Syphilis: an ancient disease in modern times

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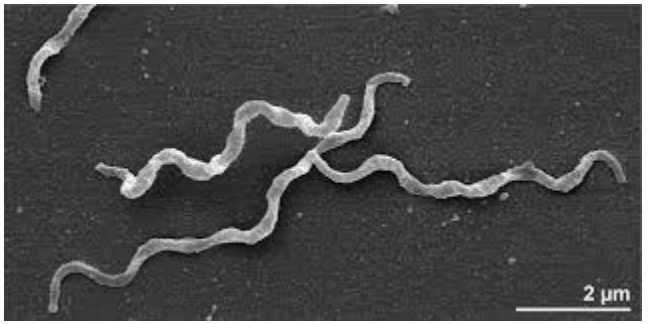
General

- Treponematoses = diseases caused by treponemes
- 4 different, chronic diseases
  - → Veneral syphilis
  - → 3 forms of non-veneral treponematoses

- No animal reservoir, strictly human disease
- Clinical and serological diagnosis



Non-veneral treponematoses

- *Treponema pallidum endemicum*
  - → Bejel, non-veneral ‘endemic’ syphilis
  - → Sub-saharan africa (also arabian peninsula): dry climate
  - → Early: Skin, oral lesions, osteitis
  - → Late: gummata, gangosa

