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section 8 Infectious diseases 1210 Lower doses are used compared to syphilis, with a recommended dose of 0.6 MU for children under 10 years and 1.2 MU for older children and adults. Treatment failure has been rarely reported fol- lowing treatment of yaws with benzathine-penicillin. The inability to distinguish treatment failure from reinfection makes these re- ports difficult to interpret and there is no good evidence of resist- ance to benzathine-penicillin developing in any of the endemic treponematoses. A landmark randomized controlled trial conducted in Papua New Guinea showed that a single oral dose of azithromycin (30 mg/kg, max 2 g) was noninferior to penicillin for the treatment of both primary and secondary yaws. Azithromycin is now the preferred first-line treatment for yaws because of ease of administration. Azithromycin has not been used in the treatment of bejel or pinta but is likely to be efficacious. Resistance to azithromycin in T. pall idum is mediated by point mutations in the 23s rRNA gene and is common in venereal syphilis, and has now been documented in yaws as well. Following treatment treponemes disappear from lesions within 8–10 hours, skin lesions begin to heal within 2–4 weeks, and nontreponemal test titres decrease 4-fold or more within 6–12 months. If treated early bony lesions may resolve but late stage scarring manifestations are irreversible. Treatment failure, either based on clinical or serological findings, is generally considered to be an indication for re-treatment Second-line agents For patients over the age of 10 years who are allergic to drugs of choice, oral tetracycline (500 mg q6h) or doxycycline (100 mg q12h) for 14 days are considered the best alternative agents. Adjunctive therapy Simple dry dressing is useful for keeping ulcerated lesions clean and protected from trauma. Pain control with nonopioid analgesics (e.g. paracetamol) is usually sufficient for managing mild discomfort related to arthralgias, osteoperiostitis, or palmoplantar keratosis. Prevention and control Social and economic development has led to the natural decline of the endemic treponematoses in many countries worldwide. As with syphilis, there is limited evidence for naturally acquired im- munity and individuals living in endemic communities can be- come repeatedly re-infected following treatment. Most cases of yaws occur in children and adults appear relatively unaffected even in hyperendemic communities, which might suggest immunity can eventually develop. Experimental studies have suggested that in- dividuals may develop some degree of protection from reinfection with homologous strains but not from infection with alternative treponemal species or subspecies. There is no currently available vaccine available for any of these human treponematoses. Yaws has been the focus of several previous large-scale control and eradication programmes. The previous eradication programme in the 1950s to 1960s resulted in a substantial reduction in the burden of disease worldwide, but focal pockets of the disease have remained, and disease prevalence has rebounded in some countries. More re- cently both Ecuador and India have achieved local elimination of yaws through government led mass

treatment and case finding pro- grammes, demonstrating that eradication should be feasible. The demonstration that azithromycin was an effective agent for the treatment of yaws has led to renewed interest in yaws eradication. A WHO eradication strategy was launched in 2012 based on com- munity mass treatment with single-dose oral azithromycin and sub- sequent clinical case detection to direct further rounds of targeted treatment. Pilot studies conducted in Ghana, Papua New Guinea, and Vanuatu demonstrated that this approach was highly effective at redu- cing the community prevalence of both clinical and latent yaws. These findings have prompted optimism that it might finally be possible to eradicate yaws worldwide. Several key areas will need to be addressed if the current eradication campaign is to be successful. In particular there is a need for a significant improvement in the accuracy of information about the current epidemiology of yaws, and for studies to understand the optimal mass treatment strategy required to achieve eradication. At present there is no specific strategy for the eradication of either bejel or pinta. It is likely that the tools developed as part of yaws eradi- cation efforts will be applicable in the control of both bejel and pinta. FURTHER READING Ayove T, et al. (2014). Sensitivity and specificity of a rapid point-of- care test for active yaws: a comparative study. Lancet Glob Health, 2, e415–e421. Cejková D, et al. (2012). Whole genome sequences of three Treponema pallidum ssp. pertenue strains: yaws and syphilis treponemes differ in less than 0.2% of the genome sequence. PLoS Negl Trop Dis, 6, e1471. Giacani L, Lukehart SA (2014). The endemic treponematoses. Clin Microbiol Rev, 27, 89–115. Marks M, et al. (2014). Haemophilus ducreyi associated with skin ul- cers among children, Solomon Islands. Emerg Infect Dis, 20, 1705–7. Marks M, et al. (2015). Challenges and key research questions for yaws eradication. Lancet Infect Dis, 15, 1220–5. Mitjà O, Asiedu K, Mabey D (2013). Yaws. Lancet, 381, 763–73. Mitjà O, et al. (2012). Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, noninferiority, randomised trial. Lancet, 379, 342–7. Mitjà O, et al. (2015). Mass treatment with single-dose azithromycin for yaws. N Engl J Med, 372, 703–10. Mitjà O, et al. (2018). Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. Lancet, 391, 1599–607. Perine PL, et al. (1984). Handbook of endemic treponematoses: yaws, endemic syphilis and pinta. World Health Organization, Geneva. 8.6.37 Syphilis Phillip Read and Basil Donovan ESSENTIALS Syphilis results from infection with the spirochaete Treponema pallidum subsp. pallidum, for which humans are the only known nat- ural host. In adults it is transmitted primarily by sexual contact. The organism gains entry into the body through small breaks in the skin

8.6.37 Syphilis 1211 or the intact mucosal surfaces of the genitals, mouth, or anus, and is able to invade and survive in a wide variety of tissues. Since the availability of penicillin, syphilis has become primarily (>90%) a disease of less affluent countries or of minority subpopulations in more affluent countries with poor access to healthcare. It is also a disease of people with rapid rates of partner change (e.g. men who have sex with men and commercial sex workers). Clinical features Syphilis can manifest in three stages: (1) primary syphilis, which occurs within a few weeks to months after infection; (2) secondary syphilis, which presents after a few months, up to a year; and (3) tertiary syphilis, which presents years to decades after primary infection. These stages can overlap, and there are frequently asymptomatic periods. Primary syphilis—this appears 9–90 days after the organism gains entry via direct inoculation through the thin skin or mucosa of the anogenital tract or mouth during sexual exposure. The resulting le- sion is typically a painless ulcer or ‘chancre’, sometimes indurated, that appears at the site of inoculation and is associated with regional lymphadenopathy; chancres can be multiple and atypical. Secondary syphilis—occurs 3–6

