8.6.22 Brucellosis 1102

8.6.22 Brucellosis 1102

section 8 Infectious diseases 1102 needed in great quantities. These realities will challenge prepared- ness planners. Challenges and future developments Methods for detection of spores in the environment, especially in the atmosphere, will improve. But specificity of these assays will remain challenging, since true-positives will be rare and false-positives will be costly and socially disruptive. The mechanisms by which anthrax toxins compromise immune responses and cause organ failure will become more clear and re- sult in improved therapies. New vaccines and simpler immunizing schedules will become available. Concern will remain that the increasing capacity to genetically modify B. anthracis strains may lead to deliberate releases with organisms that are resistant to antibiotics and/or have altered vac- cine target sites. FURTHER READING Berger T, et al. (2014). Injectional anthrax—new presentation of an old disease. Euro Surveill, 19, pii: 20877. Beyer W and Turnbull PCB (2009). Anthrax in animals. Molecular Aspects of Medicine, 30, 481–9. Brachman PS, et al. (1962). Field evaluation of a human anthrax vac- cine. Am J Public Health, 52, 632–45. CDC (2010). Use of anthrax vaccine in the United States. MMWR Morb Mortal Wkly Rep, 59, 1–30. Davies JCA (1982). A major epidemic of anthrax in Zimbabwe, part 1. Cent Afr J Med, 28, 291–8. Friedlander AM, et al. (2017). Anthrax vaccines. In: Plotkin SA, et al. (eds) Vaccines, pp. 134–48. 7th edition. Elsevier Saunders, Philadelphia, PA. Ganz HH, et al. (2014). Interactions between Bacillus anthracis and plants may promote anthrax transmission. PLoS Negl Trop Dis, 8, e2903. Hendricks KA, et al. (2014). CDC expert panel meetings on preven- tion and treatment of anthrax in adults. Emerg Infect Dis, 20, http:// dx.doi.org/10.3201/eid2002.130687 (Internet; cited 29 June 2018). Holty J-EC, et al. (2006). Systematic review: a century of inhalation an- thrax cases from 1900 to 2005. Ann Intern Med, 144, 270–80. Inglesby TV, et al. (2002). Anthrax as a biological weapon, 2002: up- dated recommendations for management. JAMA, 287, 2236–52. Keim P, et al. (2015). Whole genome analysis of injectional anthrax identifies two disease clusters spanning more than 13 years. E Bio Medicine, 2, 1613–8. Liu S, et al. (2014). Anthrax lethal and edema toxins in anthrax patho- genesis. Trends in Microbiol, 22, 317–25. Meselson M, et al. (1994). The Sverdlovsk anthrax outbreak of 1979. Science, 266, 1202–8. Plotkin SA, et al. (1960). An epidemic of inhalation anthrax, the first in the twentieth century: I. Clinical features. Am J Med, 29, 992–1001. Rasko DA, et al. (2011). Bacillus anthracis comparative genome analysis in support of the Amerithrax investigation. Proc Natl Acad Sci USA, 108, 5027–32. Sirisanthana T, et al. (1984). Outbreak of oral-pharyngeal anthrax: an unusual manifestation of human infection with Bacillus anthracis. Am J Trop Med Hyg, 39, 144–50. Turnbull PCB, Shadomy SV (2011). Anthrax from 5000 BC to AD 2010. In: Bergman NH (ed) Bacillus anthracis and anthrax, pp. 1–15. John Wiley & Sons, London. Van Ert ML, et al. (2007). Global genetic population structure of Bacillus anthracis. PLoS One, 2, e461.

