SYPHILIS

FLAME LECTURE: 167

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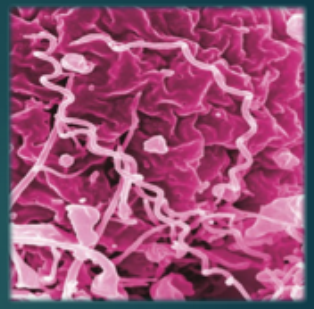
LEARNING OBJECTIVES

- To understand the cause, transmission, and stages of syphilis
- To describe the symptoms and physical exam findings associated with syphilis
- To describe initial evaluation, diagnosis, and treatment of syphilis
- Prerequisites:
  - NONE
- See also – for closely related topics
  - FLAME 92: SYPHILIS IN PREGNANCY

DEFINITIONS

- Syphilis is an infection caused by the spirochete bacterium *Treponema pallidum*
- Different stages guide diagnosis and treatment
  - Primary: local infection that develops within a few weeks of inoculation
  - Secondary: disseminated disease that begins 1-3 months after appearance of primary disease
  - Latent: early (acquired <1 year) or late (acquired >1 year) based on timing of initial symptoms
  - Tertiary: years later systemic disease (uncommon today due to effective antibiotic treatment)



T. pallidum

https://www.flickr.com/photos/nihgov/24512817196

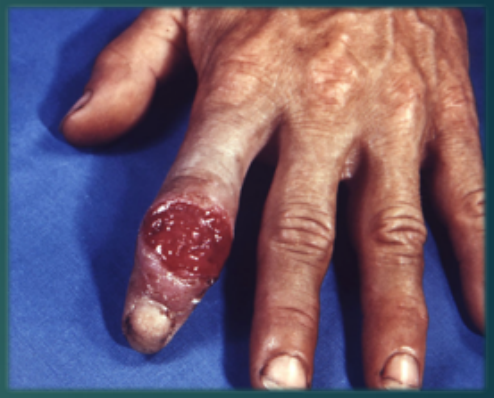
TRANSMISSION

- Syphilis is a highly infectious STI:
  - It is transmitted via direct venereal contact with active lesions (oral, breast, genital, anal)
    - Lesions include chancres, condylomata lata, gummas
  - It can also be transmitted transplacentally from an infected mother to the fetus
    - See FLAME LECTURE 92

CLINICAL PRESENTATION

PRIMARY SYPHILIS

- Average incubation period before clinical manifestations is 21 days (ranges from 3-90 days)
- Presentation:
  - Painless papule appears, which soon ulcerates into a painless chancre (1-2 cm ulcer with raised, indurated margin)
  - Chancres usually appear on the genitalia but can develop in other sites of inoculation such as posterior pharynx, anus, or extragenital
  - Chancres heal within 2-6 weeks even without treatment
  - Concurrently, there is worldwide widespread dissemination of *T. pallidum*



Extragenital chancre

https://commons.wikimedia.org/wiki/File:Extragenital_syphilitic_chancre_of_the_left_index_finger_PHIL_4147_lores.jpg

CLINICAL PRESENTATION
SECONDARY SYPHILIS

- Weeks to months later, 25% of untreated individuals develop systemic illness with a variety of symptoms
- Presentation:
  - Rash: classically diffuse, maculopapular eruption that can involve any body surface, including palms and soles
  - Condylomata lata: gray-white plaques in mucocutaneous areas such as mouth and perineum. Highly infectious!
  - Fever, headache, malaise, anorexia, sore throat, myalgia, weight loss, lymphadenopathy
  - Also: alopecia, hepatitis, GI ulcerations, synovitis, osteitis, glomerulonephritis, uveitis

CLINICAL PRESENTATION
LATENT AND TERTIARY SYPHILIS

- Latent Syphilis
  - Early or late latent syphilis: asymptomatic, but positive serology
- Tertiary syphilis can affect any organ:
  - Gummas (granulomatous lesions): may appear as ulcerative lesions on skin or internal organs
  - Cardiovascular syphilis: aortitis involving aortic root, obliterative endarteritis

CLINICAL PRESENTATION

NEUROSYPHILIS

- Although most often associated with tertiary syphilis, neurosyphilis can occur at any stage
  - Early presentations include cranial nerve involvement, ophthalmic effects (i.e. Argyll-Robertson pupil), auditory changes
  - Meningovascular disease leading to multiple small infarcts
  - Paresis, a combination of psychiatric and neurological symptoms
  - Tabes dorsalis causing ataxia, paresthesia, cognitive disturbances, incontinence, impotence

DIAGNOSIS

SCREENING TESTS

- In recent years, screening and confirmatory testing definitions have blurred; non-treponemal tests used to always be used as a screening test with treponemal tests used as confirmatory tests
  - This was 2/2 to complexity and cost
- However, now treponemal tests are increasingly automated which mediate both of these factors and thus are now more often used as a screening test
- Non-treponemal tests
  - Venereal Disease Research Laboratory (VDRL) test
  - Rapid plasma reagin (RPR) test
  - Toluidine Red Unheated Serum Test (TRUST)
- Treponemal tests
  - Fluorescent treponemal antibody absorption (FTA-ABS) test (**more commonly used**)
  - *T. pallidum* particle agglutination assay (TP-PA)
  - Microhemagglutination assay for *T. pallidum* (MHA-TP)
  - *T. pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)

