Spirochetes

All spirochetes are highly motile. Flagella are located between inner and outer membranes. Flagella are highly antigenic, making them easily visible to the immune system. Flagellar proteins are highly conserved among spirochetes, and antibodies raised against one bacteria's flagella will also recognize those of other spirochetes. 

- (E-) w/ outer & inner membrane → flagella hide within, so even though there are Abs against them, the Abs can't see them, a host wastes energy.
- Flagella are wrapped around the cell. → still have motors, etc.
- B/c flagella are helical, make cell twist & also be helical.
- W/ Elisa, easy to get reinfection, & old/new Abs may cause false +

Syphilis

* Treponema pallidum subspecies pallidum (two other subspecies discussed later)

* Very thin spirochetes, difficult to see under standard microscopy. Darkfield microscopy → bright, thick, background is black, path. are white.

Humans are only natural host.

Cannot be cultured in artificial media. Can be maintained in the laboratory by injection into rabbit testicles. Multiply only ~100-fold. Must be harvested during small window of maximum density, as rabbit will quickly clear the infection.

Difficulty in working with *T. pallidum* has complicated understanding of its pathogenic mechanisms.

* Became invasive around 1492, when Columbus sailed the ocean blue…
Virulence factors:

*T. pallidum* thought to express very few or no proteins on its surface once infection is established. Perhaps the reason why the bacteria can persistently infect immunocompetent individuals?

2 or 3 different apparent outer membrane proteins bind extracellular matrix: Laminin, fibronectin, collagen

Tomp1 (*T. pallidum Rare Outer Membrane Protein*) / TroA
Researchers arguing over whether this is an outer membrane protein or located in the periplasm. Would be good candidate for vaccine → who gets the $$$?

The recently sequenced lab strain can encode 12 different Tpr proteins (T. pallidum repeats) Functions of Tprs unknown. Antibodies to TprK correlate with resistance to reinfection

Symptoms appear to be due to immune system responses, rather than direct toxicity of bacteria. & like chlamydia & gonorrhea, over-reacts

Epidemiology

Incidence of syphilis decreased during 1970s-80s, but has dramatically increased throughout the US and many other countries, especially Eastern Europe (since collapse of the USSR, 1991, & spread of B. Europeans to west)

Homosexual males are particularly at risk

**Majority of cases are acquired through sexual contact.**

Smaller numbers via:
- non-sexual contact (e.g. contact with skin lesions of *Z* syphilis)
- congenital infection → not in birth process, but during gestation.
- blood transfusion
Pathology

Primary Syphilis

Bacteria can penetrate intact mucous membranes, or may enter through abrasions in skin.

Disseminate through blood and lymphatics within hours of infection. Blood is infectious at this time.

Bacteria replicate slowly (doubling time ~30 hours). Lesions appear after bacteria reach a high concentration in tissue, so incubation time is dependent upon infective dose. 50% infectious dose calculated to be 57 organisms.

Primary lesion (chancre) (shank-ar) or canker

Appears at site of inoculation

Painless (contrast with painful lesions of herpes and chancroid)

Begins as papule, rapidly becomes eroded

An infection arising from a small inoculum may manifest only a small, non-eroded papule. Previous exposure may to lead to small chancre

* Large initial dose = large chancre

Persists 4-6 weeks (range 2-12 weeks), then heals spontaneously.

Vaginal and anal chancre easily missed due to lack of pain

Oral chancre may be mistaken for other types of sores

Local lymphadenopathy with 1 week of chancre, nodes are hard, nonsuppurative and painless, may persist for several months
Secondary Syphilis

6-8 weeks after healing of chancre, although ~15% of patients still have chancre present (or 3-4 mo).

Lesions appear on skin and mucous membranes at other sites (syphilids or syphilides).

- 5 to 10 mm diameter
- Macular, papular or pustular
- May be subtle, ~25% of patients are unaware of lesions
- In warm, moist skin areas, papules may enlarge and erode to produce broad, moist pink-to-white condylomata lata, which are highly infectious.

Constitutional symptoms sometimes accompany secondary syphilis:
- sore throat, fever, malaise, headache, anorexia and weight loss

Other complications may occur, but less common.
- Iritis: pain, photophobia - 5-10% of patients have bacteria in aqueous humor
- Hepatitis
- Neuropathy
- Gastrointestinal manifestations
- Arthritis

Latent Syphilis

Asymptomatic, but may occasionally become infectious. Latent female may transmit T. pallidum to fetus

* no more chancre sp. — looks like infection is clear, but is still infected!! *NEED TX!!

