8.6.35 Leptospirosis 1198

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section 8 Infectious diseases 1198 8.6.35 Leptospirosis Nicholas P.J. Day ESSENTIALS Leptospirosis, caused by pathogenic spirochetes of the genus Leptospira, is a bacterial zoonosis with a worldwide impact on human and animal health. For human infection rodents are the most important reservoir; infection follows exposure to contaminated water, soil, or urine, the organism entering through skin abrasions or mucosal surfaces. Clinical features—subclinical infection is common, but symptom- atic disease usually begins with abrupt onset of fever, chills, headache, and myalgia. Conjunctival suffusion, uncommon in other causes of febrile illness, is a useful diagnostic sign. Most cases of leptospirosis are self-limiting, but in a minority (<10%) severe disease may follow with complications including jaundice and renal failure ('Weil's dis- ease'), vascular collapse, and haemorrhagic manifestations including pulmonary haemorrhage. Diagnosis—most cases are undiagnosed due to the poor avail- ability of diagnostic tests in regions where transmission occurs. The gold standard remains the serological microscopic agglutination test, but increasingly new serological and molecular tests, including rapid diagnostic tests, are becoming available. Treatment and prognosis—whether treatment of mild leptospirosis with antibiotics prevents more severe disease remains controversial, most experts recommend empirical treatment if leptospirosis is sus- pected. Mild disease can be treated with doxycycline or azithromycin. Severe disease should be treated with parenteral antibiotics (ß-lactams or doxycycline). Reported mortality in hospitalized cases of leptospir- osis ranges from 4% to 52%. Introduction Leptospirosis is a widespread zoonotic infection caused by patho- genic spirochetes of the genus Leptospira. It has a major impact on both human and animal health. A variety of domestic and wild ani- mals are reservoirs for leptospires, which are maintained in the renal tubules of infected animals and shed in the urine. Humans are inci- dentally infected following direct or indirect exposure to the urine of infected animals. Infection in humans ranges from asymptom- atic through a relatively benign febrile illness to a severe potentially fatal illness associated with jaundice, renal failure, and pulmonary haemorrhage. Severe icteric leptospirosis is known as Weil's disease after Adolf Weil, who first described the combination of abrupt high fever, jaundice, renal failure, and splenomegaly in 1886. Aetiology • Leptospirosis is caused by infection with pathogenic spirochetal bacteria of the genus Leptospira. • The genus Leptospira contains 22 species, ten of which are pathogenic. • Over 200 serovars of pathogenic Leptospira have been described, many of which are broadly associated with a particular animal host. Leptospires are highly motile, aerobic, spiral-shaped spirochetes with a typical length of 6–20 µm, width of 0.1 µm, helical amplitude of 0.1–0.15 µm and wavelength of 0.5 µm. Their corkscrew motility is driven by two endoflagella, one at each end of the cell. It is thought that the positioning and action of these endoflagella is respon- sible for the hooks that occur at one or both ends of the cell, giving leptospires their characteristic 'question mark' appearance that in- formed