weeks after the appearance of the chancre, with manifestations including fever, malaise, mucocutaneous lesions (rash, condyloma lata, mucous patches), generalized lymph- adenopathy, and (uncommonly) visceral disease. Invasion of the central nervous system is common, but usually asymptomatic. Latent syphilis—the lesions of both primary and secondary syphilis may wax and wane, but they eventually resolve; there are no signs or symptoms of active syphilis, but serological tests are positive for T. pallidum. Tertiary syphilis—affects around one-third of infected people fol- lowing a variable period of latent infection, with manifestations including: (1) neurosyphilis—which can present as: (a) aseptic meningitis, with variable features (e.g. focal neuro- logical deficits, cranial nerve palsies, hydrocephalus, or psy- chiatric symptoms); (b) meningovascular disease, with endarteritis leading to cere- bral infarction; (c) general paresis, involving changes in the parenchyma of the central nervous system that lead to the gradual onset of cog- nitive impairment, depression, and personality changes, later progressing to dementia, delirium, seizures, and delusions; (d) tabes dorsalis, with initial symptoms and signs including lightening pains and parasthesias, visceral crises, abnormal deep tendon reflexes, incontinence, ataxia with a wide- based gait, and pupillary abnormalities. (2) gummatous syphilis—destructive granulomatous lesions most commonly present on skin, mucosal surfaces, or in bone. (3) cardiovascular syphilis—most commonly asymptomatic aortitis, aortic incompetence, aortic aneurysm, and coronary ostial stenosis. Congenital syphilis—most pregnant women with early syphilis will transmit the condition to the fetus via the placenta, with congenital syphilis often resulting in fetal loss, stillbirth, or neonatal or childhood disease. Diagnosis and treatment Diagnosis—the transient nature of the lesions and the spirochetaemia limit the role of direct detection of T. pallidum, hence diagnosis usu- ally relies on serology, with tests being: (1) nonspecific (or nontreponemal or reagin)—for example, rapid plasma reagin and venereal disease research laboratory tests; de- tect phospholipid cardiolipin as an antigen; generally sensitive in early infection but tend to decline over the next several years without treatment; able to quantify disease activity and hence used for follow-up after treatment. (2) specific (or treponemal)—for example, T. pallidum haemagglutin- ation assay; use T. pallidum as the antigen; may become positive shortly before the nonspecific tests; typically remain reactive for life after successful treatment and therefore have no role in as- sessing stage of infection, ‘cure’, or reinfection. Treatment—parenteral penicillin G remains the preferred treatment for syphilis, with doxycycline providing an oral alternative. Successful treatment of early disease relies on demonstrating a fourfold de- crease in reagin (rapid plasma reagin or venereal disease research laboratory) titres over the next 6–12 months. Sexual contacts of early syphilis should be treated presumptively, regardless of their test re- sults, if the contact was within 90 days, usually with a single dose of benzathine penicillin G. Prevention The chance of acquiring syphilis following one act of intercourse with an infected person is 1–2%, which should be reduced by the use of condoms. Early treatment of disease decreases the duration of infect- ivity and thereby minimizes transmission to others, hence those at high risk of syphilis should be encouraged to undergo regular syphilis screening (as well as testing for HIV and other sexually transmissible infections). Prevention of congenital infection and serious outcomes such as stillbirth and neonatal death rely on routine antenatal screening early in the pregnancy, with prompt treatment of infected mothers. Women in high-incidence settings should be rescreened later in pregnancy. Introduction and historical perspective In the 1490s, an epidemic of a new and virulent sexually transmis- sible disease appeared in Europe following the return of Christopher Columbus and his fleet from the Americas. This led many to believe that syphilis originated in the New World. There is now molecular phylogenetic evidence for this ‘Columbian hypothesis’. Syphilis spread rapidly through Europe where it was

known by a variety of names including morbus gallicus (the French disease), lues venereum (venereal disease), and the great pox. The alternative theory proposes that syphilis was simply another variant of a preexisting treponemal infection that had adapted to sexual and congenital transmission and produced greater morbidity (the Unitarian hypothesis). A variety of yaws-like diseases that pre- dominantly affected children were present in Europe and Africa at the time, and a few persisted in Europe into the 20th century.

section 8 Infectious diseases 1212 Syphilus (the original spelling) was an afflicted shepherd in a poem by Girolamo Fracastoro published in 1530. The original text described the symptoms of syphilis, hypothesized about its origins, and mentioned the use of early remedies such as guaiacum, a com- pound derived from a Central American tree, and mercury. Following an experiment by John Hunter in 1767 it was thought that gonorrhoea and syphilis were different manifestations of the same disease until Philippe Ricord, in 1838, clarified the differences between the two infections. Soon after, the three stages of syphilis were categorized and congenital and neurological syphilis were described. Because of the toxicity and dubious benefit of the treatments available at the time, a prospective cohort study into the natural history of syphilis was conducted in Oslo between 1890 and 1920. This study followed 1978 initially symptomatic patients and demon- strated that approximately one-third developed late complications. Many of these complications proved fatal. Rapid advances in knowledge occurred around the beginning of the 20th century. In 1905, Schaudinn and Hoffman demonstrated spirochaetes in secondary syphilitic lesions. One year later, Von Wasserman devised the first serological test for syphilis. In 1910, Paul Erlich announced results for his compound 606 (salvarsan), a form of arsenic that showed activity against syphilis. The discovery of penicillin by Fleming, its development for thera- peutic use by Florey, Chain, and Heatley and the first clinical trial in 1943 by Mahoney revolutionized the treatment of syphilis. During the immediate postwar period the use of penicillin eclipsed other forms of therapy and by the mid-1950s the incidence of syphilis had fallen markedly throughout the industrialized world. Aetiology, genetics, pathogenesis, and pathology Treponema pallidum subsp. pallidum, a spiral-shaped bacterium, is a member of the order Spirochaetales and the cause of adult-acquired and congenital syphilis. Humans are the only known natural host for all T. pallidum subspecies, although an unclassified and morpho- logically indistinguishable simian pathogen, the Fribourg–Blanc treponeme, was isolated from a baboon in Guinea in 1962. The in- ability to culture T. pallidum in vitro has retarded study of its biology. T. pallidum subsp. pallidum is closely related to other pathogenic treponemes that cause nonvenereal disease: T. pallidum subsp. car ateum (pinta), T. pallidum subsp. pertenue (yaws), and T. pallidum subsp. endemicum (endemic syphilis or bejel) (see Chapter 8.6.36). Subspecies pertenue and endemicum and the Fribourg–Blanc trepo- neme have recently been demonstrated to be genetically distinct from subspecies pallidum, consistent with the lack of cross-immunity. The spirochaete is 6–20 µm long and only 0.10–0.18 µm thick, making it invisible to ordinary light microscopy. Using dark-field micros- copy, T. pallidum has 6–20 characteristic tightly wound spirals and it moves with corkscrew motility or by bending in the middle and popping back into place with a spring. Other nonpathogenic trepo- nemes tend to have fewer coils or a jerkier motion. Commensal spe- cies of treponema (T. denticola and T. oralis) can mimic T. pallidum, limiting the usefulness of dark-field microscopy of oral and anal lesions. The T. pallidum DNA genome was first published in 1998. It is small, with a single circular chromosome of 1 138 006 base pairs containing 1041 predicted protein coding sequences, consistent with its limited metabolic capabilities. The organism obtains most of its essential nutrients from the host environment, making it an obligate parasite. In vivo, T.

