

Endemic Treponematoses and Leptospirosis

Chapter 188 & 189 | Part 5: Infectious Diseases | Part 5 – Infectious Diseases: Bacterial | DETAILED EDITION

KEY CLINICAL POINTS

1. Endemic treponematoses (yaws, bejel, pinta) are caused by *Treponema pallidum* subspecies (*T. pertenuis*, *T. endemicum*, *T. carateum*) and are distinct from venereal syphilis (*T. pallidum* subsp. *T. pallidum*) by transmission mode and clinical features.
2. Yaws is the most common endemic treponematosis, found in moist tropical areas; eradication programs have reduced prevalence but resurgence is documented in Africa and Pacific Islands.
3. Bejel (endemic syphilis) is found in arid climates of West Africa and the Middle East; transmission is via mouth-to-mouth or shared utensils.
4. Pinta is the most benign, characterized by dyschromic macules (pigmented lesions) without destructive lesions; found in Central America and northern South America.
5. Leptospirosis is a zoonotic disease caused by pathogenic *Leptospira* species, with rodents as the primary reservoir; transmission occurs via contact with urine-contaminated water or soil.
6. Severe leptospirosis (Weil's syndrome) presents with the triad of jaundice, renal dysfunction, and hemorrhagic diathesis; pulmonary hemorrhage is a critical complication.
7. Diagnosis of endemic treponematoses relies on clinical manifestations and serology (same as syphilis); NAAT can identify the specific agent.
8. Treatment for yaws involves azithromycin (30 mg/kg) or benzathine penicillin G; macrolide resistance is emerging.
9. Leptospirosis treatment includes doxycycline, penicillin, or azithromycin; severe cases require supportive care and management of organ failure.
10. Conjunctival suffusion (redness without exudate) is a characteristic finding in leptospirosis; 'crab yaws' (painful papillomatous lesions on soles) is a hallmark of yaws.

FIGURES IN THIS CHAPTER

1. Transmission electron microscopic image of *Leptospira*...
2. Geographic distribution of yaws in 2022
3. Differentiation of pathogenic, intermediate, and nonpathogenic...
4. Clinical manifestations of early yaws
5. Severe pulmonary hemorrhage in leptospirosis
6. Clinical manifestations of bejel and pinta

1. DEFINITION & OVERVIEW

- The endemic treponematoses are chronic diseases that are generally transmitted by direct contact, usually during childhood, and can cause severe late manifestations years after initial infection.
- These diseases are caused by spirochete bacteria closely related to *Treponema pallidum* subspecies *pallidum*, the etiologic agent of syphilis.
- Yaws, pinta, and bejel (endemic syphilis) have traditionally been distinguished from venereal syphilis by mode of transmission, age of acquisition, geographic distribution, and clinical features; however, there is overlap for each of these factors.
- Most of the knowledge about these infections is based on observations by health care workers who have visited endemic areas during the past 70 years.
- Except for ongoing mass drug administration (MDA) programs for yaws eradication promoted by the World Health Organization (WHO), virtually no well-designed studies of the natural history, diagnosis, or treatment of these infections have been conducted.
- The four classically defined treponemal infections are compared in Table 188-1.
- Leptospirosis is a globally important zoonotic disease whose apparent reemergence is illustrated by recent outbreaks on virtually all continents.
- The disease is caused by pathogenic *Leptospira* species and is characterized by a broad spectrum of clinical manifestations, varying from asymptomatic infection to fulminant, fatal disease.
- In its mild form, leptospirosis may present as nonspecific symptoms such as fever, headache, and myalgia.
- Severe leptospirosis, characterized by the triad of jaundice, renal dysfunction, and hemorrhagic diathesis, is often referred to as Weil's syndrome.
- With or without jaundice, severe pulmonary hemorrhage is increasingly recognized as an important presentation of severe disease.

Table 1 TABLE 188-1 Classic Comparison of the Agents of the Human Treponematoses and Their Associated Diseases

| FEATURE | SYPHILIS | YAWS | BEJEL (ENDEMIC SYPHILIS) | PINTA |
|------------------------------|---|---|--|--|
| Organism | <i>T. pallidum</i> subsp. <i>pallidum</i> | <i>T. pallidum</i> subsp. <i>pertenue</i> | <i>T. pallidum</i> subsp. <i>endemicum</i> | <i>T. carateum</i> |
| Common modes of transmission | Sexual, transplacental, skin-to-skin | Skin-to-skin | Mouth-to-mouth or via shared drinking/eating utensils, skin to skin, sexuala | |
| Usual age of acquisition | Sexual maturity or in utero | Childhood | Early childhood, adulthood | Late childhood |
| Primary lesion | Mucocutaneous ulcer (chancre) | Papilloma, often ulcerative | Mucosal papule, rarely seen | Nonulcerating papule with satellites, pruritic |
| Common location | Genital, oral, anal | Extremities | Oral, occasionally sexuala | Extremities, face |

| FEATURE | SYPHILIS | YAWS | BEJEL (ENDEMIC SYPHILIS) | PINTA |
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| Secondary lesions | Cutaneous rash and mucosal lesions; condylomata lata, ocular and otic syphilis | Cutaneous papillomatous or ulcerative lesions; condylomata lata, osteoperiostitis | Mucocutaneous lesions (mucous patch, split papule, condylomata lata); osteoperiostitis | Pintides, pigmented, pruritic |
| Infectious relapses | ~25% | Common | Unknown | Unknown |
| Late complications | Gummas, cardiovascular and central nervous system involvement | Destructive gummas of skin, bone, cartilage | Destructive gummas of skin, bone, cartilage | Nondestructive, dyschromic, achromic macules |

1.1 Classification of Treponematoses

- The four classically defined treponemal infections are: Syphilis, Yaws, Bejel (Endemic Syphilis), and Pinta.
- These are modified by current knowledge and compared in Table 188-1.
- The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment.
- Repeat CSF examinations may be performed every 6 months until the cell count is normal.
- An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients.
- The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure.
- Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years.
- In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective ART.
- Thus, multiple follow-up CSF examinations may not be necessary in patients treated for neurosyphilis in whom serologic titers are falling appropriately.

1.2 Classification of Leptospirosis

- Pathogenic *Leptospira** species are divided into serovars according to their antigenic composition.
- There are more than 260 known pathogenic serovars, which are arranged in 26 serogroups.
- Leptospire are coiled, thin, highly motile organisms that have hooked ends and two periplasmic flagella, with polar extrusions from the cytoplasmic membrane that are responsible for motility.
- These organisms are 6–20 μm long and ~0.1 μm in diameter; they stain poorly but can be seen microscopically by dark-field examination and after silver impregnation staining of tissues.
- Leptospire require special media and conditions for growth; it may take weeks to months for cultures to become positive.

2. EPIDEMIOLOGY

- Generally, yaws flourishes in moist tropical areas (Fig. 188-1); bejel has been found primarily in arid climates of West Africa and the Middle East; and pinta has been found in temperate foci in the Americas.

