

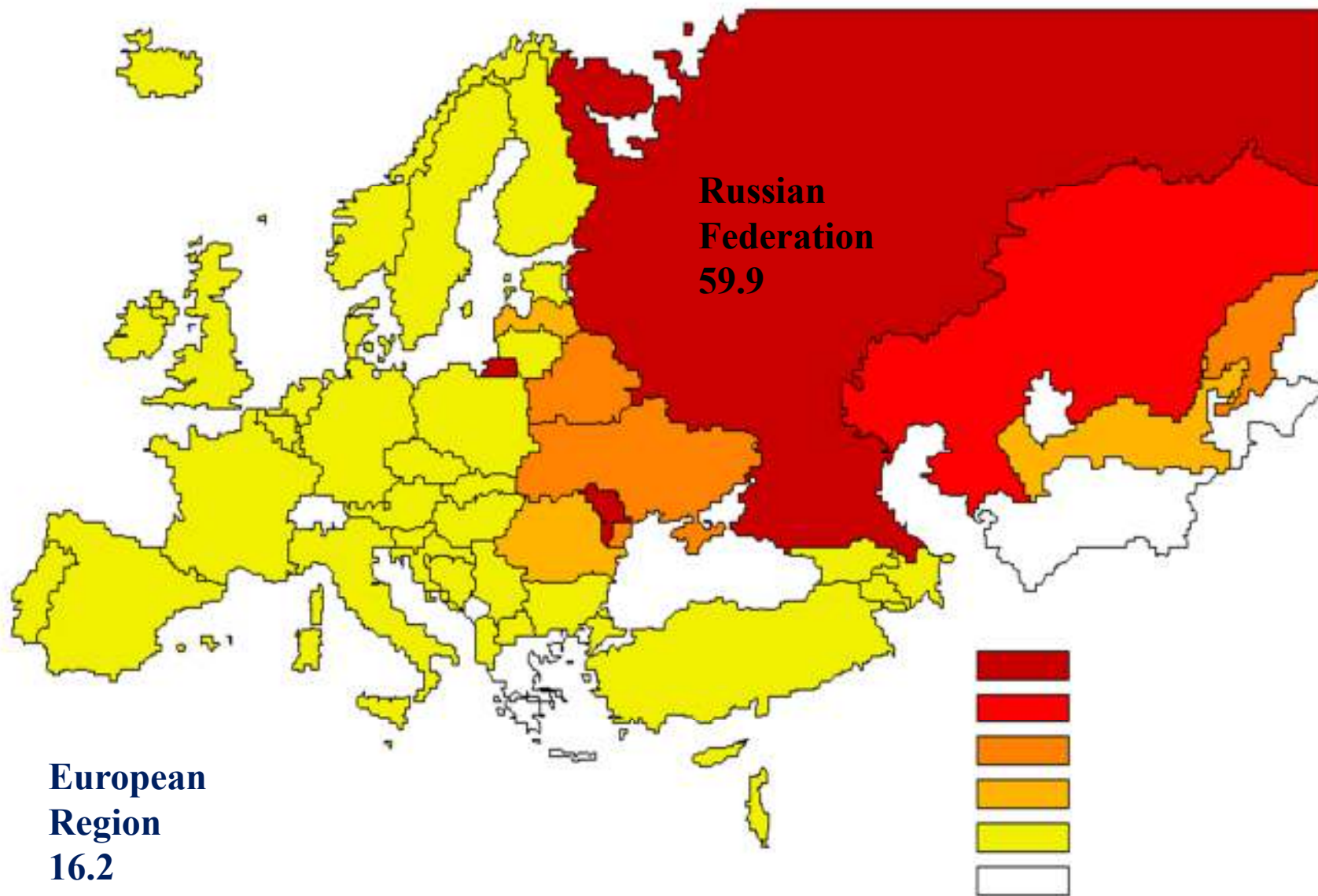
Syphilis

Background

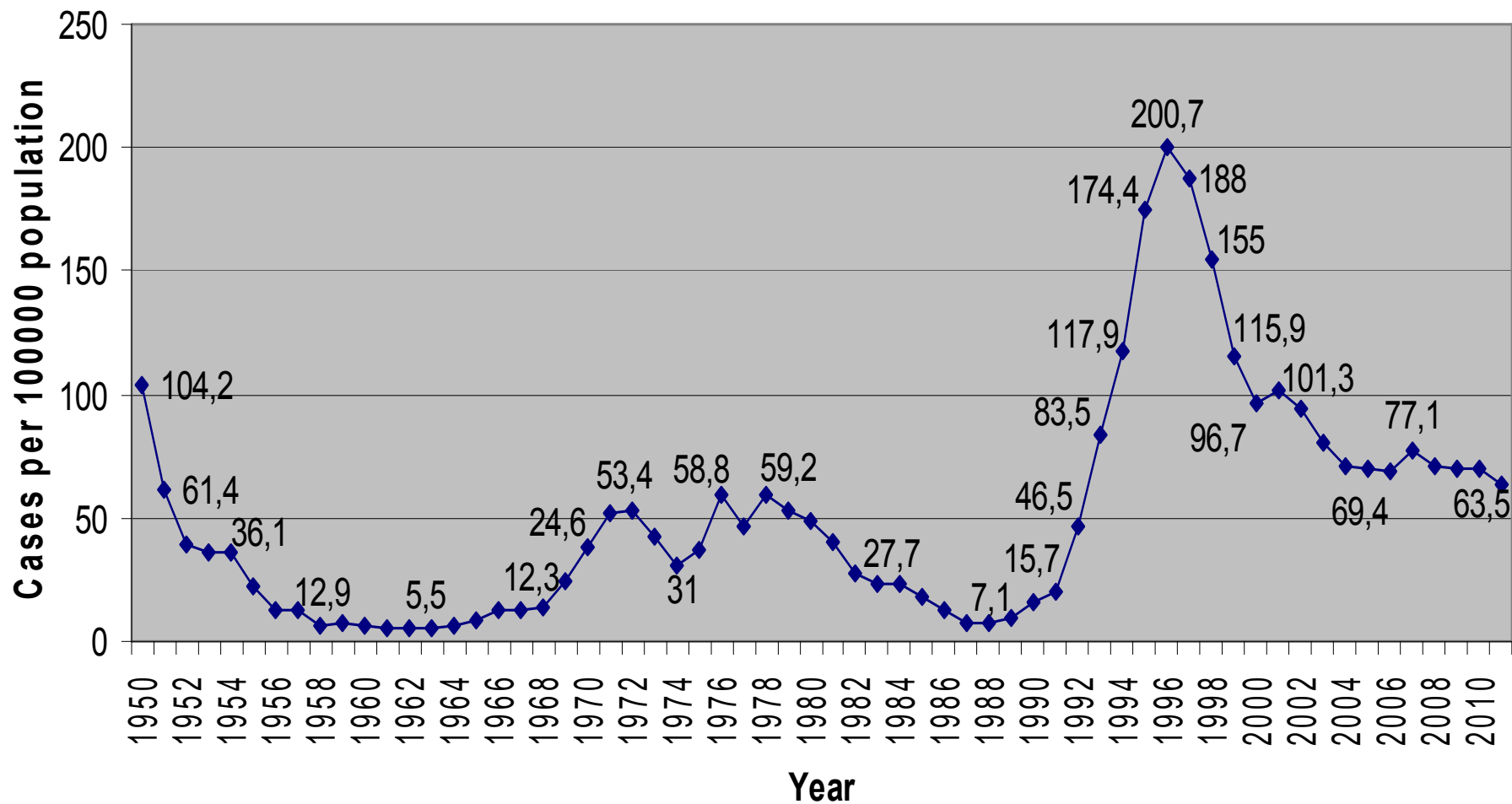
- *Treponema pallidum* is the microaerophilic spirochete that causes syphilis, a chronic systemic venereal disease with multiple clinical presentations (the great imitator).
- ***T. pallidum*** is a very small, spiral bacterium (spirochete) whose form and corkscrew rotation motility can be observed only by dark-field microscopy. The reproductive time is estimated to be 30 to 33 hours, in contrast to most bacteria, which replicate every 30 minutes.
- Serum levels of antibiotics must therefore persist for at least 7 to 10 days to expose all replicating organisms.
- The Gram stain cannot be used, and the bacteria can be grown only with sophisticated tissue culture techniques.