8.6.22 Brucellosis Juan D. Colmenero and Pilar Morata ESSENTIALS Brucellosis is a worldwide

zoonotic disease. It remains endemic in the Mediterranean basin, Northern Africa, the Middle East, Western Europe, Central and South America, sub-Saharan Africa, the Indian subcontinent, and Central Asia. There are three species especially pathogens for humans; Brucella melitensis (most commonly asso- ciated with goats, sheep, and camels), B. abortus (cattle) and B. suis (pigs). Brucellosis is usually transmitted by direct contact with infected animals, by ingestion of untreated dairy products, and less frequently by inhalation (laboratory workers) or inoculation (veterinary). Clinical features—symptoms are very nonspecific and hetero- geneous, hence epidemiological information collected in the
clinical history is very important. In most of cases the infection manifests as a febrile syndrome with no apparent focus, comprising chills, profuse sweating, asthenia, arthralgia, and myalgia. Between 20 and 40% of patients develop focal complications, which can af- fect any organ or system, especially the locomotor and genitourinary system. Diagnosis and treatment—definite diagnosis always requires la- boratory confirmation, either by isolating the organism from blood, body fluids or tissues, or by demonstration of high titres of specific antibodies or seroconversion. In addition to adequate symptomatic and supportive measures, treatment is based on the administration of doxycycline plus an aminoglycoside or rifampicin. Doxycycline plus streptomycin/gentamicin regimen is more effective and results in fewer therapeutic failures and relapses. Prevention—human brucellosis can be prevented by eradicating the disease in animals by vaccination. Other preventive measures include occupational hygiene (especially in exposed professionals such as farmers, shepherds, abattoir workers, butchers, and labora- tory workers), avoiding keeping farm animals in close proximity to houses, and avoiding the consumption of unpasteurized raw milk or its by-products. Aetiological agent The Brucella genus belongs to the Alphaproteobacteria family. Six species are recognized within the genus Brucella: B. abortus, B. melitensis, B. suis, B. ovis, B. canis, and B. neotomae. This clas- sification is mainly based on the difference in host preference

8.6.22 Brucellosis 1103 and in pathogenicity. They are small nonencapsulated nonmotile nonsporulating intracellular facultative Gram-negative aerobic ba- cilli. Several new species have recently been described, including at least two species in marine mammals (B. ceti in dolphins, porpoises, and whales, and B. pinnipedialis in seals) and an additional species, B. microti, in the common vole (Microtus arvalis). Epidemiology Brucellosis is a worldwide zoonotic disease. It remains a serious public health problem in many low- and middle-income coun- tries. In the past 15 years, the epidemiology of human brucellosis has evolved. Brucellosis continues to be endemic in some coun- tries of the Mediterranean basin, Northern Africa, the Middle East, Western Europe, Central and South America, sub-Saharan Africa, the Indian subcontinent, and Central Asia. The incidence of brucel- losis varies widely between and within countries. While some areas, such as Peru, Kuwait, and parts of Saudi Arabia, have a very high incidence, the low incidence reported in other known brucellosis endemic areas may reflect low levels of surveillance and reporting. Demographic, occupational, and socioeconomic factors may also play a role in these differences. Brucella spp. can infect a wide variety of both domesticated and feral animals. B. melitensis (goats, sheep, and camels) is the most pathogenic to humans, followed at some distance by B. abortus (cattle), and B. suis (pigs). Exceptionally, B. canis can be pathogenic for humans but no human cases have been reported due to B. ovis or B. neotomae. The pathogenicity for humans of the different marine Brucella species (B. ceti and B. pinnipediae) found in cetaceans and pinnipeds remains to be established. The control and eradication of animal brucellosis is very diffi- cult because infection is often not apparent in cattle, sheep, goats, or other ruminants, as well as