- Because of the ongoing yaws eradication programs, some survey data are available for that disease, but no epidemiologic data are available for bejel and pinta, aside from sparse case reports.
- Thus, the current extent of these infections is unknown.
- The endemic treponematoses have traditionally been limited to rural areas of developing nations and have been seen in developed countries primarily among recent immigrants from endemic regions.
- In a WHO-sponsored mass eradication campaign from 1952 to 1969, >160 million people in Africa, Asia, and South America were examined for treponemal infections, and >50 million cases, contacts, and persons with latent infections were treated.
- This campaign reduced the prevalence of active yaws from >20% to <1% in many areas.
- In subsequent decades, lack of focused surveillance and diversion of resources resulted in the documented resurgence of these infections in some regions.
- Of nearly 100 countries previously endemic for yaws, there are 16 countries with reported yaws cases during 2017–2022, and 3 others with suspected cases; there are no data for the remaining countries.
- In 2022, a total of 168,239 suspected cases were reported, primarily from Papua New Guinea, Côte d'Ivoire, Ghana, and Solomon Islands, all countries in which focused or integrated yaws detection programs and treatment trials are ongoing.
- Other areas of resurgent yaws morbidity in Africa include Cameroon, Togo, Benin, Central African Republic, Nigeria, Congo, Liberia, and Democratic Republic of the Congo.
- In Asia and the Pacific Islands, reports document active cases of yaws in Papua New Guinea, the Solomon Islands, Timor Leste, Vanuatu, the Philippines, and Indonesia.
- After years of focused programs, India was declared yaws-free in 2016.
- In the Americas, suspected yaws cases have been reported in Haiti, Colombia, and Ecuador, with no recent data for Peru, Brazil, Guyana, Suriname, and many Caribbean islands.
- The prevalence of bejel is estimated to be >10% in some regions of northern Ghana, Mali, Niger, Burkina Faso, and Senegal, although data are scarce.
- No data are available from formerly endemic regions of the Middle East.
- Recent molecular studies, however, have reported genital lesions caused by *T. pallidum* subspecies *endemicum* in persons from Cuba and Japan, and in a person with sexual contact in Pakistan.
- Pinta is thought to be limited to Central America and northern South America, where it is found rarely and only in very remote villages.
- The WHO lists 15 countries in Latin America where pinta was previously endemic; however, due to the lack of surveillance, the current prevalence of pinta is unknown.
- In the early 1980s, clinical evidence of pinta was discovered in 20% of the examined inhabitants of a remote village in Panama.
- In 1987 and 1993, pinta cases were reported from indigenous populations living in the Amazon border region of Brazil, Colombia, and Peru.
- More recently, in 1999, an active pinta lesion was identified in a Cuban tourist visiting Austria, and in 2021, a case of pinta was confirmed in southern Brazil.
- It is likely, therefore, that pinta is still endemic in some remote areas of Latin America.
- It is important to note the vast majority of the data described for the endemic treponematoses are reported as 'suspected cases' that are based on clinical diagnosis of ulcers and are not confirmed.
- Serologic confirmation is only occasionally available, and even reactive treponemal serologies may reflect past or latent treponemal infection that is unrelated to the etiology of the ulcer.
- Molecular studies of lesion swabs from Papua New Guinea indicate that ~30% of suspected yaws lesions contain *T. pallidum* DNA; most of these had *T. pallidum* DNA detected alone, while some contained both *T. pallidum* and *Haemophilus ducreyi* DNA (dual infection).

- Approximately 50% of lesions contained DNA of neither of these pathogens identified, *Streptococcus pyogenes* was the most abundant organism detected in a metagenomic analysis.
- Both *H. ducreyi* and *S. pyogenes* have been shown to be common skin and environmental contaminants in yaws-endemic areas but may also serve as primary pathogens or secondary infections.
- Thus, the accuracy of the diagnosis in 'yaws cases' reported to WHO is unclear.
- Evidence of yaws-like and genital lesions, with treponemal seroreactivity, has been found in several species of wild nonhuman primates (NHP) in sub-Saharan Africa, providing evidence that there is an animal reservoir for yaws treponemes.
- At the genomic level, these organisms are virtually identical to known human *T. pallidum* subspecies *pertenue* isolates.
- Although direct NHP-human transmission has not yet been confirmed, this finding likely has important implications for yaws eradication efforts.
- Leptospirosis has a worldwide distribution.
- Infection occurs most commonly in the tropics and subtropics because the climate and occasionally poor hygienic conditions favor the pathogen's survival and distribution.
- In most countries, leptospirosis is an underappreciated problem.
- Most cases occur in men, with a peak incidence during the summer and fall in both the Northern and Southern Hemispheres and during the rainy season in the tropics.
- Reliable data on morbidity and mortality from leptospirosis have gradually started to appear.
- Current information on global human leptospirosis varies but indicates that ~1 million severe cases occur per year, with a mean case–fatality rate of nearly 10%.
- As a zoonosis, leptospirosis affects almost all mammalian species and represents a significant veterinary burden.
- Rodents, especially rats, are the most important reservoir, although other wild mammals as well as domestic and farm animals may also harbor these microorganisms.
- Leptospire establish a symbiotic relationship with their host and can persist in the urogenital tract for years.
- Some serovars are generally associated with specific animals—e.g., *Icterohaemorrhagiae* and *Copenhageni* with rats, *Grippityphosa* with voles, *Hardjo* with cattle, *Canicola* with dogs, and *Pomona* with pigs—but may occur in other animals as well.
- Leptospirosis presents as both an endemic and an epidemic disease.
- Transmission of leptospire may follow direct contact with urine, blood, or tissue from an infected animal or, more commonly, exposure to environmental contamination.
- The dogma that human-to-human transmission is very rare is challenged by recent findings on household clustering, asymptomatic renal colonization, and prolonged excretion of leptospire.
- Both of the latter features could imply human infection sources that are not recognized.
- Because leptospire can survive in a humid environment for many months, water is an important vehicle in their transmission.
- Epidemics of leptospirosis are not well understood.
- Outbreaks may result from exposure to floodwaters contaminated by urine from infected animals, as has been reported from several countries.
- However, it is also true that outbreaks may occur without floods, and floods often occur without outbreaks.
- The vast majority of infections with *Leptospira* cause no or only mild disease in humans.
- A small percentage of infections (~1%) lead to severe, potentially fatal complications.

- The proportion of leptospirosis cases that are mild is unknown because patients either do not seek or do not have access to medical care or because the nonspecific symptoms are interpreted as an influenza-like illness.
- Reported cases surely represent a significant underestimation of the total number.
- Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry.
- Risk factors include direct or indirect contact with animals, including exposure to water and soil contaminated with animal urine.
- Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding.

