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section 8 Infectious diseases 1176 the lacrimal concretions that are usually present and local applica- tion of antimicrobials always result in prompt cure. Trueperella pyogenes (formerly Arcanobacterium, Actinomyces, or Corynebacterium pyogenes, respectively) and Arcanobacterium haemolyticum (formerly Corynebacterium haemolyticum) cause acute pharyngitis, urethritis, cutaneous or subcutaneous suppur- ations, or bacteraemia. The recently described species A. graevenit- zii, A. europaeus, A. radingae, A. turicensis, A. funkei, A. cardiffensis, A. hongkongensis, A. oricola, A. urogenitalis, A. dentalis, A. mas- siliensis, A. timonensis, and A. hominis, as well as Trueperella (Arcanobacterium, Actinomyces) bernardiae, Actinobaculum schaa- lii, and Varibaculum cambriense have been isolated from various clinical sources including abscesses and blood cultures, and may also be associated with mixed bacterial flora. A. neuii subsp. neuii and A. neuii subsp. anitratus are most frequently involved aetio- logically in abscesses and infected atheromas, but may also cause infections of skin structures, endophthalmitis, and bacteraemias including endocarditis. A. turicensis and possibly A. urogenitalis seem to be particularly common in genital infections, while A. rad- ingae was found only in patients with skin-related pathologies and A. nasicola was isolated from pus from the nasal antrum. A. euro- paeus, A. turicensis, and A. urogenitalis as well as Actinobaculum schaalii, A. urinale, and A. massiliense were detected in predomin- antly elderly patients with urinary tract or bloodstream infections, and A. radicidentis was isolated from infected root canals of teeth. FURTHER READING Bonnefond S, et al. (2016). Clinical features of actinomycosis: a retro- spective, multicentre study of 28 cases of miscellaneous presenta- tions. Medicine (Baltimore), 95, e3923. Hall V (2011). Genus V. Varibaculum Hall, Collins, Lawson, Hutson, Falsen, Inganäs and Duerden 2003, 644VP. In: Whitman WB, et al. (eds) Bergey’s manual of systematic bacteriology, 2nd edition, Vol. 5: Actinobacteria, pp. 139–40. Springer-Verlag, Dordrecht. Henssge U, et al. (2009). Emended description of Actinomyces naeslundii and description of Actinomyces oris sp. nov and Actinomyces johnsonii sp. nov., previously identified as Actinomyces naeslundii genospecies 1, 2 and WVA 963. Int J Syst Evol Microbiol, 59, 509–16. Lawson PA (2011). Genus II. Actinobaculum Lawson, Falsen, Åkervall, Vandamme and Collins 1997, 902VP. In: Whitman WB, et al. (eds) Bergey’s manual of systematic bacteriology, 2nd edition, Vol. 5: Actinobacteria, pp. 109–14. Springer-Verlag, Dordrecht. McNeil MM, Schaal KP (1998). Actinomycoses. In: Yu VL, Merigan TCJr, Barriere SL (eds) Antimicrobial therapy and vaccines, pp. 14–22. Williams and Wilkins, Baltimore, MD. Ng LSY, et al. (2012). Comparison of phenotypic methods and matrix-assisted laser desorption ionisation time of flight mass spectrometry for the identification of aero-tolerate Actinomyces spp. Isolated from soft-tissue infections. Eur J Clin Microbiol Infect Dis, 31, 1739–52. Pulverer G, Schütt-Gerowitt H, Schaal KP

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2nd edition, Vol. 1, pp. 850–905. Springer, Berlin. von Graevenitz A (2011). Actinomyces neuii: review of an unusual in- fectious agent. Infection, 39, 97–100. Yassin AF, et al. (2011). Comparative chemotaxonomic and phylo- genetic studies on the genus Arcanobacterium Collins et al. 1982 emend. Lehnen et al. 2006: proposal for Trueperella gen. nov. and emended description of the genus Arcanobacterium. Int J Syst Evol Microbiol, 61, 1265–74. Yassin AF, Schaal KP (2011). Genus III. Arcanobacterium Collins, Jones and Schofield 1983, 438VP. In: Whitman WB, et al. (eds) Bergey's manual of systematic bacteriology, 2nd edition, vol. 5: Actinobacteria, pp. 114–26. Springer-Verlag, Dordrecht. Zelyas N, et al. (2016). Infections caused by Actinomyces neuii: a case series and review of an unusual bacterium. Can J Infect Dis Med Microbiol, 2016, 6017605. 8.6.31 Nocardiosis Roderick J. Hay ESSENTIALS Nocardia species—Nocardia asteroides, N. brasiliensis, and N. otidiscaviarum—are Gram-positive, filamentous, partially acid-fast bacteria. They are occasionally detectable in environmental sources such as soil, but they rarely cause infections in humans, although they can give rise to a variety of different diseases. In healthy individ- uals, most commonly in the tropics, they can present with cutaneous abscesses or subcutaneous infections (actinomycetoma) in which the organisms are present as clusters of filaments or grains. In im- munocompromised patients they cause a disseminated or localized deep infection, with particular sites affected being the lungs or brain. Diagnosis of Nocardia infection depends on culture, although histo- pathology is very useful in Nocardia actinomycetomasiii. Antibiotic treatment is typically with a sulphonamide (often as co-trimoxazole for lung infections), but combinations of drugs are usually given be- cause the responsiveness of Nocardia species is very variable.

8.6.31 Nocardiosis 1177 Introduction Nocardiosis (nocardiasis) is the infection caused by Nocardia species; over 80 different species are now known, many of which cause human infection. Nocardia farcinica, N. brasiliensis, and the N. nova, N. abscessus, and N. transvalensis complexes are the most common. N. farcinica appears to be more virulent than the others as it is more likely to present with disseminated disease and is more resistant to antimicrobials. Molecular studies indicate that N. brasiliensis, N. otitidiscavarium, and N. transvalensis exhibit diverse characteristics and it is anticipated that new species will continue to emerge. Nocardia asteroides once the name of the most common Nocardia is still a cause of disease but many of the isolates previously identified N. asteroides have been transferred to the newer species. Nocardiosis most commonly affects the lungs (39% of cases) but may be systemic (≥2 sites involved, 32%), involve