DIAGNOSIS

SCREENING/CONFIRMATORY TESTS

- Non-treponemal serologic tests become positive for 70-80% of those exposed in 2-4 weeks after inoculation
  - The other 20-30% may take another 2-4 weeks
- Non-treponemal assays are semi-quantitative in that the amount of antibody present (both IgM and IgG) generally reflects the activity of the infection and will decrease following treatment
- Treponemal serologic testing is typically more specific
  - However, these stay positive for life, so they will still be positive in a treated patient

DIAGNOSIS

SCREENING/CONFIRMATORY ALGORITHMS

INITIAL SCREENING W/ NON-TREP SEROLOGIC TEST	INITIAL SCREENIG W/ TREP SEROLOGIC TEST
• Screen w/ RPR or VRDL; if positive, confirm w/ FTS-ABS • If both neg and asymptomatic = done • If both neg and symptomatic, re-screen in 2-4 weeks and give abx • If both positive and asymptomatic = latent syphilis • If both positive and symptomatic = primary, secondary, or tertiary syphilis, or false positive • If both positive in the setting of prior treated syphilis, 4X higher titer = new repeat infection • If positive RPR/VRDL with neg FTS-ABS, likely false positive (*more common in preg)	• *Higher false-positive rates, however more sensitive* • Screen w/ FTS-ABS or TP-EIA; if positive, confirm with RPR or VRDL • If neg and asymptomatic = done • If neg and symptomatic, re-screen in 2-4 weeks and give give abx • If FTS-ABS positive and RPR/VRDL negative, consider history of treated syphilis or late-latent syphilis (perform a second different treponemal test to confirm; if neg, maybe false positive)

DIAGNOSIS
OTHER TESTS

- Point-of-care (POC) serologic testing being studied, but not yet routinely recommended
- Dark-field microscopy and direct fluorescent antibody was the most definitive test, but now rarely done 2/2 difficulty
- CSF analysis if neurologic disease is suspected
  - Would see elevated WBC and protein, low glucose, positive VDRL
  - *Note: negative CSF VDRL does not rule out neurosyphilis as the test is not very sensitive*

DIFFERENTIAL DIAGNOSIS

- Primary syphilis chancre may be confused with:
  - Herpes simplex: multiple, painful vesicles
  - Chancroid: painful papule/pustule
  - Lymphogranuloma venereum (LGV): painless papule/vesicle
- Secondary syphilis:
  - Rash may be confused with Rocky Mountain spotted fever, viral exanthem (i.e. Coxsackie), drug eruptions
  - Systemic symptoms may be confused with HIV

TREATMENT OVERVIEW

- Gold standard is Benzathine Penicillin G, a long-acting antibiotic
  - Single dose = 2.4 million units
- Alternatives for penicillin-allergic patients:
  - Doxycycline 100 mg PO BID x 14 days
  - Tetracycline 500 mg PO QID x 14 days
  - Ceftriaxone 1-2 g IV or IM QD x 10-14 days
  - Azithromycin 2 g PO x1 dose (last choice)

- *Note: penicillin-allergic **pregnant** patients must be desensitized and treated with Penicillin G*

TREATMENT

Stage	Clinical Manifestations	Treatment	Penicillin-allergic
Primary	Painless chancre	Penicillin G (IM) x1 dose	Doxycycline x14 days
Secondary	Diffuse rash, condylomata lata, lymphadenopathy, oral lesions, hepatitis	Penicillin G (IM) x1 dose	Doxycycline x14 days
Early latent	Asymptomatic		
Tertiary (w/ normal CSF)	CV: Aortic aneurysms, aortic insufficiency, endarteritis Skin: Gummas	Penicillin G (IM) x1 dose weekly for 3 weeks	Doxycycline x14 days
Late latent	Asymptomatic		
Neurosyphilis at any stage	CNS: Tabes dorsalis, Argyll-Robertson pupil, dementia, auditory symptoms	Penicillin G (IV) x10-14 days	Ceftriaxone x14 days

TREATMENT FOLLOW UP

- All patients should receive follow-up clinical evaluation and repeat serologic testing at 6,12, 24 months after treatment
  - Most patients should also undergo HIV testing
- 4X reduction in titers using VDRL or RPR tests is evidence of an appropriate treatment response
- If response is inadequate, patients should be retreated vs. tested for reinfection (CSF analysis)

TREATMENT REACTIONS

- Jarisch-Herxheimer reaction
  - This acute febrile reaction, often with headache, tachycardia, myalgia, and exacerbation of skin lesions, may develop in some patients within the first 24 hours of starting any treatment
    - More common in primary or secondary syphilis
  - Thought to be caused when endotoxins are released into circulation by dying spirochetes, triggering a systemic release of reactive cytokines.
  - This temporary inflammatory reactions is treated symptomatically with antipyretics and analgesics
  - Usually resolves within 24 hours

SCREENING AND PREVENTION

- Screening guidelines (USPSTF)
  - Screen all pregnant women
  - Screen populations at higher risk of acquiring syphilis
    - MSM who engage in high risk behaviors
    - Commercial sex workers
    - Persons who exchange sex for drugs
    - Persons in adult correctional facilities
  - USPSTF recommends against routine screening of asymptomatic persons not in the above groups due to false positive rates
- Prevention: patient education on safe sex practices and barrier methods, test and treat sexual partners, test for HIV
- No vaccine available

REFERENCES

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4. USPSTF: Recommendation Statement: Syphilis Infection: Screening. (2017)
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