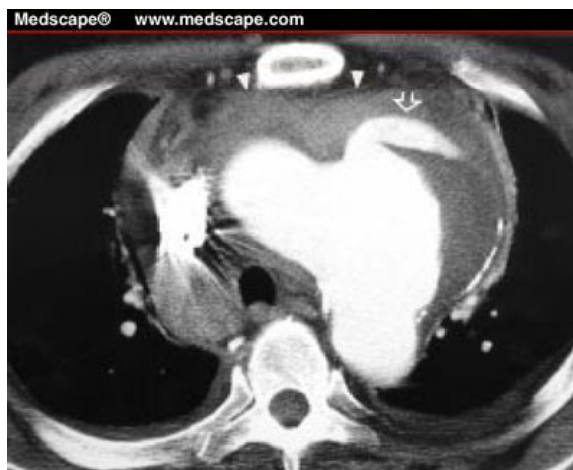


Syphilis

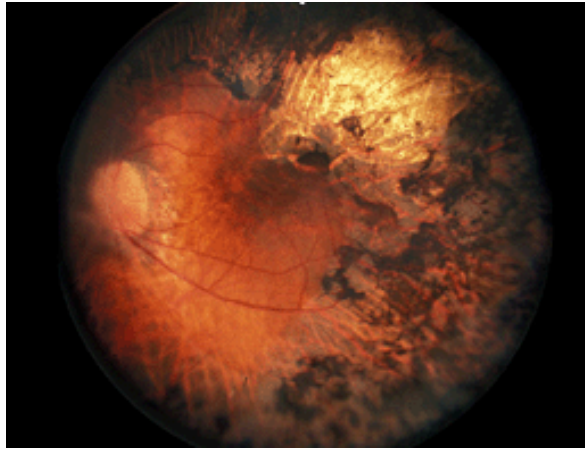
Simon J. Tsiouris, MD, MPH
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55 yo man presents to the ER with chest pain radiating to his back, shortness of breath and is found to have this on Chest CT



Aortic aneurysm rupture. Axial postcontrast image through the aortic arch reveals an aortic aneurysm with contrast penetrating the thrombus within the aneurysm (open arrow). Note the high attenuation material within the mediastinal fat (arrowheads), representing blood and indicating the presence of aneurysm rupture.

26 yo man presents to an ophthalmologist with progressive loss of vision in his Left eye, his fundoscopic exam looks like the picture on the left:



Normal

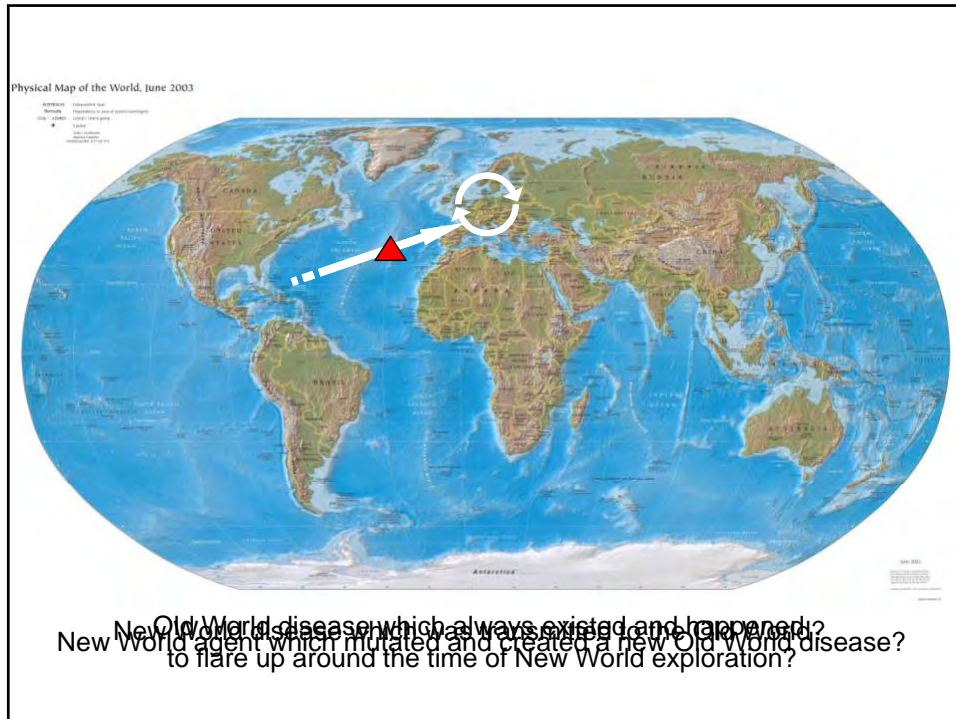
- 43 yo woman with RUQ pain is found to have a liver mass on U/S, biopsy of the mass reveals granulomas
- 26 yo man presents to the ED with new-onset seizures, a Head CT reveals an acute CVA
- 85 yo woman c/o shooting pains down her arms and in her face for 2 years duration
- 36 yo man presents to his PMD with an enlarging lymph node in his neck