the name given in the original 1907 description—Spirocheta interrogans (Fig. 8.6.35.1). The genus Leptospira currently contains 22 species, ten of which are pathogenic (Leptospira interrogans, L. kirschneri, L. noguchii, L. alexanderi, L. weilii, L. alstonii, L. borgpetersenii, L. santaro sai, L. kmetyi and L. mayottensis). Five species are considered to be of unclear or intermediate pathogenicity (L. inadai, L. fainei, L. broomii, L. licerasiae, and L wolffii), and the remaining seven are nonpathogenic free living saprophytic species (L. biflexa, L. meyeri, L. wolbachii, L. vanthielii, L. terpstrae, L. yanagawae and L. idonii). L. interrogans, L. borgpetersenii an L. kirschneri are the main patho- genic species of leptospirosis in humans and animals worldwide. There are several genetic typing schemes for identifying par- ticular strains of leptospire, including multilocus sequence typing and multiple-locus variable-number tandem repeat analysis. An older classification system based on serology is used in par- allel with the newer molecular classification, and forms the basis of the microscopic agglutination test which remains the gold standard for serological diagnosis of leptospirosis. Serovars are defined by cross-agglutination absorption testing with rabbit antiserum, and approximately 250 serovars of pathogenic leptospires grouped into 24 serogroups have been described. Many of these have regional and animal host associations and for this reason the serovar classi- fication remains epidemiologically useful. For example, serovars of the serogroup Icterohaemorrhagiae are associated with rats (Rattus species), and several serovars are associated with domestic livestock animals, such as Hardjo (with cattle and sheep) and Pomona (with pigs). Several serovars are found in multiple Leptospira species, so by convention the two classification systems are used together (e.g. Leptospira borgpetersenii serovar Hardjo). Epidemics may be caused by a particular ecologically successful pathogenic clone, such as the 1995–2005 epidemic in Thailand where most isolates were L. interrogans serovar Autumnalis of multilocus sequence typing sequence type 34. Whole genome sequencing is currently revolutionizing our under- standing of Leptospira. Pathogenic species evolved from saprophytic species through a process of gene loss (often metabolic genes neces- sary for living free in the environment) and the gain through hori- zontal transfer of genes putatively associated with adaptation to the mammalian host. Genome comparison also allows identification of genes putatively associated with disease pathogenesis. Epidemiology • Leptospirosis is a worldwide zoonosis, though more common in tropical regions.

8.6.35 Leptospirosis 1199 • Humans are incidental hosts, infected through direct or environ- mental exposure to the urine of infected reservoir animals. Leptospirosis is the most widespread human zoonosis, occurring in both temperate and tropical regions. Its incidence is around 10 times higher in tropical regions than temperate; in the tropics lepto- spirosis is mainly a disease of poverty, associated with poor sani- tation, rodent-infested slums, occupational exposure, and flooding. Information on the epidemiology of human leptospirosis and its associated global health burden is limited, as because of difficulties in diagnosis and the poor health systems in many endemic areas it is a relatively neglected and underreported disease. Based on available data from health databases and published studies on morbidity and mortality, it has been estimated recently that roughly one million cases of leptospirosis occur annually causing around 60 000 deaths. These are likely to be underestimates. The highest burdens of mor- bidity and mortality were seen in South and Southeast Asia-Oceania, the Caribbean, Andean, Central, and tropical Latin America, and East sub-Saharan Africa (Fig 8.6.35.2). A wide variety of mammals are reservoir hosts of pathogenic leptospires, with humans infected incidentally following direct or environmental exposure to infected animals or their urine. Hence the epidemiology of human leptospirosis is driven by the epidemi- ology of animal infection and the manner in which humans are ex- posed to

these animals and their urine. Animal infection Leptospirosis is a ubiquitous global disease of animals, particularly mammals. It is found in both wild and domestic animals, and as a source of human disease and cause of economic loss is an excellent example of the ‘One Health’ concept. Animals commonly infected include rodents, cattle, swine, dogs, horses, sheep, and goats. Cats are rarely infected. Animals can be maintenance hosts or, like humans, incidentally infected. Initial infection is through the mucous mem- branes (eyes, mouth, genitals), and during an initial bacteraemic phase leptospires spread haematogenously to the renal tubules. Certain serovars are well adapted as parasites in particular host ani- mals, with infection in the renal tubules lasting for many years and causing little in the way of clinical illness while maintaining the in- fection in the environment through urinary excretion. Symptomatic disease in animals can be severe; mortality in dogs is estimated at approximately 10%. Spontaneous abortion is a common outcome of leptospirosis in cattle, swine, sheep, and goats, leading to major economic consequences. Human infection Human infection results from exposure to animal urine, contam- inated water or soil, or infected animal tissue (see Box 8.6.35.1). Fig. 8.6.35.1 Leptospire seen under darkfield microscopy. Courtesy of Vanaporn Wuthiekanun. Fig. 8.6.35.2 Estimated annual morbidity of leptospirosis by country or territory. Annual disease incidence is represented as an exponential colour gradient from white (0–3), yellow (7–10), orange (20–25) to red (over 100), in cases per 100 000 population. Circles and triangles indicate the countries of origin for published and grey literature quality-assured studies, respectively. From Costa F et al. (2015) Global Morbidity and Mortality of Leptospirosis: A Systematic Review. PLoS Negl Trop Dis 9(9), e0003898.