pallidum has been grown in rabbits and reproduces itself slowly, doubling every 30–33 h. T. pallidum is able to survive better with low levels of oxygen (3–5%) and is sensitive to heat. T. pallidum is able rapidly to invade and survive in a wide var- iety of tissues after gaining entry into the body through small breaks in the skin or the intact mucosal surfaces of the genitals, mouth, or anus. The organism has a reputation as a ‘stealth’ pathogen be- cause its paucity of surface proteins and lipopolysaccharides helps it to evade the host immune response. T. pallidum induces humoral, cell-mediated, and local innate responses that appear to confer im- munity to exogenous infection in the chronically infected person (chancre immunity). However, patients treated for early syphilis can rapidly become reinfected. From the site of inoculation, T. pallidum replicates locally and spreads to regional lymph nodes, then into the blood stream from where it can traverse junctions between vascular endothelial cells. Indeed T. pallidum DNA has been isolated from blood in one-third of cases with primary syphilis. Lymphocyte, (CD4+) macrophage, and plasma cell infiltrates accompanied by vasculopathic changes, endarteritis, and periarteritis, underlie the histology of syphilitic le- sions of all stages. Silver staining of tissues might demonstrate the presence of spirochaetes, usually in the dermal–epidermal junction. In secondary syphilis, treponemes are found in many sites including visceral organs, the central nervous system, and the skin. T. pallidum can remain clinically dormant in the aortic wall, pro- ducing an endarteritis in the vasa vasorum and varying degrees of thickening, scarring, and destruction of the arterial wall. This pro- cess results in the development of arterial plaques and calcification of the vessels found in cardiovascular syphilis. In meningitis, perivascular infiltration of lymphocytes and plasma cells causes the meninges to become inflamed. In meningovascular syphilis, thickening of the intima, fibrous changes in the adventitia, and vascular narrowing cause changes in brain blood vessels with resultant infarction and cranial nerve palsies. The gummas of late syphilis are chronic granulomatous lesions consistent with a hypersensitivity response with few treponemes present. Histologically, central necrosis, peripheral lymphocytosis, perivasculitis, and obliterating endarteritis are seen. Epidemiology Since the availability of penicillin, syphilis has become pri- marily (>90%) a disease of less affluent countries or of minority subpopulations in more affluent countries with poor access to healthcare. It is also a disease of populations with rapid rates of partner change, such as men who have sex with men and commer- cial sex workers. The World Health Organization estimated that in 2008 syphilis continued to infect about 10.6 million people a year globally. The greatest number of new infections, 3.5 million, is found in Southeast and East Asia. Sub-Saharan Africa accounted for 3.4 million new cases and the Americas and Caribbean contributed 2.8 million. In Africa, between 4 and 17% of women are seropositive for syphilis in

8.6.37 Syphilis 1213 antenatal clinics, and many are coinfected with HIV. About a million pregnancies a year are seriously complicated or aborted by syphilis. The incidence of syphilis in China has risen following the political and social changes that occurred in the last part of the 20th cen- tury. In the former Soviet Union, the incidence of syphilis among the young sexually active population rose rapidly after 1991 with the degradation of the public health system. Since the beginning of the 21st century, syphilis rates in the United Kingdom, Europe, Asia, North America, Australia, and other developed countries have risen in men who have sex with men, espe- cially in those who are HIV positive. Serosorting, the phenomenon of homosexual men of similar HIV status seeking each other for un- safe sex, has been a factor. Oral sex, considered to be relatively safe in terms of transmission of HIV infection, readily transmits syphilis. Prevention Syphilis in adults is transmitted primarily by sexual contact. The chance of acquiring the infection is estimated to be between 1 and 2% following one act of intercourse with an infected person. Syphilis is found in up

to 60% of sexual partners of infected individuals. As T. pallidum is present in mucosal or cutaneous lesions, infected adults are more likely to transmit the disease during primary or secondary stages. The use of condoms to prevent syphilis has not been evaluated in controlled trials. Intuitively, condoms should have some effect in reducing transmission, but they do not provide 100% protection as they do not cover all areas of anogenital skin during intercourse. Condoms should also be used for oral sex. The early recognition and treatment of syphilis decreases the dur- ation of infectivity thereby minimizing transmission to others. As symptoms are not always present, those who are at higher risk of syphilis such as men who have sex with men and commercial sex workers are encouraged to undergo regular syphilis screening, as well as testing for HIV and other sexually transmissible infections. In order to attract those most at risk of syphilis, health services need to be accessible and culturally appropriate, confidential, and provide free or affordable diagnosis and treatment. Presumptive treatment of sexual partners and early recognition and treatment of those who may be core transmitters in a sexual network is essential in any syphilis control programme. Pilot studies have shown encouraging results of syphilis chemoprophylaxis when given to high-risk men who have sex with men. Some authorities now use the internet and dating applications to encourage men who have sex with men to have regular syphilis tests. The internet can also help these men to inform their sexual partners in a nonthreatening and confidential way. Syphilis can be transmitted via donated blood or organs, although this is rare. Thus, serological screening of donors is routine in most settings. Mother-to-child transmission of syphilis usually occurs in utero. Prevention of congenital infection and serious outcomes such as stillbirth and neonatal death rely on screening and treating for syph- ilis in the mother early in the pregnancy. In high-incidence popu- lations, rescreening around week 28 to 32 of the pregnancy and again at delivery is also recommended. With timely treatment of the mother, congenital syphilis is almost entirely preventable. Provision of comprehensive antenatal healthcare with affordable testing for syphilis should form part of a comprehensive syphilis control pro- gramme. Community education should encourage women to at- tend for healthcare early in pregnancy when treatment can be given with best effect. In high-prevalence areas, if a mother first presents at term, routine treatment of the neonate with a single dose of benzathine penicillin 50 000 units/kg is sometimes recommended if the mother has not been tested or adequate maternal treatment cannot be confirmed. Clinical features Clinical staging of syphilis is important to guide the process of con- tact tracing or partner notification. Primary, secondary, and early latent syphilis are collectively called ‘infectious syphilis’. Late latent and tertiary syphilis are generally regarded as no longer infectious for sexual partners. However, pregnant women may pose an occa- sional risk to their offspring. Treatment for later stages of syphilis is typically longer than for early syphilis. Primary syphilis The chancre, or ulcer of primary syphilis, develops at the site of in- oculation within 9 to 90 days (median 3 weeks) of infection, initially as a red macule that soon becomes papular before it ulcerates. The typical ulcer is painless, has fluid or grey slough in its centre, and a well-defined rolled edge. Mature ulcers can have a palpable indur- ated plaque deep to the lesion. However, chancres can occasionally be painful or multiple, and clinically indistinguishable from other causes of genital ulcers (Fig. 8.6.37.1). Mixed aetiologies are always possible (Fig. 8.6.37.2). Common sites for chancres in men include the distal penis, while in women the posterior fourchette, labia, and vulva are the most commonly diagnosed sites (Fig. 8.6.37.3a). The anus, mouth, and Fig. 8.6.37.1 Multiple painful chronic chancres in a man with HIV infection. Courtesy of Dr David Bradford.