19 yo man is seen at an STD clinic
for a painless ulcer on his penis



Mercutio: "... a pox on your houses!"

Romeo and Juliet, 1st Quarto, 1597, William Shakespeare



Origins of syphilis

- Pre-Colombian New World skeletal remains have bony lesions consistent with syphilis
- *T. pallidum pallidum* (cause of syphilis) and *T. pallidum pertunae* (cause of Yaws) have 100% genetic homology
- Native Americans suffered from syphilis (previously unknown to them) **after** Europeans arrived

Other names for syphilis

- Great pox
- Disease of Naples
- Italian pox
- French pox (Morbus gallicus)
- Turkish disease
- Spanish disease

Famous people who (probably) had syphilis

- Ivan the Terrible
- Henry VIII
- Cortes
- Francis I
- Charles Baudelaire
- Meriwether Lewis
- Friedrich Nietzsche
- Gaetano Donizetti
- Toulouse Lautrec
- Al Capone
- ...

The Great Pox – Syphilis in the 1500s



10. A young man afflicted with syphilis. Colored drawing
1523, by Hans Holbein the Younger.

From *Epidemics and History: Disease, Power and Imperialism* by Sheldon Watts, Yale University Press 1999

Galen's humors

- Pox diseases were associated with phlegm (one of the four humors)
- Treatments should promote spitting and sweating

Treating syphilis in the 1600s



II Guaiac wood, prepared and administered. Engraving, c. 1600, by Philip Galle after J. van der Straet.

From Epidemics and History: Disease, Power and Imperialism by Sheldon Watts, Yale University Press 1999

Other treatments

- Mercury
 - Given until patient produced copious saliva
 - Sign of mercury poisoning: copious saliva
- Arsenic
 - Arsphenamine[®], Salvarsan[®]
- Bismuth (i.e. Pepto-Bismol)
- Fever therapy
- Malaria therapy

- Penicillin --- more on this later

Syphilis and sin in the 19th century



12. Sin, syphilis and skeletons. Nineteenth-century watercolor by R. Cooper.

From Epidemics and History: Disease, Power and Imperialism by Sheldon Watts, Yale University Press 1999

Syphilis in wartime



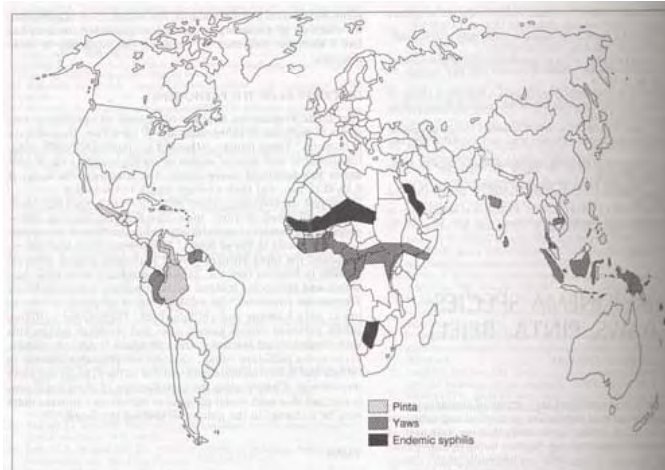
Syphilis in wartime

- World War I
 - Syphilis most common cause for rejection from service
 - Up to 10% of European theater allied soldiers had syphilis
- World War II
 - Most penicillin available was used not to treat infected wounds but to treat syphilis (so that soldiers could return to the front)

Treponemes

- Family Spirochaetaceae
 - Borrelia
 - Lyme disease, Tick-borne and louse borne relapsing fever
 - Leptospira
 - Leptospirosis
 - Treponema
 - *Treponema pallidum* subsp. *pertenue*
 - yaws
 - *Treponema pallidum* subsp. *endemicum*
 - bejel, endemic syphilis
 - *Treponema pallidum* subsp. *carateum*
 - pinta
 - *Treponema pallidum* subsp. *pallidum*
 - syphilis