ancient practices such as nomadism and the involvement of different wild animals sharing a habitat with herds. This helps to explain the re-emergence of brucellosis. Brucella spp. can survive for long periods in dust, dung, water, slurry, aborted animal fetuses, soil, meat, and dairy products. The precise duration of survival is dependent on many variables such as the nature of the substrate, number of organisms, temperature, pH, and sunlight. Brucellosis can be transmitted to humans through consumption of unpasteurized dairy products or through direct or indirect contact with infected animals, placentas, aborted fetuses, or a contaminated environment, as well as by inhalation, conjunc- tival contamination, skin cuts or abrasions, and accidental self- inoculation with live vaccines. Certain professions, such as farmers, shepherds, abattoir workers, veterinarians, and laboratory workers, are at particular risk. Human- to-human transmission by blood transfusion, tissue transplantation, or sexual contact has been reported occasionally but is nevertheless exceptional. Pathogenesis Brucella species can survive and replicate inside macrophages and nonprofessional phagocytic cells, thus explaining the tendency of brucellosis to have a prolonged clinical course and to relapse. Soon after Brucella penetrates skin or mucosa there is migration of ac- tivated macrophages to the site of invasion. Brucella later passes through the lymphatic vessels to regional lymph nodes, then via the blood stream to all organs of the body, particularly those rich in reticuloendothelial tissue. Organ localization is associated with inflammatory cellular infiltrates with or without granuloma forma- tion, necrosis, or even abscess formation. Experimental data in murine models suggest that brucella may use different strategies to evade the host immune response, including evasion of intracellular destruction by restricting fusion of type IV secretion system-dependent brucella-containing vacuoles with lysosomal compartments, inhibition of apoptosis of infected mononuclear cells, and prevention of dendritic cell maturation, antigen presentation, and activation of naive T cells. Inhibition of phagosome-lysosome fusion has been proposed as the main mech- anism for intracellular survival of brucella, and lipopolysaccharide O-antigen as the major virulence factor that governs the early be- haviour of bacteria inside macrophages. The initial response is neither antigen nor organism specific (in- nate immunity), involving γδ T-cell (Vγ9Vδ2), natural killer, and CD4 and CD8 T-cell activation. Lipopolysaccharide on the surface of brucella is recognized by these cells, which activate macrophages and facilitate phagocytosis. Activated γδ T cells may provide the initial γ-interferon (INFγ), tumour necrosis factor-α (TNFα), and other cytokine secretions which become cytotoxic for brucella- infected monocytes and the bacteria, impairing their intracellular survival. Most brucella are rapidly eliminated by phagolysosome fu- sion. Killing inside macrophages is initiated by cytokines secreted by T-helper cells. Macrophages activate TNFα secretion, initiating a complex cascade of host defence mechanisms, resulting in hydro- lytic enzymes and the peroxide–halide system (‘oxidative-burst’ or ‘oxygen-based killing’). Some brucella survive in compartments which are rapidly acidified. Brucella resists lysosome-mediated killing and phagosome acidification. The mechanism of trafficking of the brucella-containing phagosome within macrophages and the lack of fusion with the lysosome is not understood. Brucella multi- plies in the macrophage endoplasmic reticulum without affecting host-cell integrity. The organisms are released by cell lysis and ne- crosis. In the early stage of infection, brucella activates the cAMP/ PKA pathway, which regulates a variety of mechanisms favouring infection. In the first week of infection, antilipopolysaccharide IgM appears in the serum, followed one week later by IgG and IgA which peak during the fourth week. Antilipopolysaccharide anti- bodies have a limited role in host protection, but are important for diagnosis. Clinical features The incubation period of brucellosis ranges between seven days and three months, although incubation periods of as long as 10 months have been reported, thereby explaining how the symp- toms can begin at a very distant place from where the infection was

acquired. This is an important fact to consider in the case of febrile syndromes in travellers returning from countries where brucel- losis is endemic. Epidemiological data of patients with brucellosis are shown in Table 8.6.22.1. The distribution by age and gender is shown in Fig. 8.6.22.1.

section 8 Infectious diseases 1104 Brucellosis is a systemic infection with a wide clinical spectrum, ranging from asymptomatic forms to severe cases causing death. Symptoms can start suddenly or gradually. In most cases the infec- tion manifests as a febrile syndrome with no apparent focus, with chills, profuse sweating, asthenia, malaise, arthralgia, and myalgia. Table 8.6.22.2 shows the main symptoms and signs of brucellosis at the time of diagnosis. Brucellosis lacks a typical pattern of fever. Usually patients have a predominantly evening fever which is indistinguishable from other febrile syndromes. Because the clinical picture is very nonspecific, the differential diagnosis of brucellosis is very broad. Therefore, epidemiological data collected in the clinical history are very im- portant. Classifying brucellosis as acute or chronic is of no clinical interest and provides no useful information concerning diagnosis or treatment. Brucellosis can affect virtually any organ or system, causing focal forms with long clinical courses, which are considered true com- plications of the infection. In the absence of focal complications, physical examination of patients with brucellosis is nonspecific. Approximately 30% of patients have hepatomegaly and 20% spleno- megaly; less than 5% have maculopapular rash. Notable discrepancies exist in the incidence rate and clinical spectrum of focal forms. Some authors consider these discrepan- cies to be a consequence of the lesser virulence of some Brucella spp., especially B. abortus. However, this fact does not explain the low incidence of focal forms in some reports referring to B. meli- tensis. These discrepancies seem to be mainly related to the retro- spective character of the reports and the lack of uniform definitions and diagnosis of focal forms. Around 20–40% of patients with brucellosis develop a focal com- plication in the clinical course of their disease. These focal forms of brucellosis have been described in almost all organs and sys- tems, with the osteoarticular and genitourinary forms being more common and those affecting the heart and the central nervous system more severe. Table 8.6.22.3 shows the focal complications of a large cohort of adult patients with brucellosis in the Regional University Hospital in Malaga, Spain. Osteoarticular complications represent between 60 and 70% of the focal complications of brucellosis. The disease can affect the musculoskeletal system at virtually any site, but in adults the axial skeleton is the most frequently involved. Sacroiliitis and vertebral osteomyelitis (spondylodiscitis) account for more than 80% of cases with osteoarticular involvement. This tendency for axial in- volvement in adults may be related to closure of the metaphysis, change in bone vascularization, and redistribution of the bone marrow from the long to the axial bones, which occurs from the second decade of life. In vertebral osteomyelitis the lumbar segment is the most fre- quently involved, followed by the thoracic, and finally the cervical segments. Multiple level involvement is rare, accounting for less than 5% of cases. Although brucellar spondylodiscitis is considered a mild form of infectious vertebral osteomyelitis (Fig. 8.6.22.2), in our own experience a considerable percentage of patients required surgical treatment because of the development of paravertebral and/or epidural masses (Figs. 8.6.22.3 and 8.6.22.4), psoas abscess Table 8.6.22.1 Epidemiological data for brucellosis in Spaina Number of cases Percentage Gender Male Female 655 293 69.1 30.9 Origin Urban Rural 356 592 37.6 62.4 Possible source of infection Habitual or occasional contact with goats or sheep Habitual or occasional contact with goat or sheep products Consumption of unpasteurized dairy products Multiple sources of infection Other sources of infection Unknown source of infection 124 72 241 382 51 88 13.1 6.6 25.5 40.3 5.4 9.3 a Based upon 948 patients with B. melitensis infection seen at