the central nervous system (9%); cutaneous (8%), or occur at a single extrapulomonary site (e.g. eyes, bone; 12%). The nocardia are Gram-positive filamentous branching bacteria that ramify in infected tissues. They can also break up into bacil- lary forms and, in some conditions, aggregate into grains typical of mycetomas. These organisms are aerobic and partially acid fast. They grow readily on ordinary laboratory media. Pathogenesis Nocardia are found in soil, particularly where there is decaying vegetation, and in aquatic environments. They can also be isolated from the air and, in most cases, systemic infection is by the airborne route; rarely nocardiosis can be acquired after inoculation into the skin. The characteristic histopathological response to infection is the production of polymorphonuclear leucocyte abscesses without ex- tensive fibrosis. Caseation and palisading granulomas are not gener- ally seen. Dissemination to other organs such as brain and skin can occur. By contrast, in primary cutaneous infections the lesion is usu- ally localized to an abscess containing filaments at the site of inocu- lation and is accompanied by local lymphadenopathy. Mycetoma grain formation may occur in some of these infections that follow inoculation. It is not known why, in some patients, transcutaneous infection with nocardia results in the development of a mycetoma whereas in others a subcutaneous abscess containing filaments is formed. The formation of mycetomas appears to be more common with N. brasiliensis infections. Epidemiology In the early 1970s the incidence of nocardiosis was estimated to be 500 to 1000 cases per year; this is likely to be an underestimate as nocardiosis is not a notifiable disease. The current incidence is likely to be much higher as the number of immunocompromised indi- viduals at risk for nocardiosis (e.g. transplant recipients) increases. Otherwise healthy patients may be infected by Nocardia, although the frequency of subclinical exposure and sensitization in normal populations is unknown. However, most patients with systemic nocardiosis are immunocompromised, most commonly with a con- dition that affects the expression of T-lymphocyte-mediated im- mune responses. Underlying conditions include: • malignancies, including cancer and lymphoma • HIV infection and other immunodeficiency states such as chronic granulomatous disease • solid organ transplantation • other conditions that require high doses of corticosteroids, such as collagen vascular disease and rheumatoid arthritis • pre-existing pulmonary disease; alveolar proteinosis, in particular, seems to predispose to nocardiosis • tumour necrosis factor α inhibitors Inhalation of the organism is thought to be the most common route of infection and is supported by evidence that most infections involve the lung. Other modes of entry include ingestion of con- taminated food, direct inoculation into the skin (causing cutaneous disease), and nosocomial transmission (e.g. a report of a cluster of postoperative sternal wound infection caused by N. farcinica). The usual site of primary infection is the lung and the disease may remain restricted to this site. It may also be disseminated to other organs, particularly to the brain and skin. Nocardiosis can occur at any age, although it is rare, particularly in childhood. Clinical features Primary cutaneous nocardiosis This is an uncommon infection that appears to follow traumatic inoculation of organisms into a superficial abrasion. The usual primary lesion is a small nodule, ulcer, or abscess at the site of in- oculation. There may be a small chain of secondary nodules (as in sporotrichosis, see Chapter 8.7.1) along the course of a lymphatic and local lymphadenopathy is common (Fig. 8.6.31.1). Some such cases resolve spontaneously. This form of disease can be caused by a variety of different species Nocardia mycetoma This is discussed in Chapter 8.7.1; N. brasiliensis is the usual cause. Fig. 8.6.31.1 Extensive chronic nocardiosis at site of injury in a
27-year-old Peruvian man, Instituto de Medicina Tropical ‘Alexander
von Humboldt’, Universidad Peruana Cayetano Heredia, Lima, Peru. Copyright D. A. Warrell.

section 8 Infectious diseases 1178 Pulmonary nocardiosis Pulmonary infection is seen in about 75% of cases of systemic nocardiosis, even where there are disseminated lesions elsewhere. Symptoms of pulmonary nocardiosis are variable with cough, fever, and leucocytosis. In otherwise healthy individuals the changes and signs may be very similar to pulmonary tuberculosis, whereas in the immunocompromised patient the lesions present as rapidly developing single or multiple lung lesions. In HIV-infected patients symptoms are often minimal, even in the presence of extensive dis- ease. These changes are reflected by the course of the disease. In some patients progression is rapid, in others it is chronic. Chest radiographs may show segmental or lobar infiltrates, cavi- tation, nodules, or diffuse miliary infiltrates; endobronchial infec- tion has been recorded. Calcification is not common. The infection may spread locally to involve adjacent structures such as the pleural space and diaphragm or may spread to other sites. Very occasionally, Nocardia spp. can be isolated from sputum of otherwise healthy pa- tients. Whether this reflects the process of asymptomatic sensitiza- tion is not known. Disseminated nocardiosis Haematogenous spread is seen in the immunocompromised pa- tient and may occur without evidence of pulmonary infection. The most common site for dissemination is the brain where it presents with localized abscesses without meningeal involvement. The signs are those due to an intracerebral space-occupying lesion. Spread to other sites is less common, although dissemination to skin, liver, kidneys, and bone may occur. The acute disseminated forms and those with involvement of the central nervous system have the worst prognosis. Continued therapy with corticosteroids also appears to have bad prognostic signifi- cance. Infection in HIV-infected patients may not be recognized before death. Rapid diagnosis is therefore a key to successful man- agement. By contrast, pulmonary infection in otherwise healthy pa- tients is usually a chronic process and has to be distinguished from tuberculosis. Laboratory diagnosis The infection is often recognized initially by direct microscopy of pus, bronchial washings, or tissue. In Gram’s stains the organisms can be shown as fine branching filaments, although distinction from other bacteria may be difficult if short rod-like forms predominate. A modified acid-fast stain using weak acid can be used to demon- strate filaments. Nocardia grow on ordinary media aerobically but require pro- longed incubation as colonies may take 5 to 21 days to appear. The laboratory should be informed if nocardiosis is suspected as cul- tures will need prolonged incubation. Growth may be enhanced by the use of selective media such as buffered charcoal yeast ex- tract and Thayer–Martin medium. Nocardia have variable colonial morphology varying from chalky white to yellow, orange, or brown colonies. Speciation of nocardia using conventional phenotypic methods is difficult and time-consuming. Polymerase chain reaction for identification of nocardia species is more rapid and accurate than the phenotypic tests but is not available in routine diagnostic laboratories. Antimicrobial susceptibility testing should be performed for all clinically significant isolates. The optimal method is the broth microdilution method, but minimum inhibitory concentrations may be difficult to interpret. Histopathological examination is useful in some cases. Filaments stain with modified acid-fast stains using an aqueous solution of a weak acid for decolourization, but can also be highlighted with the methenamine–silver stain (Grocott’s modification). The branching nature of the organism is best appreciated in histopathological ma- terial. Other pathogens such as Pneumocystis spp. may also be pre- sent in histopathological material. Serological tests (usually counterimmunoelectrophoresis or en- zyme immunoassay) can be obtained in reference centres and are generally used to monitor the progress of therapy rather than estab- lish the diagnosis. Therapy The mainstays of therapy are sulphonamides, and the first choice is often co-trimoxazole, particularly in pulmonary forms, al- though it still unclear how helpful the trimethoprim component is, particularly in intracerebral infections. In many cases, drainage of abscesses may hasten recovery. Some species of Nocardia