 lips are all possible sites for chancres, as well as other extragenital sites. If a chancre is small or hidden in the anal canal, vagina, cervix, or mouth, it

usually passes unnoticed (Fig. 8.6.37.4). Most patients subsequently diagnosed with secondary syphilis do not recall the lesions of primary syphilis. Painless and typically rubbery, small lymph nodes are often felt in the affected region within a week of the development of the chancre (Fig. 8.6.37.3b). The chancre usually heals spontaneously in 3 to 6 weeks, but it may occasionally recur (‘chancre redux’). Secondary syphilis This disseminated stage of the infection typically occurs between 3 and 6 weeks following the appearance of the chancre, and the two stages might overlap. However, up to 60% of patients do not recall any signs or symptoms of secondary syphilis at all. The symptoms and signs of secondary syphilis are often de- scribed as protean, as listed in Table 8.6.37.1. Without treatment they resolve spontaneously only to reappear, usually in a milder form, in almost one-quarter (24%) of patients in the following 12 to 24 months (Fig. 8.6.37.5). Latent syphilis Latent syphilis is present when there are no signs or symptoms of active syphilis but serological tests are positive for T. pallidum. Latent syphilis is arbitrarily divided into early latent syphilis, when the asymptomatic infection has been present for less than 1 or 2 years, and late latent syphilis after this time. In practice, asymptomatic people diagnosed through screening are often deemed to have la- tent syphilis of unknown duration. As a precaution, such patients are treated with the longer courses of antibiotics that are used for late infections. Before the antibiotic era, approximately two-thirds of adults re- mained in the latent phase throughout their lifetime and showed no signs of tertiary syphilis. These days many common antibiotics have some activity against T. pallidum, so it is likely that antibiotics used for other conditions are also altering the natural history of, if not ac- cidentally curing, latent syphilis. Tertiary syphilis Tertiary syphilis occurred in 15–40% of those who remain un- treated in the Oslo study, with some modest differences between Fig. 8.6.37.2 Chancre against a background of primary genital herpes.
Fig. 8.6.37.4 An asymptomatic chancre on the anterior lip of the cervix in the same woman as Fig. 8.6.37.3a. (b) (a) Fig. 8.6.37.3 (a) A periurethral chancre in a woman who presented with a painless lump. (b) Chancre on thigh and inguinal lymphadenopathy of primary syphilis. Copyright D. A. Warrell.

 the sexes (Table 8.6.37.2). Partly as a result of the wide availability of antibiotics used for other purposes, gummatous and cardiovas- cular syphilis are now relatively rare compared to neurosyphilis; most oral antibiotics are unlikely to achieve cidal levels in the cen- tral nervous system. Neurosyphilis The diagnosis of neurosyphilis frequently raises clinical dilemmas because of the nonspecific nature of its clinical presentations and the absence of definitive tests. Neurosyphilis can manifest as aseptic (basilar pattern) meningitis or meningovascular disease as early as the secondary stage or up to several years after infection. As well as the usual symptoms of meningitis, syphilitic meningitis can also present with focal neurological deficits such as hemiparesis, aphasia, seizures, or psychiatric symptoms. Cranial nerve palsies accompany syphilitic meningitis in about 40% and hydrocephalus in 35% of patients. Meningovascular syphilis stems from endarteritis leading to in- farction, most commonly 5–12 years after infection. While any artery may be affected, the middle cerebral is the most frequently involved. Gradual onset and less extensive damage results from smaller arteries being involved than is usual in thrombotic stroke. Psychological changes can mimic the early stages of parenchymal disease. Confusing the diagnosis, up to 25% of individuals with early syphilis have T. pallidum in the cerebrospinal fluid demonstrated by rabbit inoculation or polymerase chain reaction (PCR). This largely asymptomatic phenomenon is known as neuroinvasion and it is be- lieved that most, but not all, will spontaneously clear T. pallidum from the cerebrospinal fluid. Studies in the preantibiotic era dem- onstrated that the degree of cerebrospinal fluid abnormalities (white cell

count, raised protein, and reactive cerebrospinal fluid (CSF)- Venereal Disease Research Laboratory (VDRL) test) in asymp- tomatic neurosyphilis predicted later progression to symptomatic neurosyphilis. Rarely, after 20–25 years, syphilitic meningitis or meningovascular disease can involve the spinal cord resulting in (often asymmetric) paresis, incontinence, hyperreflexia, extensor plantar reflexes, and loss of position, and vibration sense. Table 8.6.37.1 Clinical manifestations of secondary syphilis Features Frequency Rash Erythematous or coppery colour Nonpruritic or mildly pruritic Macular or maculopapular (50%) progressing to papular, papulosquamous, psoriasiform, annular
(dark-skinned people), pustular, or follicular Usually symmetrical, round to oval lesions, 5–20 mm across (Fig. 7.6.36.5a, b) Trunk, palms, soles, and body flexures are most commonly involved Occasionally papules around the forehead hairline (‘corona veneris’) Over 70% Condyloma lata Pale elevated moist plaques in warmer flexural areas such as perineum, perianal area, groin, axilla, perioral area, and nasolabial folds (Fig. 7.6.36.5c) Appear later than rash 15–50% Mucous patches Superficial erosions, papules, or plaques of mucosa of the oropharynx or anogenital area Involvement of the pharynx may result in hoarseness or sore throat 4–17% Constitutional Low-grade fever, malaise, headache, myalgias, arthralgias, anorexia, and nausea Occasionally severe Common, but variable Lymphadenopathy Generalized, nontender, and characteristically rubbery and discrete (Fig. 7.6.36.3b) Over 60% Hepatitis Mildly elevated transaminases Usually not clinically important Up to 10% Ocular Iritis or uveitis Occasional Alopecia Follicular disease can lead to patchy ‘moth-eaten’ alopecia of the scalp or, rarely, loss of the outer part of the eyebrows or beard Occasional Central nervous system Asymptomatic neuroinvasion occurs in up to 25% Symptomatic meningitis or meningovascular disease may be more common in HIV infection Ocular and auditory cranial nerves most commonly involved Up to 2% Kidney Asymptomatic proteinuria Nephritic syndrome Rapidly progressive glomerulonephritis Rare Heart Myocarditis Ventricular arrhythmia Rare Parotitis Rare Gastritis Gastritis and stomach ulcers resulting in nausea and abdominal pain Rare Periostitis, arthritis, or bursitis Localized Rare Malignant syphilis
(‘lues maligna’) Rapidly progressive variant with marked constitutional symptoms and disfiguring crusted necrotic ulcers Possibly more common with HIV infection and in alcohol dependant patients Rare

