Spirochaetal diseases

Summary

- Spirochaetes are very thin, spiral shaped organisms.
- There are a number of species.
- The bacteria take their name from various sources: Borrelia (after the French bacteriologist Amédée Borrel), leptospires (meaning “fine coils”), treponemes (“turning, drilling”).
- Spirilla are usually classified separately.
- As yet there is no definitive nomenclature for the various subspecies.

T. pallidum	syphilis, bejel (non-venereal syphilis)
T. pertenue	framboesia (= yaws, = pian)
T. carateum	pinta
L. interrogans	Weil’s disease and more mild forms
B. recurrentis	louse-borne borreliosis
B. duttonii, B. hispanica, B. persica and others	tick-borne borreliosis
B. burgdorferi sl	Lyme disease
B. vincenti	tropical ulcer, Plaut-Vincent’s angina, cancrum oris, Fournier’s scrotal gangrene, trench mouth (necrotising ulcerative gingivitis)
Spirillum minus	sodoku or rat bite fever
Streptobacillus moniliformis	Haverhill fever

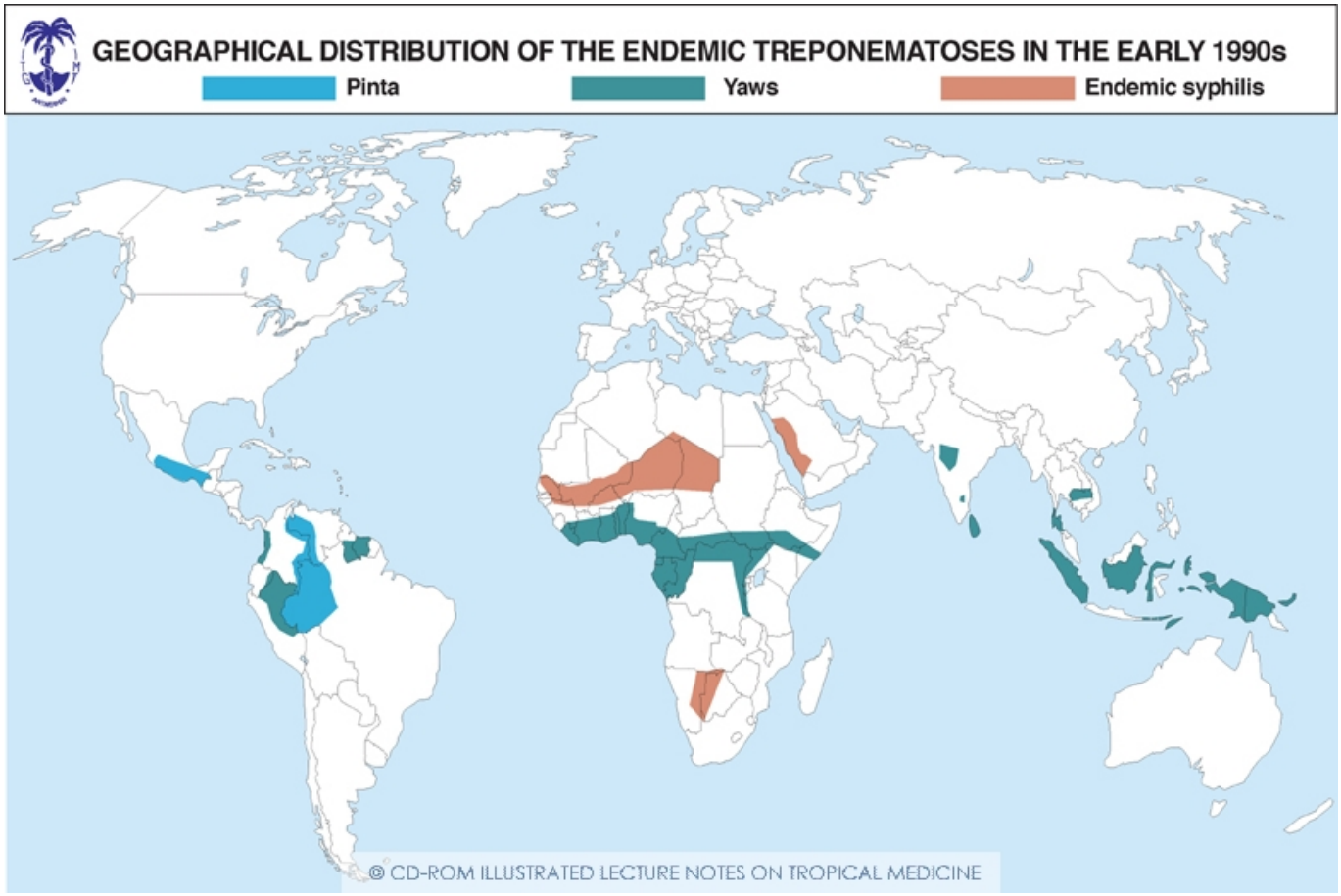
There are Treponema diseases:

1. Venereal syphilis or Lues
2. Non-venereal syphilis or Bejel
3. Framboesia or Yaws or Pian
4. Pinta

LAST UPDATED BY ADMIN ON JUNE 23RD, 2022

Non-venereal treponematoses

Treponematoses are diseases caused by treponemes. These are bacteria with a spiral structure (“trepo” = turn; “nema” = thread). They belong to the *Spirochaetaceae*. They cause 4 different chronic exclusively human diseases. There is **no animal reservoir**. The various treponemes cannot be cultured in vitro (*Treponema pallidum* can be cultured with some difficulty in tissue culture and in rabbit testicles). Morphologically **they cannot be distinguished one from another** and all give positive results on so called syphilis serology. They are all sensitive to penicillin. Prevention varies.



Geographical distribution of non-venereal treponematoses.

Bejel or Njovera or Treponarid

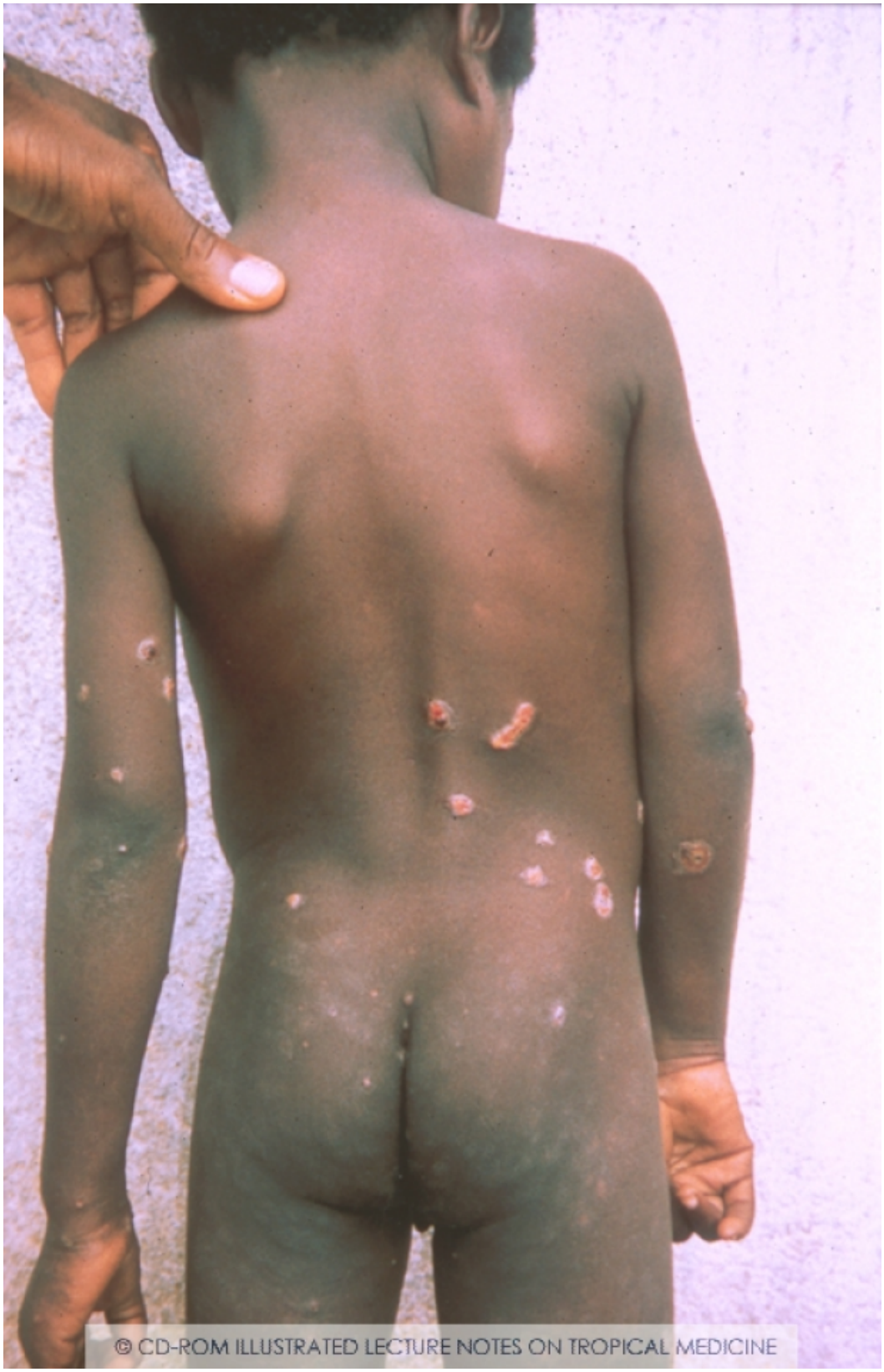
Bejel is caused by ***Treponema endemicum*** (*Treponema pallidum endemicum*). The disease occurs (occurred) in foci in sub-Saharan Africa, in the Middle East, central Australia and in Asia, in temperate to warm dry climates (e.g. Sahel area, Zimbabwe, Botswana). The disease formerly also occurred in Bosnia. Between 1950 and 1960 there were large-scale campaigns to control the disease in the Sahel countries. At present the disease has become rare.