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3. ETIOLOGY & PATHOPHYSIOLOGY

- The etiologic agents of the endemic treponematoses are listed in Table 188-1.
- These little-studied organisms are morphologically identical to *T. pallidum* subspecies *pallidum* (the agent of syphilis), and no definitive antigenic differences among them have been identified to date.
- A controversy has existed for decades about whether the pathogenic treponemes are truly separate organisms or represent a genetic continuum.
- Current genome sequencing indicates that, although yaws, bejel, and syphilis isolates clearly cluster in separate branches of phylogenetic trees, these organisms are 99.8% identical at the genomic level, and several studies support the ability of these pathogens to exchange DNA between subspecies.
- Genomic studies of many more isolates from different geographic regions are needed to further understand the genomic relationship among the pathogenic treponemes to better inform nomenclature decisions.
- Currently, three of the four etiologic agents are classified as subspecies of *T. pallidum*; the fourth (*T. carateum*) remains a separate species simply because no pinta organisms have been available for genetic studies.
- Based on analysis of a limited number of strains and clinical samples available for genetic studies, molecular signatures that can differentiate the known strains of *T. pallidum* subspecies have been identified using approaches ranging from restriction fragment length polymorphism to whole genome sequencing.
- No obvious genetic polymorphisms have been identified that might be related to any distinct clinical characteristic of these diseases.
- The rate of development of acquired resistance to *T. pallidum* after natural or experimental infection depends on both the size of the infecting inoculum and the duration of infection before treatment.
- Both humoral and cellular responses are important in the healing of early lesions.
- Cellular infiltration, predominantly by T lymphocytes and macrophages, produces an interferon γ -dominated cytokine milieu and results in the clearance of organisms by activated macrophages.

- Specific antibodies to surface antigens enhance phagocytosis.
- Antigenic variation of the *TprK* protein contributes to development of subsequent stages of syphilis, persistence of infection, and susceptibility to reinfection with another strain.
- Comparative genomic studies have revealed genes with sequence variations among *T. pallidum* strains, leading to development of molecular typing methods used to examine syphilis outbreaks.
- Several laboratories are actively working to develop effective vaccines that stimulate the relevant protective immunologic functions to attenuate or prevent lesion development and reduce dissemination of *T. pallidum* to distant anatomic sites.
- Leptospire are coiled, thin, highly motile organisms that have hooked ends and two periplasmic flagella, with polar extrusions from the cytoplasmic membrane that are responsible for motility.
- These organisms are 6–20 µm long and ~0.1 µm in diameter; they stain poorly but can be seen microscopically by dark-field examination and after silver impregnation staining of tissues.
- Leptospire require special media and conditions for growth; it may take weeks to months for cultures to become positive.
- Pathogenic *Leptospira* contain a variety of genes coding for proteins involved in motility and in cell and tissue adhesion and invasion that represent (potential) virulence factors.
- Many of these are surface proteins.
- Pathogenic *Leptospira* species are divided into serovars according to their antigenic composition.
- There are more than 260 known pathogenic serovars, which are arranged in 26 serogroups.
- The peptidoglycan layer is located close to the cytoplasmic membrane.
- The lipopolysaccharide (LPS) in the outer membrane has an unusual structure with relatively low endotoxic potency.
- However, host immunity depends on the production of circulating antibodies to serovar-specific LPS.
- It is unclear whether other antigens play a significant role in protective humoral immunity.
- Transmission occurs through cuts, abraded skin, or mucous membranes, especially the conjunctival and oral mucosa.
- After entry, the highly motile organisms proliferate, cross tissue barriers, and disseminate hematogenously to all organs (leptospiremic phase).
- During this initial incubation period, leptospire can be isolated from the bloodstream.
- Clearly, *Leptospira* can survive in the non-immune host by evading parts of the innate immune response such as complement-mediated killing and phagocytosis.
- However, earlier studies have highlighted the relation between an exaggerated proinflammatory immune response and mortality.
- During the immune phase, the appearance of antibodies coincides with the disappearance of leptospire from the blood.
- However, the bacteria persist in various organs, including liver, lung, kidney, heart, and brain.
- Autopsy findings illustrate the involvement of multiple organ systems in severe disease.
- Renal pathology shows both acute tubular damage and interstitial nephritis.
- Acute tubular lesions progress in time to interstitial edema and acute tubular necrosis.
- Severe nephritis is observed in patients who survive long enough to develop it and seems to be a secondary response to acute epithelial damage.
- The reported deregulation of the expression of several transporters along the nephron contributes to impaired sodium absorption, tubular potassium wasting, and polyuria.
- Histopathology of the liver shows focal necrosis (widespread hepatocellular necrosis is usually not found), foci of inflammation, and plugging of bile canaliculi.

- Hepatocyte apoptosis has also been documented.
- Experimental work showed infiltration of *Leptospira* in Disse space (perisinusoidal space) and migration between hepatocytes with detachment of the intercellular junctions and disruption of bile canaliculi leading to bile leakage.
- Petechiae and hemorrhages are observed in the heart, lungs (Fig. 189-4), kidneys (and adrenals), pancreas, liver, gastrointestinal tract (including retroperitoneal fat, mesentery, and omentum), muscles, prostate, testes, and brain (subarachnoid bleeding).
- Several studies show an association between hemorrhage and thrombocytopenia.
- Although the underlying mechanisms of thrombocytopenia have not been elucidated, it seems likely that platelet consumption plays an important role.
- A consumptive coagulopathy may occur, with elevated markers of coagulation activation (thrombin–antithrombin complexes, prothrombin fragments 1 and 2, D-dimer), diminished anticoagulant markers (antithrombin, protein C), and deregulated fibrinolytic activity.
- Overt disseminated intravascular coagulation (DIC) has been documented in several clinical studies.
- Elevated plasma levels of soluble E-selectin and von Willebrand factor in patients with leptospirosis reflect endothelial cell activation.
- More specifically, markers of endothelial cell activation correlate to disease severity in patients with severe leptospirosis.
- Experimental models show that pathogenic leptospires or leptospiral proteins are able to activate endothelial cells in vitro and to disrupt endothelial-cell barrier function, thus increasing permeability and promoting dissemination.
- Platelets have been shown to aggregate on activated endothelium in the human lung, whereas histology reveals swelling of activated endothelial cells but no evident vasculitis or necrosis.
- Immunoglobulin and complement deposition have been demonstrated in lung tissue involved in pulmonary hemorrhage.