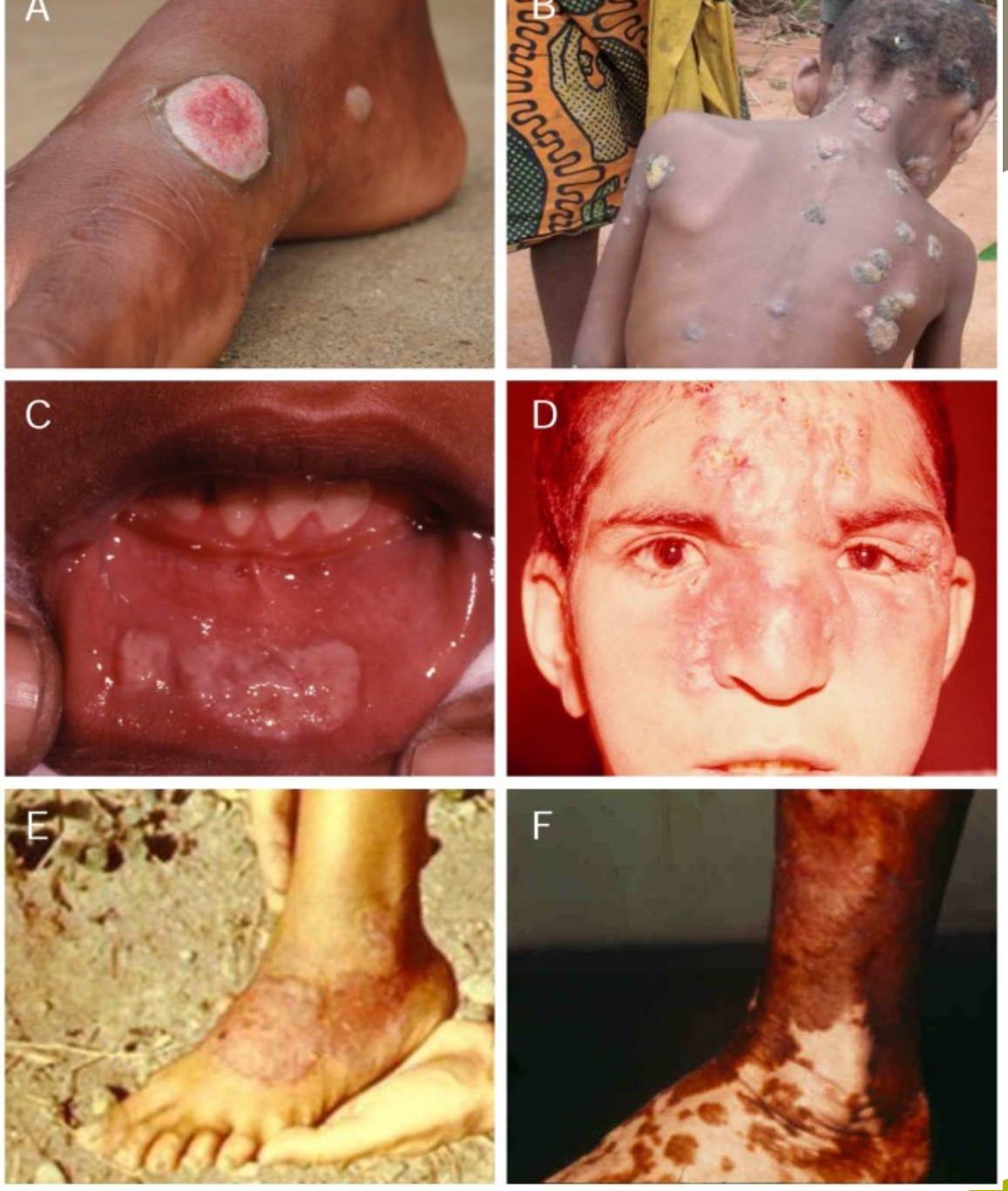
Non-veneral treponematoses

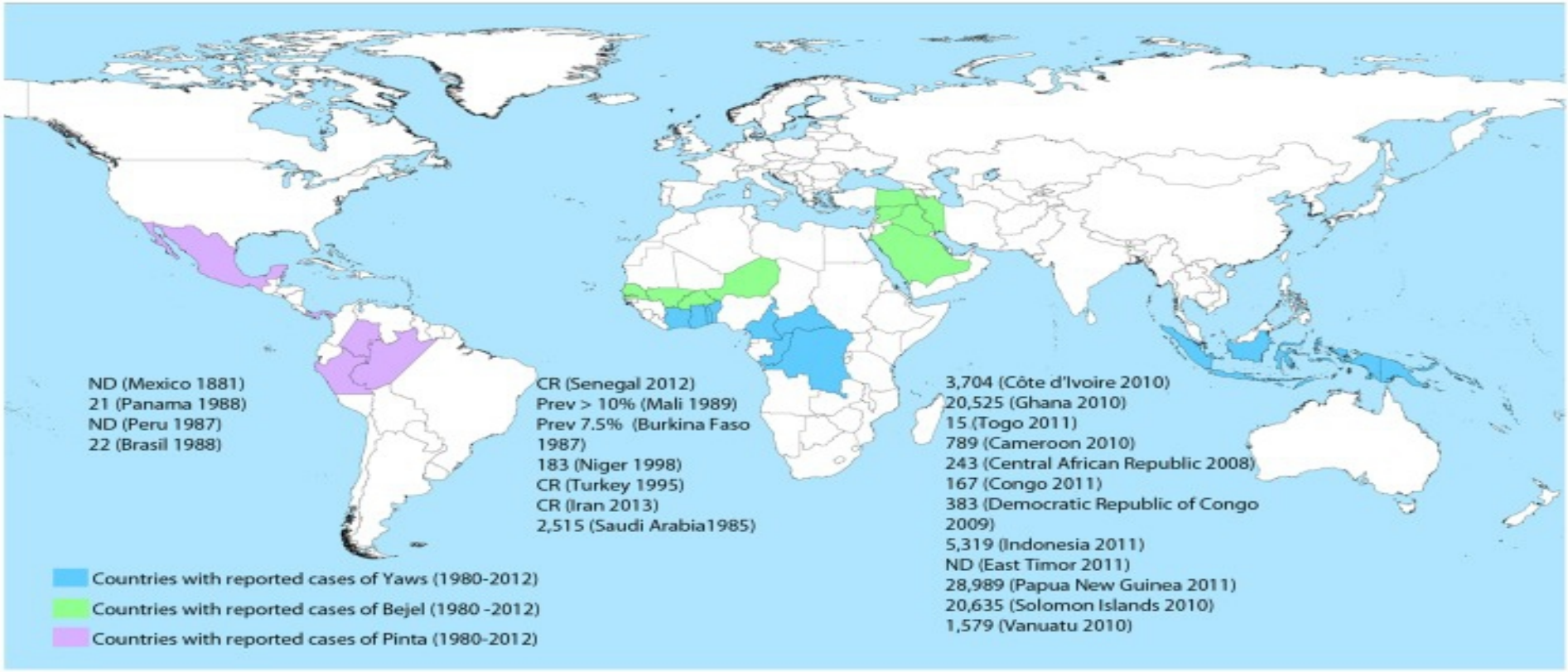
- *Treponema pallidum pertenue*
  - → Framboesia or yaws (pian)
  - → Tropical, wet climate: Africa (Ghana), Indonesia, Papua, Solomon Islands
  - → Primary 'warty' skin lesion (may ulcerate), extra-genital
  - → Multiple secondary lesions reappear, persist for months (flare-ups)
  - → Late onset (10%, after 5y) gummata, periosteitis, chronic osteitis ("sabre tibia")