Clasa Spirochetaceae

Genul	Specia	Subspecia	Maladia
Treponema	T.pallidum T.pallidum T. pallidum T.carateum T.vincentii	pallidum endemicum pertenue	Sifilis Bedjel Frambezia Pinta Angina Plaut-Vencent
Borellia	B.recurrentis B.caucasica, B.duttoni, B.persica, etc		Febra recurentă transmisă de capușe sau păduchi
	B.burgdorferi		Boala Lyme
Leptospira	Leptospira interrogans ...		Leptospiroza



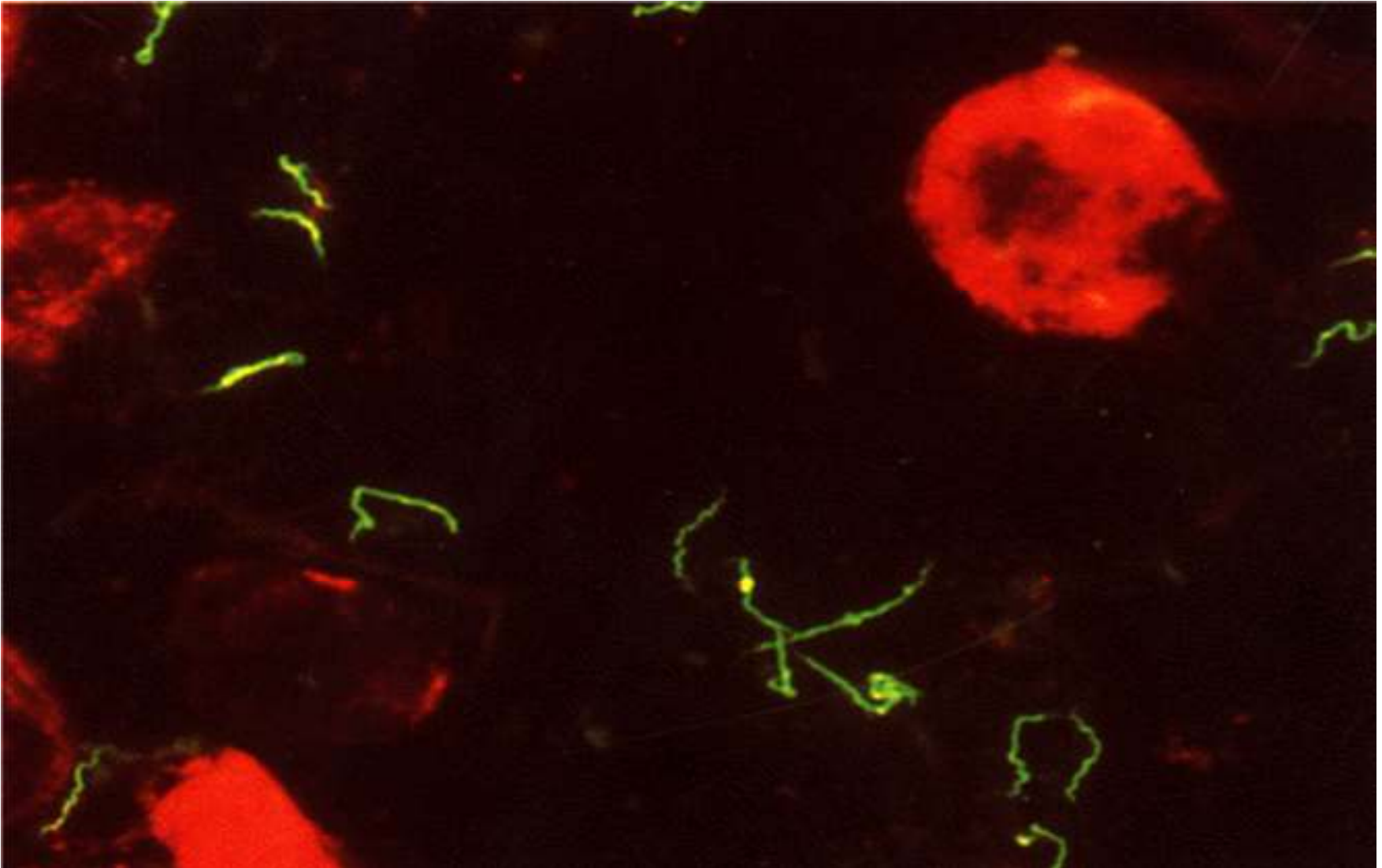
Evolutionary incidence of syphilis in Republic of Moldova during 1950-2011 period



Treponema pallidum



Treponema pallidum:
fluorescent microscopy



Background

- Syphilis is transmitted in 2 ways, either from intimate contact with infectious lesions (most common sexually) or blood transfusions (blood collected during early syphilis), or it is transmitted transplacentally from an infected mother to her fetus.
- Therefore there are 2 distinct forms of syphilis: acquired and congenital.
- Acquired syphilis is characterized by episodes of active disease (primary, secondary, tertiary stages) interrupted by periods of latency (latent syphilis).

Pathophysiology

- In acquired syphilis, the organism rapidly penetrates intact mucous membranes or microscopic dermal abrasions and, within a few hours, enters the lymphatics and blood to produce systemic infection.
- The central nervous system is invaded early in the infection; during the secondary stage, examinations demonstrate that more than 30% of patients have abnormal findings in the cerebrospinal fluid (CSF).
- During the first 5-10 years after infection, the disease principally involves the meninges and blood vessels, resulting in meningovascular neurosyphilis. Later, the parenchyma of the brain and spinal cord are damaged, resulting in parenchymatous neurosyphilis.

Pathophysiology

- Regardless of the stage of disease and location of lesions, 2 histopathologic hallmarks of syphilis have been noted including obliterative endarteritis and plasma cell–rich mononuclear infiltrates.
- Endarteritis is caused by the binding of spirochetes to endothelial cells, mediated by host fibronectin molecules bound to the surface of the spirochetes. The resultant endarteritis heals with scar tissue formation.