Infection mainly results in **skin and skeletal abnormalities**. Transmission is not via sexual intercourse but through contact. The incubation time is unknown. As a rule, non-venereal or endemic syphilis occurs in childhood. The **oral mucosae are the most important source of infection**. Children are mainly infected by objects they use such as contaminated beakers

(bacteria entering through the mouth). In this way they probably acquire immunity against *T. pallidum* before puberty and are protected against later venereal syphilis.

There is an **early stage** which lasts some 5 years. This is characterised by skin lesions and oral mucosal lesions which occur intermittently. **Osteitis and periostitis** can occur. In rare cases there are **delayed lesions (gummata)**. Gangosa is characterized by destruction of the nose, lip and palate and can lead to severe mutilation. Treatment consists of a single IM administration of 1.2 or 2.4 million units of long-acting benzathine penicillin. A single dose of azithromycin can also be used for treatment but some guidelines prefer to safeguard azithromycin as reserve antibiotic. Tetracyclines can be used as an alternative. Plastic reconstructive surgery is often needed to repair mutilations.

Framboesia or Yaws or Pian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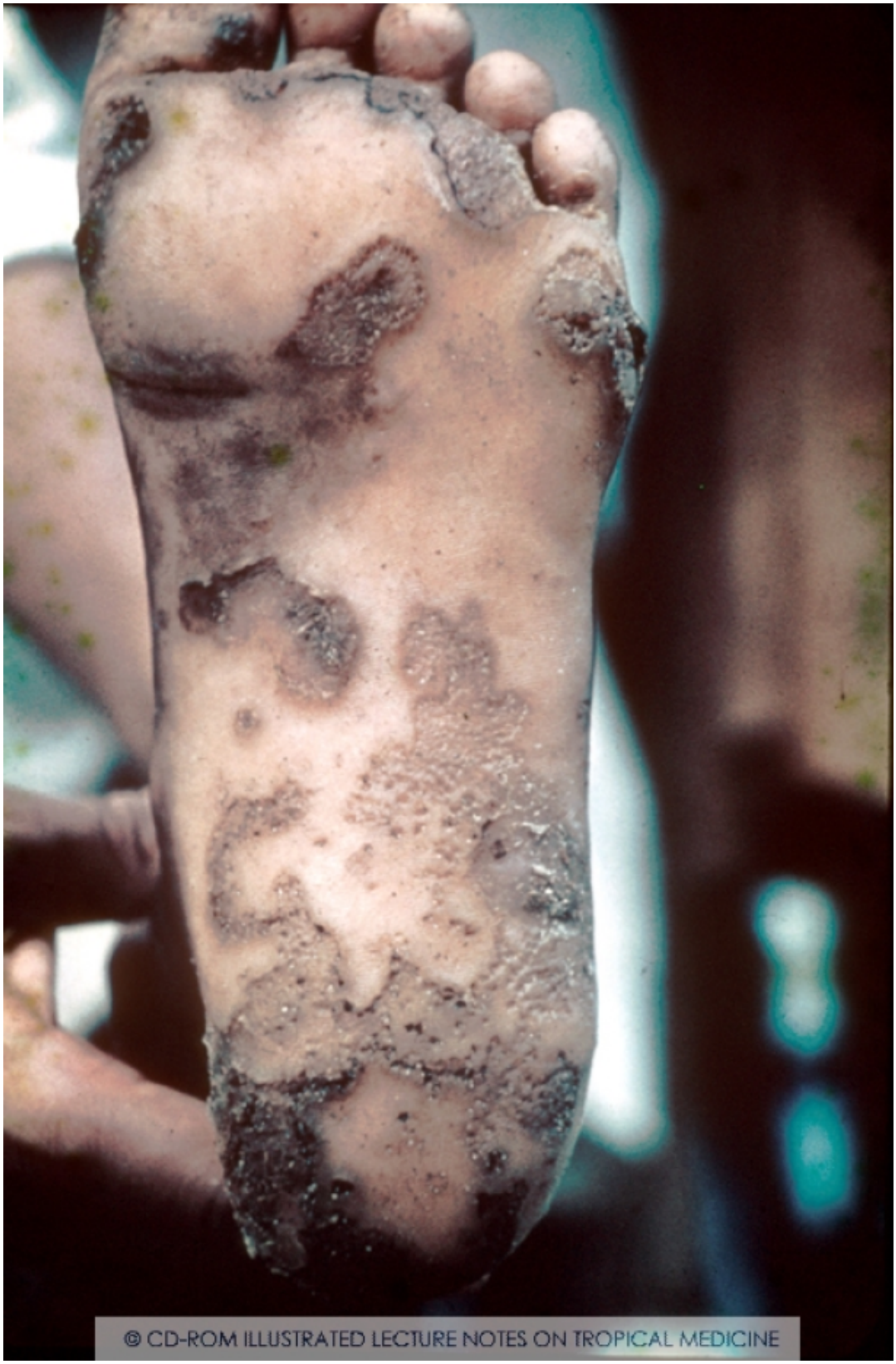
Framboesia, yaws, pian. Infection with Treponema pallidum pertenue. Copyright ITM, photo by Dr Jef Van den Ende.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Framboesia, yaws, pian. Infection with Treponema pallidum pertenue, resulting in plantar hyperkeratosis with painful cracks and fissures. Copyright ITM, photo by Dr Jef Van den Ende.

Yaws is caused by ***Treponema pertenue*** or *Treponema pallidum pertenue*. The transmission of yaws in man through inoculation was demonstrated by Paulet in 1848 and by Charlouis in 1881, predating the discovery of *T. pertenue* by Castellani in two Ceylonese patients with the disease (called “parangi” there).

This treponematosis is transmitted from person to person via **direct skin and mucous membrane contact** (small scrapes). It is a disease of poor isolated rural communities in warm, humid, tropical areas of Africa, Central and South America, and some islands in Southeast Asia. There is hardly any congenital transmission. Framboesia has currently become rare and has been eliminated in some areas (e.g. in Esmeraldas, Ecuador) but may be re-emerging in some areas. This is explained by the deterioration in clinical medical care in certain areas (it is easy to diagnose and the treatment is cheap and simple) and the lack of large-scale treatment campaigns. *T. pertenue* can infect baboons, chimpanzees and some other monkeys, but the importance of this is not clear. It is unlikely that an animal reservoir plays an important epidemiological role as far as can be judged at this time.

Clinical Aspects

The **skin and skeleton** are affected, deep organs are always spared. The disease is characterised by **wart-like skin lesions with the appearance of strawberries** (hence the name; yaw = strawberry). The skin lesions return periodically.

The primary lesion is extragenital. It may consist of one warty lesion but sometimes there is an initial **parent lesion with various satellite lesions**. In most cases the lymph nodes are swollen. If the hypertrophic, papillomatous epidermis is removed an exudate with a crust forms. There is no deep ulceration. These early lesions heal without leaving scars. After healing some residual skin discoloration may remain.

A few weeks to months after the primary lesion, more scattered secondary macular or papillomatous lesions occur. The early skin lesions which contain a great number of

treponemes, tend to be multiple and moist. They occur in flare-ups which last weeks or months in each case. Without treatment this can last 3 to 5 years. When there is a flare-up, there can be general malaise together with joint pain and fever. The skin lesions may persist for 3-6 months. On the palms of the hand and the soles of the feet the skin can thicken, become **hyperkeratotic** and itchy and painful fissures appear. These result in the characteristic gait, the so-called **"crab gait".** A severe infection with *Tunga penetrans* (sand fleas) can sometimes produce a similar picture, but on closer inspection the difference is clear. Sometimes there is involvement of the skeleton. Chronic inflammation of the bones of the fingers (dactylitis) should be distinguished from the more acute dactylitis seen in sickle cell anaemia. Since the general availability of penicillin occasionally mild forms of yaws are seen with only one or just a few small lesions, a few papules or limited hyperkeratosis. It is not known whether the pathogen has a reduced sensitivity to penicillin.

Late-onset framboesia occurs in 10% of patients (after > 5 years). Characteristic of this condition are **sporadic gummata in the skin**; deep crater-like ulcers which later heal with the formation of scars covered by a thin skin. Treponemes are very rare here and the lesions are therefore not particularly infectious. Contracture of the affected limb may occur. Joints may stiffen and chronic osteitis and periostitis can lead to bent legs (sabre tibiae).