often do not respond as well to particular antibiotics; N. otitidiscavi- arum, for instance, is generally resistant to cotrimazole. Much of the recommended drug therapy is derived from the personal ex- periences of a few cases. However, wherever possible sensitivity testing is advised. Other drugs that have been used include amikacin, ampicillin, cefotaxime, imipenem, linezolid, moxifloxacin, and minocycline. Experience of other drugs is similarly limited. It is the general prac- tice to use two antibiotics eg cotrimoxazole and cefotaxime for nocardiosis. Clustering of cases may occur occasionally, suggesting exposure to a common source of infection. In two such episodes there had been extensive construction work in the vicinity of the hospital in- volved. At present, no methods of prevention are known, although the existence of more than two cases in a single or adjacent wards should alert clinicians to the possibility of environmentally acquired infection. FURTHER READING Boiron P, et al. (1992). Review of nocardial infections in France, 1987– 1990. Eur J Clin Microbiol Infect Dis, 11, 709–14. Brown-Elliott BA, Conville P, Wallace RJ (2015). Current status of Nocardia taxonomy and recommended identification methods. Clin Microbiol Newsletter, 37, 25–32. Filice GA (2005). Nocardiosis in persons with human immunodefi- ciency virus infection, transplant recipients, and large, geographic- ally defined populations. J Lab Clin Med, 145, 156–62. Georghiou PR, Blacklock ZM (1992). Infection with Nocardia spe- cies in Queensland: a review of 102 clinical isolates. Med J Aust, 156, 692–7.

1179 8.6.32 Rat bite fevers (Streptobacillus moniliformis and Spirillum minus infection) Hay RJ (1983). Nocardial infections of the skin. J Hyg (Lond), 91, 385–91. Houang ET, et al. (1980). Nocardia asteroides infection: a transmissible disease. J Hosp Infect, 1, 31–6. Kilincer C, et al. (2006). Nocardial brain abscess: review of clinical management. J Clin Neurosci, 13, 481–5. Sakai C, Takagi T, Satoh Y (1999). Nocardia asteroides pneumonia, subcutaneous abscess and meningitis in a patient with advanced malignant lymphoma: successful treatment based on in vitro anti- microbial susceptibility. Intern Med, 38, 683–6. Wilson JW (2012). Nocardiosis: updates and clinical overview. Mayo Clin Proc, 87, 403–7. 8.6.32 Rat bite fevers (Streptobacillus moniliformis and Spirillum minus infection) Andrew F. Woodhouse ESSENTIALS Rat bite fever is usually attributable to Streptobacillus moniliformis in the Americas, Europe, and Australasia, and to Spirillum minus in Asia. Bites are increasingly common among children with pet rats, and pet shop and laboratory workers. Both bacteria are com- mensals of rats, some other rodents, and their predators. After an incubation period less than 1 week, S. moniliformis causes sudden high fever, rigors, myalgia, petechial rash, and migratory reactive or septic polyarthritis with synovial effusions. Complications can in- clude fulminant septicaemia, endocarditis, pneumonia, and meta- static abscesses.
S. minus infection (sodoku) has a longer incubation period with similarly high fever but concomitant exacerbation of the bite wound, local lymphadenopathy, papular rash, and arth- ralgia without effusions. In both diseases, fever subsides after a few days but may relapse repeatedly over months. Untreated, mor- tality is about 10% for S. moniliformis and 2 to 10% for S. minus.
S. moniliformis can be cultured (with some difficulty) and the diag- nosis confirmed by molecular methods. S. minus infection cannot be confirmed by culture or serology, but the organism may be visualized by microscopy in involved tissue and sometimes blood. Penicillin is the treatment of choice for both infections. Prevention is by controlling peri-domestic rats and avoiding bites by pet or laboratory rodents. Introduction The rat bite fevers (RBF) are zoonotic infections of humans caused by one of two distinct bacteria—Streptobacillus moniliformis or Spirillum minus. The illnesses caused by these organisms have overlapping features but are also distinct in several ways. Febrile illness developing after rat bites has been recognized for centuries and the risk of infection after a bite is reported to be as high as 10%. Despite this these infections remain rare and

underdiagnosed due to the nonspecific nature of their clinical presentation. This is compounded by the difficulty of microbiological confirmation of infection. Rats are one of the most populous mammalian species on earth and human interaction with wild rats is increasing, particularly where rat infestation occurs in deprived urban and rural commu- nities. In addition, the popularity of rats as pets and their use as laboratory animals has led to more human-animal interaction and greater likelihood of bites, scratches, and other forms of contact in more developed and affluent settings. Antibiotic treatment is generally effective and while untreated disease can be self-limiting, reported mortality of up to 10% for both forms of RBF is described. Important complications include septicaemia with multiorgan failure, endocarditis, pericarditis, meningitis, deep organ abscess development, and osteoarticular infections. Aetiology Streptobacillus moniliformis is the cause of streptobacillary RBF and Haverhill fever. It is a nonmotile, filamentous Gram-negative bacillus. It is fastidious and microaerophilic, requiring blood, serum, or ascites enriched tryptone soy agar or broth to optimize growth. Spirillum minus is the other causative agent of rat bite fever, re- sponsible for the febrile syndrome known in Japan as Sodoku (de- rived from So = rat and doku = poison). S. minus is a tightly coiled Gram-negative rod, motile by virtue of terminal flagellae. It is a spir- illum and has not been successfully cultured on artificial media but can be transferred to mice or guinea pigs by inoculation of infected tissue. The inability to grow the organism in vitro makes confirma- tory diagnosis difficult. Streptobacillus moniliformis is found in the oropharynx of most wild rats and a significant proportion of pet and laboratory rats. It has also been isolated from other rodents and animals that prey on rats, broadening the potential pool of infective sources. Spirillum minus is also a commensal of rats, estimated to be found in 25% of animals and has been found in blood and oral and respiratory tissue and secretions. Transmission of both organisms to humans occurs most often via a contaminated bite wound, but transmission without a bite is possible. Infection can occur via scratches or mucosal contact after handling either live or dead animals. Human in- fection is usually associated with rat contact, but other rodents and animals have been occasionally implicated as sources of S. moniliformis infection. Ingestion of food or fluids (e.g. water or unpasteurized milk) contaminated with S. moniliformis can lead to the form of RBF known as ‘Haverhill fever’, named after the town in Massachusetts where an outbreak of the disease was first described in 1926.