Rinaldi A (2008) Yaws: A Second (and Maybe Last?) chance for eradication. *PLoS Negl Trop Dis* 2(8): e275

Non-veneral treponematoses

- *Treponema carateum*
  - → Pinta
  - → Only skin lesions
  - → Mexico, Panama, Indian tribes Amazon (Colombia, Brazil, Peru)
  - → Initial lesion scaly papule (itchy), appears after +-1 week, enlarges over months
  - → Then generalised maculo-papular rash


A
B
C
D
E
F


ND (Mexico 1881)
21 (Panama 1988)
ND (Peru 1987)
22 (Brasil 1988)
CR (Senegal 2012)
Prev > 10% (Mali 1989)
Prev 7.5% (Burkina Faso 1987)
183 (Niger 1998)
CR (Turkey 1995)
CR (Iran 2013)
2,515 (Saudi Arabia1985)
3,704 (Côte d'Ivoire 2010)
20,525 (Ghana 2010)
15 (Togo 2011)
789 (Cameroon 2010)
243 (Central African Republic 2008)
167 (Congo 2011)
383 (Democratic Republic of Congo 2009)
5,319 (Indonesia 2011)
ND (East Timor 2011)
28,989 (Papua New Guinea 2011)
20,635 (Solomon Islands 2010)
1,579 (Vanuatu 2010)
Countries with reported cases of Yaws (1980-2012)
Countries with reported cases of Bejel (1980 -2012)
Countries with reported cases of Pinta (1980-2012)

History of veneral syphilis

- Stigmatised, disgraceful disease
- First epidemic described 1494 Naples
  → 'French – Italian' war
  → More severe , more rapidly spreading, and more atypical then nowadays
- 'French' 'Napolitan' 'Polish' 'German' 'Spanish' 'Christian' disease
- "Syphilis sive Morbus Gallicus"

Tampa M, Sarbu I, et al. Brief history of syphilis *J Med Life*, Mar 15,2014; 7(1):4-10

Hypotheses on the origin

- Columbian hypothesis
  - → Navigators in Columbus fleet brought the disease to Europe

- Unitarian/ pre-columbian hypothesis
  - → Adaptive responses of *T Pallidum* to changes in environment, cultural differences and contact between different populations

Treatment along the history

- Guaiac tree 15th century (*Guaiacum officinale*)
  → Purgatory, 'blood cleansers'
- Mercury (Paracelsus 1493-1541): topically, oral or 'fumigation'
- Bismuth salts 1884
- Arsphenamine (Salvarsan-'compound 606')
  → Arsenic compound
- *Plasmodium Vivax*
- Penicilline 1928

Case history

- 50 year old male
- Headache associated with a widespread rash
  - → Rash since 2 weeks, non-pruritic, started on abdomen
  - → Headache appeared 4 days ago: GP ‘viral exantham’ /R paracetamol
  - → Headache aggravated last 2 days, N+, V-
  - → No fever, no weight loss, no night sweats