the Regional University Hospital of Malaga between 1982 and 2013. 0 20 40 60 80 100 120 140 160 < 20 21–30 31–40 41–50 51–60 61–70 71–80 >80 year Age distribution by sex Male Female Fig. 8.6.22.1 Age and gender distribution of patients with brucellosis. Table 8.6.22.2 Summary of symptoms and signs at the time of diagnosisa Symptoms Number of cases Percentage Fever 932 98.3 Chills 802 84.6 Sweating 790 83.3 Constitutional symptomsb 678 71.5 Arthralgia 456 48.1 Myalgia 380 40.1 Spinal pain 179 18.9 Testicular pain (referred to 655 males) 49 7.5 Signs Hepatomegaly 319 33.6 Splenomegaly 183 19.3 Lymphadenopathy 65 6.9 Skin rash 24 2.5 a Based upon 948 patients with B. melitensis infection seen at the Regional University Hospital of Malaga between 1982 and 2013. b Constitutional symptoms = two or more of the following: anorexia, asthenia, malaise.

8.6.22 Brucellosis 1105 (Fig. 8.6.22.5), spinal cord or radicular compression, or instability of the column. Sacroiliitis, together with vertebral osteomyelitis, is the most frequent osteoarticular involvement in adult patients. It almost in- variably occurs unilaterally, and in those cases of bilateral involve- ment it is usually asymmetric, which helps to differentiate it from noninfectious sacroiliitis. Peripheral arthritis is a frequent form of osteoarticular brucellosis. The knee and ankle are the most fre- quently affected joints, two-thirds of which were monoarthritis and one-third oligoarthritis. The age of patients with peripheral involve- ment or sacroiliitis is significantly lower than in patients with ver- tebral osteomyelitis. Large bone osteomyelitis, relatively frequent a few decades ago, is now exceptional. After osteoarticular complications, the most common focal complications of brucellosis are those affecting the genitourinary system. Epididymo-orchitis is, without doubt, the most fre- quent genitourinary complication, affecting 2–20% of males with brucellosis. Pathogens of the genus Brucella possess great tropism for the genitourinary system of their usual hosts (cows, goats, sheep, and pigs), which has been associated with the high con- centration of erythritol in the testicular and placental tissues of these animals. This carbohydrate is a known stimulus for growth of Brucella spp. Although erythritol is not present in the male re- productive system, the high concentration of other carbohydrates could account for the incidence of human epididymo-orchitis. Although the prognosis of brucellar epididymo-orchitis is usually good, delay in diagnosis or inappropriate management may result in serious complications, such as testicular abscess, that may then require orchiectomy. Although Brucella spp. can be isolated in the urine of patients with acute infection, renal involvement is unusual. On rare occasions, renal involvement severely compromises renal function and even the life of the patient. The pathogenic mechanism of renal involve- ment is multiple. In most cases, lesions are secondary to interstitial nephritis caused by direct invasion of the bacteria. In other cases, the renal lesion has a glomerular predilection as a consequence of the deposition of circulating immune complexes. In these cases, the coexistence of an underlying endocarditis is frequent. Neurologic complications, although infrequent (2–5% in the lar- gest series of brucellosis reported) are of marked clinical importance due to their severity and important sequelae. The clinical spectrum of neurobrucellosis is variable. Different clinical pictures have been described, including meningitis, meningoencephalitis, intracerebral haemorrhage, benign intracranial hypertension, optic neuritis, arachnoiditis, polyradiculoneuritis, and myelitis. The lesions are located mainly in the meninges, where a diffuse in- flammatory infiltrate can be observed extending to the perineurium of the nerve sheaths and to the vessel walls. These pathologic findings explain the wide clinical spectrum of neurobrucellosis. Inflammatory changes in the cerebrospinal fluid are a constant feature of neurobrucellosis. Most patients have lymphocytic pleo- cytosis (between 20 and 500 cells/ml), elevated total protein, and hypoglycorrhachia. Brucella can be isolated from cerebrospinal fluid in 35–50% of cases of

