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 associated with jaundice (median reported mortality 19.1%, range 0–39.7%), renal failure (12.1%, range 0–25%) and age over 60 years (60%, range 33.3–60%). In other series of treated hospitalized cases mortality ranges from 4% to 52%. In a retrospective series of treated cases pulmonary involvement and central nervous system disease were associated with poor outcome. Where renal failure complicates leptospirosis, recovery of renal function after the acute period is generally rapid and complete, though recent reports from Sri Lanka and Taiwan suggest that leptospirosis might in some cases lead to chronic kidney disease. Prevention Vaccination Several human vaccines have been developed over the years, and although effective in certain epidemiological circumstances, all are serovar-specific and none are currently widely available. Vaccination of domestic and farm animals provides variable levels of protection but is not widely practised. Exposure avoidance Control measures for preventing human leptospirosis include ro- dent control, protection of food from contamination with animal urine, and avoiding skin and mucous membrane contact with po- tential sources of infection such as flood water and animal farm water runoff. Antimicrobial prophylaxis Oral antimicrobial prophylaxis can be given to individuals at high risk of exposure. In a randomized placebo-controlled study of 940 soldiers deployed for jungle training in Panama, significantly fewer cases of leptospirosis were observed in those who received weekly prophylaxis with doxycycline 200 mg prophylaxis compared with placebo (1 versus 20 cases). In a second study in the highly endemic flood-prone Andaman Islands 782 individuals were randomized to weekly doxycycline 200 mg or placebo. Clinical infection rates were lower among those who received doxycycline (3.1% vs. 6.8%), but there was no difference in seroconversion rates. FURTHER READING Adler B (ed) (2015). Leptospira

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8.6.36 Nonvenereal endemic treponematoses: Yaws, endemic syphilis (bejel), and pinta 1205 Introduction The human treponematoses consist of venereal syphilis, caused by Treponema pallidum subsp. pallidum, and the three nonvenereal endemic treponematoses; yaws (caused by T.p. subsp pertenue), bejel or endemic syphilis (caused by T.p. subsp. endemicum) and pinta (caused by T. carateum). Differences in the epidemiological and clinical features of the human treponematoses aid in diagnosis (Table 8.6.36.1) although newer molecular tools are being devel- oped to allow differentiation of the causative agents. All four diseases are caused by morphologically indistinguishable gram-negative spirochetes, which cannot be cultured in vitro or

differen- tiated by conventional testing. Sequencing of a limited number of trepo- nemal strains has shown the genome sequence of T.p. subsp. pallidum and T.p. subsp. pertenue to be more than 99.8% identical, with evidence of recombination between syphilis and yaws strains. Most of the identi- fied differences are restricted to six genomic regions, which are thought to contribute to the differences in pathogenicity between species. Clinically, the endemic treponematoses are characterized by multistage infection predominantly involving the skin, bones, and cartilage. The diseases vary in the incidence and severity of late stage disease. As with syphilis, penicillin has been the mainstay of treat- ment, but azithromycin has recently been shown to be effective in the treatment of yaws, prompting renewed efforts to eradicate it. Yaws Epidemiology Yaws is found in warm, humid environments, and predominantly affects children aged 2–15 years living in remote, rural popu- lations. Even in countries where yaws is endemic the disease is extremely focal. It is spread by direct skin-to-skin, nonsexual, contact often after a cut or abrasion in the lower legs. Children born to mothers with yaws are generally unaffected, and most of the evidence indicates that the disease is not acquired congeni- tally. For every clinical case of yaws, there may be as many as six to ten latent cases in the community. Treponemal infections ex- tremely closely related to yaws and syphilis have been identified in nonhuman primates, but there is limited direct evidence for zoonotic infection. Yaws is the most prevalent of the endemic treponemal diseases. In the mid-twentieth century, as many as 50 million individuals were thought to be infected by yaws. Between 1952 and 1964 a joint WHO and UNICEF programme for the control of endemic treponemal dis- eases was conducted. Approximately 300 million individuals were treated worldwide with injectable penicillin and it is believed that this reduced the global burden of diseases by as much as 98%. Following the cessation of these control programmes the disease rebounded in several countries in the 1970s and a further World Health Assembly resolution for the eradication of yaws was passed in 1978. In some countries this led to renewed control efforts but, despite these efforts, the disease was not eradicated. The number of reported cases has continued to climb in recent years but accurate prevalence and inci- dence data are lacking from most endemic countries. Yaws is currently thought to be endemic in 15 countries, mostly in West Africa, Southeast Asia, and the Pacific (Fig. 8.6.36.1). Papua New Guinea, the Solomon Islands and Ghana have each re- ported more than 15 000 suspected cases of yaws in recent years; in another eight countries transmission occurs mainly in hard-to- reach populations. A further 79 countries were previously reported to have been endemic for yaws but there are limited data on the current epidemiology of yaws from most of these countries. Yaws was previously reported to be endemic in South America and the Caribbean, but control programmes in the mid-20th century are thought to have successfully eliminated yaws from most countries in the region except Guyana. India interrupted transmission in Table 8.6.36.1 Clinical and epidemiological features of the human treponematoses Feature Venereal syphilis Yaws Endemic syphilis Pinta Organism T. pallidum subsp. pallidum T. pallidum subsp. pertenue T. pallidum subsp. endemicum T. carateum Age of infection (years) 20–40 5–15 2–10 10–30 Occurrence Worldwide Africa, South America, Oceania, Asia Africa, Middle East Central and South America Climate All Warm, humid Dry, arid Warm, rural Direct transmission: Venereal Common No Rare No Nonvenereal Rare Common Rare Common Congenital Yes No Unknown No Indirect transmission: Contaminated utensils Rare Rare Common No Reservoir of infection Adults Infectious and latent cases;
possibly nonhuman primates Infectious and latent cases Ratio infectious:latent cases 1:3 1:5–8 1:2 Unknown Late complications: Skin + + + + Bone, cartilage + + + No Neurological + No ? No Cardiovascular + No ? No