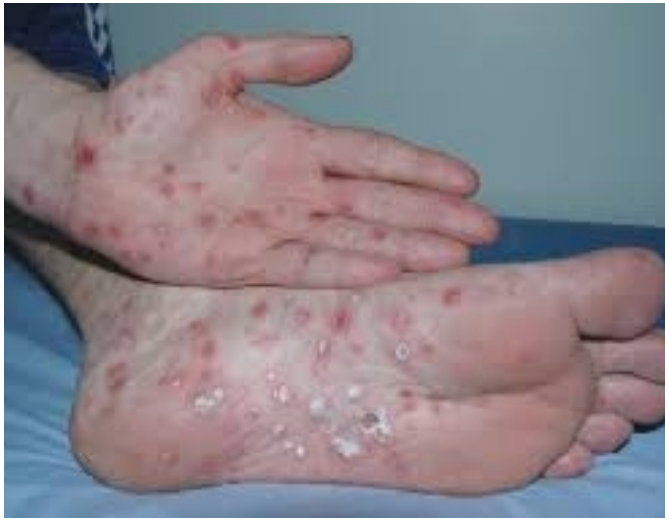
Medical history

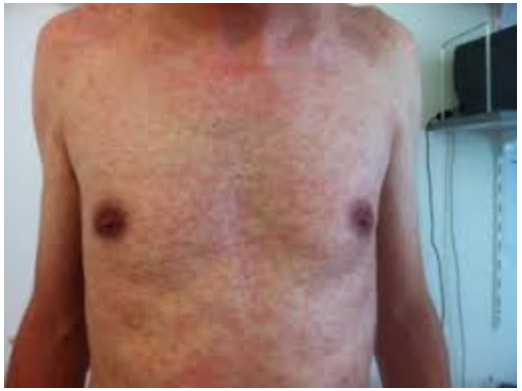
- Arterial hypertension
  → /R amlodipine 10mg q24h
- Allergic to penicilline (rash)

- No recent travel in the last 6 months
- ‘Caucasian’, belgian nationality
- Non-smoker, +-20 U alcohol/week
- New (male) partner since 2 months
- Last negative hiv test 2years ago, no drugs

Physical examination

- No fever, normal BD and HR
- Widespread, symmetrical, non-pruritic, maculo-papular rash
- Also on his palms and soles of his feet
- Purplish lesions, well circumscribed
- No oral or genital lesions
- Widespread adenopathy (not tender)
- No neck stiffness/meningism, Kernig –
- No neurological deficit, cranials nerves intact
- Clear chest, normal heart sounds, abdomen OK





Additional testing

- ER: Chest XR, blood tests, blood cultures
- /R 1dose ceftriaxone 2g IV
- CXR normal
- Lab: only slightly elevated CRP 14 mg/L, hematology, renal function, LFT all normal

What's next?

A. Ask a dermatologist for advice
B. Ask a neurologist for advice
C. Give IM penicilline and send him home
D. Yell at the ER doctor and immediately perform LP
E. Reexamine patient, CT scan and LP

Differential diagnosis

- Bacterial meningitis?
- Viral meningitis?
- Acute hiv seroconversion (rash, ADP, headache)
- Syphilitic meningitis?
- TB or cryptococcal meningitis (but what with the rash?)

Returns after CT scan (with contrast)

- CTscan = normal, no space-occupying lesions, no CI for LP
- worsening rash
- Increasingly unwell, low-grade fever, myalgia

What's next ?

A. Suspect contrast allergy
   → Give IV steroids and IM promethazine
B. Suspect antibiotic allergy
   → Give IV steroids and IM promethazine
C. Perform LP
D. Give paracetamol and perform LP

Results of the CSF

- CSF: clear, opening pressure 15 cm H_2O
- Mildly elevated protein (700 mg/L)
- Normal glucose (CSF 65 mg/L, blood 98 mg/L)
- Lymphocytic pleiocytosis (30 cells/mm^3 , 95%L)

What's next ?

