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A B FIGURE 188-3 Clinical manifestations of bejel and pinta. A. Mucous patches of early bejel. B. Pigmented macules of early pinta. (Photos reprinted with permission from the Handbook of Endemic Treponematoses, PL Perine et al, Geneva, World Health Organization, Color Plates 54, 60; 1984.) Pinta Pinta (mal del pinto, carate, azul, purupuru) is the most benign of the treponemal infections. This disease has three stages that are characterized by marked changes in skin color (Fig. 188-3B), but pinta does not appear to cause destructive lesions or to involve tissues other than the skin. The initial papule is most often located on the extremities or face and is pruritic. After 1 to many months of infection, numerous disseminated secondary lesions (pintides) appear. These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue. The secondary lesions are infectious and highly pruritic and may persist for years. Late pigmented lesions are called dyschromic macules and contain treponemes. Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance. White achromic lesions are characteristic of the late stage. ■ ■DIAGNOSIS Diagnosis of the endemic treponematoses is based on clinical manifes tations and, when available, dark-field microscopy and serologic test ing. The same serologic tests—detecting antibodies to either lipoidal or treponemal antigens—that are used for syphilis (Chap. 187) become reactive during all treponemal infections. To date there is no antibody test that can discriminate among the treponemal infections. The nonsyphilis treponemal infections should also be considered in the evalu ation of a reactive syphilis serology in any person who has emigrated from an endemic area. Sensitive nucleic acid amplification–based assays can be used to confirm treponemal infection and to identify the etiologic agent in research and selected clinical laboratories. TREATMENT Endemic Treponematoses The current WHO-recommended therapy for patients and their con tacts includes either azithromycin (30 mg/kg, up to a maximum of

2 g) or benzathine penicillin G (1.2 million units IM for adults; 600,000 units for children <10 years old); these two drugs have been shown to be equivalent for early yaws. The recommended dose of benzathine penicillin G is half of that recommended for early syphi lis, yet no controlled efficacy studies have been conducted. Evidence of genetic resistance to penicillin is lacking, although relapsing lesions have been reported after penicillin treatment in Papua New Guinea. The efficacy of single-dose azithromycin provided the WHO’s revitalized yaws eradication program with a much easier regimen for use in mass treatment. Macrolide resistance has become common in circulating strains of T. pallidum subspecies pallidum in many parts of the world (Chap. 187), and analyses of yaws samples from Papua New Guinea and elsewhere have yielded evidence of mutations con ferring resistance to macrolide antibiotics, including azithromycin,

in a small number of treated patients. Careful molecular surveil lance is essential to monitor developing resistance in yaws-endemic areas. Limited data suggest the efficacy of tetracycline for treatment of yaws, but no data exist for other endemic treponematoses. Based solely on experience with syphilis, it is likely that doxycycline, tetra cycline (at doses appropriate for syphilis; Chap. 187), or ceftriaxone are alternatives, in addition to azithromycin, for patients allergic to penicillin. A Jarisch-Herxheimer reaction (Chap. 187) may follow treatment of endemic treponematoses. Lipoidal serologic titers (in the Venereal Disease Research Laboratory [VDRL] slide test or the

rapid plasma reagin [RPR] test) usually decline after effective therapy, but patients may not become seronegative.