3.1 Treponemal Pathogenesis

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4. CLINICAL FEATURES

- All of the treponemal infections, including syphilis, are chronic and are characterized by defined disease stages, with a localized primary lesion, disseminated secondary lesions, periods of latency, and possible late lesions.
- Primary and secondary stages are more frequently overlapping in yaws and bejel than in syphilis, and the late manifestations of pinta are very mild relative to the destructive lesions of the other treponematoses.
- The current preference is to divide the clinical course of the endemic treponematoses into 'early' and 'late' stages, and this terminology is increasingly used for syphilis as well.
- Yaws Also known as pian, framboesia, or bouba, yaws is characterized by the development of one or several primary lesions ('mother yaw') followed by multiple disseminated skin lesions.
- All early skin lesions are infectious and may persist for many months; cutaneous relapses are common during the first 5 years.
- Late manifestations, affecting ~10% of untreated persons, are destructive lesions of skin, bone, and joints.
- The infection is transmitted by direct contact with infectious lesions, often during play or group sleeping, and may be enhanced by disruption of the skin by insect bites or abrasions.
- While *T. pallidum* subspecies *pertenue* DNA has been detected on flies and fomites from endemic regions, there is not yet convincing evidence of insect or fomite transmission of infection.
- After an average of 3–4 weeks, the first lesion begins as a papule—usually on an extremity—and then enlarges (particularly during moist warm weather) to become ulcerated (Fig 188-2A) or papillomatous ('raspberry-like'—thus the name 'framboesia').
- Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks of infection.
- A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or after the primary lesion, and may take several forms—macular, papular, or papillomatous (Fig. 188-2B).
- Painful papillomatous lesions on the soles of the feet result in a crablike gait ('crab yaws'), and periostitis (Fig. 188-2C) may result in nocturnal bone pain and polydactylitis (Fig. 188-2D).
- Late yaws is manifested by gummas of the skin and long bones, hyperkeratoses of the palms and soles, osteitis and periostitis, and hydrarthrosis.
- The late gummatous lesions are characteristically extensive.
- Destruction of the nose, maxilla, palate, and pharynx is termed gangosa and is similar to the destructive lesions seen in leprosy and leishmaniasis.

- The early lesions of bejel (endemic syphilis, siti, dichuchwa, njovera, skerljevo) are usually localized to mucocutaneous and mucosal surfaces.
- The infection is reportedly transmitted by direct contact, by kissing, by pre-mastication of food, or by sharing of drinking and eating utensils.
- Recently, however, *T. pallidum* subspecies *endemicum* has been identified in genital lesions (clinically diagnosed as primary syphilitic chancres) and in secondary lesions in several settings, suggesting sexual transmission.
- The initial lesion, usually an intraoral papule, may go unrecognized and is followed by mucous patches on the oral mucosa (Fig. 188-3A) and mucocutaneous lesions resembling the condylomata lata of secondary syphilis.
- This eruption may last for months or even years, and treponemes can readily be demonstrated in early lesions.
- Periostitis and regional lymphadenopathy are common.
- After a variable period of latency, late manifestations may appear, including osseous and cutaneous gummas.
- Destructive gummas, osteitis, and gangosa are more common in bejel than in yaws.
- Pinta (mal del pinto, carate, azul, purupuru) is the most benign of the treponemal infections.
- This disease has three stages that are characterized by marked changes in skin color (Fig. 188-3B), but pinta does not appear to cause destructive lesions or to involve tissues other than the skin.
- The initial papule is most often located on the extremities or face and is pruritic.
- After 1 to many months of infection, numerous disseminated secondary lesions (pintides) appear.
- These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue.
- The secondary lesions are infectious and highly pruritic and may persist for years.
- Late pigmented lesions are called dyschromic macules and contain treponemes.
- Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance.
- White achromic lesions are characteristic of the late stage.
- Leptospirosis is classically described as biphasic.
- The acute leptospiremic phase is characterized by fever of 3–10 days' duration, during which time the organism can be cultured from blood and detected by polymerase chain reaction (PCR).
- During the immune phase, resolution of symptoms may coincide with the appearance of antibodies, and leptospire can be cultured from the urine.
- The distinction between the first and second phases is not always clear: milder cases do not always include the second phase, and severe disease may be monophasic and fulminant.
- The idea that distinct clinical syndromes are associated with specific serogroups has been refuted, although some serovars tend to cause more severe disease than others.
- Mild Leptospirosis Most patients are asymptomatic or only mildly ill and do not seek medical attention.
- Serologic evidence of past inapparent infection is frequently found in persons who have been exposed but have not become ill.
- Mild symptomatic leptospirosis usually presents as a flulike illness of sudden onset, with fever, chills, headache, nausea, vomiting, abdominal pain, conjunctival suffusion (redness without exudate), and myalgia.
- Muscle pain is intense and especially affects the calves, back, and abdomen.
- The headache is intense, localized to the frontal or retroorbital region (resembling that occurring in dengue), and sometimes accompanied by photophobia.
- Aseptic meningitis may be present and is more common among children than among adults.

- Although *Leptospira* can be cultured from the cerebrospinal fluid (CSF) in the early phase, the majority of cases follow a benign course with regard to the central nervous system; symptoms disappear within a few days but may persist for weeks.
- Physical examination may include any of the following findings, none of which is pathognomonic for leptospirosis: fever, conjunctival suffusion, pharyngeal injection, muscle tenderness, lymphadenopathy, rash, meningismus, hepatomegaly, and splenomegaly.
- If present, the rash is often transient; may be macular, maculopapular, erythematous, or hemorrhagic (petechial or ecchymotic); and may be misdiagnosed as due to scrub typhus or viral infection.
- Lung auscultation may reveal crackles.
- Mild jaundice may be present.
- The natural course of mild leptospirosis usually involves spontaneous resolution within 7–10 days, but persistent symptoms have been documented.
- In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low.
- Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%.
- Higher mortality rates are associated with an age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.
- The classic presentation, often referred to as Weil's syndrome, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.
- The natural course of mild leptospirosis usually involves spontaneous resolution within 7–10 days, but persistent symptoms have been documented.
- In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low.

4.1 Yaws Clinical Features

- Yaws is characterized by the development of one or several primary lesions ('mother yaw') followed by multiple disseminated skin lesions.
- All early skin lesions are infectious and may persist for many months; cutaneous relapses are common during the first 5 years.
- Late manifestations, affecting ~10% of untreated persons, are destructive lesions of skin, bone, and joints.
- The infection is transmitted by direct contact with infectious lesions, often during play or group sleeping, and may be enhanced by disruption of the skin by insect bites or abrasions.
- While *T. pallidum* subspecies *pertenue* DNA has been detected on flies and fomites from endemic regions, there is not yet convincing evidence of insect or fomite transmission of infection.
- After an average of 3–4 weeks, the first lesion begins as a papule—usually on an extremity—and then enlarges (particularly during moist warm weather) to become ulcerated (Fig 188-2A) or papillomatous ('raspberry-like'—thus the name 'framboesia').
- Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks of infection.
- A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or after the primary lesion, and may take several forms—macular, papular, or papillomatous (Fig. 188-2B).
- Painful papillomatous lesions on the soles of the feet result in a crablike gait ('crab yaws'), and periostitis (Fig. 188-2C) may result in nocturnal bone pain and polydactylitis (Fig. 188-2D).

- Late yaws is manifested by gummas of the skin and long bones, hyperkeratoses of the palms and soles, osteitis and periostitis, and hydrarthrosis.
- The late gummatous lesions are characteristically extensive.
- Destruction of the nose, maxilla, palate, and pharynx is termed gangosa and is similar to the destructive lesions seen in leprosy and leishmaniasis.