A. Complete syphilis serology RPR, TPPA (or EIA)
B. Syphilis screening RPR
C. Syphilis screening TPPA
D. Syphilis screening EIA

Syphilis screening in Europe

- Primary screening test
  - → Option 1: a TT (TPHA, MHA-TP, TPPA or EIA/CIA)
  - → Option 2: a NTT (ideally quantitative) (RPR or VDRL)
  - → Option 3: both a TT and a NTT
- Confirmatory test(s) on the same serum if any screening test is positive
  - → Option 1: another TT of a different type AND a quantitative NTT if second TT is positive
  - → Option 2: a TT
  - → Option 3: NTT must be performed quantitatively

Janier M et al. 2014 European guideline on the management of syphilis. *JEADV* 2014, 28,1581-1593

What else do you want ?

A. HIV screening and cryptococcal Ag
B. HIV + VDRL (or RPR) on CSF
C. HIV + VL + CD4
D. HIV + VL + CD4 + VDRL(or RPR) on CSF

- HIV ELISA + (and confirmed 2nd sample)
- VL 18,000 copies/mL
- CD4 lymphocyte count 36% (556/mm³)
- RPR 1/32 TPPA + (1/20480)
- Cryptococcal Ag (serum) - , India ink –
- PCR CSF (enteroviridae, HSV 1-2) neg.
- CSF RPR + (1/8)

Secondary syphilis

- 2-3 months after acquisition
- Systemic illness
- Rash
  - → Non-pruritic
  - → Affects all the skin, including palms/soles
  - → Macular, papular or maculo-papular
  - → But often atypical (in the setting of HIV)

Secondary syphilis, less frequent presentations

- Hepatitis
- Splenomegaly
- Patchy alopecia
- Condylomata lata
- Periosteitis
- Glomerulonephritis
- Meningitis (2-5%)
- Cranial nerve palsies
- Anterior (posterior) uveitis

Neurosyphilis

- Diagnostic criteria
  - → Confirmed:
    - any stage of syphilis
    - and reactive CSF VDRL (or RPR)
  - → Presumptive:
    - any stage of syphilis
    - nonreactive CSF VDRL (or RPR)
    - and Pleiocytosis or elevated protein CSF
    - and Neurological clinical signs or symptoms consistent with syphilis

Early neurosyphilis

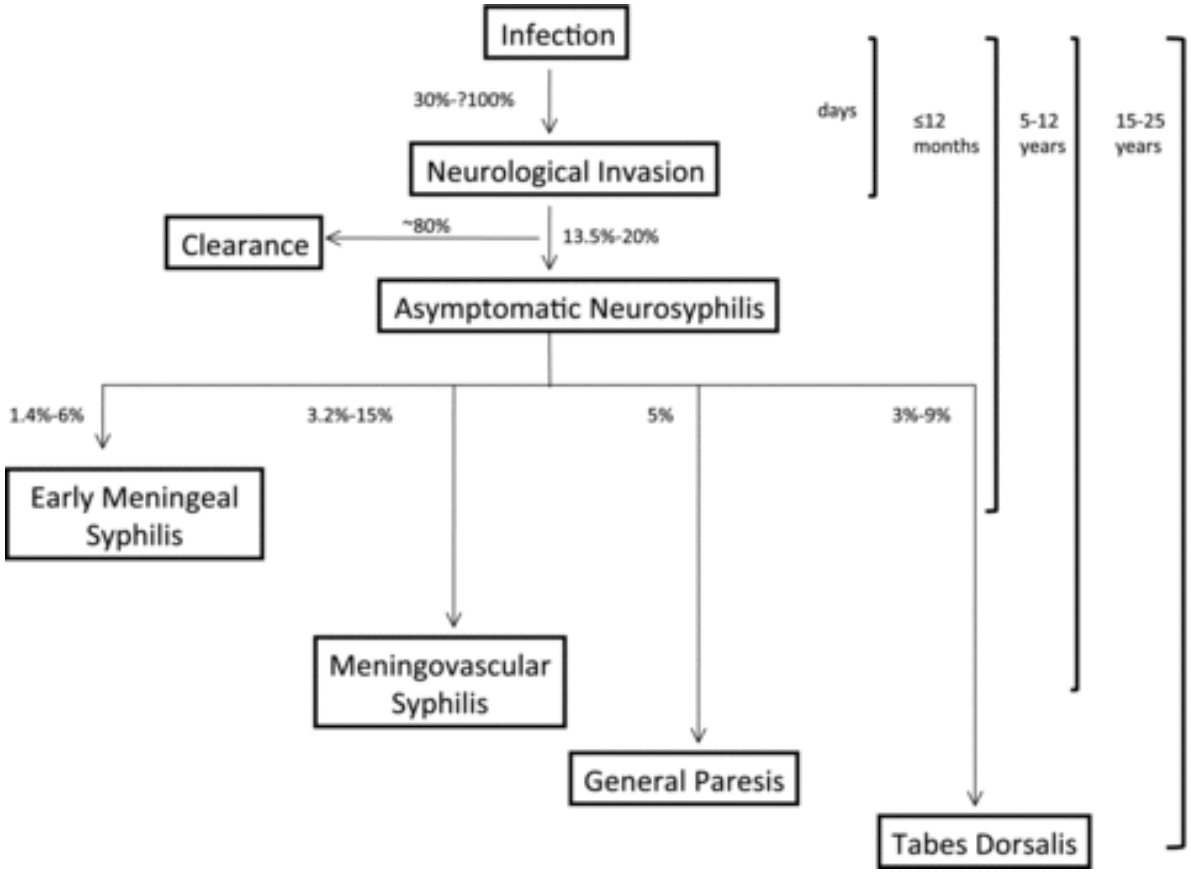
- Asymptomatic neurosyphilis (13,5 - 20%)
  → Both in early and late stages
- Early symptomatic neurosyphilis
  → Within 12 months of infection
  → Diffuse meningeal inflammation
  → Headache, photophobia, N+V+ cranial nerve palsies (occasionally seizures)