section 8 Infectious diseases 1180 Epidemiology Streptobacillus moniliformis infection occurs worldwide causing streptobacillary rat bite fever. Based on published series and case re- ports it is a more common cause of RBF than Spirillum minus in Europe, Australasia, and the Americas. Rat bite fever due to S. minus is mostly found in Asia, particularly Japan, although several case reports exist from other continents suggesting the distribution is probably worldwide. Understanding the extent of the problem of these zoonotic infections is limited by a lack of systematic reporting and data collection. In regions where rats infest human habitats, rat bites might occur at night during sleep and might not always be appreciated, with children at particular risk. Owners of pet rats, pet shop, and labora- tory workers are groups recognized to be at increasing risk of rat bite fever. Clinical features An abrupt onset systemic illness is the hallmark of the rat bite fevers. Considering the diagnosis when evaluating patients with fever and rash, and the features outlined next, is important for early recog- nition and treatment. Asking appropriate questions about potential exposures to wild or domesticated rats, directly or indirectly can be key. A history of a definite bite might not be forthcoming, but this does not rule out the diagnosis. Clinical features of Streptobacillus moniliformis infection Streptobacillary RBF presents after a short incubation, typically three to ten days after exposure. If a bite has occurred, there is usu- ally only minor

evidence of the wound. Illness is sudden in onset with high fever and rigors, headache, nausea, vomiting, and my- algia. Rash occurs within the first week of illness in up to 75% of patients. The rash is varied and can be maculopapular, vesicular (sometimes with haemorrhage), petechial, or pustular. Usually sym- metrical, it involves the limbs and often the palms and soles, which is a helpful clinical feature to aid early diagnosis. Desquamation oc- curs in about a fifth of cases. Joint involvement is common early after onset of fever with about half of patients developing a migra- tory polyarthralgia or arthritis involving large and small joints. The arthritis is often reactive but true septic arthritis can occur. Haverhill fever, (erythema arthriticum epidemicum) is similar to the illness described earlier, but vomiting and pharyngitis are more prominent symptoms in this form of RBF compared to that fol- lowing bite or mucosal inoculation. Clinical features of Spirillum minus infection In spirillary rat bite fever, the bite wound is a prominent feature of the early illness. After initial healing the area becomes swollen and painful with induration and purple discoloration after an incuba- tion period of between one and four weeks. This is associated with regional lymphadenopathy and onset of systemic symptoms with fever, headache, and malaise. The bite lesion becomes ulcerated and a generalized rash appears during the first week of symptoms, usually macular and violaceous or red-brown and involving the face and trunk as well as limbs. Arthritis and myalgia are uncommon, in contrast to streptobacillary RBF. Complications Both forms of RBF can be complicated by endocarditis but it is rare and is almost always seen in people with pre-existing valve dis- orders. A range of other complicating infections have been described including meningitis, brain and epidural abscess, spondylodiscitis, pneumonia, myopericarditis and focal abscesses, mostly associated with S. moniliformis infection. Relapsing fever If untreated both types of RBF can cause a relapsing fever. After the initial fevers resolve over a week or so, relapse may occur over intervals of days to months with S. minus infections tending to have longer fever-free periods. Cases of recurrent fevers over years have been reported. Differential diagnosis The nonspecific presentation of rat bite fevers means that a broad differential diagnosis must be considered, particularly if a history of rat exposure is not obtained. Fever with rash and joint involvement could suggest streptococcal, staphylococcal, or meningococcal in- fection. Rickettsial infection might be a consideration depending on region of residence or travel history. The rash appearance and dis- tribution might suggest secondary syphilis. Leptospirosis should be considered, particularly with a history of exposure to rats or poten- tially contaminated water. Several viruses including coxackieviruses, parvovirus B19, and even Epstein–Barr virus can present with similar features. Clinical investigations/laboratory features A neutrophil leukocytosis is usually present acutely but there are no specific haematological or biochemical abnormalities typ- ical of the RBFs. False positive nontreponemal syphilis serology is sometimes seen. Microbiological investigation Discussion with the microbiology laboratory is important if the diagnosis of RBF is suspected to optimize processing of samples. Microscopy S. moniliformis might be seen on direct gram stain of infected pus or joint fluid as a pleomorphic Gram-negative bacillus. If cultured, its pleomorphic appearance with lateral bulbar swellings on Gram stain is highly suggestive of the diagnosis. S. minus might appear as a spirochaete-like organism with Giemsa or Wright’s stain, or dark-field microscopy of aspirates or smears of infected tissue or fluid. Culture Streptobacillus moniliformis can be cultured from pus and other in- fected body fluids and tissue but requires enriched culture media to

 optimize growth. Direct isolation from blood cultures is possible but growth is inhibited by sodium polyanethol sulphonate, an anticoagu- lant found in most commercially available blood culture media, which reduces the yield. Identification by traditional

biochemical methods can be difficult but polymerase chain reaction (PCR) amp- lification of 16S ribosomal RNA sequences has been shown to be a reliable means of identifying the organism once cultured. More recently matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry analysis has been shown to suc- cessfully identify S. moniliformis. Spirillum minus is not able to be cultured. Treatment Many cases of RBF probably go undiagnosed due to the use of effective empiric antibiotics in patients presenting with non- specific fever syndromes with sepsis and rash or joint involve- ment. In the context of a suggestive illness with a supportive exposure history, starting treatment while awaiting confirmation is appropriate. Uncomplicated rat bite fever Both S. moniliformis and S. minus are susceptible to penicillin which remains the treatment of choice for suspected or confirmed RBF. There is no trial evidence to guide treatment recommendations. For uncomplicated RBF initial intravenous (IV) treatment for 5–7 days with benzyl penicillin is suggested with a switch to oral treatment to complete 14 days therapy. Recommended doses of IV penicillin G have historically been relatively low with total daily doses of 1.2–2.4 million units given in divided doses 4–6 hourly. In practice higher doses of penicillin are likely to be used initially, particularly while invasive infection and complications such as endocarditis are excluded. Oral follow on with penicillin V (500 mg four times daily) or amoxicillin (500 mg three times daily) is suitable in uncompli- cated disease. Most β-lactams are effective and ceftriaxone (1 gram daily IV) can make outpatient based intravenous antibiotic treat- ment a practical option. Alternatives for penicillin allergic patients include tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily). Macrolides, lincosamides, and glycopeptides also have good ac- tivity, with fluoroquinolones and aminoglycosides less active in vitro. Complicated infection. Recommendations for antibiotic treatment of more complicated forms of RBF are largely pragmatic, depending on the site of in- fection, and are based on the small numbers of cases published. Treatment of endocarditis due to either organism should be with higher doses of penicillin, up to 20 million units per day intraven- ously, for four to six weeks. Combination with streptomycin for the first two weeks of treatment has been recommended but there are no data to support this recommendation. Central nervous system infections will also require high dose treatment and some forms of infection (e.g. septic arthritis, spinal epidural abscess, or deep tissue collections) might need surgical intervention in addition to antibiotic therapy to ensure resolution. Prognosis/outcome Untreated infection can be self-limiting but mortality rates of 10% are recognized for both organisms with a higher likelihood of death in complicated disease such as endocarditis (50%). In general, both forms of rat bite fever respond well to antibiotic treatment. Arthralgia can be a persistent and troublesome symptom after streptobacillary disease has been treated and may take many months to settle. Prevention Preventive measures to reduce the frequency of rat bite fevers include control of wild rat populations and limiting opportunities for direct contact between feral rodents and humans. In the case of domesticated or laboratory rats, handlers and owners should use ap- propriate care when handling animals. Hand to mouth or eye contact should be avoided and hand washing encouraged following contact. Children handling pet rats should be supervised and educated about appropriate hygiene measures. Any rat bites should have the wound thoroughly cleaned and consideration given to tetanus prophylaxis. The role of pre-emptive antibiotic therapy following rat bites to prevent RBF is unproven, but several guidelines and authors advocate short courses of oral antibiotic (e.g. three days of amoxi- cillin/clavulanate or doxycycline to cover the agents of RBF and other potential contaminating bacteria). FURTHER READING Adam JK, et al. (2014). Notes from the field: fatal rat-bite fever in a child—San Diego County, California, 2013. MMWR Morb Mortal Wkly Rep, 63, 1210–1. Addidle M, et al. (2012). Epidural abscess caused by Streptobacillus moniliformis. J Clin Microbiol, 50, 3122–4.