4.2 Bejel Clinical Features

- The early lesions of bejel (endemic syphilis, siti, dichuchwa, njovera, skerljevo) are usually localized to mucocutaneous and mucosal surfaces.
- The infection is reportedly transmitted by direct contact, by kissing, by premastication of food, or by sharing of drinking and eating utensils.
- Recently, however, *T. pallidum* subspecies *endemicum* has been identified in genital lesions (clinically diagnosed as primary syphilitic chancres) and in secondary lesions in several settings, suggesting sexual transmission.
- The initial lesion, usually an intraoral papule, may go unrecognized and is followed by mucous patches on the oral mucosa (Fig. 188-3A) and mucocutaneous lesions resembling the condylomata lata of secondary syphilis.
- This eruption may last for months or even years, and treponemes can readily be demonstrated in early lesions.
- Periostitis and regional lymphadenopathy are common.
- After a variable period of latency, late manifestations may appear, including osseous and cutaneous gummas.
- Destructive gummas, osteitis, and gangosa are more common in bejel than in yaws.

4.3 Pinta Clinical Features

- Pinta (mal del pinto, carate, azul, purupuru) is the most benign of the treponemal infections.
- This disease has three stages that are characterized by marked changes in skin color (Fig. 188-3B), but pinta does not appear to cause destructive lesions or to involve tissues other than the skin.
- The initial papule is most often located on the extremities or face and is pruritic.
- After 1 to many months of infection, numerous disseminated secondary lesions (pintides) appear.
- These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue.
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- Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance.
- White achromic lesions are characteristic of the late stage.

4.4 Leptospirosis Clinical Features

- Leptospirosis is classically described as biphasic.
- The acute leptospiremic phase is characterized by fever of 3–10 days' duration, during which time the organism can be cultured from blood and detected by polymerase chain reaction (PCR).
- During the immune phase, resolution of symptoms may coincide with the appearance of antibodies, and leptospire can be cultured from the urine.
- The distinction between the first and second phases is not always clear: milder cases do not always include the second phase, and severe disease may be monophasic and fulminant.

- The idea that distinct clinical syndromes are associated with specific serogroups has been refuted, although some serovars tend to cause more severe disease than others.
- Mild Leptospirosis Most patients are asymptomatic or only mildly ill and do not seek medical attention.
- Serologic evidence of past inapparent infection is frequently found in persons who have been exposed but have not become ill.
- Mild symptomatic leptospirosis usually presents as a flulike illness of sudden onset, with fever, chills, headache, nausea, vomiting, abdominal pain, conjunctival suffusion (redness without exudate), and myalgia.
- Muscle pain is intense and especially affects the calves, back, and abdomen.
- The headache is intense, localized to the frontal or retroorbital region (resembling that occurring in dengue), and sometimes accompanied by photophobia.
- Aseptic meningitis may be present and is more common among children than among adults.
- Although *Leptospira* can be cultured from the cerebrospinal fluid (CSF) in the early phase, the majority of cases follow a benign course with regard to the central nervous system; symptoms disappear within a few days but may persist for weeks.
- Physical examination may include any of the following findings, none of which is pathognomonic for leptospirosis: fever, conjunctival suffusion, pharyngeal injection, muscle tenderness, lymphadenopathy, rash, meningismus, hepatomegaly, and splenomegaly.
- If present, the rash is often transient; may be macular, maculopapular, erythematous, or hemorrhagic (petechial or ecchymotic); and may be misdiagnosed as due to scrub typhus or viral infection.
- Lung auscultation may reveal crackles.
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- The natural course of mild leptospirosis usually involves spontaneous resolution within 7–10 days, but persistent symptoms have been documented.
- In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low.
- Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%.
- Higher mortality rates are associated with an age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.
- The classic presentation, often referred to as Weil's syndrome, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.

5. DIFFERENTIAL DIAGNOSIS

- The endemic treponematoses should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.
- Sensitive nucleic acid amplification–based assays can be used to confirm treponemal infection and to identify the etiologic agent in research and selected clinical laboratories.
- Diagnosis of the endemic treponematoses is based on clinical manifestations and, when available, dark-field microscopy and serologic testing.
- The same serologic tests—detecting antibodies to either lipoidal or treponemal antigens—that are used for syphilis (Chap. 187) become reactive during all treponemal infections.
- To date there is no antibody test that can discriminate among the treponemal infections.
- The non-syphilis treponemal infections should also be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.

- Mild leptospirosis may be misdiagnosed as due to scrub typhus or viral infection.
- The rash in leptospirosis may be misdiagnosed as due to scrub typhus or viral infection.
- Lung auscultation may reveal crackles, which may be confused with other causes of pulmonary hemorrhage.
- Conjunctival suffusion (redness without exudate) is a characteristic finding in leptospirosis that may be confused with other causes of conjunctival injection.

5.1 Treponemal Differential Diagnosis

- The endemic treponematoses should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.
- Sensitive nucleic acid amplification–based assays can be used to confirm treponemal infection and to identify the etiologic agent in research and selected clinical laboratories.
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5.2 Leptospirosis Differential Diagnosis

- Mild leptospirosis may be misdiagnosed as due to scrub typhus or viral infection.
- The rash in leptospirosis may be misdiagnosed as due to scrub typhus or viral infection.
- Lung auscultation may reveal crackles, which may be confused with other causes of pulmonary hemorrhage.
- Conjunctival suffusion (redness without exudate) is a characteristic finding in leptospirosis that may be confused with other causes of conjunctival injection.

6. INVESTIGATIONS & DIAGNOSIS

- Diagnosis of the endemic treponematoses is based on clinical manifestations and, when available, dark-field microscopy and serologic testing.
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- Sensitive nucleic acid amplification–based assays can be used to confirm treponemal infection and to identify the etiologic agent in research and selected clinical laboratories.
- The endemic treponematoses should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.
- The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment.
- Repeat CSF examinations may be performed every 6 months until the cell count is normal.
- An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients.
- The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure.
- Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years.

- In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective ART.
- Thus, multiple follow-up CSF examinations may not be necessary in patients treated for neurosyphilis in whom serologic titers are falling appropriately.
- Leptospirosis diagnosis relies on serology, PCR, and culture.
- Specimens 1 and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup.
- CSF, cerebrospinal fluid.
- Culture/PCR Urine.
- Serology 1 2 3 4 5.
- Phases Leptospiremia Leptospiruria and immunity.