Late Neurosyphilis

- Meningovascular syphilis
  - → Endarteritis, thrombosis, infarction
  - → 5-12 year after infection
  - → Sudden onset ‘apoplexy’: hemiplegia, hemianesthesia, hemianopsia, aphasia
  - → Syphilitic meningomyelitis: spastic weakness, sphincter disturbances, senory loss

(Very) Late neurosyphilis or Parechymatous Syphilis

- General paresis , “dementia paralytica”
  - → 15-20 years after infection
  - → Atrophy frontal and temporal lobe
  - → Personality changes, forgetfulness, headache
  - → Later on impaired memory, disorientation/confusion
  - → Psychiatric: depression, delirium and psychosis
  - → Dysarthria, tremor
- Tabes dorsalis
  - → 20-25 years after infection
  - → Degeneration posterior roots and columns
  - → Ataxia, lightning/shooting pains and paresthesias, bladder dysfunction and failing vision (optic atrophy)
  - → Argyll-Robertson , ↓ reflexes, ↓vibratory sense/proprioception, ocular palsies, Charcot’s joints


Infection
30%-?100%
Neurological Invasion
~80%
Clearance
13.5%-20%
Asymptomatic Neurosyphilis
1.4%-6%
3.2%-15%
5%
3%-9%
Early Meningeal Syphilis
Meningovascular Syphilis
General Paresis
Tabes Dorsalis
days
≤12 months
5-12 years
15-25 years

What's next ?

A. Penicilline 4,000,000 U IV q4h 10-14 D
B. Ceftriaxone 2g q24h 10-14 D
C. Doxycycline 200 mg q24h 14 D
D. Doxycyline 200 mg q12h 28 D

Treatment options early syphilis

- Early syphilis (Primary, Secondary and Early latent, i.e. acquired ≤1 year previously)
- First line therapy option
  - → Benzathine penicillin G (BPG) 2.4 million units intramuscularly (IM) (one injection of 2.4 million units or 1.2 million units in each buttock) on day 1 [Ib; A]
- Penicillin allergy or parenteral treatment refused
  - → Doxycycline 200 mg daily (either 100 mg twice daily or as a single 200 mg dose) orally for 14 days [III; B]
  - → or azithromycin 2 g orally single dose [I; B]

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Treatment options neurosyphilis