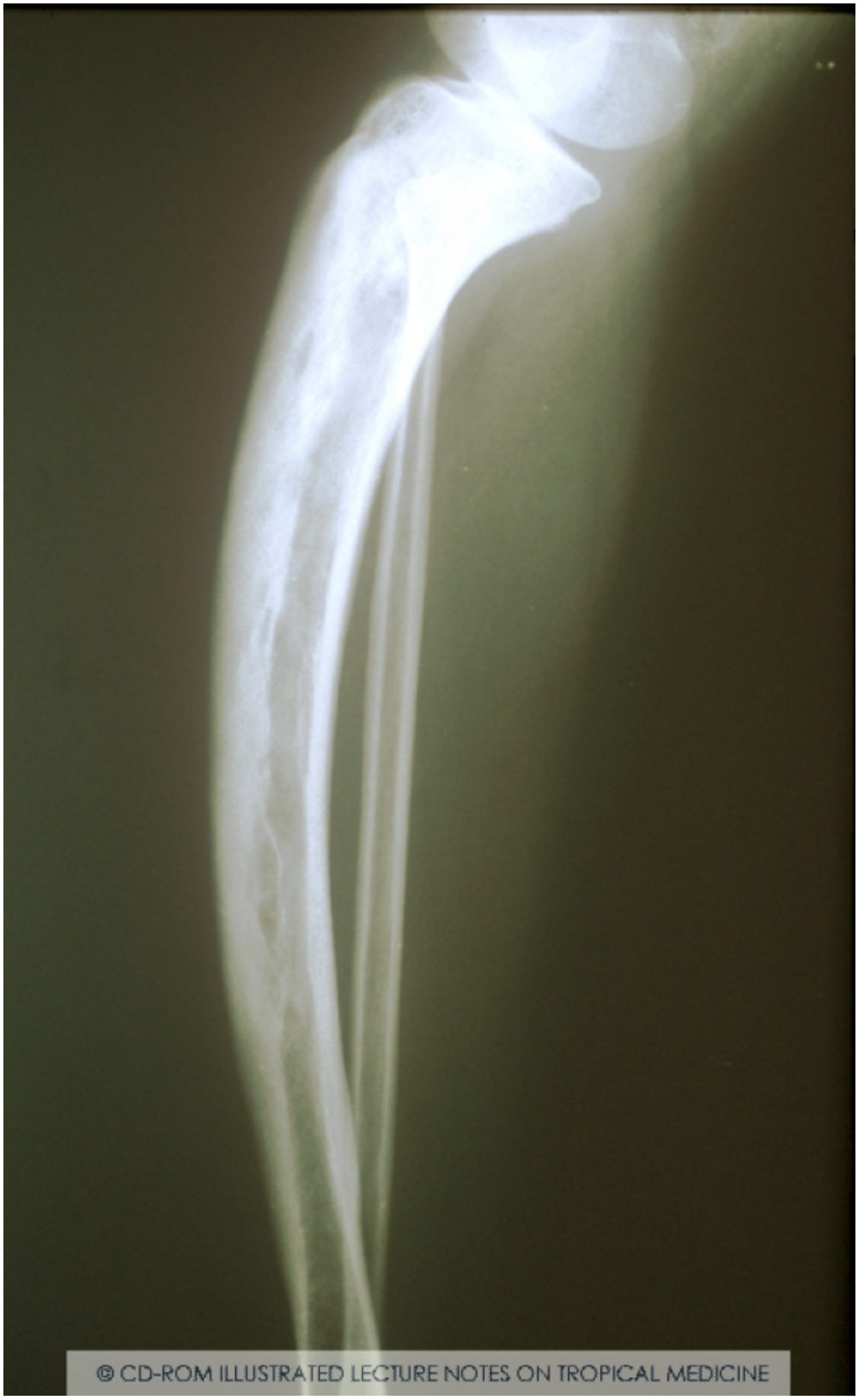
A number of secondary lesions occur in framboesia:

•**Nodules**: mainly around joints. Hard nodules which are loose from the skin and the deep tissue on the extensor side of elbows, wrists also on trochanters, ankles and sacrum. The aetiology is unclear and a differential diagnosis has to be made with onchocerciasis.

•**Gangosa**: this is rapid tissue loss from the nose, palate and upper lip, caused by a gumma in this area. To be differentiated from espundia (mucocutaneous leishmaniasis), deep mycosis (e.g. blastomycosis), leprosy and noma (= cancrum oris associated with among other things, malnutrition caused by infection with *Borrelia sp*. and fusobacteria).

•**Goundou**: swelling of the nose and upper jaw bones due to inflammation of the bones of the nose (osteitis). The rare fungal infection rhinoentomophthoromycosis can sometimes be confused with this.

- **Gumma**: a subcutaneous gumma can manifest itself as a cold abscess.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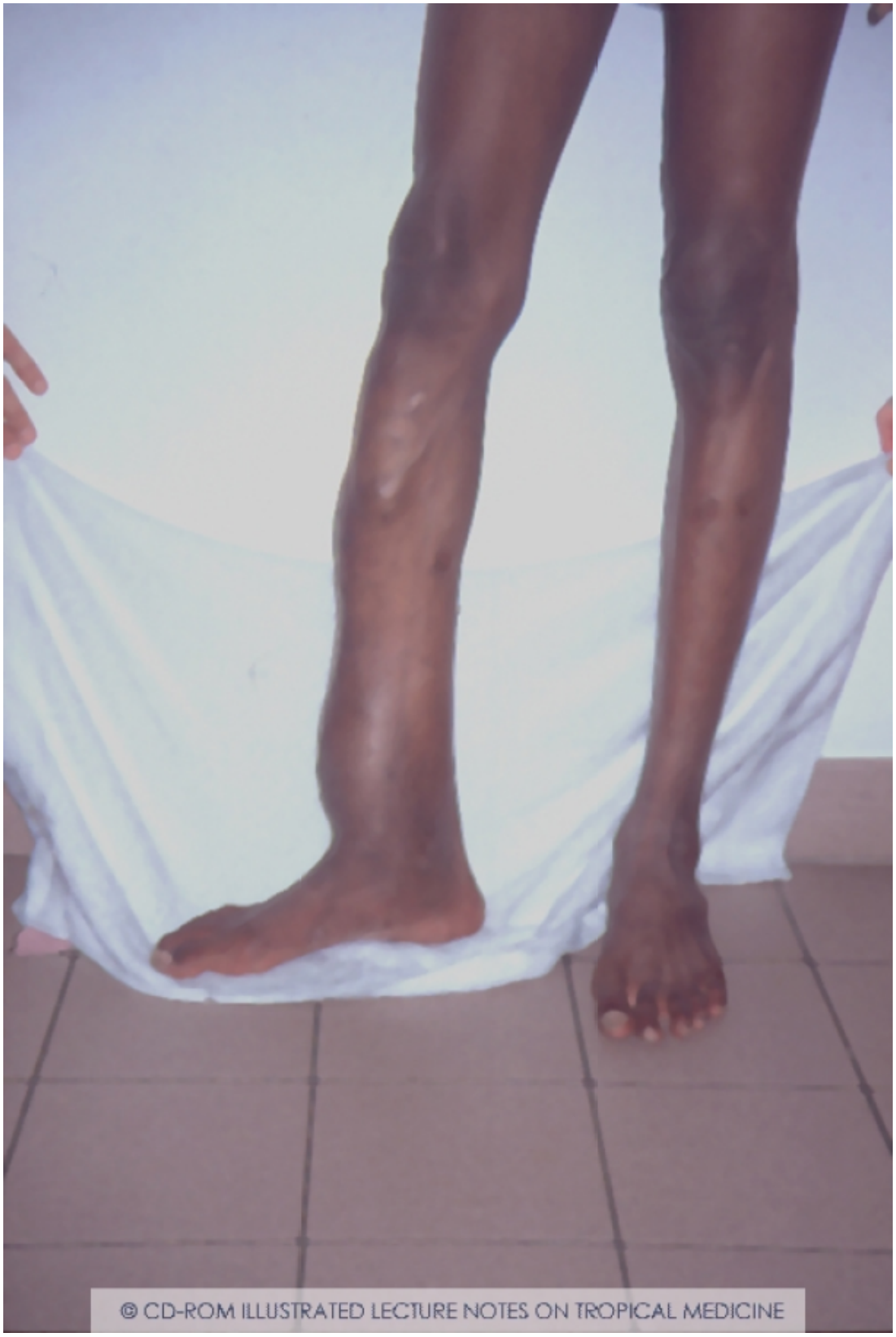
Framboesia, yaws, pian. Infection with Treponema pallidum pertenue. Deformed tibia, the so-called sabre tibia.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Melorheostosis can resemble Treponema pertenue sequellae, such as sabre tibiae. The radiological lesions often look like dripping candle wax. Copyright ITM


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Framboesia, yaws, pian. Infection with Treponema pallidum pertenue. Notice the deformed tibiae, the so-called sabre tibiae. Copyright ITM, photo by Dr Jef Van den Ende