Eisenberg T, et al. (2015). Phenotypic and genotypic characteristics of members of the genus Streptobacillus. PLoS One, 10, e0134312. Eisenberg T, et al. (2016). Approved and novel strategies in diagnostics of rat bite fever and other Streptobacillus infections in humans and animals. Virulence, 7, 630–48. Elliot SP (2007). Rat bite fever and Streptobacillus moniliformis. Clin Microbiol Rev, 20, 13–22. Gaastra W, et al. (2009). Rat bite fever. Vet Microbiol, 133, 211–28. Rupp ME (1992). Streptobacillus moniliformis endocarditis: case report and review. Clin Infect Dis, 14, 769–72. 8.6.33 Lyme borreliosis Gary P. Wormser, John Nowakowski, and Robert B. Nadelman ESSENTIALS Lyme borreliosis is a zoonotic bacterial infection caused by Borrelia burgdorferi sensu lato, a spirochaetal agent transmitted

section 8 Infectious diseases 1182 by certain species of Ixodes ticks. Small rodents and birds serve as reservoirs. It is the most common vector-borne infection in the United States of America and an important infection in many countries throughout the temperate regions of Europe and nor- thern Asia, where a wider variety of borrelia species account for differences in clinical manifestations in Eurasia compared with the United States. Clinical features—the most common and earliest clinical mani- festation is erythema migrans, a distinctive cutaneous lesion that occurs at the site of deposition of the spirochaete by the vector tick, beginning 7–14 days later as a red macule or papule, with the rash then expanding over days to weeks, with or without central clearing. This may be associated with ‘viral’ symptoms, fever, and regional lymphadenopathy. Later manifestations include (1) card- itis—usually manifested by fluctuating degrees of atrioventricular block; (2) neurological involvement—including cranial neuropathy (typically cranial nerve VII palsy), radiculopathy, and meningitis; (3) arthritis—typically migratory monoarthritis or asymmetric oligoarthritis; (4) acrodermatitis chronica atrophicans—a swollen, bluish-red appearing skin lesion in which the involved skin ultim- ately atrophies. Diagnosis—the diagnosis of erythema migrans is purely clinical in geographical areas endemic for Lyme borreliosis: serological testing is not recommended because it is insufficiently sensitive on acute phase serum samples. In patients with suspected later clin- ical manifestations, serological testing is essential because clinical findings alone lack sufficient specificity. Polymerase chain reaction testing of joint fluid and/or cerebrospinal fluid can be helpful in some cases. Treatment—most people treated for Lyme borreliosis re- spond well to a 2-week course of antibiotic therapy (preferred oral regimen usually amoxicillin, doxycycline, or cefuroxime). Symptomatic treatment is recommended for patients who have or develop subjective complaints of unclear aetiology despite successful resolution of the objective manifestation of Lyme borreliosis following antibiotic therapy, since randomized double- blind placebo-controlled trials have shown that additional anti- biotic treatment is not helpful. Prevention—measures include avoiding exposure to ticks by limiting outdoor activities in tick-infested locations, using tick repellents, tucking in clothing to decrease exposed skin surfaces, and frequent inspection of the skin for early detection and removal of ticks. Introduction Lyme borreliosis (also called Lyme disease) is named after Lyme, Connecticut, United States of America. It is caused by the spirochaete Borrelia burgdorferi sensu lato which is transmitted to humans by the usually asymptomatic bite of certain ticks of the genus Ixodes (Fig. 8.6.33.1). Borrelia burgdorferi sensu stricto (hereafter referred to as B. burgdorferi) causes the disease in North America, while in Europe, several species of Borrelia in addition to B. burgdorferi (a) (b) (c) Fig. 8.6.33.1 (a) Adult female (right) and nymphal (left) Ixodes scapularis ticks. Adult female (b) and nymph (c) of Ixodes ricinus, the vector tick in Europe.

8.6.33 Lyme borreliosis 1183 cause this infection, including B. garinii which is probably the most common cause of classic Lyme neuroborreliosis (Bannwarth’s syn- drome) and B. afzelii the most common cause of acrodermatitis chronica atrophicans, a late cutaneous complication. The entire chromosome and associated plasmids of multiple different strains of B. burgdorferi have been completely sequenced. Representative strains of other pathogenic species, such as B. afzelii and B. garinii, have also been sequenced. Epidemiology In North America more than 25 000 new cases of Lyme borreliosis are reported each year, making it the most common vector-borne disease. It occurs in north-eastern, mid-Atlantic, north-central, and far western regions of the United States of America and in limited foci in Canada (mainly in eastern Ontario). Elsewhere, it occurs in much of the temperate regions of Europe and northern Asia. Ticks acquire this borrelial infection in a complex tick–vertebrate trans- mission cycle. The white-footed mouse is the most important res- ervoir for B. burgdorferi in North America. White-tailed deer, an important host for adult Ixodes ticks, are not a competent reservoir for Lyme borrelia. In Europe a wide variety of small rodents and birds serve as reservoirs. Migrating birds might play a role in the spread of B. burgdorferi to new geographical locations. Lyme borreliosis occurs slightly more frequently in males than in females. There is a bimodal age distribution with the highest rates in children between 5 and 9 years old and in adults 55–59 years old. Clinical manifestations The somewhat different manifestations of Lyme borreliosis in Eurasia compared with North America (Table 8.6.33.1) may be explained by the wider variety of borrelia species causing infec- tion in Eurasia. Clinical features are generally similar in adults and children. Erythema migrans Erythema migrans (Figs. 8.6.33.2, 8.6.33.3), the clinical hallmark of Lyme borreliosis, is recognized in approximately 90% of patients with objective clinical manifestations of B. burgdorferi infection. Typically, erythema migrans begins as a red macule or papule at the site of a tick bite that occurred 7–14 days earlier. The rash expands over days to weeks. Central clearing might or might not be present. Secondary cutaneous lesions can develop because of haematogenous spread of spirochaetes to other cutaneous sites. Erythema migrans must be distinguished from local tick bite reactions, tinea, insect and spider bites, bacterial cellulitis, and plant dermatitis. Lesions eventu- ally resolve spontaneously, but might recur if antimicrobial therapy is not given. Systemic symptoms, such as fatigue, myalgia, arthralgia, head- ache, fever, and/or chills, and stiff neck, are less common in pa- tients with erythema migrans caused by B. afzelii compared to either B. burgdorferi or B. garinii. Prominent respiratory and/or gastrointestinal symptoms are so infrequent that their presence should suggest an alternative diagnosis or coinfection with an- other tick-borne pathogen. Aside from the erythema migrans skin lesion itself, the most common objective physical findings are regional lymphadenopathy and fever. Occasional cases of a viral-like illness without erythema migrans have been attributed to Lyme borreliosis. Carditis Typically, cardiac disease develops within weeks to months after infection, sometimes together with erythema migrans. It is usu- ally manifested by fluctuating degrees of atrioventricular block that might cause the patient to complain of dizziness, palpi- tations, dyspnoea, chest pain, or syncope. Myocarditis can be present but pericarditis with effusion is rarely observed, and endocarditis is absent. The incidence of cardiac manifestations (as measured by electrocardiogram confirmed heart block) has been observed to be low in both the United States of America (<1%) and Europe (<4%). Neurological disease The incidence of neurological Lyme disease in Europe might be higher than in the United States of America. One explanation could be the greater neurotropism of B. garinii (a genospecies which has not been isolated in North America). The principal early neuro- logical manifestations are cranial neuropathy (typically peripheral seventh nerve palsy, which can be bilateral), radiculopathy, and meningitis, which might occur alone or together. Erythema migrans Table 8.6.33.1 Lyme borreliosis in North