- Neurosyphilis, ocular and auricular syphilis.
- First line therapy option
  - → Benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 h during 10–14 days [III; B]
- Second line therapy option (if hospitalization and IV benzyl penicillin is impossible)
  - → Ceftriaxone 1–2 g IV daily during 10–14 days [III; B]
  - → Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both during 10–14 days [IIb; B]
- Penicillin allergy
  - → Desensitization to penicillin followed by the first line regimen [III; B]

Syphilis and HIV

- Serological test are reliable for diagnosis and follow-up
- Respons rate VDRL/RPR may be slower
- High clinical suspicion but negative serology: repeated sample (supplementary treponemal test)
- HIV/early syphilis: increased risk for symptomatic neurosyphilis

Jarish-Herxheimer reaction

- Acute febrile illness, headache, myalgia resolving within 24 h.
- Common in early syphilis but is usually not important
- CAVE
  - → ophthalmic involvement (optic neuritis or uveitis),
  - → in neonates or in pregnancy when it may cause fetal distress and premature labour.

- Uncommon in late syphilis but can potentially be life threatening if involvement of strategic sites (e.g. coronary ostia, larynx, nervous system).

- Management:
- Antipyretics
- CAVE:
  - → If cardiovascular or neurological involvement (including optic neuritis) exists, inpatient management
  - → Prevention of Jarisch–Herxheimer reaction: Prednisolone 20–60 mg daily for 3 days, starting antitreponemal treatment after 24 h of commencing prednisolone [IV; C]

Follow-up

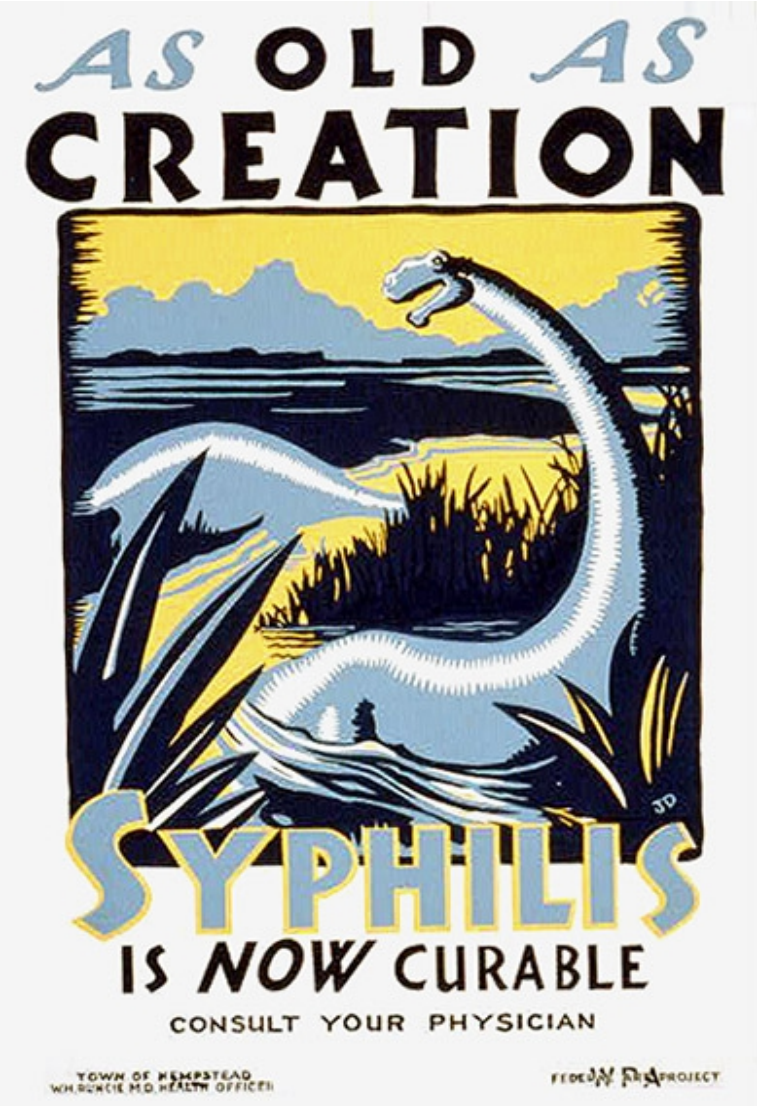
- cure vs. reinfection or relapse
- Early syphilis: (VDRL/RPR) at 1, 3 months then at 6 and 12 months.
  - → After treatment of early syphilis the titre of a NTT (e.g. VDRL and/or RPR) fourfold within 6 months.
  - → If a fourfold decrease of the titre of a NTT does not occur after 6–12 months: additional treatment with one weekly injection of BPG 2.4 million units for 3 weeks [IV; C].
  - → TT may remain positive for life