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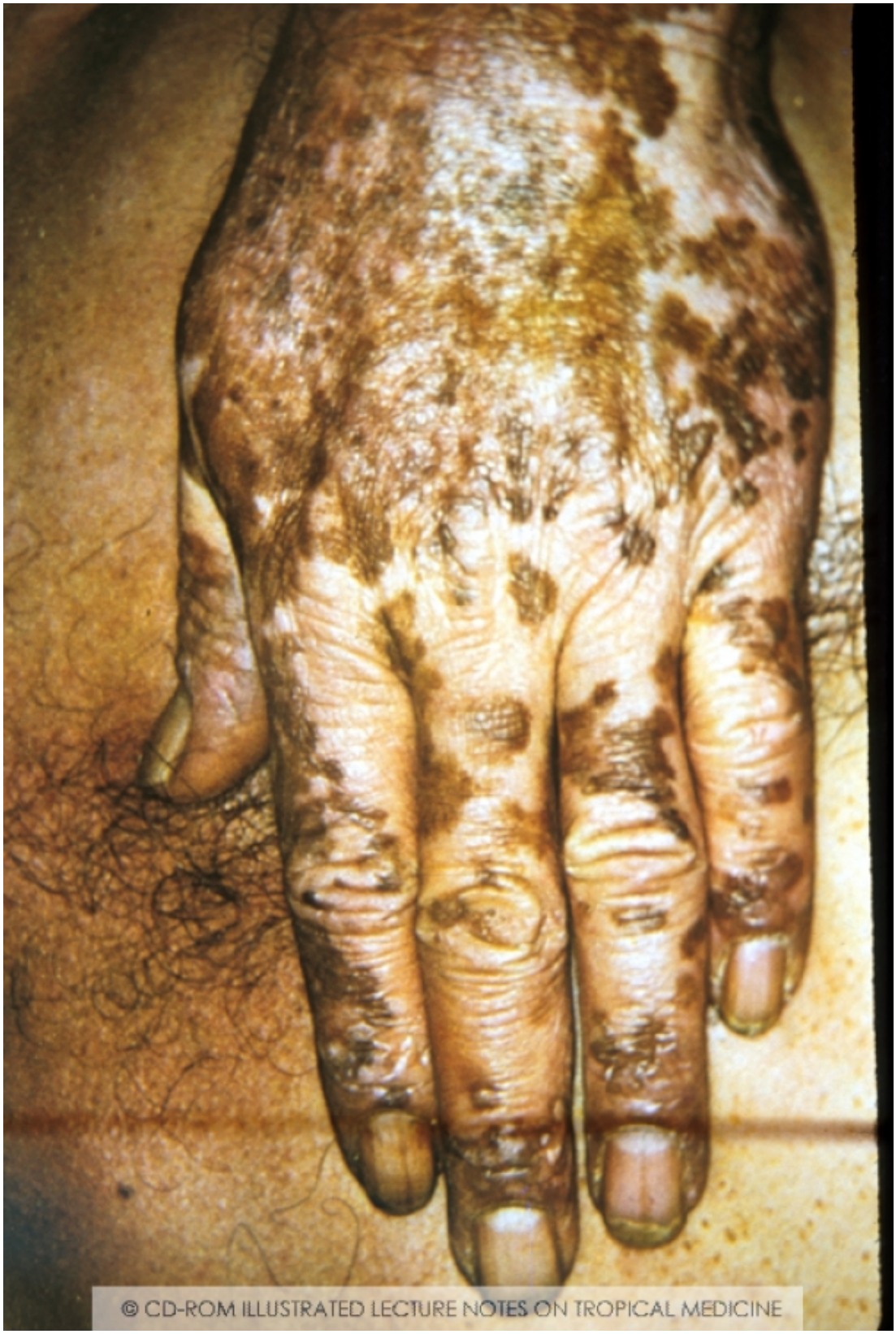
Framboesia, infection with Treponema pertenue. The name gangosa refers to the ulcerative destruction of the centre of the face. If a child survives noma, similar lesions can be found in adults.

Treatment

In patients over 10 years of age, a **single IM injection of 2.4 million units of benzathine penicillin** or a **single dose of azithromycin 30 mg/kg (max 2 gr)** is sufficient. Half the dose of penicillin should be used in younger children. In the early stages this produces fairly spectacular results. All individuals who have been in contact with the patient should also be treated. Doxycycline can be used for one week as an alternative. Erythromycin is less active. Azithromycin has been successfully used in mass treatment programs to enable yaws elimination. In certain areas the eradication of framboesia has been followed by an increase in venereal syphilis.

After successful treatment titers of nontreponemal serological tests become negative within less than 2 years.

Pinta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Pinta, depigmented skin lesions. Infection with Treponema carateum. Photo Cochabamba, Bolivia

Pinta is caused by *Treponema carateum*. This treponematosis is limited to a few foci in Central America, Colombia and southern Mexico. Cases of pinta are becoming less and less frequent. Only the skin is affected. Transmission is through contact. The primary lesion is a scaling papule which is often itchy. This appears within ten days after exposure. The papule increases in size over the following 2 to 3 months and forms a flat, scaly plaque. There is no latency period, unlike other treponematoses. A few months to more than one year later, a mild itchy maculopapular rash develops. The spots are distributed randomly over the whole of the body. They have abnormal changing pigmentation: initially blue to purplish then brown. They still contain treponemes. Later the lesions become atrophic and fade. After treatment with penicillin the lesions remain discoloured. The main problem is cosmetic, to be distinguished from other causes of hypopigmentation such as vitiligo and leprosy. There are no ulcers and no bone lesions. Pinta does not protect against the other treponematoses.

Summary

	Syphilis	**Bejel**	**Yaws**	**Pinta**
Point of entry	Genitalia	mouth	skin	skin
Congenital	yes	no	no	no
Bone lesions	sometimes	sometimes	often	never
Visceral lesions	yes	no	no	no

LAST UPDATED BY ADMIN ON JULY 14TH, 2022

Leptospirosis

Summary

- Leptospirosis: bacterial zoonosis
- Transmission via contact with contaminated freshwater
- Fever, muscle pain, cough, red eyes
- Hepatomegaly, icterus, hemorrhagic tendency, meningitis, nephritis
- Difficult clinical diagnosis: water contact, leukocytosis, urine analysis, lumbar puncture
- Serology and direct detection of bacteria are difficult to carry out
- Treatment tetracyclines, penicillin

General

Leptospirosis is the most widespread zoonosis worldwide, caused by the spirochetes of the genus *Leptospira*. An estimated one million people are infected annually, with 60.000 deaths. It is most prevalent in tropical regions, but there are occasional cases in Belgium and the Netherlands. Leptospires are the only pathogenic spirochaetes that are **free-living in the environment**. In comparison, *Treponema pallidum* is only found in humans, and *Borrelia* spirochaetes are only found in arthropods and mammals.

The severe form of leptospirosis was described in 1886 by the German Adolf Weil, Professor of Medicine at the University of Heidelberg. It is therefore still called **Weil's disease**. In 1907 Stimson discovered the organism in kidney tissue from a patient who died during a yellow fever epidemic (see Clinical aspects).

Clinically it is indeed **tough** to differentiate between yellow fever and leptospirosis. In regions where scrub typhus and hantavirosis are endemic, differentiation between *Orientia tsutsugamushi*, hantavirus infection and leptospirosis on clinical criteria alone is impossible.

Taxonomy

The bacteria are very delicate and spiral-shaped. They have a typical terminal hook (Gr. leptos = delicate, slender, speira = spiral, interrogans = question mark). The bacteria are so

thin that they cannot be detected with normal light microscopy. They can be seen using phase contrast or dark-field microscopy (urine) and using silver staining of tissue sections. Leptospires have a characteristic **double membrane architecture with features of both Gram-positive and Gram-negative bacteria**. Traditionally, the genus *Leptospira* contained two species: *Leptospira interrogans* sensu lato, which was pathogenic and *L. biflexa* sensu lato which was non-pathogenic for man. However, the taxonomy of *Leptospiro* has undergone significant changes due to large-scale whole-genome sequencing. There are currently 64 species, split into two clades (pathogenic 'P' and saprophytic 'S') and four subclades. 17 Pathogenic species are classified in subclade P1 (*L. mayottensis, L. alexanderi, L. kirschneri, L. kmetyi, L. alstonii, L. adleri, L. barantonii, L. ellisii, L. dzianensis, L. gomenensis, L. putramalaysiae, L. tipperaryensis, L. borgpetersenii, L. interrogans, L. noguchii, L. santarosai, L. weilii*). Subclade P2 comprises 20 species of intermediate or unclear pathogenicity (*L. broomii, L. licerasiae, L. fainei, L. venezuelensis, L. wolffII, L. haakeii, L. hartskeerlii, L. saintgironsiae, L. neocaledonica, L. perolatii, L. zoumogneensis, L. fletcheri, L. fluminis, L. johnsonii, L. koniamboensis, L. langatensis, L. sarikeiensis, L. selangorensis, L. semungkisensis, L. andrefontaineae, L. inadai*). The previously categorized saprophytes are subdivided in subclades S1 (*L. terpstrae, L. vanthielii, L. yanagawae, L. brenneri, L. harrisiae, L. levettii, L. kemamanensis, L. bandrabouensis, L. bourretii, L. bouyouniensis, L. congkakensis, L. ellinghausenii, L. jelokensis, L. kanakyensis, L. montravelensis, L. mtsangambouensis, L. noumeaensis, L. perdikensis, L. biflexa, L. meyeri, L. wolbachii, L. idonii*) and S2 (*L. ilyithenensis, L. kobayashii, L. ognonii, L. ryugenii*), with 22 and 5 species, respectively. In the older classification, 300 serovars, which can be differentiated by cross-agglutination absorption testing, are grouped into 32 serogroups.

Transmission

The pathogenic bacteria can **survive in freshwater** but die in seawater. Infected animals retain **bacteria in their kidneys for a long time and eliminate them in the urine**. Transmission follows contact with fresh water contaminated with the urine of infected animals. **Rats** form the main reservoir, but other animals, such as cattle, dogs, cats and pigs may also become infected.

Leptospires are killed by gastric acid and bile salts. They penetrate the body via wounds and

the mucosa of the mouth, nose and eyes (conjunctivae). **Water** is the most important transmission route, but direct contact with infected animals may also be significant (slaughterhouse workers, veterinary surgeons). It is a disease associated with **certain occupations**, e.g. workers in paddy fields or on sugar cane plantations, farmers, workers in sewers and canals, gold prospectors (gold dust obtained from water courses). People who bathe or swim in infected surface water are at increased risk of this zoonosis. Now that rafting, kayaking and adventure sports in tropical regions have become popular, there is an increase in leptospirosis in tourists. Ideal conditions for transmission are produced when dirty streets with large rat populations are flooded. Heavy rainfall or flooding in endemic areas can lead to large outbreaks of leptospirosis, especially in areas with poor housing and sanitation. Outbreaks have also been reported in triathlon participants where the swimming was in fresh water.