Table 2 TABLE 188-1 Classic Comparison of the Agents of the Human Treponematoses and Their Associated Diseases

| FEATURE | SYPHILIS | YAWS | BEJEL (ENDEMIC SYPHILIS) | PINTA |
|------------------------------|--|---|--|--|
| Organism | <i>T. pallidum</i> subsp. <i>pallidum</i> | <i>T. pallidum</i> subsp. <i>pertenue</i> | <i>T. pallidum</i> subsp. <i>endemicum</i> | <i>T. carateum</i> |
| Common modes of transmission | Sexual, transplacental, skin-to-skin | Skin-to-skin | Mouth-to-mouth or via shared drinking/eating utensils, skin to skin, sexuala | |
| Usual age of acquisition | Sexual maturity or in utero | Childhood | Early childhood, adulthood | Late childhood |
| Primary lesion | Mucocutaneous ulcer (chancre) | Papilloma, often ulcerative | Mucosal papule, rarely seen | Nonulcerating papule with satellites, pruritic |
| Common location | Genital, oral, anal | Extremities | Oral, occasionally sexuala | Extremities, face |
| Secondary lesions | Cutaneous rash and mucosal lesions; condylomata lata, ocular and otic syphilis | Cutaneous papillomatous or ulcerative lesions; condylomata lata, osteoperiostitis | Mucocutaneous lesions (mucous patch, split papule, condylomata lata); osteoperiostitis | Pintides, pigmented, pruritic |
| Infectious relapses | ~25% | Common | Unknown | Unknown |
| Late complications | Gummas, cardiovascular and central nervous system involvement | Destructive gummas of skin, bone, cartilageb | Destructive gummas of skin, bone, cartilageb | Nondestructive, dyschromic, achromic macules |

6.1 Treponemal Investigations

- Diagnosis of the endemic treponematoses is based on clinical manifestations and, when available, dark-field microscopy and serologic testing.
- The same serologic tests—detecting antibodies to either lipoidal or treponemal antigens—that are used for syphilis (Chap. 187) become reactive during all treponemal infections.
- To date there is no antibody test that can discriminate among the treponemal infections.
- Sensitive nucleic acid amplification–based assays can be used to confirm treponemal infection and to identify the etiologic agent in research and selected clinical laboratories.
- The endemic treponematoses should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area.
- The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment.
- Repeat CSF examinations may be performed every 6 months until the cell count is normal.
- An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients.
- The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure.
- Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years.
- In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective ART.
- Thus, multiple follow-up CSF examinations may not be necessary in patients treated for neurosyphilis in whom serologic titers are falling appropriately.

6.2 Leptospirosis Investigations

- Leptospirosis diagnosis relies on serology, PCR, and culture.
- Specimens 1 and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup.
- CSF, cerebrospinal fluid.
- Culture/PCR Urine.
- Serology 1 2 3 4 5.
- Phases Leptospiremia Leptospiruria and immunity.

7. MANAGEMENT & TREATMENT

- The current WHO-recommended therapy for patients and their contacts includes either azithromycin (30 mg/kg, up to a maximum of 2 g) or benzathine penicillin G (1.2 million units IM for adults; 600,000 units for children <10 years old); these two drugs have been shown to be equivalent for early yaws.
- The recommended dose of benzathine penicillin G is half of that recommended for early syphilis, yet no controlled efficacy studies have been conducted.
- Evidence of genetic resistance to penicillin is lacking, although relapsing lesions have been reported after penicillin treatment in Papua New Guinea.
- The efficacy of single-dose azithromycin provided the WHO's revitalized yaws eradication program with a much easier regimen for use in mass treatment.
- Macrolide resistance has become common in circulating strains of *T. pallidum* subspecies *pallidum* in many parts of the world (Chap. 187), and analyses of yaws samples from Papua New Guinea and

elsewhere have yielded evidence of mutations conferring resistance to macrolide antibiotics, including azithromycin.

- Although subsequent treatment with benzathine penicillin G was able to contain the spread of resistant organisms, such evidence suggests that there may be only a short window of time during which countries can successfully use azithromycin for yaws eradication.
- Antibiotic resistance is of particular concern because multiple rounds of MDA are likely to be required.
- Further, given the ongoing campaigns against trachoma using low-dose azithromycin MDA, often in populations also at high risk for yaws, more widespread macrolide resistance seems inevitable.
- Lastly, the possible animal reservoir needs to be evaluated, particularly in Africa.
- Yaws elimination will require rapid implementation and scale-up of high-level drug coverage in endemic areas, and continued careful surveillance by local health centers will be essential for success of this timely and important effort.
- Limited data suggest the efficacy of tetracycline for treatment of yaws, but no data exist for other endemic treponematoses.
- Based solely on experience with syphilis, it is likely that doxycycline, tetracycline (at doses appropriate for syphilis; Chap. 187), or ceftriaxone are alternatives, in addition to azithromycin, for patients allergic to penicillin.
- A Jarisch-Herxheimer reaction (Chap. 187) may follow treatment of endemic treponematoses.
- Lipoidal serologic titers (in the Venereal Disease Research Laboratory [VDRL] slide test or the rapid plasma reagin [RPR] test) usually decline after effective therapy, but patients may not become seronegative.
- Re-treatment should be considered if serologic responses are not adequate or if clinical signs persist or recur.
- The CSF may be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal.
- Patients treated for late latent syphilis frequently have low initial VDRL or RPR titers and may not have a fourfold decline after therapy with penicillin.
- In such patients, re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear.
- Because treponemal tests may remain reactive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.
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- Because treponemal tests may remain reactive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.
- Leptospirosis treatment includes doxycycline, penicillin, or azithromycin.
- Severe cases require supportive care and management of organ failure.

7.1 Treponemal Treatment

- The current WHO-recommended therapy for patients and their contacts includes either azithromycin (30 mg/kg, up to a maximum of 2 g) or benzathine penicillin G (1.2 million units IM for adults; 600,000 units for children <10 years old); these two drugs have been shown to be equivalent for early yaws.
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- In such patients, re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear.
- Because treponemal tests may remain reactive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.

7.2 Leptospirosis Treatment

- Leptospirosis treatment includes doxycycline, penicillin, or azithromycin.
- Severe cases require supportive care and management of organ failure.

8. PROGNOSIS & COMPLICATIONS

- Late manifestations, affecting ~10% of untreated persons, are destructive lesions of skin, bone, and joints.
- The late gummatous lesions are characteristically extensive.
- Destruction of the nose, maxilla, palate, and pharynx is termed gangosa and is similar to the destructive lesions seen in leprosy and leishmaniasis.
- Destructive gummas, osteitis, and gangosa are more common in bejel than in yaws.
- The natural course of mild leptospirosis usually involves spontaneous resolution within 7–10 days, but persistent symptoms have been documented.
- In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low.
- Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%.
- Higher mortality rates are associated with an age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.
- The classic presentation, often referred to as Weil's syndrome, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.

8.1 Treponemal Prognosis

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- Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%.
- Higher mortality rates are associated with an age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias.
- The classic presentation, often referred to as Weil's syndrome, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.