Map of endemic treponemal diseases



Yaws: *Treponema pertenue*



Bejel: *Treponema endemicum*



Geographical distribution of endemic trepanomatoses in 1950 and 20 years later



Pinta: *Treponema carateum*



Treponema pallidum subsp. *pallidum*

- Slender, tightly coiled, helical
- Undulating movement about its center (flexuose) distinguish it from nonpathogenic treponemes on darkfield microscopy
- Cannot be cultured in vitro
 - Rabbits
- Unlike other pathogenic bacteria, genome lacks apparent transposable elements
 - PCN sensitivity
 - Paucity of genes involved in biosynthesis of nutrients or energy production: scavenger



Darkfield microscopy



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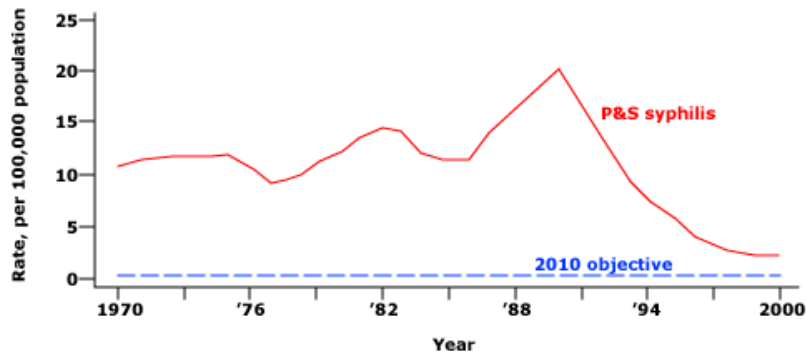
World Health Organization estimates, new adult cases 1999

- 100,000 North America
- 140,000 western Europe
- 100,000 eastern Europe
- 100,000 central Asia
- 370,000 in north Africa and the Middle East
- 3-4 million each in
 - Latin America
 - the Caribbean
 - sub-Saharan Africa
 - south and southeast Asia

Epidemiology

- Early syphilis is reportable
- Mini-epidemic in the US in the late 80s to early 90s
 - case rates that were higher than at any time since the introduction of penicillin

Syphilis incidence in the US



Specific populations

- MSM
 - The CDC estimates that in 2004, approximately 64 percent of all cases of primary and secondary syphilis were in MSM.
- 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 were HIV-infected MSM

Definitions

- Disease stages
 - Early (<1 year since infection), more likely to be infectious
 - Primary
 - Secondary
 - Early latent
 - Late latent (>1 year since infection, or unknown duration), less infectious but more difficult to treat
 - A.k.a. tertiary syphilis

Natural History (1)

- Oslo, Norway
 - 1400 patients with syphilis in the late 19th century, untreated
 - 10 percent developed cardiovascular syphilis
 - 16 percent developed gummatous syphilis
 - 6.5 percent developed symptomatic neurosyphilis



Natural History (2)

- Tuskegee, Macon County, Alabama
 - 431 black men with syphilis between 1932 and 1972, untreated
 - PCN discovered in 1947, not offered
 - 1972: news stories and public outcry, study closed
- 1974:
 - National Research Act was signed into law
 - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
 - Legislation passed that required researchers to get voluntary informed consent from all persons taking part in studies done or funded by the Department of Health, Education, and Welfare (DHEW).
 - They also required that all DHEW-supported studies using human subjects be reviewed by Institutional Review Boards
 - 1979 Belmont Report
 - Respect for Persons
 - Beneficence
 - Justice



Transmission

- Transmission of *Treponema pallidum* usually occurs via direct contact with an infectious lesion during sex.
 - the spirochete gains access via disrupted epithelium at sites of minor trauma.
- Early lesions are all very infectious
 - Chancres
 - mucous patches
 - condyloma lata
- It has been estimated that transmission occurs in approximately one-third of patients exposed to these lesions
 - Need as few as 60 organisms to infect

Clinical manifestations primary syphilis

- Incubation
 - median 21 days (range 3 to 90 days)
- Primary syphilis
 - ★ – Papule develops into classic chancre lesion at the site of inoculation
 - Clean based ulcer
 - Indurated and **painless**
 - Heals spontaneously in 3-6 wks
 - Wide dissemination of spirochete occurs