meningitis or meningoencephalitis. Cardiac involvement in brucellosis is rare. The prevalence of car- diovascular involvement in large series of adult brucellosis ranges from 1 to 2%. Endocarditis is the most common cardiovascular com- plication, and a large proportion of cases (over 50% in some series) involve a previously healthy native valve. The aortic valve is involved in more than 75% of cases. Although a complete cure has occasion- ally been achieved with medical treatment alone, most patients require surgical treatment because of haemodynamic instability. Pericardial and myocardial involvement is relatively common in pa- tients with Brucella endocarditis, though this can also happen as an isolated event, in which case the prognosis is more favourable. Liver involvement is very frequent in brucellosis, although it is usually limited to soft, painless hepatomegaly, or slight increases in levels of aminotransferases. These clinical and biochemical abnor- malities are completely reversed with adequate treatment. We do not believe they represent a true complication of the disease. The con- cept of hepatic complication should be reserved for those cases with clinical expression (right upper quadrant pain and/or jaundice) in the presence of severe disturbances of the biochemical liver param- eters or liver abscess. Defined in these terms, 2–4% of adult patients have hepatic complications. Table 8.6.22.3 Description of focal complications in patients with active brucellosisa Location Number of cases Percentage Osteoarticular 208 21.9 Genitourinary 47 4.9 Neurologic 19 2.0 Hepatic 17 1.8 Cardiovascular 12 1.3 Other focal complications 20 2.1 More than one focal complication 26 2.7 Total 323 34.1 a Based upon 948 patients with B. melitensis infection seen at the Regional University Hospital of Malaga between 1982 and 2013. Fig. 8.6.22.2 Early brucellar lumbar vertebral osteomyelitis. Decreased height of the intervertebral disc with anterior superior epiphysitis.

section 8 Infectious diseases 1106 Among the hepatosplenic focal forms of brucellosis, the presence of chronic hepatosplenic abscesses is an uncommon, but severe, complication. Chronic hepatosplenic abscess appears to be a clin- ical entity with its own characteristics, which clearly differentiate it from splenic infarctions with abscesses, occasionally associated with endocarditis, and from small, asymptomatic abscesses detected in acute bacteraemic forms of brucellosis. The diagnostic yield of abdominal CT in hepatosplenic abscess is very high (Fig. 8.6.22.6), not only because it enables 100% of the lesions to be detected, but also because it defines with much greater precision than ultrasound the extent of the lesion, some of which present such a characteristic morphology that their finding in endemic areas should lead us to consider the diagnosis of brucellosis. Fig. 8.6.22.3 Brucella melitensis vertebral osteomyelitis. A, T1-weighted MR sagittal image showing decreased signal with poor definition of the upper end plate. B, T2-weighted MR showing increased disk signal and osteolysis, corresponding to a more evolved vertebral osteomyelitis. Fig. 8.6.22.4 Psoas abscess secondary to lumbar brucellar vertebral osteomyelitis. Fig. 8.6.22.5 T1-weighted MR sagittal image after gadolinium administration showing an epidural abscess in a patient with Brucella melitensis vertebral osteomyelitis.