 General paresis involves changes in the central nervous system parenchyma, characterized by fibrosis and atrophy, and occurs much later, approximately 15–25 years after the initial infection. Parenchymatous central nervous system lesions can present with, usually gradual, onset cognitive impairment, depression, and per- sonality changes, later progressing to dementia, delirium, seizures, and delusions. Neurological signs can include irregular, often large, pupils that become unresponsive to light yet still accommodate (Argyll Robertson pupils), dysarthria, facial or hand tremor, loss of facial expression, hypotonia, and hyperreflexia or loss of reflexes. Tabes dorsalis involves parenchymatous changes in the dorsal root tracts and posterior columns of the spinal cord 15–35 years after primary infection. Initial symptoms and signs can include lightening pains and paraesthesias, visceral crises, abnormal deep tendon reflexes, incontinence, ataxia with a wide-based gait, and papillary abnormalities. Rarely, gummas involve the cerebrum or the spinal cord. (a) (c) (b) Fig. 8.6.37.5 (a, b) Rash of secondary syphilis on palms and scalp. (c) Papular lesions of secondary syphilis. Copyright D. A. Warrell. Table 8.6.37.2 Frequency of late complications of syphilis from the Oslo study in the preantibiotic era Form of tertiary syphilis Men (%) Women (%) Benign late (gummatous) syphilis 14.4 16.7 Cardiovascular

syphilis 13.6 7.6 Neurosyphilis 9.4 5.0

8.6.37 Syphilis 1217 Gummatous (late benign) syphilis Gummas are destructive granulomatous lesions that most com- monly present on skin (70%), on mucosal surfaces (10%), or in bone (10%). They can occur a few years or decades after primary infection. On the skin gummas start as painless nodules that pro- gressively become necrotic, leaving punched-out ulcers. The face, legs (Fig. 8.6.37.6), buttocks, trunk, and scalp are common sites. Gummatous involvement of the oropharynx can lead to perfor- ations and severe scarring of the palate, pharynx, or nasal septum. Tongue involvement can lead to glossitis, swelling, and leucoplakia. Fractures can occur with gummas of bone. Other organs occasionally affected include the liver, central ner- vous system, eyes, stomach, lungs, and testes. Cardiovascular syphilis Now rare, cardiovascular syphilis develops decades after primary in- fection. The most common forms are asymptomatic aortitis, aortic incompetence, (usually proximal) aortic aneurysm, and coronary ostial stenosis. Congenital syphilis Mother-to-child transmission occurs via the placenta at any stage of gestation. Because the transmission is haematogenous there is no primary lesion (chancre) and it is a disseminated infection from the outset. If the mother has early syphilis, transmission is almost certain; infectivity progressively declines to below 10% in late latent infection. Fetal wastage from syphilis might manifest as first or second trimester abortion or still birth with a large pale, fibrosed pla- centa or a macerated fetus. Of the infected babies that sur- vive, only 30% have specific symptoms in the neonatal period, though almost all will exhibit symptoms by 3 months. Many of the early (at birth or in the first 2 years) lesions resemble sec- ondary syphilis in the adult (Fig. 8.6.37.7). Failure to thrive in the first few months can be the first sign. Affected infants tend to be small or premature, irritable, snuffly, and cry feebly. The skin is often dry and wrinkled. Generalized rubbery lymphadenop- athy is common, often accompanied by hepatosplenomegaly and haematological abnormalities. Early deaths can be due to diffuse pulmonary infiltration. Painful osteochondritis or epiphysitis of the long bones, and sometimes periostitis, can occur in the first 6 months with charac- teristic radiological appearances. Late (after 2 years, but rarely beyond 30 years) congenital syphilis is analogous to tertiary syphilis in adults. However, gum- matous disease might be more common while cardiovascular disease is rare compared to adult syphilis. Interstitial keratitis is the most common form of late congenital syphilis. From the fifth year of life onward, the child might develop bilateral eye pain and photophobia, and scleral vascularization. Gumma can lead to perforation of the palate. Periostitis might lead to deformity of the tibia (sabre tibia), the skull (Parrot’s nodes), the scaphoid, and the clavicle. The stigmata of congenital syphilis are permanent deformities or scars left by early or late disease. Sometimes stigmata can help to explain unexpected positive serological tests in adults, as the pa- tient may be unaware of their prior infection. The bony deformities tend to persist, while T. pallidum can also invade tooth buds af- fecting the permanent teeth (Hutchinson’s teeth) but not the milk teeth. The molars might be deformed with dwarfed cusps, while the incisors might be small, peg-shaped, and notched at the tip. Previous interstitial keratitis can be demonstrable for life on slit- lamp examination. Differential diagnosis Syphilis is often described as the great imitator due to the vast number of illnesses that it mimics. Screening for syphilis was once considered routine for medical and psychiatric hospital admissions. A high index of suspicion is required for the diagnosis. Primary syphilis Chancres can resemble anogenital ulcers from any cause, and more than one condition may be present (Fig. 8.6.37.2). Other causes of genital ulcers include herpes simplex virus infections, chancroid, lymphogranuloma venereum, and donovanosis. An anal chancre can be painful and clinical indistinguishable from an ordinary anal fissure. Liberal use of the laboratory to exclude other

causes of ulcers Fig. 8.6.37.6 Ulcerating nodular lesions of gummatous syphilis in a man with HIV infection. Initially thought to be Kaposi’s sarcoma, the diagnosis was made by biopsy. Courtesy of Professor David Cooper. Fig. 8.6.37.7 Bullous syphilis lesions in a neonate.