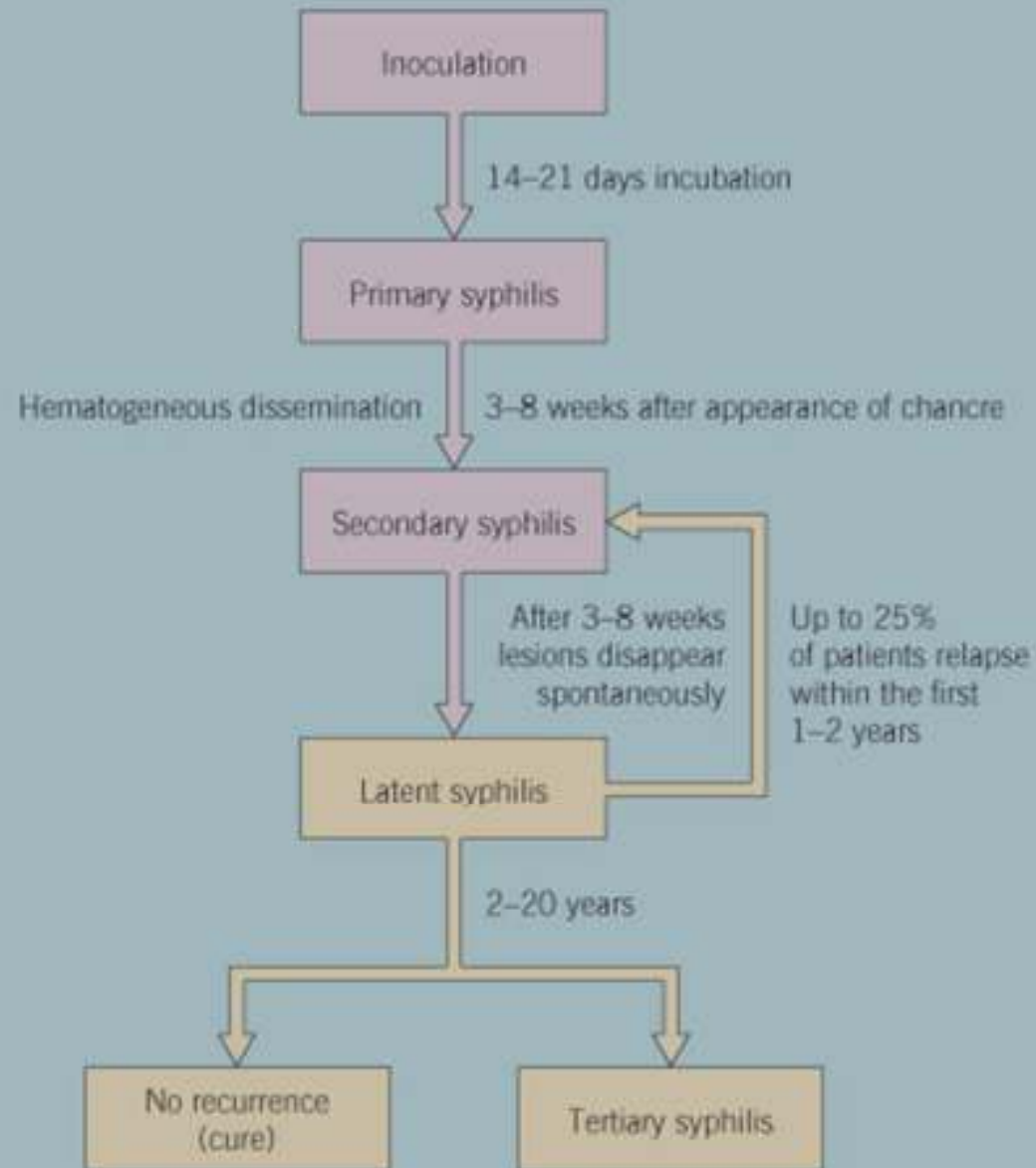
Pathophysiology

- The mononuclear infiltrates reflect a delayed-type hypersensitivity response to *T pallidum*, and in certain individuals with tertiary syphilis, this response by sensitized T lymphocytes and macrophages results in gummatous ulcerations and necrosis. Antigens of *T pallidum* induce host production of treponemal antibodies and nonspecific reagin antibodies.
- Immunity to syphilis is incomplete. For example, host humoral and cellular immune responses may prevent the formation of a primary lesion (chancre) on subsequent infections with *T pallidum*, but they are insufficient to clear the organism. This may be because the outer sheath of the spirochete is lacking immunogenic molecules, or it may be because of down-regulation of helper T cells of the TH1 class.

Frequency

- Syphilis remains prevalent in many developing countries and in some areas of North America, Asia, and Europe, especially Eastern Europe.
- In some regions of Siberia, as of 1999, prevalence was 1300 cases per 100,000 population.
- In Republic of Moldova, as of 2000 and of 2004, incidence was 97,8 and 71,1 respectively per 100,000 population.

NATURAL HISTORY OF UNTREATED SYPHILIS



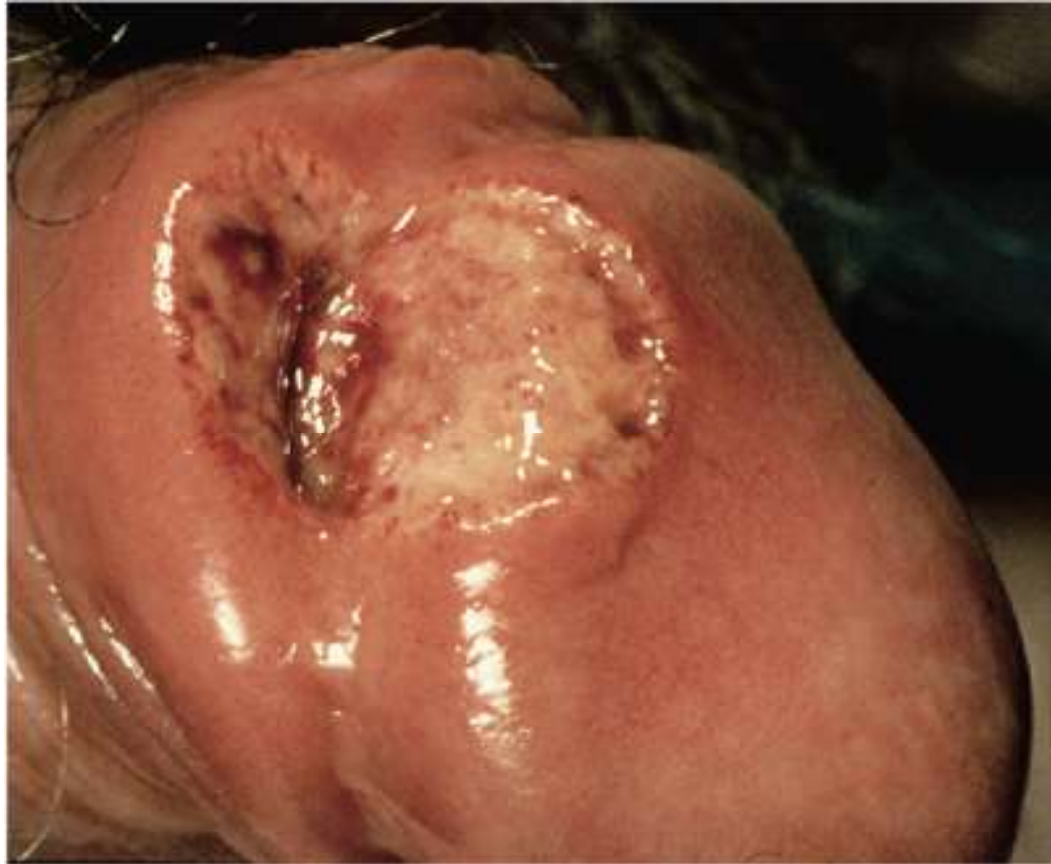
Acquired syphilis stages defined

- Untreated syphilis may pass through three stages, beginning with the infectious cutaneous primary and secondary stages, which may terminate without further sequela or may evolve into a latent stage that lasts for months or years before the now-rare tertiary stage, marked by the appearance of cardiovascular, neurologic, and deep cutaneous lesions.
- Highly infectious syphilis includes the early forms of syphilis – stages of primary, secondary, and early latent syphilis of less than 2 year's duration;
- Less infectious syphilis includes late forms of syphilis – tertiary syphilis (cardiovascular, neurosyphilis, gummatous) and late latent syphilis more than of 2 years duration.