Penile ulcer



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Early pathophysiology

- Infection initiated when *T. pallidum* gains access to subcutaneous tissues via microscopic abrasions
- Evades early host immune responses and establishes the initial ulcerative lesion
 - some organisms establish infection in regional draining lymph nodes

Early pathophysiology

- Widespread dissemination of spirochetes despite apparent effective immune control (i.e. resolution of chancre)
- Early lesional infiltration of PMNs → replaced by T lymphocytes
 - Secondary syphilis lesional fluid is enriched for CD4+ and CD8+ T cells and dendritic cells
 - Many of these dendritic cells also expressed HIV coreceptors (eg, CCR5)
- Humoral immune responses lead to the development of a variety of antibodies that can be detected relatively early in the course of syphilis.

Clinical manifestations secondary syphilis - 1

- Systemic illness a few months after chancre
 - Rash
 - Any type except vesicular
 - Classically is symmetric macular or papular
 - discrete red or reddish-brown lesions 0.5 to 2 cm in diameter
 - ★ • **palms and soles** involvement is an important clue to the diagnosis of secondary syphilis.



Rash of secondary syphilis



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Clinical manifestations secondary syphilis - 2

- Other rashes
 - Condyloma lata
 - Mucous patches
- Systemic symptoms
- Lymphadenopathy
- Alopecia
- protean manifestations
 - Hepatitis
 - GI, MS, Renal abnormalities
 - Neurologic manifestations
 - Ocular manifestations

Mucous patches



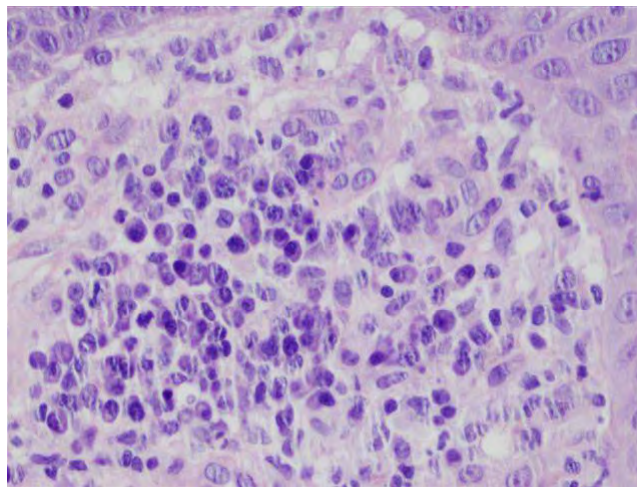
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Condyloma lata

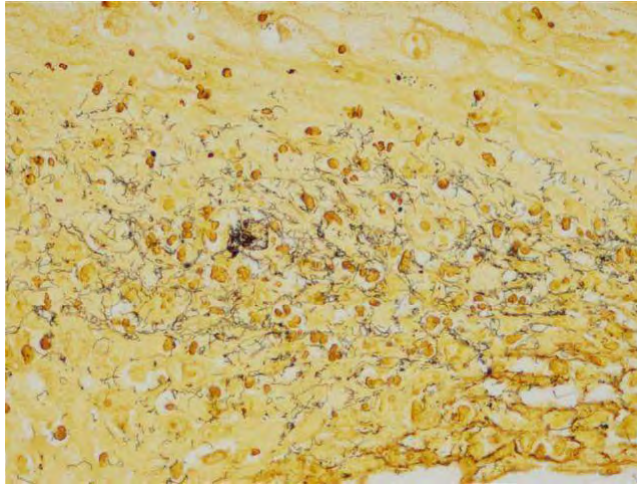


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Pathology of secondary syphilis skin lesions