8.6.22 Brucellosis 1107 Other digestive system complications of brucellosis are excep- tional, although cholecystitis, ileitis, colitis, and pancreatitis have been reported. Diagnosis Due to its heterogeneous and poorly specific clinical symptom- atology, the diagnosis of brucellosis always requires laboratory con- firmation, either by isolating the pathogen or by demonstration of high titres of specific antibodies or seroconversion. The definitive diagnosis of brucellosis requires the isolation of the organism from the blood, body fluids, or tissues. Peripheral blood is the clinical sample most commonly used for isolation of Brucella spp. In acute forms produced by B. melitensis the yield of blood cultures is usually high, reaching 70–80% of cases. This is not- ably reduced,

however, in cases of long illness, in patients with focal complications and in patients with infections caused by B. abortus and B. suis. Occupational acquisition has occurred in laboratory workers handling blood cultures containing brucella. If the infection is suspected, cultures should be handled in a safety hood to reduce this risk. The semi-automated methods (BACTEC 9204 or Bac/Alert) considerably shorten the time taken for detection; the presence of brucella can be detected between the third and seventh day of incubation. Recently, some authors have proposed polymerase chain reaction (PCR)-based assays for the direct detection of Brucella organisms in blood and other clinical samples. Some studies have shown that real-time PCR assays are far more sensitive than conventional cul- tures, and this, coupled with its speed and reduction in risk to laboratory workers, could make this technique a very useful tool not only for the initial diagnosis of brucellosis, but also for the diagnosis of focal complications and the differentiation between active and past brucellosis. Despite the apparent advantages that PCR-based methods have over conventional microbiological tests for the diag- nosis of human brucellosis, their application in clinical practice re- mains very limited. More experience is still needed before deciding whether this can replace the traditional cultures. Despite the important advances made in the diagnosis of human brucellosis following the introduction of new semi-automated methods for blood culture processing, diagnosis of this disease is still based mostly on the demonstration of specific antibodies by means of different serological techniques. This is mainly because the greatest incidence of brucellosis is found in underdeveloped coun- tries with poor technical resources, as well as the fact that it tends to occur in rural communities. The major brucella antigen useful for diagnosing human brucel- losis is the smooth lipopolysaccharide of the outer cell membrane. Several serological tests are available for the diagnosis of human brucellosis, including the Rose Bengal test (RBT), standard agglu- tination, Coombs anti-Brucella test, immunocapture-agglutination test, and ELISA. All of these have good sensitivity, but lack the de- sired specificity in highly endemic areas, in occupationally exposed patients, or those with a recent history of brucellosis. Moreover, all these serological tests can produce cross-reactions with other bac- teria, including Yersinia enterocolitica O:9, Escherichia coli O:157, Francisella tularensis, Salmonella urbana O:30 and Vibrio cholera. The strategy most widely used for the serological diagnosis of brucellosis consists of a combination of a rapid screening test, such as the RBT, and a confirmation test, such as standard agglutination, Coombs anti-Brucella test, immunocapture-agglutination test, or ELISA. The RBT is a simple and rapid plate agglutination test that uses a suspension of B. abortus in an acid buffer. It can detect agglutinating and nonagglutinating antibodies and avoids the prozone phenom- enon. The sensitivity of the RBT is greater than 95%, regardless of the stage of the disease. The serum (tube) agglutination test (SAT) is a very useful test for the diagnosis of human brucellosis when it is performed with a standardized antigen preparation. The RBT can be used qualitatively or quantitatively. The quantitative RBT test demonstrates sensitivity and specificity equivalent to that achievable by performing SAT. The immunocapture-agglutination test (Brucellacapt®) has re- cently been introduced in the diagnosis of human brucellosis. A good correlation between the results of Brucellacapt and Coombs antibrucella test has been reported, though the immunocapture- agglutination test is technically easier to perform and to interpret. In our experience, RBT titres ≥1/4, SAT ≥1/160, or immuno- agglutination test ≥1/320 in patients with a compatible clinical pic- ture can be considered diagnostic of active brucellosis. In highly endemic areas, in patients with a history of brucellosis or with focal complications, the serological diagnosis often requires the com- bined use of RBT, SAT, and the immunocapture-agglutination test. Treatment Brucella species are sensitive in vitro to many antimicrobial drugs. However, the results of routine susceptibility tests do not always cor- relate with clinical efficacy. Tetracyclines,

aminoglycosides, and ri- fampicin are the mainstay of treatment of brucellosis. Trimethoprim/ sulfamethoxazole and quinolones are also useful alternatives. Acute uncomplicated brucellosis almost invariably responds well to appropriate antimicrobial treatment. Unfortunately, the results achieved with monotherapy in the treatment of brucellosis have been suboptimal. For this reason, the usual treatment is based on a combination of two antimicrobial drugs. Fig. 8.6.22.6 Abdominal CT with oral and intravenous contrast showing a brucellar splenic abscess.