Primary syphilis

- From 10-90 days after exposure (incubation), a primary lesion, the chancre, develops at the site of initial contact.
- **The chancre** is characterized by a cutaneous ulcer or erosion, is acquired by direct contact with an infectious lesion of the skin or the moist surface of the mouth, anus, or vagina.
- Chancres are usually solitary, but multiple lesions are not uncommon. Extragenital chancres account for 6% to 7% of all chancres, and most occur on the lips and in the oral cavity and are transmitted by kissing or orogenital sex.
- The lesion begins as papule that undergoes ischemic necrosis and erodes, forming an 0,3 to 2,0 cm, painless, hard, indurated ulcer or erosion; the base is clean, with a clear, yellow, serous discharge.
- Because the chancre began as a papule, the borders of the ulcer are raised, smooth, and sharply defined.
- Painless, hard, discrete **regional lymphadenopathy** occurs in 1 to 2 weeks; the lesions never coalesce or suppurate unless there is a mixed infection. **Lymphangitis** is the third symptom of primary triad.
- Without treatment the chancre heals with scarring in 4 to 8 weeks, that is total duration of primary syphilis.
- The differential diagnosis includes ulcerative genital lesion such as chancroid, herpes progeneralis, aphtae, and traumatic ulcers such as occur with biting.

Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: The chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre



Primary Syphilis: the chancre-edema



Primary Syphilis: the chancre-edema



Primary Syphilis: chancre-tonsillitis



Primary Syphilis: balanitis



Primary Syphilis: phimosis



Primary Syphilis: chancre gangrened



Primary Syphilis: chancre phagedenic



Primary Syphilis: regional lymphadenitis



Secondary syphilis

- Secondary syphilis is characterized by muco-cutaneous lesions, a flu-like syndrome, and generalized adenopathy. The healing primary chancre may remain present in 15-25% of patients.
- Asymptomatic dissemination of *T.pallidum* to all organs occurs as the chancre heals, and the disease then resolves in approximately 75% of cases.
- In the remaining 25%, the clinical signs of the secondary stage begin approximately 6 weeks after the chancre appears and last for 2 to 10 weeks (duration of the first episode – recent secondary syphilis). The following episodes (recurrent secondary syphilis) can occur within 2-3 years (duration of secondary syphilis).
- Cutaneous lesions are preceded by a flu-like syndrome and generalized, painless lymphadenopathy.
- The cutaneous and mucosal lesions are varied and may be confused with numerous other skin diseases.
- The rash is usually non-itching, bilateral and symmetric.

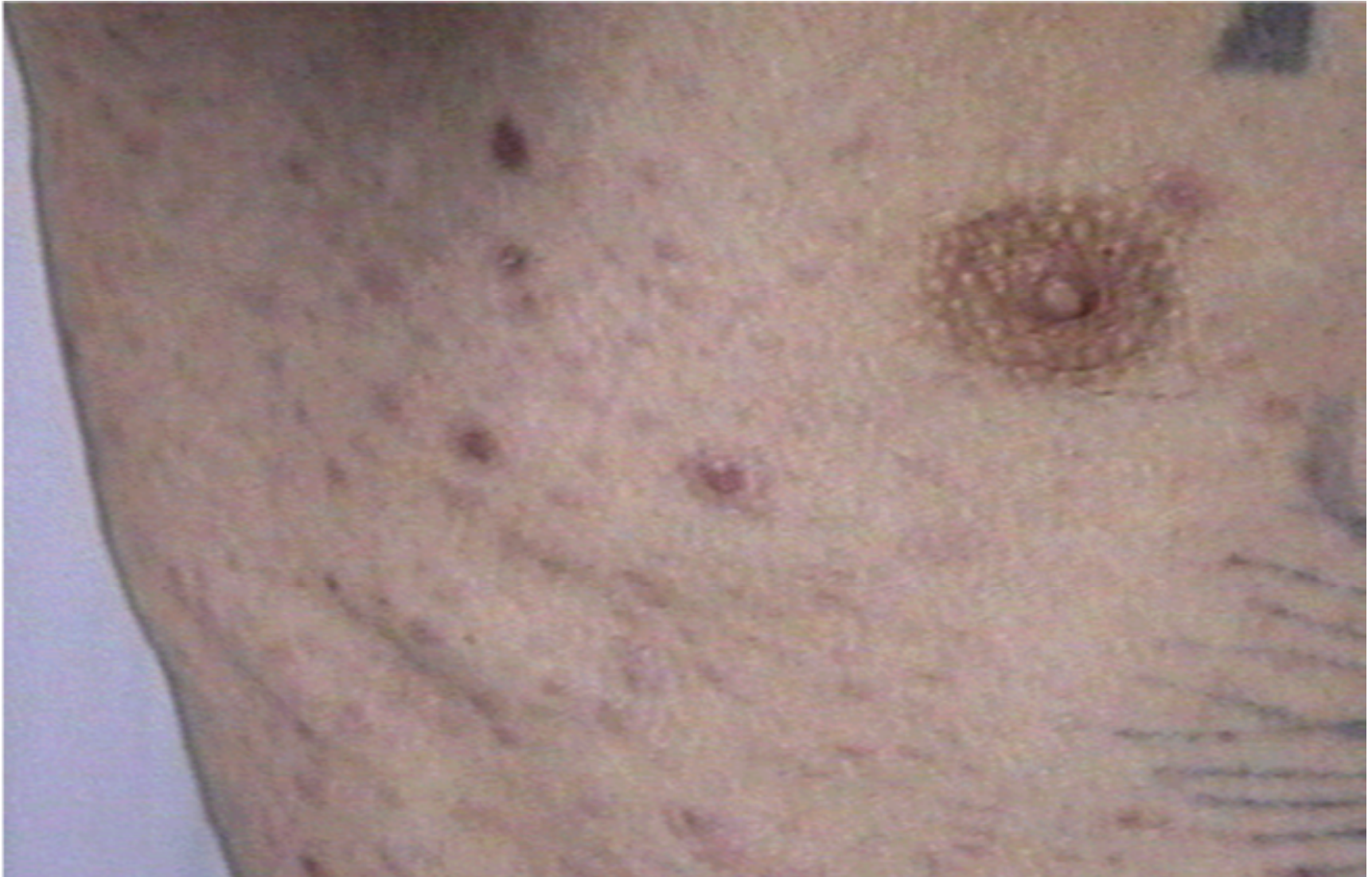
Secondary syphilis – lesions

- Initial lesions are bilaterally symmetric, pale red to pink (in light-skinned persons) or pigmented (in dark-skinned persons), discrete, round macules that measure 5-10 mm in diameter and are distributed on the trunk and proximal extremities – **syphilitic roseola**.
- After several days or weeks, red papular lesions 3-10 mm in diameter appear. These lesions often become necrotic and are distributed widely with frequent involvement of the palms and soles – **syphilitic papule**.
- In 10% of patients, highly infectious papules develop at the mucocutaneous junctions and, in moist intertriginous skin, become hypertrophic and dull pink or gray – **condyloma lata**.
- From 10-15% of patients with secondary syphilis develop superficial mucosal erosions on the palate, pharynx, larynx, glans penis, vulva, or in the anal canal and rectum. These mucous patches are circular silver-gray **eroded papules** with a red areola.
- **Syphilitic pustules** can occur in malignant, unfavorable evolution: impetigo-, acne- and chickenpox-like as superficial or ecthyma- and rupia-like as deep lesions.
- Tiny papular follicular syphilids involving hair follicles may result in patchy alopecia (alopecia areolaris). In addition to the classic moth-eaten alopecia, a diffuse alopecia also has been reported – **syphilitic alopecia**.
- In recurrent secondary syphilis hypopigmented patches surrounded by a hyperpigmented background can occur on the chest and neck – **syphilitic leukomelanoderma (Venus necklace)**.
- Ocular abnormalities, such as iritis, are a rare clinical finding, although anterior uveitis has been reported in 5-10% of patients with secondary syphilis.
- Less common findings include periostitis, arthralgias, meningitis, nephritis, hepatitis, and ulcerative colitis.