Clinical aspects

Given the many species of leptospires, **a broad spectrum of diseases is possible**. Symptoms range from mild fever with a 'flu'-like syndrome to atypical pneumonia, myocarditis, aseptic meningitis or the severe Weil's disease with liver and kidney failure, meningitis and hemorrhage.

The disease course has **three phases**: the first **septicaemic**, the second with **leptospiruria** (leptospires in the urine) and the third **convalescence** phase. During the first phase, the leptospires are present in the blood in low numbers (too low to be detected in a blood smear using phase contrast microscopy). Subsequently, the organisms disappear from the blood due to the formation of antibodies. The cellular defense also clears the bacteria from the various tissues. Leptospires persist in the kidney. In the renal tubules, the organisms can multiply and cause renal damage. Bacteria are eliminated with the urine, although the concentration is quite low: $< 10^4$/ml urine. The bacteria may remain in the kidneys for months, even after clinical recovery. Leptospires might also persist in the choroid plexus of the brain.

Most cases of leptospirosis are mild and self-limiting or asymptomatic. Mild forms are often atypical and are generally missed unless they are specifically sought for. The acute phase of leptospirosis usually starts 5 to 14 days after exposure (maximal incubation range 2 to 30

days).

Fever, rigors, myalgias (mainly in the calves and lower back), headache and general malaise usually last two to nine days. Patients can sometimes pinpoint within the hour when the illness began. Next, the fever may subside for a few days and then increase once more (biphasic fever) during the “immune” phase. The absence of this fever pattern does not rule out the disease. Significant muscle pain is almost always present. If it is absent, the diagnosis is improbable.

There is sometimes a sore throat and a dry cough, later possibly hemoptysis. In 10 to 30% of patients, the lower legs have a spotty skin rash. [This was initially described as “Fort Bragg Fever” caused by *L. interrogans autumnalis*]. The eyes are often bloodshot due to dilation of conjunctival blood vessels causing conjunctival erythema. Pus discharge is absent, unlike in purulent conjunctivitis. Subconjunctival hemorrhage can occur on top of the **conjunctival suffusion**. During the immune phase, anterior uveitis presenting as acute onset pain and redness of the eye(s) may occur. Posterior uveitis (chorioretinitis) is less common and presents with decreased vision or floaters. Two-thirds of patients suffer nausea and/or vomiting. Swollen lymph nodes are only present in a minority of patients. The spleen is swollen in 20% of cases.

Marked elevation of CK levels indicates **muscle damage** and occurs only in severe cases. Muscle pain, predominantly in the calves, can lead to local swelling, which can be so severe that patients cannot walk anymore. Pectoral, back and abdominal muscles may also be involved.

Palpation of the calves tends to be painful. The injured muscles heal without scarring. CK levels and muscle symptoms usually diminish in the second week of illness. Rhabdomyolysis seems to be secondary to direct muscle cell invasion with cell necrosis and small intramuscular hemorrhages.

Myocarditis occurs and often leads to congestive heart failure and cardiogenic shock. Electrocardiographic abnormalities are common.

Weil’s disease is a syndrome characterized by icteric leptospirosis with fever, jaundice and

renal failure. Lung bleeding with ARDS, myocarditis and rhabdomyolysis may accompany this syndrome. **Involvement of the liver** is characterized by hepatomegaly, jaundice and a hemorrhagic tendency. Scleral icterus and jaundice are accompanied by a marked conjugated bilirubin elevation with normal or slightly elevated aminotransferases. The gall bladder may become inflamed (acute cholecystitis). Liver failure is rare.

Atypical pneumonia with possible blood-tinged sputum can be expected in severe cases. Pulmonary lesions are primarily hemorrhagic rather than inflammatory. Patients are at risk for secondary bacterial pneumonia.

Kidney damage leads to proteinuria, hematuria and uremia. Hypovolaemia and poor renal circulation may further exacerbate renal damage. Hypovolaemia is characterized by oliguria, low blood pressure, diminished skin turgor and flat neck veins. If it is not corrected by giving fluids, tubular necrosis will follow. Temporarily hemodialysis is needed in severe renal failure. Sterile pyuria, proteinuria, granular casts, myoglobinuria and enlarged kidneys occur in some patients. The haem part of myoglobin separates form the globin moiety in an acid environment (pH < 5,4). Renal tubular obstruction due to the precipitation of myoglobin is dangerous. Myoglobin is less toxic if there is no dehydration or acidosis. Therefore alkalinization of the urine is essential.

Meningism may occur early but is more frequent in the immune phase. Neck stiffness is present in half the patients with **aseptic meningitis**. The CSF typically has a neutrophilic or lymphocytic pleocytosis with mild proteinorachia. CSF pleocytosis may last for up to three months. Meningitis is attributed to the immune response rather than a true CNS infection. However, recent studies could *Leptospira* in the CSF by polymerase chain reaction.

In severe leptospirosis, the total period of illness is approximately three weeks to one month. The mortality is between 5 and 30 %; severe icterus has a poor prognosis. If the patient survives, there is usually no residual damage. A long convalescent period is typical.

Differential diagnosis:

This is **very broad because of the variable symptoms**. It includes Hantavirus infection, influenza, gastro-enteritis, meningitis, malaria, hepatitis, cholangitis, rickettsiosis (e.g. scrub

typhus), borreliosis, typhoid fever, Reye's syndrome, arboviroses such as yellow fever, Rift valley Fever, Crimean-Congo hemorrhagic fever and West Nile fever as well as arenaviroses. In the case of hemorrhagic tendency, Gram-negative bloodstream infections and various viral hemorrhagic fevers should be considered.

Diagnosis

Confirming leptospirosis is quite **difficult**, and the disease is often missed. The disease should be clinically suspected in patients exposed to endemic or outbreak settings who present with systemic febrile illness without an alternative explanation. **Exposure** to potentially contaminated water (occupation, accident, swimming, recent travel to flooded areas etc.) and rat exposure should be enquired. Aseptic meningitis, uveitis, jaundice, acute febrile kidney injury, pulmonary hemorrhage and conjunctival suffusion should raise the suspicion for leptospirosis.

Microscopy of Leptospira sp., bacteria that cause leptospirosis. Photo Cochabamba, Bolivia

There is proteinuria, pyuria and microscopic haematuria. The cerebrospinal fluid initially contains neutrophils. Later, lymphocytes predominate, together with elevated protein and normal glucose.

In general, there is significant leukocytosis, but this is not constant. Thrombocytopenia is common. Early in the disease, leptospires can rarely be found in the blood, urine or cerebrospinal fluid (the tests are not very sensitive). Subsequently, the bacteria are only found in the urine.

Since these are very thin organisms (0.1 µm diameter), a dark-field microscope is needed to detect them in a blood smear. Indirect illumination is used in this method instead of direct illumination so that fine structures can be detected which are not visible with the traditional microscope. This method is not very sensitive and has been responsible for many errors (many false positives and false negatives).

Serology can be performed. The traditional serology using micro-agglutination test or MAT requires a well-functioning laboratory, which will not be available in practice in low resources settings. A single positive or negative IgM or IgG cannot confirm or rule out infection, even though a single IgG titer (>1:800 on MAT) strongly supports infection. A second sample 7 to 14 days after the first antibody test should be obtained, and a four-fold increase in IgG titer confirms infection. Antibody tests that do not detect all serovars may produce false negative results. The interpretation of MAT serology results to identify the responsible serovars is rather difficult because the highest titer does not necessarily correlate with the actual serovar responsible for the infection.

Culture of the bacteria is the gold standard but is **not practical in most settings**. The culture of leptospires is complex and requires non-standard equipment. Special media such as Fletcher’s, Ellinghausen’s, or polysorbate 80 media are required for isolation. Blood and CSF specimens are positive during the first ten days of the illness. Urine cultures become positive during the second week of illness and remain so for up to 30 days after the resolution of symptoms.

In high-resource settings, **PCR** is used on blood samples, urine, CSF and tissue biopsies. Whereas PCR detects leptospires during the first week of symptoms, urine samples are particularly valuable beyond the first week of illness. The sensitivity of PCR ranges from 40 to 60 percent in blood samples; the specificity exceeds 95 percent.

Antigen detection using a monoclonal antibody-based direct ELISA (anti-*LipL32* antibodies) on blood has shown promising results in Sri Lanka but needs validation in larger international studies.

Treatment

Most patients with leptospirosis will recover without antibiotics. Although robust evidence is lacking, **early treatment initiation** might prevent evolution to severe disease. Antibiotics such as tetracyclines within the first 4 days are assumed to shorten the illness. Sometimes leptospires persist in urine, despite the correct treatment. Oral doxycycline 200 mg per day for 1 week is the preferred regimen for mild infections. If there is vomiting, IV penicillin is used. For severe infections, ceftriaxone can also be used. This allows for once-daily dosing, which is more practical than the multiple dosing schemes using penicillin. Azithromycin and ampicillin are also active against leptospires. Chloramphenicol is not. Most patients with critical illness will have been placed on an empirical antibiotic treatment. However, since the pathophysiology suggest an exaggerated immune reaction, the beneficial effect in severe disease remains controversial.

The immune-triggered second phase suggests a role for corticoids in Weil’s disease. Some studies suggest a possible benefit, but more studies are needed.