section 8 Infectious diseases 1108 Currently, the optimal treatment of uncomplicated brucellosis should be based on a six-week regimen of doxycycline (100 mg/12 h, orally) combined with streptomycin for 2–3 weeks. With this thera- peutic schedule, the time to disappearance of fever is usually less than a week. Although gentamicin, in a dose of 5 mg/kg/day intra- venously or intramuscularly, administered for 7–10 days in combin- ation with doxycycline yielded good results in one study, experience with this regimen is too limited to justify its use over doxycycline plus streptomycin. The relapse and treatment failure rates with doxy- cycline/streptomycin are around 5–7% and 1–2%, respectively. The need for parenteral administration of aminoglycosides may compli- cate the use of this regimen. The combination of doxycycline plus rifampicin (600–900 mg/ day orally), with both drugs administered for six weeks, is a good alternative. All other regimens/combinations should be considered second-line. The data available allow us to conclude that the regimen of doxy- cycline plus streptomycin is more effective than doxycycline plus ri- fampicin. A possible explanation of treatment failures and relapses with this latter regimen could be related to the fact that rifampicin might enhance the plasma clearance of doxycycline, thus resulting in subtherapeutic levels. In any case, the fact that doxycycline plus rifampicin is an oral regimen might allow for better implementation in clinical practice in areas with a less well- developed health infra- structure. Nevertheless, it should be borne in mind that the use of this therapeutic schedule also poses problems in developing coun- tries due to its potential to induce resistance to rifampicin in other infections, mainly tuberculosis. Most authors continue antibiotic therapy for 45 days. Shorter treatment periods yield inferior results, while longer periods do not offer clear advantages. Some osteoarticular focal forms, such as sacroiliitis, do not appear to require longer treatment. In contrast, orchiepididymitis, vertebral osteomyelitis, endocarditis, and other local complications of brucel- losis require prolonged therapy, such as the continuation of doxy- cycline for eight weeks. The treatment of central nervous system complications of brucel- losis poses a special problem because of the need to achieve suitable concentrations of drugs in the cerebrospinal fluid. Since doxycycline and aminoglycosides have a low blood/brain barrier penetration it is recommended that drugs which achieve this concentration, such as rifampicin or co-trimoxazole, be added to the standard regimen of doxycycline plus streptomycin. The optimal duration of treatment for neurobrucellosis has not been determined, though it should not be less than 8–12 weeks and possibly longer, depending on the clin- ical response. The optimal therapy for brucellosis during pregnancy has not been determined with certainty. Co-trimoxazole plus rifampicin for at least 45 days has been used in individual cases with reported success. Despite the long duration of brucellosis treatment, the side effects of the standard medication are mild or moderate, and only rarely require treatment withdrawal. Prevention Brucellosis is a zoonosis with a strong correlation between animal and human disease. Prevention of human brucellosis is therefore based on elimination of the disease from animals. This goal is very difficult to achieve in countries with limited resources. The most successful method for prevention and control of brucellosis in animals is through herd management, hygiene, and vaccination. Although there is no completely effective and safe vaccine, the at- tenuated strains of B. melitensis strain Rev.1 for sheep and goats and B. abortus strain 19 or RB51 for cattle, have proven to be superior to all

others. Vaccine efficacy is limited and offers an animal protection rate of 65–90%. Given that at the present time there is no effective vaccine for human use and bearing in mind that the main source of infection is through direct or indirect exposure to infected animals or their products and ingestion of contaminated food products, the pre- vention of human brucellosis should be based on the following two pillars; first, occupational hygiene, especially in exposed profes- sionals such as farmers, stockmen, shepherds, abattoir workers, but- chers, dairymen and laboratory workers; and second, food hygiene, avoiding consumption of unpasteurized raw milk or its by-products.

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