Secondary syphilis: roseola



Secondary syphilis: papules



Secondary syphilis: papules



Secondary syphilis: papules



Secondary syphilis: condylomata lata



Secondary syphilis: condylomata lata



Secondary syphilis: eroded papula



Secondary syphilis: papules on palms



**Secondary syphilis:
papules on palms and soles**



Secondary syphilis: pustula



Secondary syphilis: ecthyma



Secondary syphilis: leucoderma



Secondary syphilis: alopecia





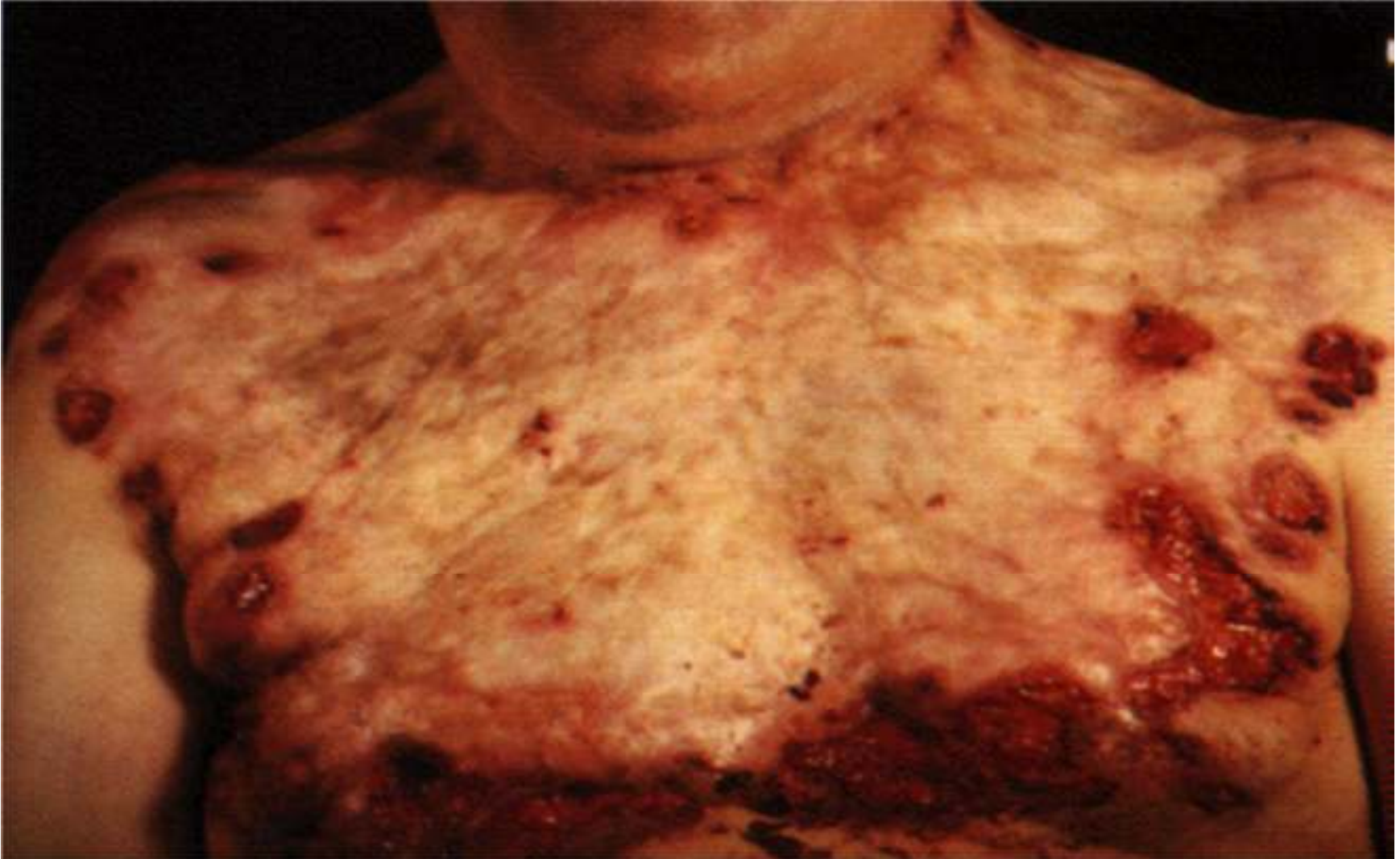
Tertiary syphilis

- The lesions of benign tertiary syphilis usually develop within 3-10 years of infection. The typical lesion is a **gumma** or **tuberculum**, and patient complaints usually are secondary to bone pain, which is described as a deep boring pain characteristically worse at night. Trauma may predispose a specific site to gumma involvement. **Tertiary erythema** is the third cutaneous lesion of tertiary syphilis.
- CNS involvement may occur, with presenting symptoms representative of the area affected, ie, brain involvement (headache, dizziness, mood disturbance, neck stiffness, blurred vision) and spinal cord involvement (bulbar symptoms, weakness and wasting of shoulder girdle and arm muscles, incontinence, impotence).
- Some patients may present up to 20 years after infection with behavioral changes and other signs of dementia, which is indicative of neurosyphilis.

Tertiary syphilis – lesions

- Gummas may be identified on the skin, in the mouth, and in the upper respiratory tract. They appear most commonly on the leg just below the knee.
- Gummas may be multiple or diffuse but usually are solitary lesions that range from less than 1 cm to several centimeters in diameter.
- Cutaneous gummas are indurated, nodular, papulosquamous or ulcerative lesions that form characteristic circles or arcs with peripheral hyperpigmentation.
- The most common clinical finding on cardiovascular examination is a diastolic murmur with a tambour quality, secondary to aortic dilation with valvular insufficiency.
- Symptomatic neurosyphilis produces various clinical syndromes that develop in approximately 5% of patients with syphilis who remain untreated. The most common presentation of meningovascular syphilis (diffuse inflammation of the pia and arachnoid along with widespread arterial involvement) is an indolent stroke syndrome involving the middle cerebral artery.
- Cranial nerve palsies and pupillary abnormalities occur with basilar meningitis.
- Argyll Robertson pupil, which occurs almost exclusively in neurosyphilis, is a small irregular pupil that reacts normally to accommodation but not to light.
- Tabes dorsalis presents with signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia (eg, ataxic wide-based gait and foot slap, areflexia and loss of position, deep pain and temperature sensations). Deep ulcers of the feet can result from loss of pain sensation.
- Rare findings include iritis, with possible adhesion of the iris to the anterior lens, producing a fixed pupil (not to be confused with Argyll Robertson pupil).