Symptomatic and supportive therapy is vital. If there is myoglobinemia, alkalinization of the urine is essential to limit renal damage. In severe disease, hemodialysis, mechanical ventilation and blood products can be life-saving.

Prevention

Since **rats** form the main reservoir and contaminate surface water and drains, their control is important for prevention. Nevertheless, it should not be forgotten that the animal reservoir is

much broader (e.g. dogs etc.) and **cannot be eradicated completely**. Avoiding sources of infections, such as water contaminated with animal urine, is advised. Wearing boots when working in stagnant water is advisable. **Chemoprophylaxis** of 200 mg doxycycline per week may be taken as a preventative in high-risk situations like flooding in an endemic region. After infection, there is protection against the infecting serovar but no cross-immunity. Human vaccines have been developed, but they are serovar-specific, and none of them is widely available. Animal vaccination can provide variable levels of protection for animals and humans.

LAST UPDATED BY ADMIN ON JANUARY 27TH, 2025

Borreliosis

Relapsing fever

Summary

- Spiral shaped bacteria, transmitted by ticks (endemic) or lice (epidemic)
- Recurrent fever, rash, hepatosplenomegaly, red eyes, haemorrhagic diathesis, muscular pain, coughing, confusion, neurological complications
- Thick film test positive, esp. in beginning of attack
- Treatment with penicillin or tetracyclines (e.g. doxycycline)

General

Borrelia sp. are very thin, spiral shaped bacteria. They are **larger, longer and have looser coils** than treponemes or leptospires. They are responsible for major diseases, including **recurrent or relapsing fever**. In 1868 the German Otto Obermeier identified the microorganisms during an epidemic in Berlin. The pathogenic potential was demonstrated in 1874 by Gregor Münch, who inoculated himself with *Borrelia recurrentis* and survived the subsequent relapsing fever. The French microbiologists Sergent and Foley identified the body louse as the vector. The British pathologist Joseph Dutton (famous because of *B. duttoni*)

discovered an alternative vector: the Argasid soft tick *Ornithodoros moubata*. He injured himself while performing an autopsy on a patient who had died from borreliosis and died himself from relapsing fever. During his research into East Coast fever in East Africa, Robert Koch discovered that transovarial transmission took place in these ticks. Charles Nicolle and co-workers established that *Borrelia recurrentis* disappeared from the intestine of the louse 24 hours after a blood-meal, to appear again suddenly in the haemolymph of the insect after 6-8 days. Experimental animals such as rats and mice can be inoculated successfully. *Borrelia recurrentis* can be grown in chicken embryos and since 1994 in-vitro.

There are two types of borreliosis: relapsing fever, **louse-borne borreliosis (*Borrelia recurrentis*)** and **tick-borne borreliosis** (***Borrelia duttoni*** and many other varieties, depending on the geographical region). The bacteria are morphologically identical. The name "tick-borne borreliosis" sometimes causes confusion, as *Borrelia burgdorferi* is also transmitted by ticks, but this organism does not cause relapsing fever.

Epidemic, louse-borne relapsing fever

In the **epidemic** form of borreliosis the bacterium ***Borrelia recurrentis* is transmitted by lice**. The vector is the common body louse (*Pediculus humanus corporis*). [The body louse is also the vector of epidemic typhus and of *Bartonella quintana*. This insect is not to be confused with the pubic louse (Phthirus pubis)]. The head louse (*P. h. capitis*) hardly ever plays a part in transmission. There is no transovarial transmission of *Borrelia recurrentis* in the louse. **Humans are the reservoir** of the disease.

The louse is infected by sucking blood at the time the patient has an outbreak of fever. At this time the levels of bacteria in the blood are at their highest. The bacteria penetrate the insect's intestine and multiply in the haemolymph ["blood"] of the louse. The bacteria do not penetrate the salivary glands. The disease is not transmitted by the bite itself. **If an infected louse is crushed on the skin when scratching, the bacteria can penetrate into the skin**. Lice do not like high temperatures and will readily leave a person who has a fever. In the event of poor hygiene and close physical contact between people lice can pass from a sick person to a healthy person

The disease is **rare but can occur all over the world**. The geographical distribution of

LBRF has declined due to improvements in living standards. Currently the disease is primarily found in limited endemic foci in Ethiopia but also in Somalia and Sudan. The disease has also been recorded in the rural Andean community in Peru and in northern China. Epidemics occur in conditions of poor hygiene, overcrowding and malnutrition, such as in floods, mass migration, earthquakes, concentration camps and refugee camps, war, and in the slum districts of large towns. Body lice multiply rapidly and a population can increase by 11% per day. Infection is more frequent in the cold months. People live closer together then, wear more clothes, so there are more lice and consequently more transmission. **Mortality can be very high (30 to 80%).** Between 1910 and 1945 there were 7 large epidemics in Africa, Eastern Europe and Russia with 15 million cases and 5 million dead.

Endemic, tick-borne relapsing fever

This is a sporadic, endemic disease in a number of areas caused by *Borrelia duttoni* and related bacteria. The vectors are **soft ticks** (*Ornithodoros sp.*). In West Africa *O. erraticus* is responsible for the transmission of *B. hispanica*. In Central, Eastern and Southern Africa *Ornithodoros moubata* is the main vector (*B. duttoni*). These latter ticks infect people through their saliva and through coxal fluid. It is mainly an infection of rodents. These animals are the principal reservoir. Because the bacterium in ticks passes from one generation to the next by transovarial transmission, the ticks themselves also form a reservoir. People can be infected by ticks for example when walking through grass or bushes. In Central Africa there is a domestic variety whereby the ticks live in cracks in the walls of mud huts and are therefore more likely to bite humans. The people who are infected are then the main reservoir. Ticks can live for a number of years (exceptionally up to 15 years) unlike lice (a maximum of 2 months). They can survive for a long time without a blood-meal. **Mortality in man is lower with tick-borne borreliosis (2 to 5%) than with the epidemic form**. The local population builds up immunity from repeated infections; they usually have a mild form. The bacteria can cross the placenta to the fetus.

Over the course of an infection in a single human host *Borrelia sp*. regularly display **antigenic variation**, mainly by changing various surface proteins (“variable large proteins and variable small proteins”).

Clinical Aspects

After an incubation period **of 4 to 14 days (1 week on average),** the patient suddenly develops a **violent fever** (39° to 41°C). This is accompanied by a **high bacteraemia**: 10^{6-8}/ml. The concentration of bacteria is so high that they can be detected with the **thick film test or a thin blood smear** (in classical Gram-negative bacteraemia (e.g. *E. coli*) the concentration of bacteria is much lower). The patient suffers from headache, muscular pain and pain in the joints. There is often a dry cough and dyspnoea, which can be quite severe. The patient sometimes suffers from abdominal pain and diarrhoea. The patient is frequently jaundiced. The spleen, the liver and the lymph nodes are often swollen. Neurological abnormalities occur. The conjunctivae are often red. Sometimes (in 4 to 50% of cases) there is a discrete rash which usually appears when the first fever peak subsides. Diffuse intravascular coagulation (DIC) and thrombocytopenia, petechiae and haemorrhaging can occur, e.g. epistaxis (nose bleeds). Sometimes (1/3) a considerable leucocytosis can be present, but leukopenia can also occur. The cerebrospinal fluid can contain an increased number of lymphocytes (mainly in endemic tick-borne borreliosis). The fever suddenly disappears after 2 to 8 days on average 5 days. This is usually accompanied by an aggravation of the symptoms, hypotension and sometimes death. The prognosis is worse with louse-borne borreliosis, when there is manifest jaundice, hypotension and high bacteraemia (which can be objectivised in a thin blood smear). There is high neonatal mortality (50%).

The first febrile episode is followed by a period **of 3 to 30 days (on average 9 days) without fever**. In 60% of patients this is followed by a second febrile period, which is somewhat less severe than the first and also lasts for a shorter time (on average 2 days). This can be repeated a number of times: maximum 4 times in case of louse-borne borreliosis, maximum 11 times in case of tick-borne borreliosis. This characteristic explains why it is called “relapsing fever”.

Complications are meningo-encephalitis with as sequelae facial paralysis, deafness and paralysis of the eye muscles (mainly endemic tick-borne borreliosis). Most spirochaetes are neurotropic. Myocarditis and abortion may also occur. If a pregnant woman has relapsing fever she has around a 50% risk of going into labour.

Diagnosis

The clinical **signs and symptoms are not specific** apart from the **recurrent bouts of fever**. At the beginning of a febrile episode bacteria are found in the blood. These very thin spiral shaped bacteria (0.5µm) can be seen in an unstained unfixed preparation because of their typical mobility. They can also be stained with Giemsa and Wright stain. Staining with Diff-Quik (xanthene thiazine stain) is an alternative. They are found between the red blood cells. The fact that the bacteria can be seen in peripheral blood is explained by the very high density of the bacteria. *Borrelia* spp can be cultured through animal inoculation or in vitro cultivation in a Barbour-Stoenner-Kelly (BSK) medium. PCR and serology are only available in a few reference laboratories.

The differential diagnosis includes **many febrile conditions** including malaria, typhoid fever, hepatitis, amoebic hepatic abscess, leptospirosis, rat bite fever, septicaemia, arbovirosis, ehrlichiosis and anaplasmosis, babesiosis, rickettsial diseases (can also be transmitted by lice and ticks).