Early latent syphilis: generally within 1 year of acquiring infection, good possibility of secondary symptoms occurring. ~90% of relapses occur in first year. (after 5yrs disappear)

Late latent syphilis: later than early. Almost all relapses occur within 4 years of infection.
- If it's been 10yrs, very slim chance of relapse

Patient may never have another manifestation of syphilis, or may develop:
Tertiary Syphilis → Serious, disseminated problem

Neurosyphilis - risk greater if patient had neurologic symptoms in earlier stages of disease

Meningeal syphilis: may resemble stroke
Paresis - changes to personality, affect, reflexes, eyes (loss of pupil reflexes), speech, intellect, sensorium (delusions, hallucinations)

Cardiovascular tertiary syphilis was very common before antibiotics, now rare
10-40 years after infection

Optic lesions - Iritis, photophobia

Late Benign Syphilis

Formation of gumma (granulatormous lesions) on skin and throughout body
Microscopic to several centimeters in size → Tissue destruction
May heal spontaneously with scarring
May be very destructive
Painless in skin, painful in bone

* These lesions help archaeologists trace evol. of syphilis

Congenital Syphilis

May occur at any time during pregnancy → across placenta

Risk 75-95% with early untreated syphilis, ~35% with later latent syphilis → blc Pt may have cleared syphilis

Lesions appear after ~ 4 months of gestation → ie, 2 wk embryo won't show it
* Once fetus recog. syphilis as bed, then will start dtz
May result in spontaneous abortion or death shortly after birth
Most often due to pulmonary hemorrhage, hepatitis or secondary infection

Petechiae and other skin rashes, bone, liver and spleen abnormalities common
Diagnosis of Syphilis

Dark-field microscopy examination of lesion exudate requires special microscope, live bacteria appear white on black background (used for photography of bacteria in video shown at beginning of class)

Serologic testing

Reagin tests examine for nontreponemal antibodies induced during syphilis (cardiolipin-cholesterol-lecithin complexes) VDRL, TRUST, etc.

*T. pallidum-specific antigens

Direct immunofluorescence with fluorescence-tagged anti T. pallidum antibodies easy but expensive

Treatment of Syphilis

Penicillin G drug of choice, T. pallidum is very sensitive to β-lactams

Jarisch-Herxheimer reaction may occur as bacteria are killed → sudden release of endotoxins

Endemic Treponematoses

Extremely closely related to T. pallidum pallidum Rare in US

Endemic syphilis (betel): T. pallidum subsp. epidemicum
Spread by casual contact, cooking utensils, etc.
Oral lesions common, skin lesions rare
Fewer late complications than venereal syphilis → even w/ chronic inf.
Foci in tropical/subtropical eastern hemisphere, incl. eastern Mediterranean

Yaws: T. pallidum subsp. pertenue
Skin to skin transmission
Nondestructive lesions of skin
Foci in Caribbean & South America, Africa

Pinta: T. carateum
Skin to skin transmission
Skin lesions (pintides) initially red, turn darker upon exposure to sun
Western hemisphere disease

* Bac. can be cleared naturally, but unlikely → it is NEVER too late for Tx.

* Need close observation w/ Tx!!
Oral Treponemes

Normal flora of mouth includes many species of spirochetes, including Treponema denticola, T. vincentii, T. socranskii and other Treponema spp.

Oral treponemes are associated with periodontal disease, although their roles in development of disease are unknown.

*T. vincentii (sometimes called Borrelia vincentii) associated with Vincent's angina - "trench mouth"

Many oral spirochetes have never been cultivated, known as "PROS"- pathogen related oral spirochetes. PROS are a very heterogeneous group, so the terminology is basically meaningless.

Produce many degradative enzymes, such as protease dentilysin of T. denticola —> degrade ECM
*form biofilm; break down host tissue

Sera of many people contain antibodies against proteins of oral treponemes, from previous clinical or subclinical infections. (20-30% are sero+) These include antibodies that recognize the flagellar components. Such antibodies can give false positive results in serological tests for other spirochetes.

*How specific is this test