Tertiary syphilis: tubercles



Tertiary syphilis: gummas (nodular ulcer type)



Tertiary syphilis: nose gummas



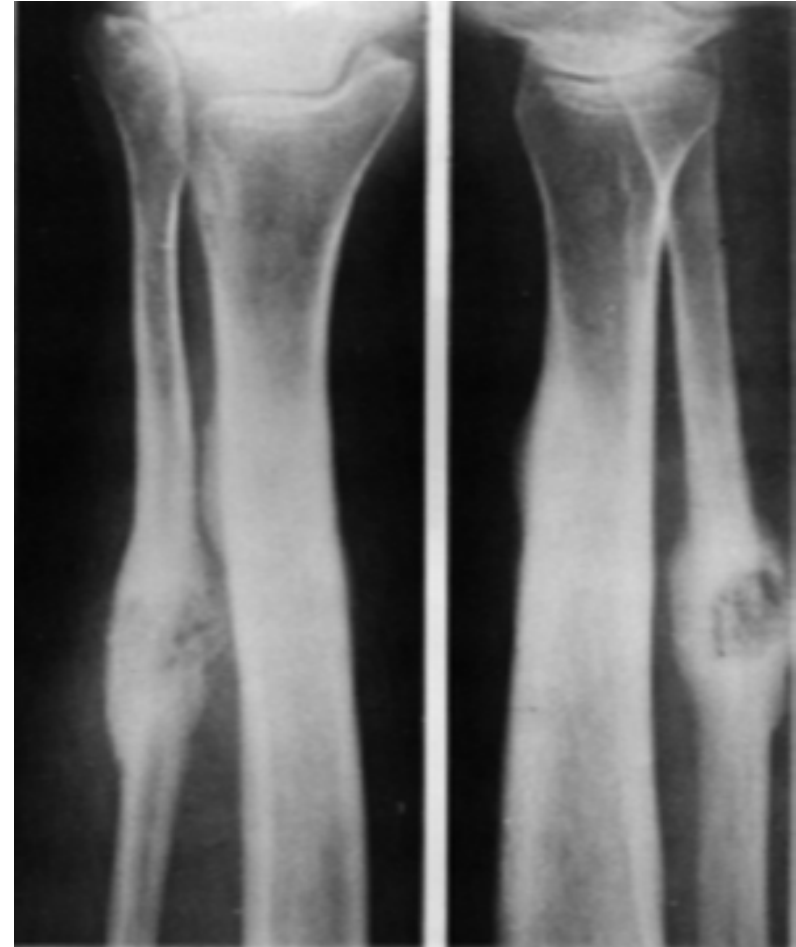
Tertiary syphilis: hepato-splenomegaly



Tertiary syphilis: mesaortitis



Tertiary syphilis: periostitis



Tertiary syphilis: saddle nose



Latent syphilis

- A patient has latent disease if a positive serologic result is discovered without evidence of active disease.
- In latent syphilis, one depends on the accuracy of the patient's history that there were characteristic signs and symptoms or that the blood test, the result of which has been discovered to be positive, was nonreactive at a specific time in the past.
- Often the physician is unable to confirm the specific time interval.
- By convention, early latent syphilis is of 2 years or less and late latent syphilis is more than 2 years duration.
- The periods of 2 years were established to help predict a patient's chance of relapsing with signs of secondary infectious syphilis.
- Approximately 25% of untreated patients in the early latent stage may have a relapse, most of them (approximately 90%) during the first year, a small percentage in the second year, and almost none after that.

Congenital syphilis

- *T. pallidum* can be transmitted by an infected mother to the fetus in utero. In untreated cases stillbirth occurs in 19% to 35% of reported cases, 25% of infants die shortly after birth, 12% are without symptoms at birth, and 40% will have late symptomatic congenital syphilis.
- *T. pallidum* can cross the placenta at 4th month during pregnancy. Adequate therapy of the infected mother before the sixteenth week of gestation usually prevents infection of the fetus.
- Treatment after 18 weeks may cure the disease but not prevent irreversible neural deafness, interstitial keratitis, and bone and joint changes in the newborn.
- The fetus is at greatest risk when maternal syphilis is of less than 2 years duration. The ability of the mother to infect the fetus diminishes but never disappears in late latent stages.
- The manifestations of untreated congenital syphilis can be divided into those that are expressed prior to age 2 years (early congenital syphilis) or after age of 2 years (late congenital syphilis).

Congenital syphilis – early manifestations

- Early signs and symptoms include development of a diffuse eruption characteristic of secondary syphilis, such as maculopapular rash and desquamating erythema of the palms, soles and skin around the mouth and anus (**Hochzinger's diffuse papulous infiltration**).
- **Osteochondritis** with the 'sawtooth' metaphysis seen on radiographs and **periostitis** appears with tender limbs and joints (Parrot's pseudo-paralysis).
- Blistering especially on palms and soles (**syphilitic pemphigus**).
- Rhinitis with highly infectious nasal discharge (**syphilitic rhinitis**).
- Hepatomegaly, splenomegaly, petechiae and other skin rashes, anemia, lymphadenopathy, jaundice, etc.
- A classic mucocutaneous sign is depressed linear scars radiating from the orifice of the mouth and termed rhagades (**Parrot-Robinson-Fournier lines**).

Congenital syphilis: pemphigus syphiliticum



Congenital syphilis: macules and papules



Congenital syphilis: macules and papules



**Congenital syphilis:
condylomata lata**



Congenital syphilis: syphilitic rhinitis



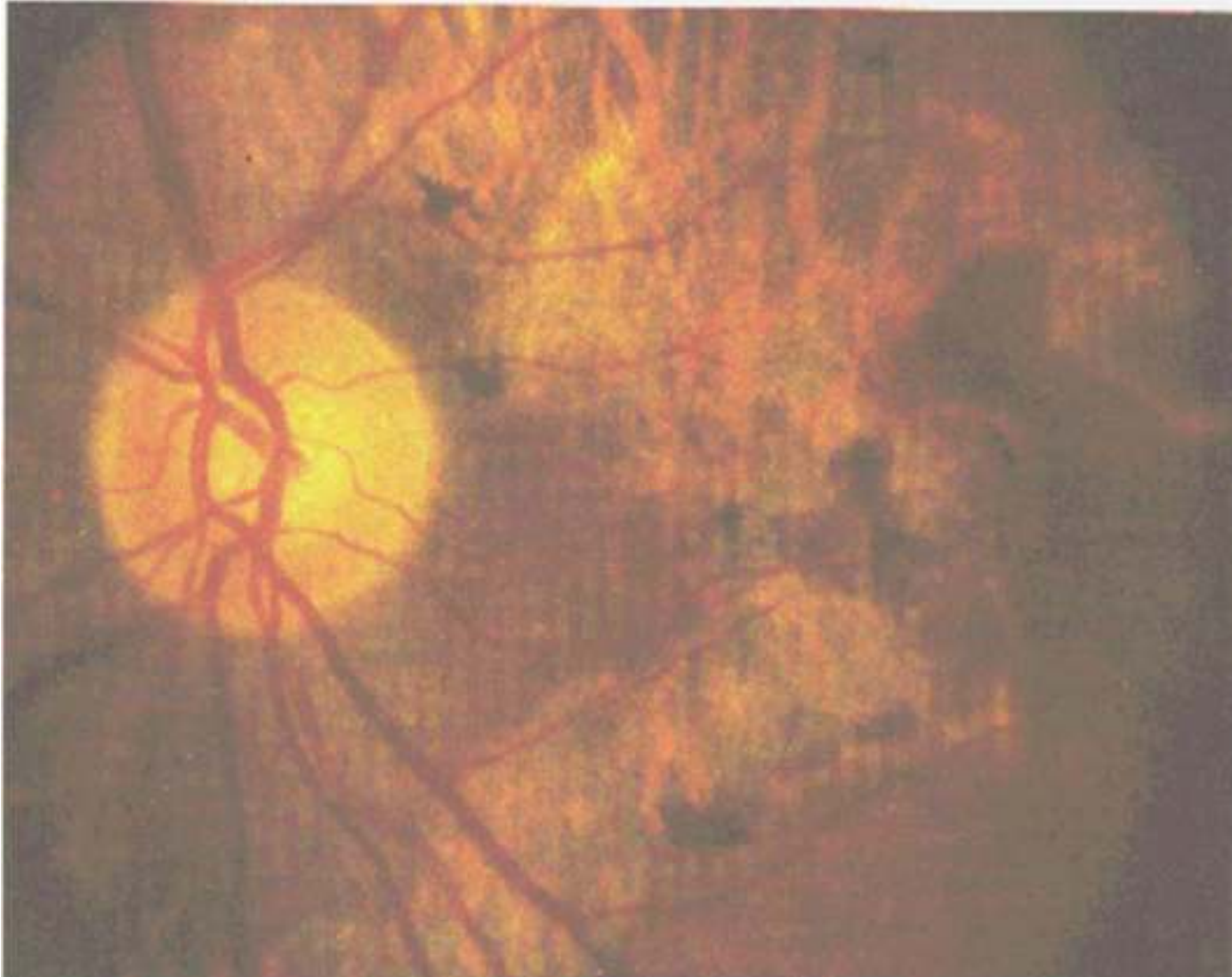
Congenital syphilis: parenchymatous organs involvement