Treatment

Tetracyclines are the first choice, e.g. doxycycline. A single administration is often sufficient. Alternatively erythromycin can be given. In the case of louse-borne borreliosis, in ± 90% of patients a spectacular deterioration in the symptoms is seen 1 to 3 hours after starting therapy: headache and muscular pain, tremor, very high fever, tachypnoea, tachycardia and initial hypertension. This is followed shortly after by excessive perspiration and hypotension and sometimes shock. This is a so-called **“Jarisch-Herxheimer”** reaction which usually lasts 6 to 12 hours. This reaction rarely occurs (1%) with tick-borne borreliosis. The reaction was first described in syphilis patients who were being treated with mercury chloride or penicillin. It can also occur when treating other infections caused by intracellular bacteria (such as Brucella, Q fever). It has a mortality rate of about 5%. It is thought that it develops from various substances being released from the destroyed bacteria, together with high concentrations of certain cytokines (e.g. TNF alpha, IL-6 and IL-8). Steroids are not effective in preventing the reaction. It has been shown that treatment with anti-tumour necrosis-alpha antibodies mitigates the Herxheimer reaction. The patient must be kept under close supervision (bed rest, IV infusion). Penicillin is less frequently associated with

Herxheimer reactions but is less effective (often further recurrences).

Prevention

There is no vaccination and no lasting immunity after a patient has had the infection. In the case of an epidemic (louse-borne borreliosis) mass delousing is often carried out (2 x with an interval of 2 weeks) for example in refugee camps. This is based on the use of insecticides and hot sterilisation (boiling and washing) of clothes.

Borrelia vincenti

It is not clear whether this bacterium is itself a pathogen or whether it is present as a saprophyte in necrotic material. The bacteria can, unlike the other *Borrelia* be cultured in an anaerobic environment. In combination with certain anaerobic bacteria (fusobacteria = anaerobic Gram-negative "fusiform bacteria") this bacterium is suspected of causing ulcerative damage in the:

- **throat**: *Plaut-Vincent's angina.* This results in a major throat infection with localised necrosis. DDx: diphtheria of the throat, local anthrax or plague.
- **gums**: *Trench mouth or Vincent's stomatitis*, a necrotising and ulcerative gingivitis of the cheek. This occurs in malnourished children and sometimes after herpes simplex.
- **cheeks / lips**: *Cancrum oris (noma)* is characterised by pain and extensive tissue destruction. Treatment consists of penicillin, correct nutrition and treatment of any underlying disorder (e.g. kala-azar, etc). Plastic surgery will be needed.
- **scrotum**: Gangrene of the scrotum (*Fournier's gangrene*).
- **skin**: Painful (in the acute stage), purulent, foul-smelling ulcers, mainly on the legs or feet (*phagedenic or tropical ulcer*). Ulcers such as this can drag on for years or sometimes heal spontaneously. In some patients a spinocellular carcinoma develops which is invasive locally and can metastasise to the local lymph nodes. Treatment consists of penicillin and metronidazole. Local wound cleaning, antiseptics and non-adhesive dressings are important. Dry dressings should be avoided because they prevent the forming of new epithelium (when the dressing is removed the new cells are pulled off).

Rat Bite Fever

Summary

- Infection by bacteria: *Streptobacillus moniliformis* or *Spirillum minus*
- Rate bite fever is named sodoku in Asia, caused by *S. minus*
- Haverhill fever is rat bite fever caused by *Streptobacillus moniliformis* after ingestion of food or water contaminated with rat faeces
- Rat bite wound followed by fever, lymphadenopathy, migrating arthralgia, skin rash and muscle pain
- If transmitted via infected drink: episodic fever, throat pain, rash, muscle and joint pain
- Systemic complications possible: myocarditis, pneumonia, abscesses, meningitis
- Treatment with penicillin

General

Rat bites may give rise to infection with various bacteria but two deserve special attention. *Spirillum minus* is a systemic zoonosis occuring mainly in Asia. Rat bite fever caused by *Streptobacillus moniliformis* has a more cosmopolitan distribution and is mainly recognised in Europe and North America. A third species causing rat bite fever – *Streptobacillus notomytis* – has only been reported rarely. Infection in third world countries will probably be discovered as soon as better diagnostic facilities are available. Rat bite fever may trigger intermittent fever which may make it similar to other infections.

Clinical aspects

Spirillum minus is a small spiral-shaped bacterium and is usually classified as a spirochaete and is unable to be cultured. The bacterium has flagellae and moves quickly unlike *Streptobacillus moniliformis*.

Streptobacillus moniliformis is a difficult to culture pleomorphic non-motile Gram-negative rod-shaped bacterium. Its name refers to the necklace like morphology exhibited by the bacteria that form thin branched filaments.

The disease caused by *S. minus* is known as sodoku in Asia (a Japanese name: *so*: rat, *doku*: poison). Infection may follow a rat bite or the consumption of water or milk contaminated by rat urine or faeces.

Streptobacillus moniliformis infection occurs after ingestion of food or water contaminated with infected rat faeces. The disease is known as **Haverhill Fever**. The name Haverhill refers to a small town in Massachusetts where an epidemic broke out in 1926 following the consumption of contaminated unpasteurized milk. The bacteria occur naturally in the nasopharynx of rats and are found in 50 to 100% of rats living in the wild. The risk of rat bite fever due to *S. moniliformis* after a rat bite is estimated to be 10%. Not only rats, but also other rodents such as mice, gerbils, squirrels or carnivores or omnivores which eat rodents (cats, dogs, pigs, weasels, ferrets) can transmit the bacteria. People who work with animals (laboratory staff, some biologists) are at increased risk.

The incubation time is 1 to 30 days, usually approximately 1 week. If infection (*S. minus and S. moniliformus*) is transmitted orally, there are no skin wounds. A bite wound of*S. minus* causes local inflammation and even tissue necrosis with enlarged regional lymph nodes and its initial wound may reappear at the onset of systemic illness. *Streptobacillus moniliformis* bite wounds heal spontaneously.

After the wound has healed, intermittent chills, extreme fatigue, vomiting, diffuse muscle and joint pain and headache follow. Arthritis is not common in *S. minus* infection. *S. moniliformis* infection may give rise to an asymmetrical non-purulent poly-arthritis in up to 50% of patients. Generally the large joints are affected, such as the knees, ankles, elbows, wrists, shoulders and hips. Purulent arthritis is rare. If a patient is bitten on a finger, a neighbouring interphalangeal joint may exhibit impaired function.
Approximately two to four days after the beginning of the fever a skin rash occurs. This may have a morbilliform, pustular or petechial character. The rash is most pronounced on the hands and feet. Desquamation may occur. Somewhat later the patient develops painful pharyngitis. After an average of five days spontaneous improvement is seen. The fever disappears and the other lesions improve over the course of a few weeks.

After an irregular period of time there might be a relapse which resembles a picture of fever of unknown origin. This recurrence may persist for two years.

Complications include ulcerative endocarditis, subacute myocarditis, pericarditis, meningitis, pneumonia, amnionitis and anaemia. Abscesses may occur in any organ. In epidemics the name erythema arthriticum epidemicum is used.

Differential diagnosis:

Differential diagnosis includes coxsackievirus (hand-foot-mouth syndrom) or an aspecific viral exanthema, meningococcal septicaemia, leptospirosis, erythema multiforme, secondary syphilis, rickettsiosis (RMSF [Rocky Mountain spotted fever]), tularaemia, *Bartonella henselae* (cat scratch disease) and infections which typically occur after bites, such as *Capnocytophaga canimorsus*, *Eikenella corrodens* or *Pasteurella multocida* infections. If joint problems are prominent, Lyme disease, acute rheumatic fever, brucellosis, gonococcal infection, septic arthritis, infectious endocarditis and auto-immune disorders may have to be excluded.

Diagnosis

A diagnosis may be reached clinically: unexplained (relapsing) fever or sepsis, maculopapular rash and/or polyarthritis in patient with rat exposure. But even if there has been a rat bite, this will not always be reported when taking the history. Nevertheless this detail will be an important guiding factor. Some patients have a normal blood count, while others have significant leukocytosis (to 30,000) with left shift. Confirming a diagnosis microbiologically is extremely difficult: *Spirillum minus* can be demonstrated using dark-field microscopy of a little fluid from the site of the bite but cannot be cultured yet in vitro. *Streptobacillus moniliformis* can be cultured on specially enriched anaerobic media.

Serology (ELISA) may be carried out in specialised laboratories.

Treatment

Empirical therapy should be started instantly if rat bite fever is suspected since mortality may reach 13% in untreated patients and laboratory confirmation is strenuous and time consuming. The treatment is based on penicillin (or a tetracycline in patients allergic to penicillin) preferably given for 14 days. There may be a Jarisch-Herxheimer-like reaction at

the beginning of treatment. Ceftriaxone is also effective.