section 8 Infectious diseases 1218 is essential. Alternatively, in resource-poor environments that must rely on syndromic management of genital ulcers, antibiotic combin- ations need to cover all the common causes of genital ulcers in that region. Secondary syphilis The rash of secondary syphilis can resemble a drug eruption, pityr- iasis rosea, tinea versicolour, seborrhoeic dermatitis, erythema multiforme, scabies, lichen planus, psoriasis, fungal infections, and leprosy. Other infections causing generalized rashes include primary HIV infection, measles, rubella, and meningococcemia. Condyloma lata can be confused with genital warts. Syphilitic alopecia can re- semble alopecia areata or fungal scalp infections. Generalized lymphadenopathy, sore throat, and fever are also seen in infectious mononucleosis, rubella, toxoplasmosis, lymphoma, acute hepatitis, and, most importantly, primary HIV infection. Symptoms of meningitis might also be present in HIV infection, bacterial meningitis, enterovirus infections, and primary herpes simplex virus infection. Latent syphilis Childhood treponemal infections such as yaws and pinta, as well as prior congenital syphilis, can be serologically indistinguishable from adult-acquired syphilis and the specific tests are likely to re- main positive for life. People from endemic treponemal areas or who may be at risk of congenital infection with positive syphilis ser- ology should be examined for stigmata of these conditions. False- positive nonspecific tests (VDRL and rapid plasma reagin (RPR)) occur in 1–2% of the population (see ‘Nonspecific serological tests’). Confirmation with a specific treponemal test is essential for asymptomatic people. Neurosyphilis Symptoms and signs of meningovascular syphilis are similar to those in other causes of stroke or cerebrovascular accidents due to haemorrhagic or thrombotic mechanisms. Gummas in the brain can be mistaken for tumours and abscesses, particularly in HIV infection. General paresis should be considered in the differential diagnosis of dementia, psychosis, seizures, delirium, and person- ality changes. Gummatous syphilis Other granulomatous diseases such as sarcoidosis, tuberculosis, and neoplastic lesions can be confused with gummatous syphilis. Cardiovascular syphilis Signs and symptoms of cardiovascular syphilis are similar to those of atherosclerotic disease and aortic aneurysms are more commonly due to hypertension. Other causes of aortic regurgi- tation without stenosis include Marfan’s syndrome and infective endocarditis. Clinical investigation Direct detection of the organism As with all bacterial infections, ideally T. pallidum should be directly detected (Table 8.6.37.3) because a serological response may take days to weeks to evolve. However, the transient nature of the lesions and the spirochaetaemia limit the role of direct detection, leading to reliance on serology or, in resource-poor environments, syndromic management. The role of PCR testing of the CSF has yet to be de- termined because asymptomatic and transient neuroinvasion by T. pallidum correlates poorly with standard criteria for diagnosing neurosyphilis. The role of PCR in the diagnosis of early syphilitic lesions is well established. PCR testing is increasingly available in many settings, and can be performed on primary and secondary lesions. The sen- sitivity for primary lesions ranges between 78 and 90%, and it may precede seroconversion. Typical PCR targets are the polA gene, or the tpp47 gene; both appear equally sensitive and specific. Table 8.6.37.3 Methods of direct detection of T. pallidum Method Brief description Role Animal inoculation Fresh (or flash-frozen to less than −78°C) lesion material or cerebrospinal fluid is usually inoculated by intratesticular or intradermal means into rabbits. The animals are then monitored for the development of skin lesions, orchitis, or serological response. The most sensitive test (approaching 100%), but only used as a gold standard to evaluate other tests in the research setting Dark-field

microscopy Fresh serous fluid with motile organisms is collected by gentle pressure on the lesions and pressed under a coverslip. An on-site microscope with a reflecting dark-field condenser and a skilled microscopist are required. Diagnostic criteria include morphology and motion of the organisms. Only appropriate for specialist services. Not for oral or anal lesions. Patient must attend service in person. Immediate result DFA test Specimen collected as for dark-field microscopy, air dried on a glass slide, and stained with labelled anti-T. pallidum globulins immediately before fluorescence microscopy. Specimen does not need to be fresh, so can be transported to laboratory. High sensitivity (>90%) if the specimen is well collected. Suitable for oral lesions DFAT test DFA test adapted to histology specimens, usually transported in 10% buffered formalin. Skin, brain, placenta, umbilical cord, or gastrointestinal biopsy specimens can be tested PCR test Suspected chancres or lightly abraded lesion swabs in PCR transport medium. Possibly cerebrospinal fluid and placental blood. Very sensitive for moist primary and secondary lesions, but only available in referral laboratories DFA, direct fluorescent antibody; DFAT, direct fluorescent antibody tissue; PCR, polymerase chain reaction.

8.6.37 Syphilis 1219 Serology Broadly there are two types of serological tests for syphilis, nonspecific (or nontreponemal or reagin) tests and specific (or treponemal) tests. Although less sensitive for some stages of syphilis as well as being less specific, nonspecific tests require less expertise, are cheaper, and are more indicative of active infection so they were often initially favoured for screening. Specific tests usually remain positive after treatment, limiting their ability to detect reinfection (Fig. 8.6.37.8). However, specific tests have now become first line screening assays in most settings, and are followed by reflex non specific testing if the specific test is reactive, Nonspecific serological tests The RPR and VDRL tests are flocculation tests targeting the phospholipid cardiolipin as an antigen. They are relatively sensi- tive in early infection (77 to 88% for primary syphilis and 100% for secondary syphilis), but tend to decline over the next several years without treatment (Fig. 8.6.37.8). Nonspecific tests are used for follow-up after treatment because they are readily able to quantify disease activity. In general, a fourfold change in titre is taken as evi- dence of cure, relapse, or reinfection. Broadly equivalent, RPR tests can be read macroscopically while VDRL tests require a microscope. The toluidine red unheated serum test (TRUST) is a variant of the RPR test. The VDRL test is the only syphilis test recommended for CSF evaluation. Such antilipoidal antibodies may be produced by other forms of acute or chronic tissue damage, so confirmation with a specific test is needed if there is no other sign of syphilis. Acute false-positive results are associated with acute infections such as hepatitis, herpes virus infections, measles, and malaria, as well as immun- izations and pregnancy. Chronic (exceeding 6 months) false- positive reactions are associated with connective tissue disorders, immunoglobulin abnormalities, drug injecting, ageing, malaria, and malignancy. Specific serological tests These tests use T. pallidum as the antigen and may become posi- tive shortly before the nonspecific tests. The specific tests typically (more than 85%) remain reactive for life after successful treatment and they do not provide meaningful quantitative results, so they have no role in assessing stage of infection, ‘cure’, or reinfection. They are technically more difficult and expensive than nonspecific tests, so they may not be available for confirmation in resource-poor environments. Examples of specific tests include the T. pallidum haemagglutination assay (TPHA), the T. pallidum particle agglu- tination assay (TPPA), and the microhaemagglutination assay for antibodies to T. pallidum (MHA-TP). The fluorescent treponemal antibody absorption (FTA-ABS) test is often used as a confirmatory test and may be the first serological test to become positive in pri- mary syphilis, so it may be added to the nonspecific test to investi- gate a genital ulcer. Newer multiantigen enzyme

immunoassays (EIAs) for IgG antibodies against T. pallidum are becoming increasingly common in high-volume laboratories because they are more objective and can be automated. The EIAs appear to have com- parable sensitivity (70–90% for primary and 100% for secondary syphilis) and specificity to the other specific tests. There is con- siderable overlap in the causes of false-positive specific and non specific tests. As IgM antibodies are large and considered unable to cross the placenta, FTA-ABS, and EIA versions of the IgM test have been used on neonates to assess possible congenital infection. The use of IgM tests is not established, and a negative IgM test does not exclude con- genital syphilis. Available only in reference laboratories, western blot can detect IgG or IgM antibodies and appears to be at least as sensitive as other specific tests for syphilis. The IgM western blot looks promising as an aid to diagnosing congenital syphilis with a specificity over 90% and a sensitivity over 83%. Several rapid point-of-care tests have been developed for syph- ilis. The majority are qualitative, and rely on detection of specific serological markers. Sensitivity compared to conventional EIA or TPPA testing is between 80 and 100%. Some point-of-care tests also include a qualitative assessment of nonspecific reactivity to help distinguish active from prior infection, and perform rela- tively well (sensitivity 80–90%) when the RPR titre is greater than 1:4. These tests have a particular role in developing country settings. Criteria for diagnosis Primary syphilis The direct detection of T. pallidum (Table 8.6.37.3) from an ulcer confirms a diagnosis of primary syphilis. Alternatively, a clinic- ally suspicious ulcer and any positive serological test are accepted as a confirmed diagnosis, although more than one serological test is normally ordered if resources permit. If initially seronegative, patients with suspicious ulcers should have repeat serology in 2–4 weeks. Secondary syphilis Treponemes may be demonstrated in moist mucocutaneous lesions of secondary syphilis, although suggestive symptoms or signs (Table 8.6.37.1) plus a positive RPR test are sufficient for the diagnosis. The nonspecific tests are normally reactive at high titres. 0 1 2 3 64 32 16 8 4 2 Years Primary Secondary Latent/tertiary Treatment Titre RPR TPHA FTA (Abs) EIA Fig. 8.6.37.8 Serological response to syphilis and its treatment.