Congenital syphilis: pseudo-paralysis Parrot



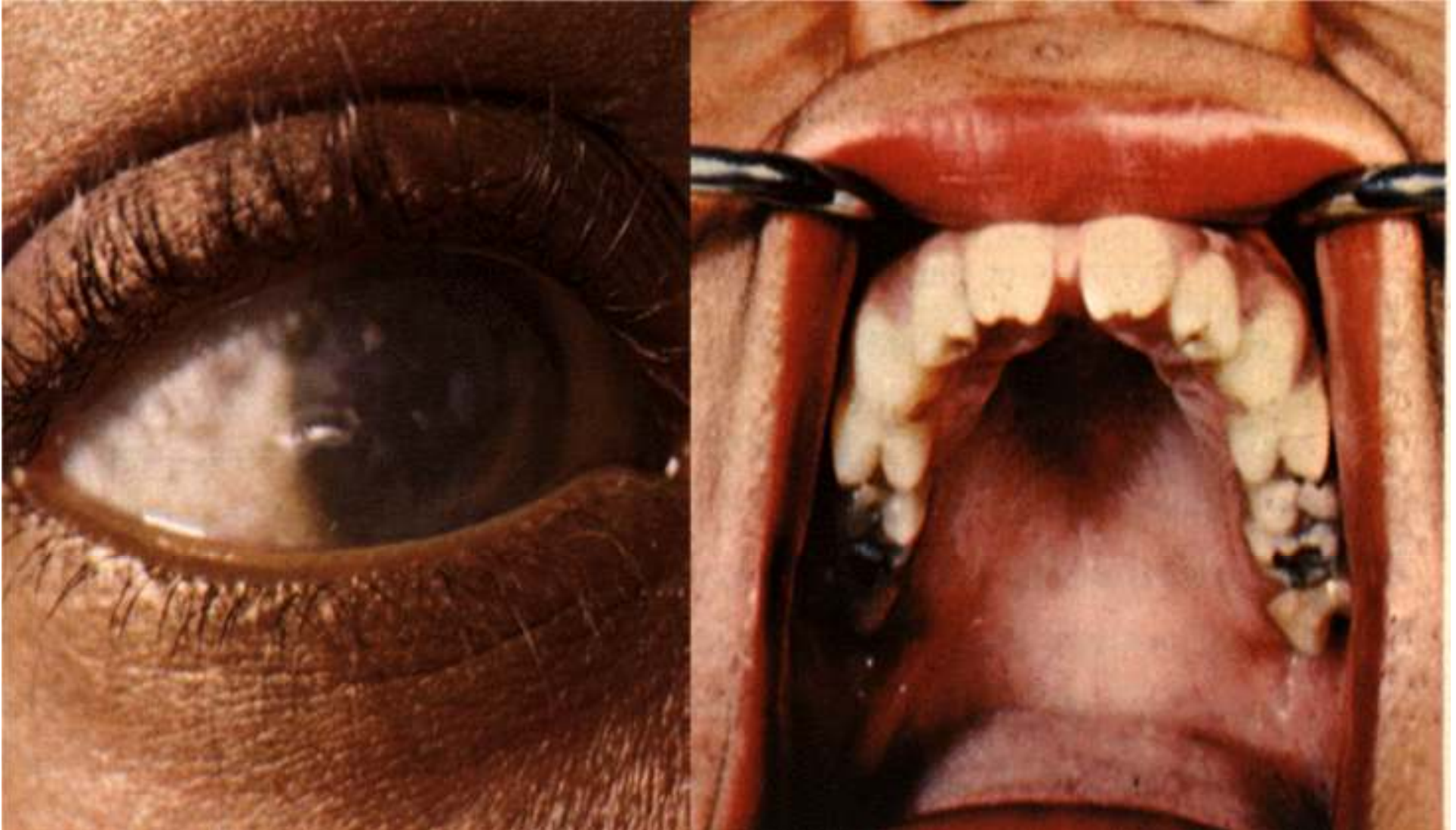
Congenital syphilis: retinitis



Congenital syphilis – late manifestations

- Late signs and symptoms are rare and, if encountered, usually involve complications including interstitial keratitis, cranial nerve VIII deafness, corneal opacities, and/or recurrent arthropathy.
- The clinical manifestations of untreated congenital neurosyphilis present in 25% of patients older than age 6 years and correspond to those of adult neurosyphilis.
- Gummatous periostitis occurs in patients aged 5-20 years and tends to cause destructive lesions of the palate and nasal septum (saddle nose).
- Dental abnormalities may be evident, such as centrally notched and widely spaced, peg-shaped, upper central incisors (Hutchinson teeth) and sixth-year molars with multiple poorly developed cusps (mulberry molars).
- Peculiar bone findings include frontal bossing of Higoumenakis-Avsitidiisky sign, which is unilateral irregular enlargement of the sternoclavicular portion of the clavicle secondary to periostitis.
- **The great late congenital syphilis Hutchinson triad: Hutchinson teeth, interstitial keratitis and deafness.**