America compared to Eurasia North American Lyme borreliosis Eurasian Lyme borreliosis Vector Ixodes(dammini) scapularis or Ixodes pacificus Ixodes ricinus or Ixodes persulcatus Aetiological agent B. burgdorferi sensu stricto B. burgdorferi sensu stricto, B. afzelii, B. garinii, B. spielmanii Clinical features Erythema migrans is the most common manifestation Erythema migrans is the most common manifestation Systemic symptoms frequently present in patients with erythema migrans (up to 80%) Systemic symptoms infrequently present in patients with erythema migrans (<35%) Other skin manifestations such as borrelial lymphocytoma and acrodermatitis chronica atrophicans are much less common than
in Europe Other skin manifestations such as borrelial lymphocytoma and acrodermatitis chronica atrophicans are much more common than in North America (acrodermatitis chronica atrophicans is much less common in children compared with adults) Cranial nerve palsy (usually 7th) with or without meningitis is the most common neurological manifestation Painful meningoradiculoneuritis with or without cranial palsy is the most common neurological manifestation

section 8 Infectious diseases 1184 might be present concomitantly. Late neurological manifestations are uncommon and include peripheral neuropathy, encephalopathy, and encephalomyelitis. Antibiotics appear to hasten the resolution of meningitis but most studies are uncontrolled. The rate of resolution of motor dysfunc- tion, which is fully reversible in the vast majority of cases, is not en- hanced by antimicrobial therapy. Symptoms of encephalopathy and peripheral neuropathy improve or do not progress after treatment with antibiotics. Rheumatological disease Lyme arthritis occurs in both North America and Europe. In a study of 55 untreated patients with erythema migrans diagnosed in the United States of America between 1977 and 1979 and followed for a mean duration of 6 years, objective arthritis developed in more than one-half, occurring within 1 year for 90%. Most of these pa- tients developed intermittent attacks of migratory monoarthritis or asymmetric oligoarthritis, lasting a mean of 3 months per episode (range 3 days to 11.5 months). The knee was affected at some point in almost all patients, but other large and (less often) small joints could be affected. Temporomandibular joint involvement occurred in 11 (39%) of 28 patients with arthritis in one series. Although large effusions can occur, joint pain and erythema are often minimal. Baker’s cysts might develop. Typically, synovial fluid analysis reveals a modestly elevated white cell count (median 24 250 white cells/mm3 in one study) with a polymorphonuclear predominance and a normal glucose level. Synovitis lasting 1 year or more might ensue for a minority of United States patients, sometimes associated with joint destruction. Although B. burgdorferi DNA can be detected by polymerase chain reaction (PCR) in the synovial fluid of up to 85% of untreated patients with Lyme arthritis, B. burgdorferi has rarely been successfully cultured from joint fluid. Acrodermatitis chronica atrophicans This cutaneous manifestation of late Lyme disease develops insidi- ously on a distal extremity, mainly in elderly women. It is a swollen bluish-red appearing skin lesion in which the involved skin ultim- ately atrophies. One-third of patients have an associated (usually sen- sory) polyneuropathy. B. burgdorferi has been recovered from a skin biopsy specimen of an acrodermatitis chronica atrophicans lesion of more than 10 years duration. Since the usual causative agent B. afzelii does not occur in the United States of America, acrodermatitis chronica atrophicans is essentially a European disease. Miscellaneous clinical manifestations Borrelia lymphocytoma, principally caused by B. afzelii and B. garinii, is a tumour-like nodule which typically appears on the pinna of the earlobe or on the nipple or areola of the breast. Lesions will eventually resolve spontaneously but disappear within a few weeks after antibiotic therapy. This lesion is extremely rare in North America. Direct involvement of the eye (e.g. uveitis, keratitis, vitritis, optic

neuritis) has been attributed to B. burgdorferi infection. However, (a) (b) Fig. 8.6.33.2 Erythema migrans skin lesions from patients who were culture-positive for borrelia: (a) skin lesion with target-like appearance; (b) skin lesion with more homogeneous appearance. (a) (b) Fig. 8.6.33.3 English patient with typical erythema migrans. Copyright D. A. Warrell.