section 8 Infectious diseases 1200 Portals of entry include cuts or abraded skin, and mucous mem- branes such as the eyes. It is unclear whether Leptospira can pene- trate intact skin. Rarely, infection might be acquired by eating food contaminated with urine or via aerosols. Human infection does involve a period of leptospire shedding in the urine, so human to human transmission is possible but very rare. Sexual transmission has been reported, as has transplacental infection during active maternal infection which often leads to abortion, stillbirth, or neo- natal infection. In tropical regions endemic leptospirosis is mainly a disease of poverty, associated with low quality rodent-infested urban slum housing with poor sanitation, with occupational exposure such as subsistence farming, and with environments susceptible to flooding. Outbreaks affecting thousands of people and causing hundreds of deaths are common, often associated with increased rainfall or flooding—which presumably increase the chances of exposure to contaminated water. Pathogenesis/Pathology • Leptospirosis has features of both an acute bacteraemic infection and a systemic vasculitis. • As accidental hosts, the human innate immune system is not well adapted to protection from leptospirosis and consequently bac- terial loads in blood are high. • Leptospires spread haematogenously to the liver, kidney, and lungs, which are the major target organs in severe leptospirosis. • The pathological consequences of infection are probably mediated by a combination of a direct toxic effect of the leptospires and the resulting immune response. • Activation of the inflammasome plays a major role in the patho- genesis of severe leptospirosis. Leptospires penetrate tissue barriers through abraded skin, the conjunctivae, or the oral cavity and can be found in the blood stream within 48 hours of initial exposure. Unlike other pathogenic spiro- chetes, such as Treponema pallidum and Borrelia burgdorferi, they form no infected lesions at the site of entry. Bacteraemia lasts from 2 to 9 days, and ends with the appearance of agglutinating antibodies. The concentration of leptospires in the blood can be as high as 106/ml, which is similar to that seen in the B. recurrentis spirochetaemia of relapsing fever and several orders of magnitude higher than seen in bloodstream infections caused by