Congenital syphilis: Hutchinson triad



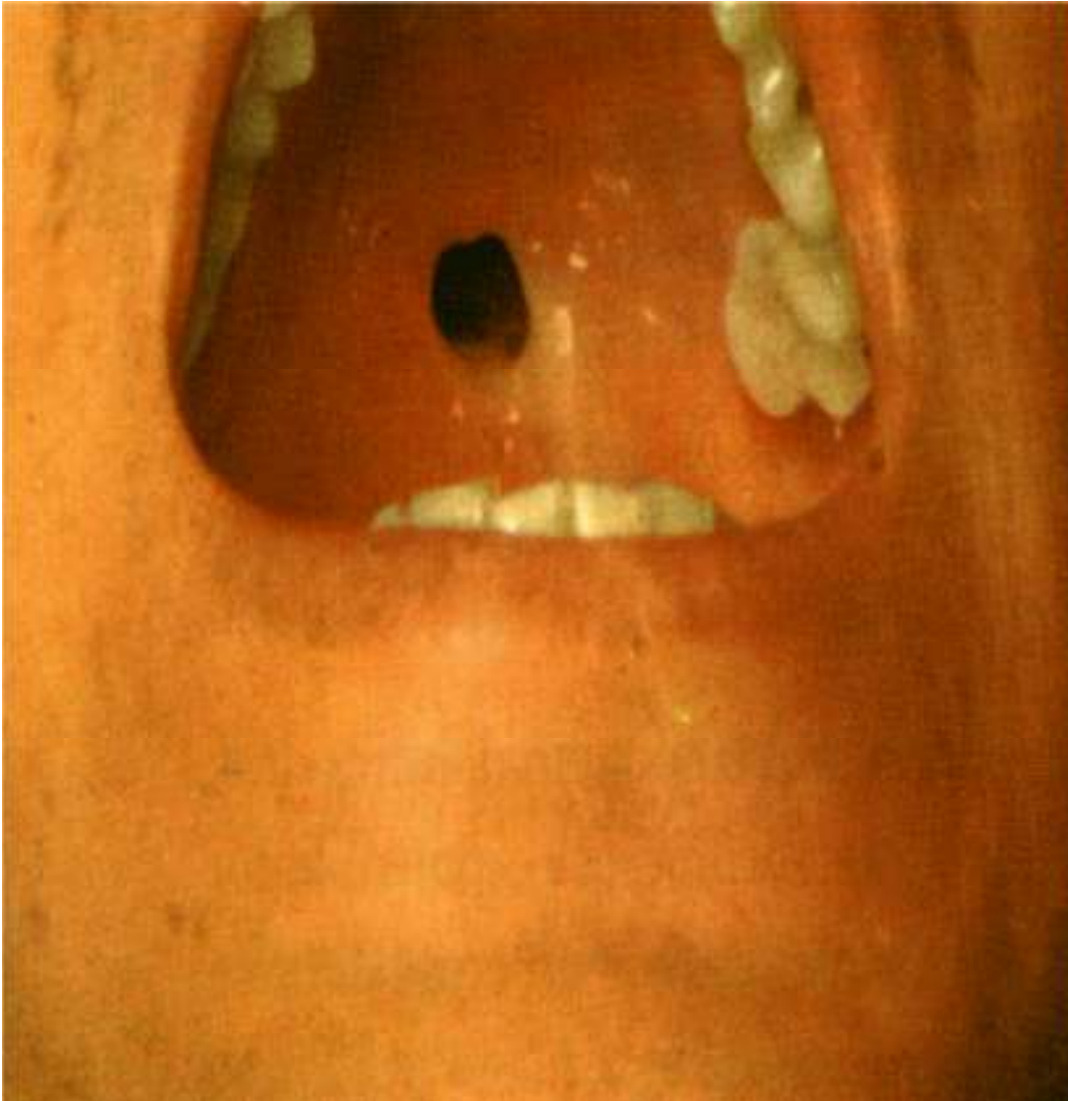
Congenital syphilis:
scimitar-shape shins; Parrot's scars



**Congenital syphilis:
Carabelli tubercle; gothic palate**



Congenital syphilis: palatine gumma perforation; saddle nose



Basic Lab Studies

- In suspected acquired syphilis, perform nontreponemal serology screening using Venereal Disease Research Laboratory (VDRL) test, rapid plasma reagin (RPR) test or Bordet-Wassermann test – these are screening tests.
- Then, test sera yielding a positive reaction by the *Treponema pallidum* hemagglutination assay (TPHA), fluorescent treponemal antibody-absorption (FTA-ABS) test, or microhemagglutination assay *Treponema pallidum* (MHA-TP) test – these are confirmatory tests.
- Dark-field microscopy is essential in evaluating moist cutaneous lesions, such as the chancre of primary syphilis or the condyloma lata of secondary syphilis. When dark-field microscopy is not available, direct immunofluorescence staining of fixed smears (direct fluorescent antibody *Treponema pallidum* [DFA-TP]) is an option. Both procedures detect the causative organism at a rate of approximately 85-92%.
- For evaluation of infants with suspected congenital syphilis, the 19S immunoglobulin M FTA-ABS serology test or the Captia Syphilis-M test currently is recommended.
- Every pregnant woman should undergo a nontreponemal test at her first prenatal visit, and women at high risk of exposure should have a repeat test in the third trimester and again at delivery.

Other Studies

- **Imaging Studies:**

- Radiologic abnormal findings commonly seen with advanced gummas of bone include periostitis, destructive osteitis, or sclerosing osteitis.
- For cardiovascular complications of tertiary syphilis, linear calcification of the ascending aorta on chest films suggests asymptomatic syphilitic aortitis.
- Angiography may be useful to distinguish between abdominal aneurysms of syphilitic versus arteriosclerotic origin since 10% of syphilitic aneurysms occur superior to the renal arteries, while arteriosclerotic abdominal aneurysms usually are found inferior to the renal arteries.

- **Other Tests:**

Echocardiogram and ECG may help confirm cardiovascular syphilis.

- **Procedures:**

- Biopsy may be necessary to differentiate gummas from coincidental granulomatous conditions.
- Lumbar puncture for CSF examination is indicated in the following situations: neurologic signs or symptoms, treatment failure or plans to administer treatment other than penicillin, a serum reagin titer of greater than or equal to 1:32, seropositive HIV, and other changes indicative of active syphilis (eg, gumma, aortitis). Additionally, the only means by which the occurrence of asymptomatic neurosyphilis in latent syphilis can be excluded is via CSF examination.

Syphilis Treatment

- Penicillin is the mainstay of treatment, the standard by which other modes of therapy are judged, and the only therapy that has been used widely for neurosyphilis, congenital syphilis, or syphilis during pregnancy. On rare occasions, *T pallidum* has been found to persist after adequate penicillin therapy; however, no indication exists that *T pallidum* has acquired resistance to the drug.
- Tetracycline, erythromycin, and ceftriaxone have shown antitreponemal activity in clinical trials but currently are recommended only as alternative treatment regimens in patients allergic to penicillin.

Syphilis Treatment Regimens

Drug Name

Penicillin G benzathine (Retarpen, Extencilline, Penidural, Bicillin LA) -- Interferes with synthesis of cell wall mucopeptides during active multiplication, which results in bactericidal activity.

Adult Dose

Disease for <2 years: 2.4 million U IM 2 doses (day 1 and 8) in 2 injection sites

Disease for >2 years: 2.4 million U in 2 injection sites qwk for 3 doses (day 1, 8 and 15)

Neurosyphilis: 12 million U IV qd for 10-14 d

Pediatric Dose

Disease for <2 years: 50,000 U/kg IM once; not to exceed 2.4 million U

Disease for >2 years: 50,000 U/kg IM qwk for 3 weekly doses; not to exceed 2.4 mil. U

Precautions

Jarisch-Herxheimer reaction (syndrome of influenza-like symptoms) may follow initiation of penicillin treatment, usually subsiding within 24 h; however, patients with syphilitic general paresis or high CSF cell count may experience serious complications, including seizures, hemiplegia, or monoplegia

Follow-up (further outpatient care)

- Patients with treated primary or secondary syphilis
 - Perform quantitative VDRL testing at 1, 3, 6, and 12 months following treatment.
 - If the VDRL titer of 1:8 or more fails to fall at least 4 fold within 12 months or if the titer starts to rise, consider more intensive retreatment, and examine the CSF.
 - If all clinical and serologic examinations remain satisfactory for 2 years following treatment, the patient can be reassured that cure is complete, and no further follow-up care is needed.
- Patients with latent syphilis
 - Perform quantitative reagin testing for up to 2 years.
 - Schedule annual follow-up visits for an indefinite period of time for patients with persistently positive serologic tests.
- Patients with benign tertiary or cardiovascular syphilis: Patients should be observed by the physician for the rest of their lives to monitor for complications.
- Patients with neurosyphilis (both symptomatic and asymptomatic): Examine the CSF (cell count, protein, reagin titer) every 3-6 months for 3 years or until CSF findings return to normal.