8.6.33 Lyme borreliosis 1185 since ophthalmological disorders have almost never been associated with the isolation of B. burgdorferi in culture, the actual pathogen- esis in these cases is uncertain. Conjunctivitis, originally described in 11% of patients with erythema migrans, was rare (<5%) in re-cent studies of culture-positive patients and might be unrelated to borrelia infection. Case reports have suggested that adverse outcomes might be associated with pregnancies complicated by maternal Lyme borreliosis. However, prospective and epidemiological studies suggest that the risk of transplacental transmission of B. burg- dorferi is probably minimal when appropriate antibiotics (Tables 8.6.33.2, 8.6.33.3) are given to pregnant women with Lyme borreliosis. There are no published data to support a congenital Lyme borreliosis syndrome. Laboratory diagnosis Where Lyme borreliosis is endemic, the diagnosis of erythema migrans is purely clinical. Laboratory testing is neither necessary nor recommended. In patients with suspected extracutaneous Lyme borreliosis, serological testing is essential to support the diagnosis. Culture of B. burgdorferi has been a highly insensitive diagnostic technique for this group of patients, presumably because of inaccessibility of tissues containing the microorganism. PCR testing of joint fluid and sometimes of cerebrospinal fluid might aid in diagnosis, provided appropriate care is taken in performing the assay accurately. A two-step approach to serological diagnosis is used in both the United States of America and Europe to increase the accuracy of a positive test. A positive or equivocal first-step test (usually an enzyme-linked immunosorbent assay (ELISA) or an indirect im- munofluorescence assay) is followed on the same serum sample by a second-stage test (immunoblot). Two-step testing, however, is not indicated for those with little or no clinical evidence of Lyme borreliosis because of a low positive predictive value. Since IgM and IgG antibodies to B. burgdorferi can persist in serum for years after clinical recovery, serology has no role in measuring response to treatment. Patients with extracutaneous Lyme borreliosis almost always have diagnostic serum antibodies at time of presentation. In some patients with early neuroborreliosis, however, antibodies to Lyme borrelia might be present in cerebrospinal fluid before they are de- tected in serum. Coinfection Ixodes scapularis ticks (Fig. 8.6.33.1a) are the vectors for sev- eral other infections that can be transmitted separately or Table 8.6.33.2 Recommended antimicrobial regimens for treatment of patients with Lyme borreliosis Drug Dosage for adults Dosage for children Preferred oral regimens Amoxicillin 500 mg three times dailya 50 mg/kg per day in three divided doses (maximum 500 mg per dose)a Doxycycline 100 mg twice dailyb <8 years: not recommended ≥8 years: 4 mg/kg per day in two divided doses (maximum 100 mg/dose) Cefuroxime axetil 500 mg twice daily 30 mg/kg per day in two divided doses (maximum 500 mg per dose) Alternative oral regimens The following dosing regimens are specifically for patients with erythema migrans or borrelial lymphocytoma: Selected macrolidesc Azithromycin 500 mg orally daily for 7–10 days, clarithromycin 500 mg orally twice daily for 14–21 days (if not pregnant), or erythromycin 500 mg orally four times per day for 14–21 days Azithromycin 10 mg/kg daily (maximum of 500 mg per day), clarithromycin 7.5 mg/kg twice daily (maximum of 500 mg per dose), or erythromycin 12.5 mg/kg four times daily (maximum of 500 mg per dose) Preferred parenteral regimen Ceftriaxone 2 g intravenously once daily 50–75 mg/kg intravenously once daily (maximum 2 g) Alternative parenteral regimens Cefotaxime 2 g intravenously every 8 hd 150–200 mg/kg per day intravenously in 3 or 4 divided doses (maximum 6 g per day)d Penicillin

G 3–4 million units intravenously every 4 hd 200 000–400 000 units/kg per day divided into six doses given every 4 hd (not to exceed 18–24 million units/day) a Although higher dosage given twice daily might be equally as effective, in view of the absence of data on efficacy, twice daily administration is not recommended. b Tetracyclines are relatively contraindicated in pregnant or lactating women and in children less than 8 years of age. c Due to their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins. Patients treated with macrolides should be closely followed to ensure resolution of the clinical manifestations. d Dosage should be reduced for patients with impaired renal function. Modified from Wormser GP, et al. (2006). The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis and babesiosis. Clinical practices guidelines by the Infectious Diseases Society of America. Clin Infect Dis, 43, 1089–134.

section 8 Infectious diseases 1186 simultaneously with B. burgdorferi, such as Babesia microti and the rickettsial agent Anaplasma phagocytophilum that causes human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis). In Europe, species of Babesia and Anaplasma are present in Ixodes ricinus ticks (Fig. 8.6.33.1b, c), which are also vectors of the flavivirus causing tick-borne enceph- alitis. Coinfection may alter the clinical presentation and response to treatment of Lyme borreliosis. Reinfections Reinfection with Lyme borrelia can often be recognized clinically by the development of a repeat episode of erythema migrans occurring at a different skin site during the months when the vector tick is plentiful in the environment. The clinical manifestations of reinfec- tion in Lyme borreliosis patients who have erythema migrans are indistinguishable from initial infection. Table 8.6.33.3 Recommended therapy for patients with Lyme borreliosisa Indication Treatment Duration (days) Range (days) Tick bite in the USA Doxycycline 200 mg (4 mg/kg in children ≥8 years of age)
and/or observation Single doseb Erythema migrans Oral regimenc, d 14 10–21e Early neurological disease Meningitis or radiculopathy Parenteral regimen or oral regimen with doxycyclinec, f 14 10–28 Cranial nerve palsyg Oral regimenc 14 14–21 Cardiac disease Oral regimenc, h or 14 14–21 Parenteral regimenc, h 14 14–21 Borrelial lymphocytoma Oral regimenc, d 14 14–21 Late disease Arthritis without neurological disease Oral regimenc 28 28 Recurrent arthritis after oral regimen Oral regimenc, i 28 28 Parenteral regimenc, i 14 14–28 Antibiotic-refractory arthritisj Symptomatic therapyk Central or peripheral nervous system disease Parenteral regimenc 14 14–28 Acrodermatitis chronica atrophicans Oral regimenc 21 14–28 Post-treatment Lyme disease syndrome Consider and evaluate other potential causes of symptoms,
if none found then symptomatic therapy a Regardless of the clinical manifestation of Lyme disease, complete response to treatment might be delayed beyond the treatment duration. Relapse can occur with any of these regimens; patients with objective signs of relapse might need a second course of treatment. b A single dose of doxycycline can be offered to adult patients and to children ≥8 years of age in the United States of America only when all of the following circumstances exist: (a) the attached tick can be reliably identified as an adult or nymphal I. scapularis tick that is estimated to have been attached for ≥36 h based on the degree of engorgement of the tick with blood or on certainty about the time of exposure to the tick; (b) prophylaxis can be started within 72 h of the time that the tick was removed; (c) ecological information indicates that the local rate of infection of these ticks with B. burgdorferi is ≥20%; and (d) doxycycline is not contraindicated. For patients who do not fulfil these criteria, observation is recommended. c See Table 8.6.33.2. d For adult patients intolerant of amoxicillin, doxycycline, and cefuroxime axetil, a macrolide can be given (Table 8.6.33.2). Patients treated with macrolides should be closely followed to ensure