section 8 Infectious diseases 1206 2004 and declared elimination in 2006, following a sustained pro- gramme which began in 1996. Pathogenesis Knowledge of the pathogenesis of the treponematoses has been predominantly derived from animal models. Bacteria are acquired through breaches in the skin or mucous membranes. Following the initial infection, treponemes disseminate to lymph nodes where they multiply rapidly. The immune response is responsible for much of the pathology associated with the treponematoses and is medi- ated by both cellular and humoral immune responses. There is no naturally acquired immunity to treponemal infections and, fol- lowing successful treatment, individuals in endemic communities are at risk of reinfection. Clinical features Primary yaws The initial lesion of primary yaws is a papule which appears at the site of inoculation after approximately 21 days (range 9–90 days). This lesion, often referred to as a 'Mother Yaw', may then evolve ei- ther into an exudative papilloma, 2–5 cm in size, or degenerate to form a single, crusted, nontender ulcer (Fig. 8.6.36.2). Lower limbs are the most frequent site for lesions of primary yaws, but other parts of the body can also be affected. Genital lesions are extremely uncommon. In the absence of treatment primary lesions may heal spontaneously over a period of 3–6 months with the formation of a pigmented scar. On occasion primary lesions may still be present in patients who develop secondary manifestations of yaws. Secondary yaws The secondary manifestations of yaws result from haematogenous and lymphatic dissemination of treponemes, and typically occur 1– 2 months (up to 24 months) after the initial infection. Secondary yaws predominantly affects the skin and bones and may be accom- panied by general malaise and lymphadenopathy. A variety of skin manifestations have been described in sec- ondary yaws. These include disseminated papillomatous and ul- cerative lesions, scaly macular lesions, and hyperkeratotic lesions of the palms and soles. The latter may crack and become secondarily infected giving rise to severe pain and an abnormal gait, so called crab yaws (Fig. 8.6.36.3a). Involvement of the mucous membranes is uncommon in secondary yaws. Alongside the skin, involvement Countries reporting yaws (1982—2018) Countries reporting bejel (1982—2018) Countries reporting pinta (1982—2018) Fig. 8.6.36.1 Current known distribution of the endemic treponemal diseases. (a) (b) Fig. 8.6.36.2 Lesions of primary yaws. (a) Ulcerative lesion of primary yaws. (b) Papilloma of primary yaws. Images courtesy of O Mitjà.

 of the bones is one of the cardinal features of secondary yaws. The most common manifestation is osteoperiostitis. In most patients multiple bones are involved, most commonly the fingers (resulting in dactylitis), or the long bones (forearm, fibula and tibia) which results in bony swelling and pain (Fig. 8.6.36.3b). Latent yaws Untreated patients may develop latent infection, with positive ser- ology but no clinical signs. Latent cases can relapse, usually in the first 5 years (rarely up to 10 years) after infection. Relapsing lesions tend to occur around the axillae, anus, and mouth. At present no diagnostic test can distinguish between true latent infection and serofast status following successful treatment. Tertiary yaws Destructive lesions of tertiary yaws were previously reported to af- fect up to 10% of untreated patients. For reasons that are unclear these late stage manifestations are now seen less frequently. The skin, cartilage, and bones are most commonly affected. The lesions of late yaws contain relatively few treponemes and are not infectious. Nodular lesions may occur near joints and ulcerate, causing tissue necrosis. Destructive lesions of the face are some of the most marked manifestations of tertiary yaws. Gangosa, a destructive os- teitis of the palate and nasopharynx, results in mutilating facial ul- ceration. Goundou, which was rarely reported even when yaws was hyperendemic, is characterized by exostoses of the maxillary bones. Yaws is not thought to cause cardiovascular or neurological disease. Attenuated disease In some