section 8 Infectious diseases 1220 Latent syphilis The diagnosis of latent syphilis requires two positive serological tests, at least one of them a specific test. Recent symptoms sug- gestive of primary or secondary (Table 8.6.37.1) syphilis, or a history of a negative test in the last 1 or 2 years, indicates early latent syphilis. The sexual risk history should be consistent with this clinical staging. Generally, nonspecific reactive test titres are higher in early latent than in late latent infection. In many cases a diagnosis of late latent syphilis or latent syphilis of unknown dur- ation is a diagnosis of last resort after risk and symptom history, clinical examination, and serological picture are judged together. Past childhood treponemal infection remains a possible explan- ation in some cases. Neurosyphilis Neurosyphilis is defined as a reactive CSF-VDRL or a CSF mono- nuclear pleocytosis of more than 5 cells/μl, or both. While a re- active CSF-VDRL is very specific it has limited sensitivity (up to 70%) in detecting neurosyphilis. CSF protein concentration may be elevated. Because HIV can cause a CSF pleocytosis anyway, against a background of HIV infection a cut-off of more than 20 cells/μl has sometimes been used for a neurosyphilis diagnosis. A bloody tap might confound the diagnosis, while symptoms or signs of neurosyphilis add confidence to the diagnosis. CT or MRI of the brain or spinal cord might demonstrate lesions compatible with tertiary syphilis. Gummatous syphilis Gumma can be diagnosed clinically (Fig. 8.6.37.6) with reactive ser- ology but, as clinical experience is limited, histological confirmation is usual. Cardiovascular syphilis Aortic valve disease or proximal aortic aneurysm with reactive syphilis serology strongly suggest cardiovascular syphilis. However, aneurysm and calcification of the aortic wall are found in other con- ditions such as hypertension. Coronary angiography demonstrates ostial stenosis. Congenital

syphilis The diagnosis of congenital syphilis is often problematic, and many neonates are treated before it can be confirmed because of the high risk of serious disease. Direct detection of T. pallidum from the placenta or nasal discharge or skin lesions of a newborn infant is definitive but rarely achievable. Usually the diagnosis relies on clinical signs (if present) and serology. Positive serological tests in the neonate may reflect passive antibody transfer from the mother, but a positive nonspecific test is useful if present in higher titres than the mother. An alternative approach to the management of a normal-looking baby of an infected mother is to perform serial quantitative nonspecific serology and treat if the titre rises. More experience is needed with PCR and western blot IgM antibody testing. As clinically indicated, long-bone and chest radiology, lumbar puncture, cranial ultrasonography, and ophthalmic examination may contribute to the diagnosis where available. Treatment Choice of antibiotics Parenteral penicillin G is the original, and remains, the preferred treatment for syphilis globally. In most parts of the world this takes the form of long-acting benzathine penicillin G injections, although some prefer daily injections with procaine penicillin, sometimes boosted with probenecid, because treponemicidal CSF levels might be achieved (Table 8.6.37.4). However, daily injections raise adher- ence and resource issues. No penicillin regime has demonstrated su- periority in controlled trials. Table 8.6.37.4 Treatment of syphilis Form of syphilis US Centers for Disease Control and Prevention (CDC) Notable variations Adult, early Benzathine penicillin G 2.4 million units (equivalent to 1.8 g) intramuscularly in one dose UK guidelines offer as an alternative: procaine penicillin G 750 mg (600 000 U) intramuscularly once a day for 10 days; or if patient averse to injections, amoxicillin 500 mg plus probenecid 500 mg orally four times a day for 14 days; or if allergic to penicillin, doxycycline 100 mg orally twice a day for 14 days Adult, late; excluding neurosyphilis Benzathine penicillin G 2.4 million units intramuscularly weekly for three doses UK alternative: procaine penicillin 750 mg intramuscularly once a day for 14 days; or if patient averse to injections, amoxicillin 2 g plus probenecid 500 mg orally four times a day for 28 days; or if allergic to penicillin, doxycycline 100 mg orally twice a day for 28 days Neurosyphilis Aqueous crystalline penicillin G 18– 24 million units intravenously per day (as 3–4 million units every 4 h or as a continuous infusion) for 10–14 days UK alternative: procaine penicillin 2.4 g intramuscularly once a day plus probenecid 500 mg orally four times a day for 14 days; or if patient averse to injections, amoxicillin 2 g plus probenecid 500 mg orally four times a day for 28 days; or if penicillin allergic, doxycycline 200 mg orally twice a day for 28 days Syphilis in a pregnant woman As per stage of adult syphilis Desensitize if allergic to penicillin (see CDC guidelines); doxycycline is contraindicated in pregnancy Congenital and childhood syphilis Aqueous crystalline penicillin G 100 000–150 000 units/kg intravenously in divided doses for 10 days UK and CDC alternative if active disease: procaine penicillin 50 000 units/kg intramuscularly once a day for 10 days; older children with primary or secondary syphilis, benzathine penicillin G 50 000 units/kg (up to 2.4 million units) in one dose; three doses if late infection or unknown duration of infection; child-protection assessment is essential CDC, Centers for Disease Control and Prevention (United States of America).