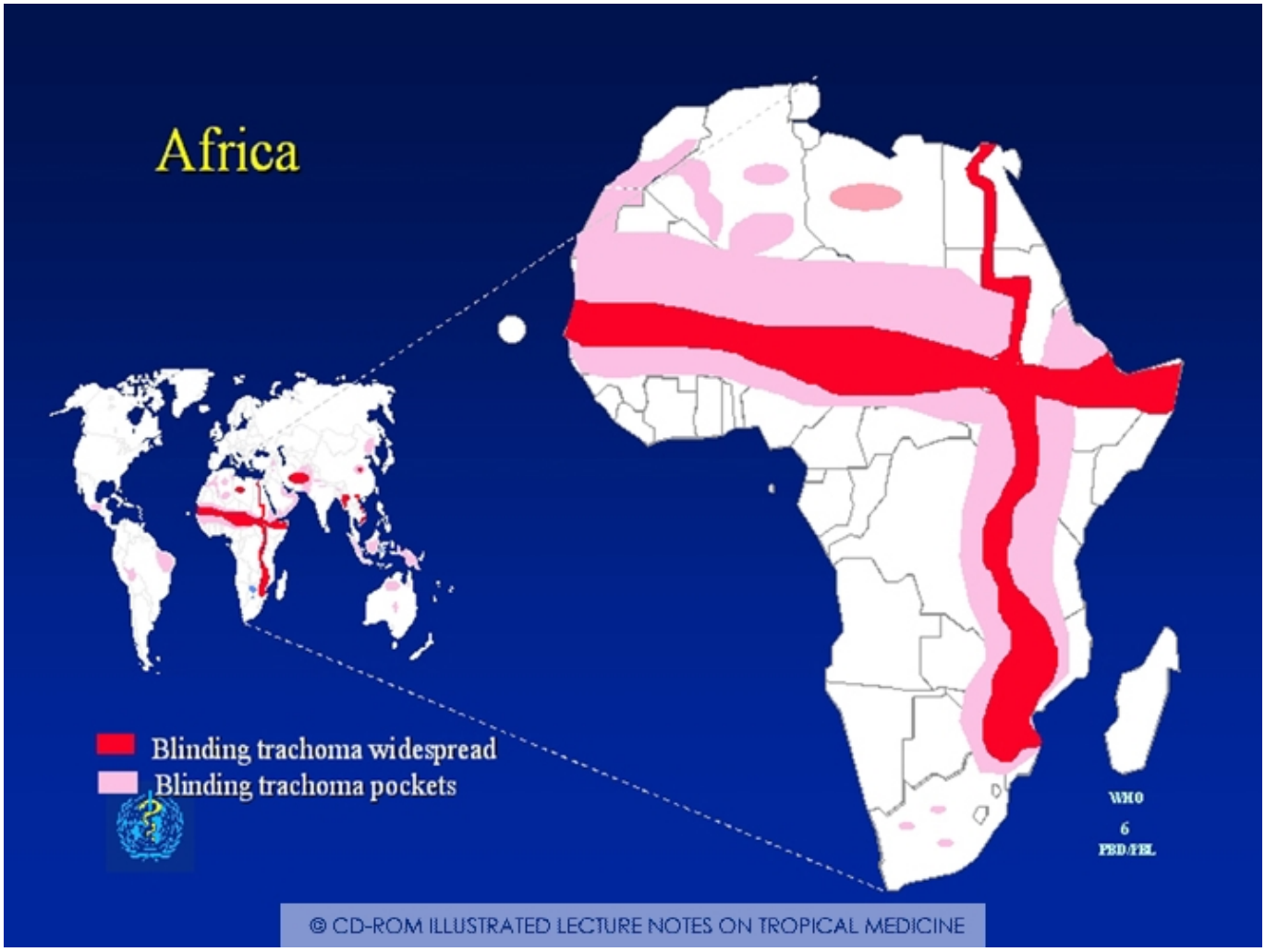
LAST UPDATED BY ADMIN ON JANUARY 27TH, 2025

Trachoma

Summary

- TTrachoma: important cause of blindness
- Chronic follicular keratoconjunctivitis caused by serotype A, B, Ba and C of *Chlamydia trachomatis*
- Inflammation of the upper eyelid, followed by pannus of the cornea, entropion and trichiasis
- Treatment by tetracyclines or azithromycin
- Prevention by better hygiene, water, soap and fly control

General



Trachoma, map. Chlamydia trachomatis. Copyright WHO

The three most important diseases which lead to blindness in the tropics are onchocerciasis, vitamin A deficiency and trachoma. Other frequent causes are trauma, diabetes, leprosy, cataract, macular degeneration and chorioretinitis. The name trachoma refers to the raw appearance of the eyelid (Gr. “trachoma” = rawness). The term was first used by the Greek Pedanius Dioscorides (AD 50-70). Trachoma is a chronic form of conjunctivitis which is caused by some serotypes of *Chlamydia trachomatis.* Repeated reinfections are probably important in the ultimate pathology. The infection is characterised by progressive exacerbations and remissions, with follicular hyperplasia, corneal neovascularisation and scarring of the conjunctivae, cornea and eyelids. The disease occurs predominantly in dry areas of Africa

(except for Congo), the Middle East, India and Southeast Asia. The disease is rare in the New World. The lack of water and soap for elementary hygiene plays an important role in transmission. Transmission takes place by hand-to-eye contact. Even sharing infected utensils can lead to transmission. The role of flies (*Musca* sp.) was underlined by Jones, who showed that fluorescein-labelled eye secretions can be transmitted from child-to-child by these insects.

Chlamydia trachomatis

Chlamydiae are very small bacteria which have to live intracellularly. They were originally considered to be viruses, but it is now known that they contain both DNA and RNA and are structurally related to Gram-negative bacteria. Several species are known in the genus Chlamydia: *C. psittaci*, the pathogen of psittacosis; *C. pneumoniae* (old name TWAR), which provokes atypical pneumonia; and *C. trachomatis*, which has many serotypes. Serotypes A, B, Ba, and C cause trachoma. Serotypes D to K cause inclusion conjunctivitis in the newborn ("paratrachoma"), Reiter's syndrome, non-gonococcal urethritis, epididymitis, cervicitis and P.I.D. (pelvic inflammatory disease). Neonatal conjunctivitis and pneumonia can be caused in the newborn by these bacteria. Serotypes L_1 and L_2 cause the sexually-transmitted disease lymphogranuloma venereum. L_3 causes pneumonia in mice. *C. trachomatis* is considered to be responsible for 20% of the pharyngitis symptoms in adults.

Clinical aspects

After an incubation period of approximately 7 days, four different clinical stages can be distinguished. These stages overlap. Reinfection can occur and makes the classification rather artificial.

Stage 1: there is bilateral redness of the conjunctivae. Photophobia, eyelid oedema and lacrimation follow. Small (2-3 mm) lymphoid follicles develop on the tarsal conjunctivae which increase in size over the course of one month. The inner side of especially the upper eyelid then becomes granular. This follicular-papular hypertrophy stage can last from several months to years.

Stage 2: After several months small blood vessels begin to grow into the uppermost part of

the cornea. This process starts in the upper limbus of the cornea. The combination of blood vessels and infiltrate is known as a pannus. The mucus-producing cells in the conjunctiva are destroyed, leading to “dry eye” (sicca syndrome). Corneal ulcerations can occur. If left untreated the cornea becomes cloudy with functional blindness as the ultimate result. In rare cases the corneal neovascularisation regresses without treatment.

Stage 3: Linear scarring appears in the tarsal conjunctiva. Follicles are replaced by small white lines. The conjunctiva becomes smooth, white and avascular. The conjunctiva of the lower eyelid may take on a milky appearance. The craters of the ruptured follicles are lined with epithelium and form a series of lacunae in the limbus, known as Herbert’s pits. The pannus regresses.

Stage 4: In this stage there is no longer any active infection. The scar tissue contracts and deforms the upper eyelid so that entropion follows. Due to the turning inward of the eyelid, the eyelashes scratch the cornea (trichiasis) and cause mechanical trauma. Bacterial superinfection can occur. The epithelium of the cornea becomes dull and thickened, which is made even worse by chronic exposure to dust and sand. This promotes further neovascularisation.

Diagnosis

In most endemic areas trachoma will be a clinical diagnosis. Chlamydia trachomatis can be cultured but the infrastructure for this is beyond the capabilities of most hospitals. PCR is more sensitive than culture. In the early stages small basophilic cytoplasmic inclusions can be seen with Giemsa staining in scrapings of the tarsal conjunctival epithelium. In clinical practice it is not necessary to provide formal proof of infection. Trachoma has to be distinguished from chronic allergic conjunctivitis. This is not always easy but eosinophilia and milky flat-topped papillae are present whereas basophilic inclusions are not found. Under field conditions the diagnosis of trachoma is likely to be correct if at least two of the following criteria are present:

1. Follicles on the upper palpebral conjunctiva in the mid-tarsal region
2. Linear scars of the tarsal conjunctiva (Arlt’s syndrome)
3. Active keratitis

4. Follicles in the limbus or their sequelae (Herbert's pits)
5. Pannus in the upper third of the cornea.

Treatment

The treatment used to rely on the administration of tetracycline eye ointment or taking doxycycline 100 mg bid for 4 weeks (erythromycin for children). Currently the treatment of choice is a single administration of azithromycin (Zitromax®), which greatly simplifies treatment. At present WHO recommends annual mass azithromycin treatment for 3 years in communities in which the prevalence of "trachomatous inflammation – follicular" in children between 1 and 9 years of age is 10% or more. However the presence of clinical trachomatous follicular inflammation disappears more slowly than the implied by PCR results of conjunctival swabs. Further field-based study of estimating the prevalence of active infection is needed. Deformities of the eyelid, such as entropion or trichiasis have to be treated surgically. Reinfection can occur and further treatment forms part of a control programme.

Inclusion conjunctivitis (serotype D-K), a sexually transmitted disease has to be treated in the child and the mother as well as her sexual partners. It is important to make people aware of the fact that removing eyelashes which face inwards may bring some temporary relief, but that it can make the situation worse. The eyelashes grow back and the short stubby hairs scratch the cornea resulting in still more damage.

Trachoma is disappearing in many parts of the World even in the absence of specific control programs, probably due to the high background of antimicrobial drug use for other reasons.

LAST UPDATED BY ADMIN ON JULY 14TH, 2022