countries the clinical manifestations of yaws appear to be less florid than has been previously described. In many Pacific coun- tries the destructive lesions of tertiary yaws are now rarely seen. There is no agreed definition of attenuated yaws. Improvements in living standards, use of treponemocidal antibiotics for other infec- tions and mutations in T. p subsp. pertenue have all been proposed as explanations for why the features of the diseases may be less severe than previously. Bejel Epidemiology Bejel (endemic syphilis) is found predominantly in children aged 2–15 years living in dry, arid environments. The disease has been reported in the Arabian peninsula and in the Sahel region of Africa (Fig. 8.6.36.1). A limited number of case reports suggest ongoing transmission in isolated, rural populations but there is limited sys- tematic data on the current distribution of bejel. The disease was previously reported to be present in several countries in northern Europe, the Balkans, Russia, and the eastern Mediterranean. Social and environmental improvements are thought to have contributed to a natural decline in the number of cases, while mass treatment campaigns are thought to have contributed to local elimination in some countries. Alongside direct inoculation via skin-to-skin con- tact, indirect inoculation in to mucous membranes via shared uten- sils has been reported to occur in bejel. Clinical features Primary lesions of bejel are rare, and if present often go undetected as small painless ulcers of the oropharynx and nasopharynx (Fig. 8.6.36.4a) and may only be noted when secondary lesions develop, which typically occurs 3–6 months after initial infection. Secondary bejel is characterized by widespread lesions of the mu- cous membranes which are frequently accompanied by regional lymphadenopathy, condylomata lata, and a diffuse maculopapular rash (Fig. 8.6.36.4b). Clinically it can be difficult to distinguish sec- ondary bejel from venereal syphilis. Painful osteitis and periostitis, similar to that seen in yaws, may also be seen in secondary bejel. The late stages of bejel are characterized by destructive gumma- tous nodules that affect the skin and can progress to form infiltrated, (a) (b) (c) Fig. 8.6.36.3 Lesions of late yaws. (a) Hyperkeratotic plantar lesion of secondary yaws. (b) Dactylitis of secondary yaws. (c) Gangosa seen in tertiary yaws. Images A and C reprinted from Handbook of endemic treponematoses: yaws, endemic syphilis and pinta, Perine PL et al., Copyright © World Health Organization 1984; B courtesy of O Mitjà.

 pigmented lesions. Gummata of the nasopharnyx may result in a de- structive rhinopharyngitis (gangosa) which is also seen in tertiary yaws. As with the other endemic treponemal diseases, cardiovas- cular and neurological manifestations are not seen in late bejel. Pinta Epidemiology Unlike the other endemic treponemal diseases pinta predominantly affects young adults. The disease is restricted to Latin America, in particular Mexico and Colombia (Fig. 8.6.36.1). There is limited re- cent data on the prevalence of pinta in any of the countries where it was previously reported, although there are believed to be remaining foci of infection among tribes living in the Amazon. Clinical features Pinta is the most benign of the endemic treponematoses. Disease manifestations are limited to the skin and the destructive late stage manifestations of yaws and bejel are not seen. The initial lesions of primary pinta form as papules or ery- thematous plaques. These lesions may become pigmented and hyperkeratotic and are frequently accompanied by regional lymph- adenopathy (Fig. 8.6.36.5a). Exposed skin, most commonly the arms and legs, are the most frequent sites involved. Constitutional symptoms are not a feature of pinta. The early lesions of pinta normally resolve spontaneously but are followed after several months by the appearance of multiple smaller lesions (‘pintids’). These secondary lesions are characterized by al- terations in skin pigmentation. As treponemes are present in these lesions for many years these patients remain infectious. Late stage pinta is characterized by abnormally pigmented le- sions, which may contain areas of both hypo- and hyperpigmenta- tion.