resolution of the clinical manifestations. e If doxycycline is used, 10 days of therapy is effective; the efficacy of 10-day regimens with the other first-line agents is unknown. f Data from European studies of neuroborreliosis indicate that oral doxycycline and parenteral antibiotic therapy are equally effective in Lyme meningitis. Similar studies have not been conducted in the United States of America. For nonpregnant adult patients, the recommended dosage of doxycycline, 200 mg/day orally (or intravenously if unable to take oral medications) in one dose or in two divided doses, may be adequate. For children ≥8 years of age the recommended dosage of doxycycline for this indication is 4 mg/kg per day in one dose or in two divided doses (maximum daily dosage of 200 mg). g Most patients can be treated successfully with an oral regimen. Parenteral antibiotic therapy is recommended for patients with both clinical and laboratory evidence of coexistent meningitis who cannot be treated with doxycycline. Systematic studies of oral antibiotic therapy in patients with cranial nerve palsy have only evaluated doxycycline. Other oral agents such as amoxicillin or cefuroxime axetil might be effective in patients who should not receive or cannot tolerate doxycycline, but clinical trials with these antibiotics are lacking. Most of the experience in the use of oral antibiotic therapy is for patients with seventh cranial nerve palsy. Whether oral therapy would be as effective for patients with other cranial neuropathies is unknown. The decision between oral and parenteral antimicrobial therapy for patients with other cranial neuropathies should be individualized. h A parenteral antibiotic regimen is recommended at the start of therapy for patients who have been hospitalized for cardiac monitoring; an oral regimen can be substituted to complete a course of therapy or to treat ambulatory patients. A temporary pacemaker is sometimes required for patients with advanced heart block. i A second course of oral antibiotic therapy is preferred for the patient whose arthritis has substantively improved but has not yet completely resolved. Consideration of retreatment
of such patients is often postponed for several months because of the anticipated slow resolution of inflammation after antibiotic treatment. During this interval use of nonsteroidal anti-inflammatory agents (NSAIDs) might be beneficial. Parenteral antibiotic therapy is reserved for those patients whose arthritis failed to improve at all or worsened. j Antibiotic-refractory Lyme arthritis is operationally defined as persistent synovitis for at least 2 months after completion of a 1-month course of intravenous ceftriaxone (or at least 1 month after completion of two 4-week courses of an oral antibiotic regimen for patients unable to tolerate cephalosporins); in addition, PCR on synovial fluid (and synovial tissue if available) is negative for B. burgdorferi nucleic acids. k Symptomatic therapy might consist of NSAIDs, intra-articular injections of corticosteroids, or other medications. If persistent synovitis is associated with significant pain or if it limits function, arthroscopic synovectomy should be considered. Modified from Wormser GP, et al. (2006). The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis and babesiosis. Clinical practices guidelines by the Infectious Diseases Society of America. Clin Infect Dis, 43, 1089–134.

8.6.33 Lyme borreliosis 1187 Treatment Although most manifestations of Lyme borreliosis resolve spontan- eously, antibiotics might speed the resolution of some and will al- most certainly prevent the progression of disease. An approach to treatment is summarized in Tables 8.6.33.2 and 8.6.33.3. Presently available fluoroquinolones, sulphonamides, first-generation ceph- alosporins, rifampicin, and aminoglycosides have no appreciable activity against B. burgdorferi and should not be used. There is no evidence to support combination antimicrobial therapy, prolonged (more than 1 month) or repeated courses of antibiotics, and ‘pulse’ or intermittent antibiotic therapy. Within 24 h after initiation of antibiotics, approximately 15% of patients with erythema migrans develop transient intensification of signs (e.g. rash and fever) and symptoms (e.g. arthralgias) consistent

with a Jarisch–Herxheimer reaction. Treatment is symptomatic. Most people treated for Lyme borreliosis have an excellent prognosis. Although a minority of patients treated for erythema migrans in recent series continue to have a variety of mild non- specific complaints following antibiotic therapy, the development of objective extracutaneous disease after treatment is extremely rare. When such complaints are disabling and last for 6 months or more they have been referred to as post-treatment Lyme disease syndrome. Randomized double-blind placebo-controlled antibiotic treatment trials of patients with post-treatment Lyme disease syn- drome have failed to show evidence that the benefit of additional antibiotic therapy outweighs the complications of such treatment. Symptomatic therapy is recommended. Patients with neurological disease tend to do well, but may sometimes have residual deficits (e.g. mild seventh nerve palsy) after treatment. In patients with arthritis, clinical recovery oc- curs typically with oral antibiotic therapy (often in conjunction with a nonsteroidal anti-inflammatory medication (NSAID)). Occasionally patients with Lyme arthritis with subtle signs of neuroborreliosis who are treated with oral antibiotics will develop overt late neuroborreliosis and require parenteral therapy. A small number of American patients with Lyme arthritis continue to have synovial inflammation for months or even several years after the apparent eradication of B. burgdorferi from the joint following antibiotic therapy (based on negative PCR testing). Such patients have improved after intra-articular corticosteroid injections, use of NSAIDS or disease-modifying antirheumatic drugs, such as hydroxychloroquine or methotrexate, or synovectomy. An im- munological mechanism rather than active infection appears to be responsible for the continued inflammatory response in these patients. In North America predominantly, but also in Europe, sev- eral patients with a variety of symptoms of uncertain aetiology, including pain and fatigue syndromes, have been labelled as having ‘chronic Lyme disease’, irrespective of tick exposure in an endemic area for Lyme borreliosis or credible clinical or labora- tory evidence of infection due to Lyme borrelia. There is no sci- entific evidence that such patients have active infection due to borreliae. Prevention Preventive measures include avoiding exposure by limiting out- door activities in tick-infested locations, using tick repellents, tucking in clothing to decrease exposed skin surfaces, bathing within 2 hours after tick exposure, and frequent skin inspec- tions for early detection and removal of ticks. Use of acaricides on property and construction of deer fences have also been proposed. Antibiotic prophylaxis with single-dose doxycycline given after recognized I. scapularis tick bites has been shown to be 87% effective in reducing further the low (less than 5%) risk of ac- quiring Lyme borreliosis after tick bites in the United States of America. Vaccination with a single recombinant outer surface protein A (OspA) preparation has been found to be safe and ef- fective for preventing Lyme borreliosis in the United States of America, but this vaccine is no longer available. Canine vaccines for prevention of Lyme borreliosis, however, are widely used in North America. FURTHER READING Aguero-Rosenfeld M, et al. (2005). Diagnosis of Lyme borreliosis. Clin Microbiol Rev, 18, 484–509. British Infection Association (2011). The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: a position statement by the British Infection Association. J Infect, 62, 329–38. Cerar D, et al. (2011). Subjective symptoms after treatment of early Lyme disease. Am J Med, 123, 79–86. Eikeland R, et al. (2011). European neuroborreliosis: quality of life 30 months after treatment. Acta Neurol Scand, 124, 349–54. Feder HM Jr, et al. (2007). A critical appraisal of ‘chronic Lyme disease’. N Engl J Med, 357, 1422–30. Halperin JJ, et al. (2007). Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 69, 91–102. Klempner MS, et al. (2001). Two controlled trials of antibiotic treat- ment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med, 345, 85–92. Ljostad U, et al. (2008). Oral doxycycline versus intravenous ceftriaxone for European

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