

1- Blood – 1st week only- and Urine – 2nd week of disease-for microscopic examination and culture

2- Serology: The diagnosis is confirmed serologically. Agglutinating antibodies first appear by the end of 1st week & increase till 4th week of disease. The use of live organisms can be hazardous. The test is highly sensitive.
Serovar-specific immunity follows infection, but reinfection with different serovars may occur.

**Spirochetes of the Normal Mouth & Mucous Membranes**

A number of spirochetes occur in every normal mouth (eg, *Borrelia buccalis*). On normal genitalia, a spirochete called *Borrelia refringens* is occasionally found that may be confused with *T pallidum*. Most of them are strict anaerobes organisms and are harmless saprophytes under ordinary conditions.