Enterobacteraceae such as E. coli. Leptospires subsequently disseminate haematogenously to target organs including the liver, lung, and kidney, leading in severe cases to multiorgan dysfunction and death. Pathogen-associated molecular patterns including lipopolysac- charides and outer membrane proteins activate the innate immune response through TLR2- and TLR4-dependent pathways. The rela- tive inability of human TLR2 to recognize leptospiral lipopolysac-charides (as opposed to lipopolysaccharides from Enterobacteraceae) might be responsible for the relatively high levels of bacteraemia seen in leptospirosis. This hypothesis is supported by the superior ability of murine TLR4 to recognize leptospiral lipopolysacchar- ides; the mouse is a natural reservoir of leptospirosis and resistant to fatal infection. In severe leptospirosis, patients experience a 'cyto- kine storm' with very high levels of pro-inflammatory cytokines such as IL-6 and TNFα. IL-6 and the anti-inflammatory cytokine IL-10 are independent predictors of fatal outcome, suggesting that an initial protective Th-1 response is counteracted by overproduc- tion of IL-10. Histopathologically, leptospires are seen in large and medium- sized blood vessels and in the capillaries and interstitial spaces of affected organs. A diffuse systemic vasculitis is suggested by the presence of polymorphonuclear cells adherent to the endothelium and signs of endothelial cell damage. Disorders of coagulation are common in severe leptospirosis. Thrombocytopenia is common, and prothrombin time and activated partial thromboplastin time are frequently prolonged. Fibrinogen, D-dimer, thrombin-antithrombin III complexes, and prothrombin fragment 1 + 2 are often elevated. In one study from Thailand al- most half of severe cases met the criteria for overt disseminated intravascular coagulation. Whereas multiple organs and systems are affected in leptospirosis, with myocarditis, meningoencephalitis, and uveitis all occurring in severe disease, the most important target organs are the liver, kidney, and lung. Liver Autopsy studies show congested hepatic sinusoids and distention of the space between the sinusoidal endothelium and hepatocytes (the space of Disse). In a hamster model of leptospirosis leptospires were observed infiltrating Disse's space and migrating between hepato- cytes, detaching the intercellular junctions and disrupting the bile canaliculi. Jaundice likely results from the consequent leakage of bile from bile canaliculi into sinusoidal blood vessels. Kidney The kidney of reservoir animals plays a key role in the leptospiral life cycle, with the proximal renal tubular lumen the major site of colonization. In humans leptospiral lipoproteins, such as LipL32, are recognized by TLR2 on tubular epithelial cells triggering an inflammatory response leading to interstitial nephritis. Autopsy studies show damage to the tubular epithelium and luminal dis- tension with hyaline casts and cellular debris. While most severe in the proximal convoluted tubule, tubular damage is more ex- tensive and less focal than seen in acute tubular necrosis from other causes. The pattern of tubular damage seen in leptospir-osis and its effects on sodium, potassium and water handling might explain the polyuria seen in mild leptospirosis, and the nonoliguric potassium wasting renal failure often seen in more severe disease. Box 8.6.35.1 Risk factors for acquiring leptospirosis • Occupational exposure—farmers, ranchers, abattoir workers, veterin- arians, loggers, sewer workers, rice farmers, pet traders, rat catchers/ merchants, military personnel, laboratory workers • Recreational activities—freshwater swimming (e.g. triathlons), canoeing, kayaking, trail biking • Household exposure—rodent infestation, pet dogs, domesticated livestock • Other—Walking barefoot through surface water, particularly during floods, skin lesions, contact with wild rodents, accidental laboratory exposure

 Lungs Autopsy specimens are usually congested, with focal or mas- sive haemorrhage occurring in both the alveolar septa and intra-alveolar spaces. Using immunohistochemistry leptospiral antigen has been detected in macrophages in both pulmonary septa and alveoli, suggesting that leptospires exert a local direct destructive action. Pathogenesis

might also involve an immune component; in a guinea pig model, which closely replicates the pulmonary haemorrhage seen in humans, extensive deposition of immunoglobulin and complement was seen along the alveolar basement membrane. The coagulation abnormalities ubiqui- tous in severe leptospirosis might also contribute to pulmonary haemorrhage. Clinical features • The clinical course of human leptospirosis is very variable. Most cases are mild or subclinical, but some are severe and potentially fatal. • Conjunctival suffusion in febrile patients strongly suggests a diag- nosis of leptospirosis. • Jaundice is a common feature of severe leptospirosis and is often associated with renal failure (Weil's disease). • Pulmonary haemorrhage is the most serious complication of leptospirosis and is associated with a high risk of death. Leptospirosis is usually described as a biphasic illness, with an acute bacteraemic phase lasting 2–9 days, then defervescence and several days of improvement, followed by an 'immune' phase with renewed fever and the onset of complications. Clinically, however, the two phases often merge, particularly in severe disease. Symptoms After an incubation period of 3–26 days (average 10 days), the illness usually presents nonspecifically with an abrupt onset of fever, rigors, myalgias, and headache. Nausea, vomiting, and diarrhoea occur in around 50% of cases, and a nonproductive cough occurs in around a third. Less common symptoms include arthralgias, bone pain, sore throat, and abdominal pain. Signs Conjunctival suffusion is uncommon in other infections but pre- sent in 55% of leptospirosis patients in one case series, and is hence an important clue to a diagnosis of leptospirosis. Subconjunctival haemorrhages can also occur (Fig. 8.6.35.3). Other clinical signs of bleeding such as petechiae, ecchymoses, and epistaxis are relatively common. Muscle tenderness (characteristically involving the calves and lower back), muscle rigidity, splenomegaly, hepatomegaly, lymphadenopathy, pharyngitis, abnormal respiratory signs, or an erythematous skin rash may be present. Aseptic meningitis is common, present in 50–85% of patients if cerebrospinal fluid (CSF) is examined after seven days of illness. This might be due to the host immune response, though in one series Leptospira DNA was detectable by polymerase chain reaction (PCR) in the CSF of 90% of serologically confirmed cases with CSF abnormalities. Complications Weil's disease, a severe, potentially fatal illness characterized by jaundice and renal failure, occurs in less than 10% of symptomatic leptospirosis cases. The renal failure is often nonoliguric and asso- ciated with a marked hypokalaemia. The hepatic involvement signi- fied by jaundice is generally reversible and not a cause of death. Leptospirosis-associated severe pulmonary haemorrhage syn- drome is the most lethal complication of leptospirosis, associated with massive haemoptysis and pathophysiological features of acute respiratory distress syndrome (Fig. 8.6.35.4). It can occur either with or without jaundice and renal failure and is associated with a very high mortality (71% in one case series). Acalculous chole- cystitis and pancreatitis have been described and can cause severe abdominal pain. Fig. 8.6.35.3 Jaundice, haemorrhage, and conjunctival suffusion in acute leptospirosis. Fig. 8.6.35.4 Chest radiograph of a European traveller with leptospirosis-associated severe pulmonary haemorrhage syndrome acquired in Sabah (Malaysia). Copyright D. A. Warrell.