- In late (latent) syphilis the serological response of NTTs is often absent.
  - → In non-HIV-infected late latent syphilis patients with a reactive NTT, which remains stable in the lowest titre range, follow-up after treatment is generally not indicated.

- An increase in ≥2 dilution steps (fourfold) in a NTT suggests reinfection or reactivation.
  - → Reinfection or relapse should be retreated preferably with supervised treatment schedules to ensure compliance and sexual partners should be rescreened.

- Follow-up examination of cerebrospinal fluid should be performed 6 weeks–6 months after treatment of neurosyphilis.

Questions?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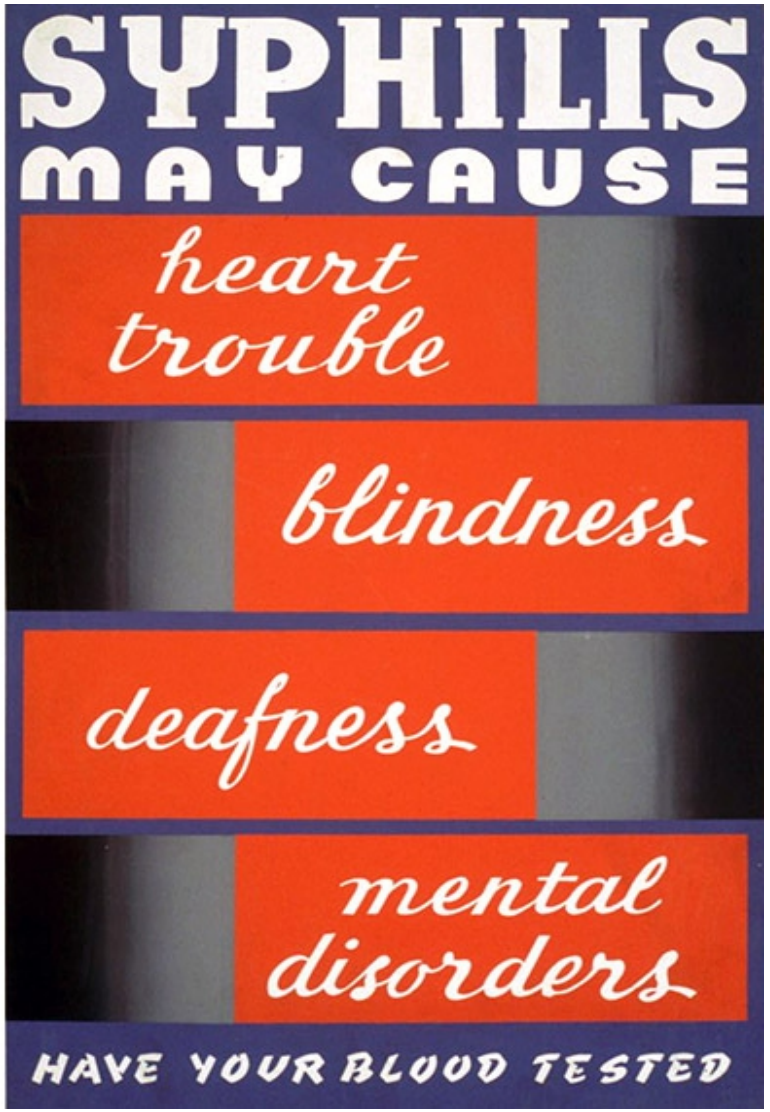
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