9. SPECIAL CONSIDERATIONS

- The endemic treponematoses have traditionally been limited to rural areas of developing nations and have been seen in developed countries primarily among recent immigrants from endemic regions.
- The WHO lists 15 countries in Latin America where pinta was previously endemic; however, due to the lack of surveillance, the current prevalence of pinta is unknown.
- In the Americas, suspected yaws cases have been reported in Haiti, Colombia, and Ecuador, with no recent data for Peru, Brazil, Guyana, Suriname, and many Caribbean islands.
- In the early 1980s, clinical evidence of pinta was discovered in 20% of the examined inhabitants of a remote village in Panama.
- In 1987 and 1993, pinta cases were reported from indigenous populations living in the Amazon border region of Brazil, Colombia, and Peru.
- More recently, in 1999, an active pinta lesion was identified in a Cuban tourist visiting Austria, and in 2021, a case of pinta was confirmed in southern Brazil.
- It is likely, therefore, that pinta is still endemic in some remote areas of Latin America.
- It is important to note the vast majority of the data described for the endemic treponematoses are reported as 'suspected cases' that are based on clinical diagnosis of ulcers and are not confirmed.
- Serologic confirmation is only occasionally available, and even reactive treponemal serologies may reflect past or latent treponemal infection that is unrelated to the etiology of the ulcer.
- Molecular studies of lesion swabs from Papua New Guinea indicate that ~30% of suspected yaws lesions contain *T. pallidum* DNA; most of these had *T. pallidum* DNA detected alone, while some contained both *T. pallidum* and *Haemophilus ducreyi* DNA (dual infection).
- Approximately 50% of lesions contained DNA of neither of these pathogens identified, *Streptococcus pyogenes* was the most abundant organism detected in a metagenomic analysis.
- Both *H. ducreyi* and *S. pyogenes* have been shown to be common skin and environmental contaminants in yaws-endemic areas but may also serve as primary pathogens or secondary infections.
- Thus, the accuracy of the diagnosis in 'yaws cases' reported to WHO is unclear.
- Evidence of yaws-like and genital lesions, with treponemal seroreactivity, has been found in several species of wild nonhuman primates (NHP) in sub-Saharan Africa, providing evidence that there is an

animal reservoir for yaws treponemes.

- At the genomic level, these organisms are virtually identical to known human *T. pallidum* subspecies *pertenue* isolates.
- Although direct NHP-human transmission has not yet been confirmed, this finding likely has important implications for yaws eradication efforts.
- Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding.
- Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry.
- Risk factors include direct or indirect contact with animals, including exposure to water and soil contaminated with animal urine.
- Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding.

9.1 Geographic Distribution

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- At the genomic level, these organisms are virtually identical to known human *T. pallidum* subspecies *pertenue* isolates.
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9.2 Occupational & Environmental Risk

- Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding.
- Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry.
- Risk factors include direct or indirect contact with animals, including exposure to water and soil contaminated with animal urine.
- Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding.

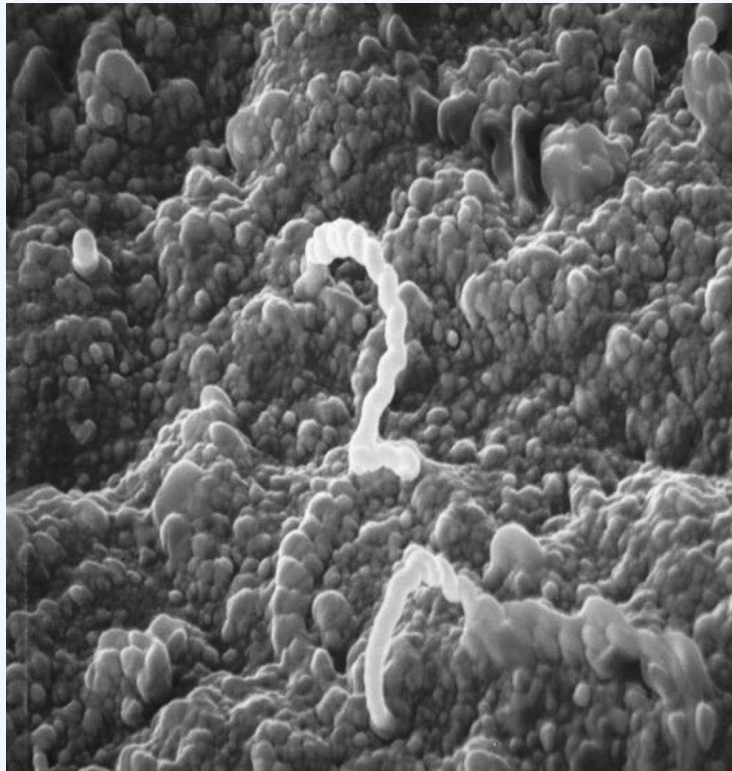
10. KEY PEARLS & CLINICAL TRAPS

- Endemic treponematoses are chronic diseases that are generally transmitted by direct contact, usually during childhood, and can cause severe late manifestations years after initial infection.
- Yaws is the most common endemic treponematoses, found in moist tropical areas; eradication programs have reduced prevalence but resurgence is documented in Africa and Pacific Islands.
- Bejel (endemic syphilis) is found in arid climates of West Africa and the Middle East; transmission is via mouth-to-mouth or shared utensils.
- Pinta is the most benign, characterized by dyschromic macules (pigmented lesions) without destructive lesions; found in Central America and northern South America.
- Leptospirosis is a zoonotic disease caused by pathogenic *Leptospira* species, with rodents as the primary reservoir; transmission occurs via contact with urine-contaminated water or soil.
- Severe leptospirosis (Weil's syndrome) presents with the triad of jaundice, renal dysfunction, and hemorrhagic diathesis; pulmonary hemorrhage is a critical complication.
- Diagnosis of endemic treponematoses relies on clinical manifestations and serology (same as syphilis); NAAT can identify the specific agent.
- Treatment for yaws involves azithromycin (30 mg/kg) or penicillin; macrolide resistance is emerging.
- Leptospirosis treatment includes doxycycline, penicillin, or azithromycin; severe cases require supportive care and management of organ failure.
- Conjunctival suffusion (redness without exudate) is a characteristic finding in leptospirosis; 'crab yaws' (painful papillomatous lesions on soles) is a hallmark of yaws.

10.1 Diagnostic Clues

- Conjunctival suffusion (redness without exudate) is a characteristic finding in leptospirosis.
- 'Crab yaws' (painful papillomatous lesions on soles) is a hallmark of yaws.
- Gangosa (destruction of the nose, maxilla, palate, and pharynx) is a characteristic finding in late yaws and bejel.
- The classic presentation of severe leptospirosis, often referred to as Weil's syndrome, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.

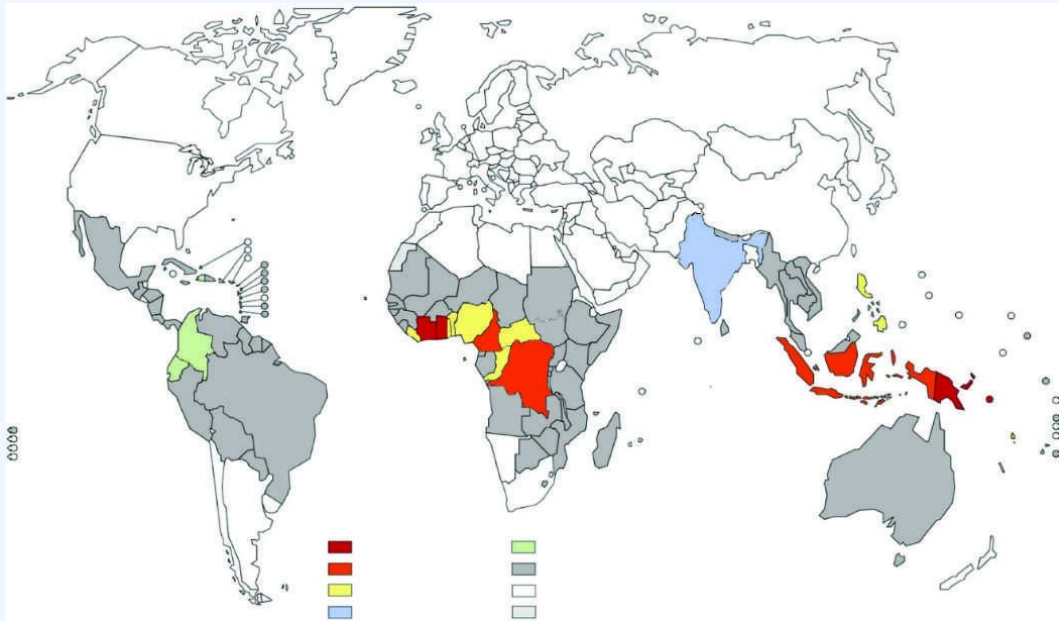
FIGURES & ILLUSTRATIONS — FROM HARRISON'S