 Other complications include uveitis, optic neuritis, periph- eral neuropathy, myocarditis, rhabdomyolysis, and gastrointes- tinal bleeding with haematemesis and/or melaena. Vasculitis with necrosis of the extremities can be seen in severe cases. An acute haemolytic anaemia might also complicate leptospirosis, particu- larly in patients with G6PD deficiency. Differential diagnosis Undifferentiated fever Leptospirosis is a common cause of undifferentiated fever, particu- larly in tropical areas, and is often difficult to distinguish clinically from other sympatric causes. Conjunctival suffusion (as opposed to conjunctivitis), when present, is

a useful almost pathognomonic sign as it rarely occurs in other infections. Common causes of fever that can present in a very similar manner to leptospirosis include malaria, dengue, scrub typhus, murine typhus, spotted fever group rickettsioses, chikungunya, Zika, ehrlichiosis, and enteric fever. As in temperate regions, cosmopol- itan viral infections such as infectious mononucleosis and influenza can be indistinguishable clinically from leptospirosis. In nontropical areas where leptospirosis is relatively uncommon suspicion that it may be the cause of undifferentiated fever is usually prompted by a history of exposure to freshwater. Severe disease Hepatitis A and E infection, malaria, and viral haemorrhagic fevers should be considered in cases of febrile jaundice. Severe malaria can present as jaundice with renal failure, and hantavirus infection is a cause of hepatorenal syndrome and pulmonary haemorrhage. Clinical investigations Routine tests Routine blood tests are usually nonspecific, with hyponatraemia, mild to moderately raised transaminases, mildly raised white blood cell count, and thrombocytopenia all common. An elevated creatine kinase occurs in around 50% of patients. In severe cases bilirubin and creatinine can be elevated, often markedly so. The bilirubin is usually conjugated, though a mixed conjugated/unconjugated bilirubinaemia can occur in cases complicated by haemolytic anaemia. Urinalysis often shows proteinuria, white cells, granular casts, and occasionally microscopic haematuria. The cerebrospinal fluid (CSF) may have elevated lymphocytes and/or neutrophils with minimal to moderately elevated protein concentrations and a normal or occa- sionally low glucose. A chest X-ray might demonstrate pulmonary involvement with consolidation or a ground glass appearance, which can indicate pul- monary haemorrhage or acute respiratory distress syndrome. Specific diagnostic tests Leptospirosis can be diagnosed by direct detection of the organism or its constituents in body fluids, by culture isolation of the organism, or by detection of specific antibodies. There is no gold standard diag- nostic test for leptospirosis. The microscopic agglutination test and bacterial culture are both relatively insensitive, even when combined (55.5% sensitivity, though 98.8% specific). The diagnostic utility of each method depends on the timing and nature of the test sample, with culture and molecular testing on blood most sensitive in the first week of illness and serological methods and urine culture more sensitive from the end of the first week onwards. Serological tests The microscopic agglutination test is the most commonly used diagnostic test, and when applied to paired acute and convalescent samples is considered the reference standard. However, it is labour-intensive and complex to perform—hence only available at reference centres—and serovar dependent. Recently developed rapid IgM ELISAs and lateral flow diagnostic tests are increasingly available but perform variably in the field, particularly in endemic areas. Molecular tests Molecular tests based on real-time PCR and loop-mediated iso- thermal amplification show considerable promise for rapid, accurate diagnosis in the acute phase of the illness, but are not yet widely available. Gene targets used include housekeeping genes (rrs, gyrB or secY) and pathogen specific genes (lipL32, lig, or lfb1). Whole genome sequencing of CSF has been used to make a diagnosis of leptospirosis. Culture Leptospires can be cultured using special medium from clinical spe- cimens including blood, urine, and CSF. Growth is usually observed in one to two weeks, but may take up to three months. A recently developed solid agar (LVW media) facilitates more rapid growth, isolation of single colonies, and simplified antimicrobial sensitivity testing. Treatment Antimicrobial therapy See Box 8.6.35.2 for suggested antibiotic treatment regimens. Mild disease Although most cases of leptospirosis are mild and self-limiting, ap- propriate antibiotic therapy should be given empirically to all symp- tomatic patients suspected of having leptospirosis with the intention of reducing the duration of illness and the shedding of leptospires in the urine. Early antibiotic treatment may prevent progression to severe disease. In one retrospective case-control study from New Caledonia, risk factors for the development of severe leptospirosis included a delay in the