Pathology of secondary syphilis skin lesions



Lymphadenopathy



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Alopecia

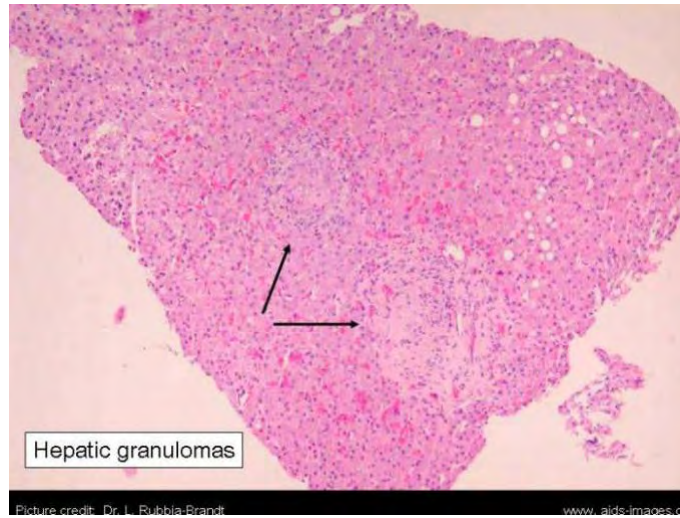


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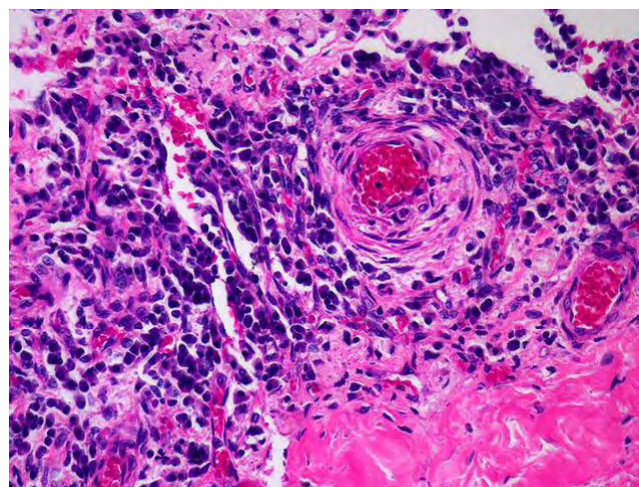
Clinical manifestations of late syphilis

- Gummatous syphilis
 - The Great pox (as opposed to the small pox)
 - Uncommon nowadays
- Cardiovascular syphilis
 - ascending thoracic aorta resulting in a dilated aorta and aortic valve regurgitation
- Syphilis of the CNS

Hepatic granulomas



Syphilitic aortitis





Diagnosis of primary syphilis

- Darkfield microscopy of chancre scraping
 - corkscrew-shaped organisms with tightly wound spirals
 - forward and backward motion with rotation
 - Soft side-to-side bending and twisting
 - Specific but not sensitive
- Direct fluorescent antibody test of specimen (DFA-TP)
 - Not widely used

Darkfield microscopy



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Diagnosis of syphilis

- Gold Standard:
 - Culture of *T. pallidum* by *in vivo* intratesticular inoculation of rabbits
 - Not done routinely

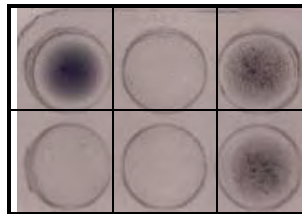


Diagnosis of syphilis

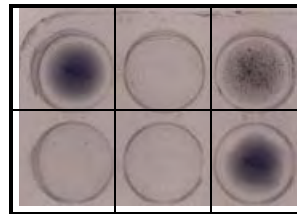
- Serologic tests
 - Non-treponemal
 - Venereal Disease Research Laboratory (VDRL) test (less commonly used except on CSF)
 - Rapid Plasma Reagin (RPR) test
 - Tests for auto-antibodies to cardiolipin, a tissue lipid
 - Easy and cheap, used for screening
 - Reported as a titer
 - Used to follow treatment
 - Sensitive except in late syphilis, specific

RPR

Negative control serum		Positive control serum
		Test



positive

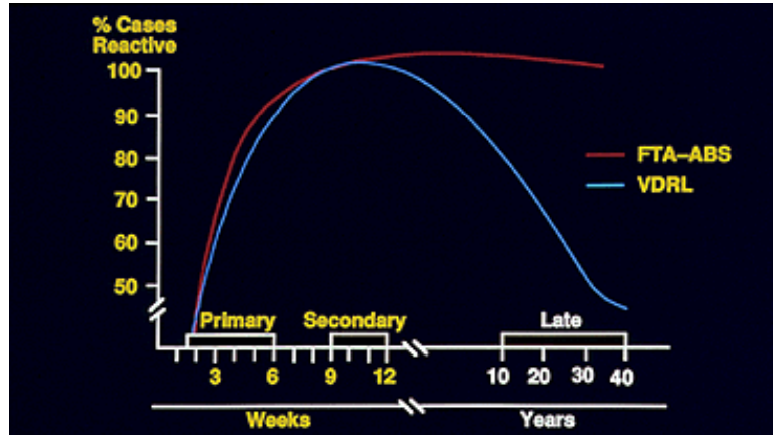


negative

Diagnosis of syphilis

- Serologic tests
 - Treponemal
 - Fluorescent treponemal antibody absorption (FTA-ABS) test
 - Microhemagglutination test for antibodies to *Treponema pallidum* (MHA-TP)
 - *Treponema pallidum* particle agglutination assay (TPPA)
 - More sensitive and more specific, even in late syphilis
 - Reported as positive or negative