0.3 μ m

Harrison's 22e · Figure 1

FIGURE 189-2 Transmission electron microscopic image of Leptospira interrogans several transporters along the nephron invading equine conjunctival tissue. (Image kindly provided by Dr. JE Nally, National absorption, tubular potassium wasting, Animal Disease Center, U.S. Department of Agriculture, Ames, IA.) of the liver shows focal necrosis is usually not found), foci of Recreational exposure and domestic-animal contact are prominent liculi. Hepatocyte apoptosis has also sources of leptospirosis. Recreational freshwater activities, such as work showed infiltration of Leptospira in canoeing, windsurfing, swimming, and waterskiing, place persons at space) and migration between risk for infection. Also, several out- breaks have followed sporting events. Approximate time scale Week 1 2 3 4 — FIGURE 188-1 Geographic distribution of yaws in 2022. Map showing countries with suspected cases, previously endemic countries, and non-endemic countries. (Reproduced with permission from World Health Organization.)



Harrison's 22e · Figure 2

FIGURE 188-1 Geographic distribution of yaws in 2022. (Reproduced with permission — FIGURE 188-2 Clinical manifestations of early yaws. A. Primary ulcer. B. Secondary papillomata. C. Periostitis. D. Polydactylitis. Photos taken during a yaws elimination trial in Papua New Guinea.

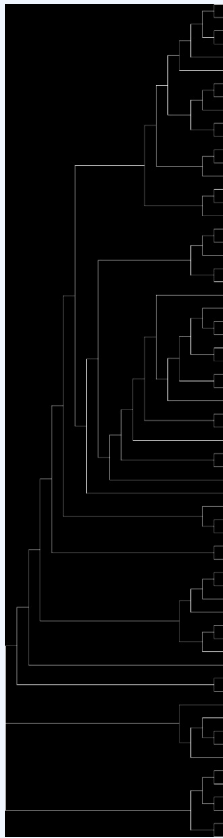


FIGURE 189-1 Differentiation of pathogenic, intermediate, and nonpathogenic (saprophytic) Leptospira species by molecular phylogenetic analysis using core genomes comparison (CgMLST). (Reproduced with permission from Dr. A Ahmed, Leptospirosis Reference Center, Academic Medical Center, Medical Microbiology, to Amsterdam, The Netherlands.) or workers in the fishing industry. Risk factors include direct or indirect contact with animals, including exposure to water and soil contami- — *FIGURE 188-3 Clinical manifestations of bejel and pinta. A. Mucous patches of early bejel. B. Pigmented macules of early pinta. Photos reprinted with permission from the Handbook of Endemic Treponematoses.*



*FIGURE 188-2 Clinical manifestations of early yaws. A. Primary ulcer. B. Secondary elimination trial in Papua New Guinea and are published with permission from Dr. Oriol — FIGURE 189-1 Differentiation of pathogenic, intermediate, and nonpathogenic (saprophytic) *Leptospira* species by molecular phylogenetic analysis using core genomes comparison (CgMLST).*

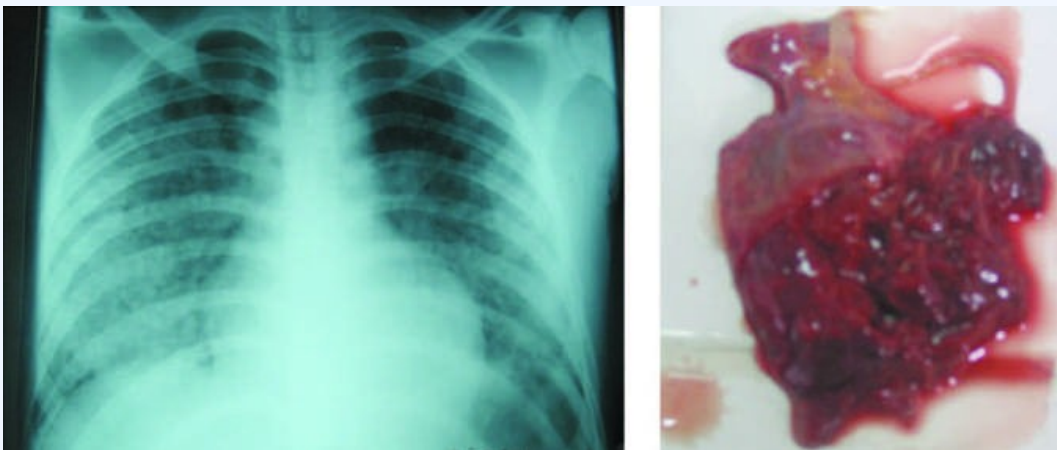


FIGURE 189-4 Severe pulmonary hemorrhage in leptospirosis. Left panel: Chest x-ray. appearance of right lower lobes of lung at autopsy. This patient, a 15-year-old from the city of Iquitos, died several days after presentation with acute illness, jaundice, and yielded *Leptospira interrogans* serovar Copenhageni/Icterohaemorrhagiae. (Adapted E Segura et al: *Clin Infect Dis* 40:343, 2005. © 2005 by the Infectious Diseases Society of intercellular junctions and disruption of bile canaliculi leading to bile leakage. Petechiae and hemorrhages are observed in the heart, lungs (Fig. 189-4), kidneys (and adrenals), pancreas, liver, gastrointesti- — FIGURE 189-2 Transmission electron microscopic image of *Leptospira interrogans** invading equine conjunctival tissue. Image provided by Dr. JE Nally, National Animal Disease Center.



Harrison's 22e · Figure 6

FIGURE 188-3 Clinical manifestations of bejel and pinta. A. Mucous patches of early bejel. B. Pigmented macules of early pinta. (Photos reprinted with permission from the *Handbook of Endemic Treponematoses*, PL Perine et al, Geneva, World Health Organization, Color Plates 54, 60; 1984.) — FIGURE 189-3 Biphasic nature of leptospirosis and relevant investigations at different stages of disease. Timeline showing incubation, acute leptospiremic phase, immune phase, and convalescent phase with corresponding lab tests (serology, PCR, culture).