initiation of antibiotics of more than 2 days following the start of symptoms. Although rapid diagnostic tests are improving in both diagnostic accuracy and availability, even if a rapid test is negative treatment should still be commenced. Most treatment will be started before a definitive diagnosis is made, so the empirical regimen chosen should cover other possible diagnoses. In patients in or returning from the tropics malaria should be excluded and empirical treatment should

8.6.35 Leptospirosis 1203 cover rickettsial diseases. Fluoroquinolones are not effective in scrub typhus so should not be used. In vitro studies have shown that leptospires are susceptible to tetracyclines, macrolides, ß-lactams, fluoroquinolones, and streptomycin. In 1984 a small randomized double-blind study of 29 patients showed that doxycycline 100 mg bd reduced the duration of illness by 2 days when compared to placebo, and also decreased symptom severity and prevented leptospiruria. In a 2007 study in Thailand 296 patients with suspected leptospirosis or scrub typhus were random- ized to receive doxycycline (200 mg initially followed by 100 mg or- ally every 12 hours for seven days) or azithromycin (2 g on the first day followed by 1 g daily for two more days). There was no difference in fever clearance times, but oral azithromycin was better tolerated than doxycycline. Severe disease In the 1980s there were two small placebo-controlled trials of intra- venous penicillin in severe leptospirosis. One from the Philippines recruited 41 patients and demonstrated a reduction in fever duration, abnormal renal function, and hospitalization in the penicillin group. The second randomized 79 patients in Barbados and showed no difference in clinical outcome. Leptospiruria was prevented in the penicillin group in both studies. Studies from Thailand have shown comparable efficacy for paren- teral penicillin, ceftriaxone, cefotaxime, and doxycycline for treat- ment of severe leptospirosis. In one study of 173 patients with severe leptospirosis, patients were randomized to penicillin G (1.5 million units IV qds for 7 days) or ceftriaxone (1 g IV od for 7 days). In a second study, 540 patients with suspected severe leptospirosis (264 serologically confirmed) were randomized to cefotaxime (1 g IV gds for 7 days), penicillin G (1.5 million units IV qds for seven days), or doxycycline (200 mg IV initially followed by 100 mg IV every bd for 7 days). In both studies, all regimens had similar efficacy for leptospirosis. Ideally an adequately placebo-controlled trial should be con- ducted, but this is unlikely to happen because of ethical consid- erations. In one retrospective intensive care unit (ICU) series of leptospirosis cases prior treatment with ceftriaxone was associated with lower mortality, suggesting treatment may have a positive effect on disease progression. Leptospirosis appears to be much less prone to a Jarisch-Herxeimer reaction to treatment than other spirochetal diseases, and antibiotics should not be withheld out of fear of this complication, which, if it exists, is rare and mild. Role of corticosteroids Intravenous corticosteroid therapy has been proposed in severe leptospirosis, particularly where there is pulmonary involvement. Some reports have suggested a possible benefit to use of steroids as an adjunct to antibiotic therapy, but there is currently insufficient evidence to support their routine use. Supportive therapy Management of patients with acute kidney injury and/or acute respiratory distress syndrome should in general follow that of other cases of severe sepsis with these complications. Continuous haemofiltration has been shown to be more effective than peri- toneal dialysis in treating infection-associated hypercatabolic renal failure. Peritoneal dialysis, however, may be the only option in resource-limited settings. There is some nonrandomized evidence that early initiation of dialysis without waiting for optimization of fluid status is associated with significantly lower mortality in lepto- spirosis patients with both acute respiratory distress syndrome and renal failure. In acute respiratory distress syndrome low net fluid in- take and lung-protective ventilation practices to prevent pulmonary haemorrhage have been recommended, though there is no random- ized

