74 - 188 Endemic Treponematoses

188 Endemic Treponematoses

Rates of decline of serologic titers appear to be slower, and serologi cally defined treatment failures more common among HIV-infected patients than among those without HIV co-infection; however, effective ART may reduce these differences. 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.

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 exami nations 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 pres ence 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. PART 5 Infectious Diseases IMMUNITY TO SYPHILIS The rate of development of acquired resistance to T. pallidum after nat ural 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. Cel lular 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 antibod ies 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. Sev eral 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. ■ ■FURTHER READING Hamill M et al: State of the art review: Neurosyphilis. Clin Infect Dis 78:e57, 2024. Luetkemeyer A et al: Postexposure doxycycline to prevent bacterial sexually transmitted infections. N Engl J Med 388:1296, 2023. Lukehart S et al: Immunization with a tri-antigen syphilis vaccine significantly attenuates chancre development, reduces bacterial load, and inhibits dissemination of T. pallidum. Vaccine 40:7676, 2022. Tantalo L et al: Antimicrobial susceptibility of Treponema pallidum subspecies pallidum: An in-vitro study. Lancet Microbe 4:e994,

)23.
Workowski K et al: Sexually transmitted infections treatment guide lines, 2021. MMWR Recomm Rep 70:39, 2021.

Sheila A. Lukehart, Lorenzo Giacani

Endemic Treponematoses The endemic treponematoses are chronic diseases that are generally trans mitted by direct contact, usually during childhood and, like syphilis, 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 (Chap. 187). Yaws, pinta, and bejel (endemic syphilis) have traditionally been distinguished from venereal syphilis by mode of transmission, age of acquisition, geo graphic distribution, and clinical features; however, there is overlap for each of these factors. Most of our “knowledge” about these infections is based on observations by health care workers who have visited endemic areas during the past 70 years. Except for the ongoing programs of mass drug administration (MDA) 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, modified by current knowledge, are compared in Table 188-1. ■ ■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 sub sequent 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 vil lages. The WHO lists 15 countries in Latin America where pinta was previously endemic; however, due to the lack of surveillance, the cur rent prevalence of pinta is unknown. In the early 1980s, clinical evi dence of pinta was discovered in 20% of the examined inhabitants of a

TABLE 188-1 Classic Comparison of the Agents of the Human Treponematoses and Their Associated Diseases FEATURE SYPHILIS YAWS BEJEL (ENDEMIC SYPHILIS) PINTA Organism T. pallidum subsp. pallidum T. pallidum subsp. pertenue T. pallidum subsp. endemicum T. carateum 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, adulthooda 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 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 aSexual transmission has been recently postulated for bejel (see text). bCentral nervous system involvement and congenital infection in the endemic treponematoses have been postulated by some investigators (see text). remote village in Panama. In 1987 and 1993, pinta cases were reported in indigenous populations living in the Amazon border region of Bra zil, 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 trepone mal 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 Number of reported cases, 2022 ≥ 10,000 1,000 – 9,999 < 1,000 Interrupted transmission FIGURE 188-1 Geographic distribution of yaws in 2022. (Reproduced with permission from World Health Organization.)

Skin-to-skin Mucocutaneous lesions (mucous patch, split papule, condylomata lata); osteoperiostitis Pintides, pigmented, pruritic from H. ducreyi, but not T. pallidum. Data from other sites confirm these approximate proportions. Of the 20% of lesions that had 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 environmen tal 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. CHAPTER 188 Evidence of yaws-like and genital lesions, with treponemal serore activity, has been found in several species of wild nonhuman primates (NHP) in sub-Saharan Africa, providing evidence that there is an ani mal reservoir for yaws treponemes. At the genomic level, these organ isms 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. Endemic Treponematoses

Countries with suspected cases Previously endemic countries (current status unknown) Non-endemic countries Not applicable

■ ■MICROBIOLOGY

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 patho genic 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 phyloge netic 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 differ ing geographic regions are needed to further understand the genomic relationship among the pathogenic treponemes to better inform nomen clature decisions. Currently, three of the four etiologic agents are classi fied 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 poly morphisms have been identified that might be related to any distinct clinical characteristic of these diseases. ■ ■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 over lapping 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. PART 5 Infectious Diseases Historically, the major clinical distinctions made between syphilis and the other human treponematoses are the apparent lack of congenital transmission and of central nervous system (CNS) involvement in the “nonvenereal” infections. It is not known whether these distinctions are entirely accurate. Because of the high degree of genetic

relatedness among the organisms, there is little biologic reason to think that T. pal lidum subspecies endemicum and T. pallidum subspecies pertenue would be unable to cross the blood–brain barrier or to invade the placenta. These organisms are like T. pallidum subspecies pallidum in that they obviously disseminate from the site of initial infection and can persist for decades. The lack of recognized congenital infection may be because childhood infections often reach the latent stage (characterized by a low to undetectable bacterial load) before girls reach sexual maturity, thus reducing the likelihood of fetal infection. Neurologic involvement may go unrecognized because of the lack of trained medical personnel in endemic regions, the delay of many years between infection and possible CNS manifestations, or a low rate of symptomatic CNS disease. Some D C B A FIGURE 188-2 Clinical manifestations of early yaws. A. Primary ulcer. B. Secondary papillomata. C. Periostitis, D. Polydactylitis. (Photos were taken during a yaws elimination trial in Papua New Guinea and are published with permission from Dr. Oriol Mitjà.)

published evidence supports congenital transmission as well as cardio vascular, ophthalmologic, and CNS involvement in yaws and endemic syphilis. Although the reported studies have been small, have failed to control for other causes of CNS abnormalities, and in some instances have not included serologic confirmation, it may be erroneous to accept unquestioningly the frequently repeated belief that these organisms fail to cause such manifestations. 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 transmis sion 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 pap illomatous (“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 general ized lymphadenopathy, appears either concurrent with or after the primary lesion, and may take several forms—macular, papular, or papil lomatous (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, hyperkerato ses 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. Bejel 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, sug gesting 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, oste itis, and gangosa are more common in bejel than in yaws.

Revision #1
Created 2026-01-06 16:33:21 UTC by Omar Ayman
Updated 2026-01-06 16:33:21 UTC by Omar Ayman