Time course of antibody development during syphilis



Courtesy of Charles B Hicks, MD; modified from the VD Program, Centers for Disease Control, US Public Health Service.

Specificity

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

Screening for syphilis

- Risk factors
 - MSM who engage in high risk behaviors
 - CSWs
 - persons who exchange sex for drugs
 - adult correctional facilities
- ★• Two step process
 - Non-treponemal test followed by a confirmatory treponemal test if positive



Treatment - 1

- Prolonged antibiotics necessary since *T. pallidum* divides slowly
 - one doubling in vivo per day
- Long-acting preparations
- Highly sensitive to penicillin



Treatment - 2

- Early syphilis
 - Benzathine penicillin G 2.4 million units intramuscularly x 1
- Late latent syphilis or latent syphilis of unknown duration
 - Benzathine penicillin G 2.4 million units intramuscularly every week for 3 weeks

Other antibiotics

- Doxycycline
- Azithromycin
- Ceftriaxone



Jarisch-Herxheimer reaction

- acute febrile reaction during first 24 hrs of therapy
- headache and myalgias
- most common among patients with early syphilis
- antipyretics can be used for symptomatic treatment

Monitoring the response to treatment

- Monitor changes in the titer of reagin antibodies
 - Use the same testing method (eg, RPR or VDRL)
- Patients with primary and secondary syphilis:
 - Expect a fourfold decline by six months
 - Expect an eightfold decline by 12 months
- Slower rate of decline among patients with early latent syphilis
 - Expect fourfold decline by 12 months
- ★• If expected change does not occur, test for HIV



Neurosyphilis (1)

- Examine CSF if:
 - latent syphilis and any of the following
 - Ophthalmic signs or symptoms
 - Evidence of active tertiary syphilis
 - Treatment failure (including failure of nontreponemal tests to fall appropriately)
 - HIV infection with late latent syphilis or syphilis of unknown duration

Neurosyphilis (2)

- CSF analysis:
 - cell count
 - protein concentration
 - CSF-VDRL titer
- Expect:
 - moderate mononuclear pleocytosis
 - elevated protein concentration
 - Positive CSF-VDRL
 - very specific, not sensitive

Neurosyphilis (3)

- Early
 - Transient or persistent asymptomatic meningitis
- Early symptomatic (weeks to years)
 - Symptomatic meningitis
 - Ocular findings
 - Stroke
- Late symptomatic meningitis (years to decades)
 - Paresis
 - Dementia
 - Personality change
 - Tabes Dorsalis

Tabes dorsalis (aka locomotor ataxia)

- Less common in antibiotic era
- Disease of the posterior columns of the spinal cord and of the dorsal roots
- Ataxia and lancinating pains
- Pupillary irregularities
 - ★– Argyll-Robertson pupil
 - small
 - does not respond to light
 - contracts normally to accommodation and convergence
 - dilates imperfectly to mydriatics
 - dilate in response to painful stimuli.



Neurosyphilis (4)

- Treatment
 - ★ – Penicillin G 3 to 4 million units IV every four hours or 24 million units continuous IV infusion for 10 to 14 days
 - Neurologic examination and lumbar puncture
 - three to six months after treatment
 - every six months thereafter
 - CSF WBC count should normalize and CSF VDRL should become nonreactive by 2 years after treatment
 - Failure to respond or a worsening of CSF WBC should prompt re-treatment.



Syphilis serology in HIV

- More false positive non-treponemal tests
- Higher non-treponemal titers than non-HIV infected
- Loss of reactivity in late HIV disease
- Slower decline of titers on treatment

Syphilis in pregnancy

- Sequelae of congenital infection
 - Perinatal death
 - Premature delivery
 - Low birth weight
 - Congenital anomalies
 - Active congenital syphilis in the neonate

“He who knows syphilis,
knows medicine”

-Sir William Osler