leptospirosis-specific evidence to support this. Hypokalaemia is a common feature of leptospirosis-associated nonoliguric renal failure, and should be corrected. Prognosis/outcome Most cases of leptospirosis are mild and self-limited. In a recent systematic review of 35 studies reporting untreated mortality rates, mortality rates for untreated anicteric patients with leptospirosis were low (median 0%, range 0–1.7%). High case fatality rates were Box 8.6.35.2 Antimicrobial treatment of leptospirosis Outpatients with mild disease Adults Either Doxycycline 100 mg orally twice daily for 7 days Or Azithromycin 500 mg orally once daily for 3 days Children ≥8 years of age Either Doxycycline 2 mg/kg orally per day in two equally divided doses, not to exceed 200 mg daily, for 7 days Or Azithromycin 10 mg/kg orally on day one (maximum dose 500 mg/ day) followed by 5 mg/kg/day orally once daily for two further days (max- imum dose 250 mg/day) Children less than 8 years and pregnant women Either Azithromycin orally for 3 days Or Amoxicillin orally 25–50 mg/kg per day in three equally divided doses, maximum 500 mg per dose, for 7 days Severe disease Adults Either Penicillin 1.5 million units intravenously (IV) 6 hourly for 7 days Or Doxycycline 100 mg IV twice daily for 7 days Or Ceftriaxone 1–2 g IV once daily for 7 days Or Cefotaxime 1 g IV 6 hourly for 7 days Children ≥8 years of age Either penicillin 250 000 to 400 000 units/kg IV per day in 4 to 6 divided doses (maximum 6 to 12 million units daily) for 7 days Or Doxycycline 4 mg/kg IV per day in two equally divided doses (max- imum dose 200 mg/day) for 7 days Or Ceftriaxone 80–100 mg/kg IV once daily; maximum dose 2 g daily for 7 days Or Cefotaxime 100–150 mg/kg IV per day in 3 to 4 equally divided doses Children less than 8 years old and pregnant women Doxycycline should probably be avoided in children less than 8 years of age unless there are no other treatment options. For children less than 8 years of age with severe disease and β-lactam hypersensitivity: Azithromycin 10 mg/kg IV on day one; maximum dose 500 mg/day, followed by 5 mg/kg/day IV once daily for two further days (maximum dose 250 mg/day) Pregnant women with severe leptospirosis can be treated with IV peni- cillin, ceftriaxone, cefotaxime, or azithromycin. Doxycycline should be avoided.

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