 Injectable ceftriaxone has been used with short-term success al- though the exact dose, frequency, and length of course are uncer- tain. Oral doxycycline provides an alternative for those with an allergy to penicillin, when there is no access to clean needles, or when the patient is averse to injections. Neither of these agents has been well studied. Macrolides such as erythromycin and azithromycin have also been used, but the rapid emergence of high-level resistance on four con- tinents, attributable to a single mutation in the T. pallidum genome, makes this group of antibiotics inappropriate in most settings. Some physicians use oral corticosteroids to

reduce the adverse ef- fects of the Jarisch–Herxheimer reaction in neurological and cardio- vascular syphilis although there is no systematic evidence to support this practice. Contacts Sexual contacts of early syphilis should be treated presumptively re- gardless of their test results if the contact was within 90 days, usu- ally with a single dose of benzathine penicillin G. Contacts beyond 90 days can be treated according to the clinical picture and serology results unless follow-up is uncertain. Follow-up The goals of treatment are to cure symptoms and signs of infection if present, to render the patient noninfectious, and to prevent late complications occurring or progressing. In primary or secondary syphilis, lesions and constitutional symptoms should be well on the way to resolving within days. However, some symptoms of early neurosyphilis may persist for several months. Antibiotic therapy halts further damage in cardiovascular, neurological, and gumma- tous syphilis but is usually unable to repair tissue damage that has already occurred. Follow-up serology can be performed at 3, 6, and 12 months from treatment. Defining successful treatment of early syphilis relies on demonstrating a fourfold decrease in reagin (RPR or VDRL) titres over the next 6–12 months. If there is ongoing risk, reinfection may be impossible to separate from relapse; both are defined as a fourfold rise in reagin titres on at least two occasions. In late infections, where reagin titres are typically low, no drop in titre may be demonstrable. Frequently, a persistently low or nonreactive reagin test, an absence of current symptoms, and a history of adequate treatment must be accepted as a cure. Regular reagin testing is recommended for those at ongoing risk of reinfection. Jarisch–Herxheimer reaction The Jarisch–Herxheimer reaction can occur in up to 50% of those with primary syphilis and more than 70% of patients with sec- ondary syphilis, but it is uncommon in late syphilis. This transient influenza-like reaction occurs between 4 and 24 h (median 8 h) after the first dose of antibiotics and lasts for several hours with malaise, low-grade fever, flushing, and tachycardia. Early and late lesions might transiently flare, secondary rashes might appear for the first time (and be mistaken for penicillin allergy), and cranial nerve and cardiovascular symptoms might worsen. In rare cases, premature labour and fetal distress have been induced. The reaction can result from the release of endotoxin-like substances from killed T. pallidum. Patients should be warned in advance and advised to stay home for the first night with paracetamol at hand. Prognosis Since the advent of penicillin, the late complications of tertiary syphilis are relatively rare and adult mortality is almost never seen. However, in resource-poor environments or where antenatal screening is not routine, fetal wastage and serious congenital disease remain common. With treatment all mucocutaneous syphilis lesions rapidly re- solve, sometimes leaving an atrophic scar. Deformities of bones and teeth generally persist for life. The symptoms of early neuro- syphilis usually resolve although this can take several months. The symptoms and signs of late neurosyphilis generally persist but they should not progress. Follow-up CSF examination should docu- ment a declining pleocytosis (if present initially) by 6 months, al- though the CSF-VDRL might take longer to normalize. Areas of controversy The role of lumbar puncture Lumbar puncture is indicated if neurological or ophthalmic symp- toms or signs are present. The role of lumbar puncture in the diag- nosis, treatment, and follow-up of other patients with syphilis has been debated. Resource and patient consent issues can be difficult. Many experts believe that if using a treatment regimen that is likely to enter the CSF such as daily procaine penicillin, then a lumbar puncture before treatment does not alter management of the case and can be omitted. Lumbar puncture can then be limited to cases where investigation might alter management, such as in cases of difficult differential diagnosis or possible relapse. HIV infection HIV and syphilis are both transmitted sexually so it is not sur- prising that both infections often coexist. Additionally, syphilis lesions can facilitate both the transmission and acquisition of HIV infection. Early syphilis can lead to a moderate decline in periph- eral CD4 cell counts and an

elevation of plasma HIV-1 viral load in HIV-infected people; both phenomena resolve with syphilis treatment. No unique clinical syphilis syndromes have been reported in people with concurrent HIV infection. Limited, largely anecdotal, evidence suggests some more aggressive clinical manifestations of syphilis in HIV infection, but this is the exception rather than the rule. Early neurosyphilis might be more common but the diagnosis is compounded by the HIV infection itself causing neurological symptoms and CSF abnormalities. Higher CSF lymphocyte counts (20 rather than the usual 5 cells/μl) have been used to diagnose neurosyphilis because HIV commonly causes a CSF pleocytosis without syphilis. Higher serum RPR titres (≥1:32) and a lower peripheral CD4 cell count (<350 cells/μl) have been shown to be predictive of neurosyphilis, making these tests relative indica- tions for lumbar puncture particularly if both are present. Some

section 8 Infectious diseases 1222 have argued for routine lumbar puncture for HIV-infected people with syphilis, while others, noting that neurosyphilis remains un- common even in this group, advocate limiting lumbar puncture to people with neurological or ocular symptoms, treatment failure, or late latent syphilis. Despite some early reports of HIV-coinfected patients with nega- tive serological tests in early syphilis, larger studies have failed to show any significant difference and standard syphilis testing proced- ures are recommended in HIV infection. In general, authorities such as the United States Centers for Disease Control and Prevention recommend routine treatment with benzathine penicillin G (Table 8.6.37.4) in HIV infection. A higher rate of serological treatment failure (defined as a four- fold decrease in RPR titre at 6–12 months) has been documented in HIV infection (c.20%) compared to HIV-uninfected people (5%). However, the clinical significance of this finding is unknown, and reinfection is always a possibility. Likely developments in the near future Nucleic acid amplification tests such as PCR will aid the aetiological diagnosis of genital ulcers if they can be made widely available in multiplex form (i.e. testing for all serious causes of genital ulcers in a single test). PCR technology, including multi-locus sequence typing, has also led to the delineation of different subtypes of syphilis, and this intraspecies variation might go some way to explaining the dif- ferent phenotypes exhibited in clinical practice. PCR testing may also improve the diagnosis of congenital syphilis. At a more mundane level, improving the availability of low-skill temperature-stable rapid syphilis tests that do not require refriger- ation or even electricity could achieve a great deal in resource-poor environments where syphilis is most common. Early experience with immunochromatographic test strips coated with T. pallidum antigens that give results in 8–20 minutes have been encouraging. The sequencing of the genome might eventually enable the devel- opment of a vaccine, but funding for syphilis research would need to be dramatically increased. The role of chemoprophylaxis, typically using doxycycline, as a prevention intervention during a syphilis epidemic has been in- vestigated in a number of studies and has shown promising results among high risk men-who-have sex with men in Western countries. Further research is required to determine if this is a useful and safe intervention at a population level. Finally, the impact of HIV pre-exposure prophylaxis on con- sistent condom use among men who have sex with men and the con- sequent effect on STI transmission, including syphilis, needs careful monitoring. FURTHER READING Bristow C, et al. (2015). A review of recent advances in rapid point-of- care tests for syphilis. Sex Health, 12, 119–25. British Association for Sexual Health and HIV (2015). UK national guidelines on the management of syphilis. https://www.bashh.org/ guidelines Cates W Jr, Rothenberg RB, Blount JH (1996). Syphilis control: the historical context and epidemiological basis for interrupting sexual transmission of Treponema pallidum. Sex Transm Dis, 23, 68–75. Centers for Disease Control and Prevention (2015). Sexually trans- mitted diseases treatment guidelines 2015. MMWR Recommen dations and Reports, 64, 1–140. Centurion-Lara A, et al. (2006). Molecular

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