These changes may be accompanied by both skin atrophy and hyperkeratosis (Fig. 8.6.36.5b). Lesions of the bones and cartilage are not seen in pinta. Differential diagnosis The differential diagnosis of the endemic treponematoses varies between the different diseases and the stages of each disease. Venereal syphilis is a key differential diagnosis for all three en- demic treponematoses. The early lesions of yaws must be distin- guished from other ulcerative skin diseases including tropical ulcers, cutaneous leishmaniasis, and pyoderma. The mucous membrane lesions of bejel may be mistaken for oral herpes sim- plex, aphthous ulceration, or syphilis. Dactylitis due to yaws must be distinguished from that of sickle cell disease. The late stage manifestations of both diseases maybe confused with syphilis, fungal, and mycobacterial infections, psoriasis, and eczema. The lesions of early pinta may be confused with eczema, psoriasis, tinea versicolor, pellagra, syphilis, and leprosy, while the dyschromic late stage lesions may be confused with vitiligo, leprosy, and fungal infections. Of particular importance, several studies have recently identi- fied Haemophilus ducreyi as a common cause of nongenital skin lesions in children in yaws endemic communitites. These lesions are found in individuals who are both sero-negative and sero- positive for yaws and clinical differentiation has not been shown to be reliable for distinguishing between ulcers caused by T.p. subsp. pertenue from those caused by H. ducreyi. (a) (b) Fig. 8.6.36.4 Lesions of primary and secondary bejel. (a) Oral ulcer of primary bejel. (b) Chronic skin lesion of seconday bejel. Images reprinted from Handbook of endemic treponematoses: yaws, endemic syphilis and pinta, Perine PL et al., Copyright © World Health Organization 1984.

Diagnosis The diagnosis of the endemic treponematoses is based on a com- bination of the clinical and epidemiological features combined with microbiological evidence of infection, most frequently serology. In endemic settings the diagnosis may be relatively straightforward, although the epidemiological and serological overlap with venereal syphilis can be a diagnostic challenge. Diagnostic quandaries arise when individuals who have emigrated from an endemic area are found to have reactive serology. Clinicians need to consider the possibility that the reactive serology reflects either a previous infection with an en- demic treponemal infection or venereal syphilis. The social and medical history of the patient should be carefully reviewed. If there is clinical doubt, then treatment with benzathine-penicillin should be offered. Serology Serology remains the mainstay of diagnosis for all of the human treponematoses. Traditional serological testing combines a specific- treponemal assay with a less specific nontreponemal assay. No cur- rently available serological test can distinguish between the different human treponematoses. The most commonly used treponemal tests include the T. pallidum haemagglutination and the T. pallidum par- ticle agglutination assays. These tests are highly specific but remain positive for life following infection. Nontreponemal tests include the venereal disease research laboratory (VDRL) and rapid plasma re- agin (RPR) tests. These detect several antigens including cardiolipin, lecithin, and cholesterol. Although nonspecific, VDRL/RPR titres best reflect disease activity. Titres fall after treatment and may be- come zero, especially after treatment of early infection. There is limited access to routine diagnostic testing in many of the remote communities where the endemic treponematoses are most common. A rapid diagnostic test combining both a treponemal and a nontreponemal component, originally developed for the diagnosis of venereal syphilis, has been validated for the diagnosis of yaws and is likely to also be of value for the diagnosis of bejel and pinta. Microscopy Treponemes can be demonstrated in exudates from early lesions by darkfield examination, and they can also be found in biopsy speci- mens processed with silver or immunoperoxidase stains. However, these techniques are not routinely available in settings where

these diseases are prevalent. Molecular techniques Polymerase chain reaction (PCR)-based assays have become rou- tinely available for the diagnosis of syphilis in high-income coun- tries. Commercial PCR assays cannot distinguish subspecies of pathogenic treponemes, but real-time PCR assays are now available at research laboratories which can achieve this. Susceptibility in vitro and in vivo Studies to examine the in vitro and in vivo susceptibility of T. pall idum subspecies to antimicrobial agents are all laborious and tech- nically challenging since the bacteria cannot be grown in culture media. T. pallidum pertenue has been found to be sensitive to peni- cillin, chloramphenicol, tetracycline, and erythromycin, while it is insensitive to streptomycin and rifampicin. Treatment Long-acting injectable benzathine-penicillin has been the standard of care for the endemic treponematoses for more than 50 years. (a) (b) Fig. 8.6.36.5 Lesions of primary and secondary pinta. (a) Erythematous plaque of early pinta. (b) Hyperpigmented lesion of late pinta. Images reprinted from Handbook of endemic treponematoses: yaws, endemic syphilis and pinta, Perine PL et al., Copyright © World Health Organization 1984.

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