■ ■CONTROL Buoyed by the successful elimination of yaws in India and the avail ability of an inexpensive, single-dose oral drug for treatment, in 2012, the WHO renewed its efforts to eradicate yaws globally by 2020. Based on the results of several pilot programs of MDA, however, the target year for eradication was extended to 2030. Initial enthusiasm has been dampened by several factors: (1) Pilot studies have indicated that a very high level of MDA coverage must be achieved and that multiple rounds of MDA are needed in the affected areas. Treatment must be followed by careful case detection and targeted treatment of cases and contacts. (2) Azithromycin resistance has emerged during MDA studies in Papua New Guinea. Although subsequent treatment with benzathine penicillin G was able to contain the spread of resistant organisms, such evidence suggests that there may be only a short window of time during which countries can successfully use azithromycin for yaws eradica tion. Antibiotic resistance is of particular concern because multiple rounds of MDA are likely to be required. Further, given the ongoing campaigns against trachoma using low-dose azithromycin MDA, often in populations also at high risk for yaws, more widespread macrolide resistance seems inevitable. (3) Lastly, the possible animal reservoir needs to be evaluated, particularly in Africa. Yaws elimination will require rapid implementation and scale-up of high-level drug coverage in endemic areas, and continued careful surveillance by local health centers will be essential for success of this timely and important effort. CHAPTER 189 Leptospirosis ■ ■FURTHER READING Giacani L, Lukehart SA: The endemic treponematoses. Clin Micro biol Rev 27:89, 2014. Janecková K et al: The genomes of the yaws bacterium, Treponema pallidum subsp. pertenue, of nonhuman primate and human origin are not genomically distinct. PLoS Negl Trop Dis 17:e0011602, 2023. John LN et al: Trial of three rounds of mass azithromycin administra tion for yaws eradication. N Engl J Med 386:47, 2022. Marco Goeijenbier, Jiři F. P. Wagenaar

Leptospirosis Leptospirosis is a globally important zoonotic disease whose appar ent reemergence is illustrated by recent outbreaks on virtually all continents. The disease is caused by pathogenic Leptospira species and is characterized by a broad spectrum of clinical manifestations, varying from asymptomatic infection to fulminant, fatal disease. In its mild form, leptospirosis may present as nonspecific symptoms such as fever, headache, and myalgia. Severe leptospirosis, characterized by the triad of jaundice, renal dysfunction, and hemorrhagic diathesis, is often referred to as Weil’s syndrome. With or without jaundice, severe pulmonary hemorrhage is increasingly recognized as an important presentation of severe disease.

 workers in the fishing industry. Risk factors include direct or indirect contact with animals, including exposure to water and soil contami nated with animal urine.

Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat and mouse populations are expanding. FIGURE 189-1 Differentiation of pathogenic, intermediate, and nonpathogenic (saprophytic) Leptospira species by molecular phylogenetic analysis using core genomes comparison (CgMLST). (Reproduced with permission from Dr. A Ahmed, Leptospirosis Reference Center, Academic Medical Center, Medical Microbiology, Amsterdam, The Netherlands.) ■ ■ETIOLOGIC AGENT Leptospira species are spirochetes belonging to the order Spirochaetales and the family Leptospiraceae. Traditionally, the genus Leptospira com prised two species: the pathogenic L. interrogans and the free-living L. biflexa, now designated L. interrogans sensu lato and L. biflexa sensu lato, respectively. Sixty-four Leptospira species with pathogenic (17 spe cies), intermediate (21 species), and nonpathogenic (26 species) status have now been described based on phylogenetic analyses (Fig. 189-1). Genome sequences of all Leptospira species have been published, and this will undoubtedly lead to a better understanding of the pathogen esis of leptospirosis. However, classification based on serologic differ ences better serves clinical, diagnostic, and epidemiologic purposes. Pathogenic Leptospira species are divided into serovars according to their antigenic composition. There are more than 260 known patho genic serovars, which are arranged in 26 serogroups. Leptospires are coiled, thin, highly motile organisms that have hooked ends and two periplasmic flagella, with polar extrusions from the cytoplasmic membrane that are responsible for motility (Fig. 189-2). These organisms are 6–20 μm long and ~0.1 μm in diameter; they stain poorly but can be seen microscopically by dark-field examination and after silver impregnation staining of tissues. Leptospires require special media and conditions for growth; it may take weeks to months for cultures to become positive. ■ ■EPIDEMIOLOGY Leptospirosis has a worldwide distribution. Infection occurs most commonly in the tropics and subtropics because the climate and occa sionally poor hygienic conditions favor the pathogen’s survival and distribution. In most countries, leptospirosis is an underappreciated problem. Most cases occur in men, with a peak incidence during the summer and fall in both the Northern and Southern Hemispheres and during the rainy season in the tropics. Reliable data on morbidity and mortality from leptospirosis have gradually started to appear. Current information on global human leptospirosis varies but indicates that ~1 million severe cases occur per year, with a mean case–fatality rate of nearly 10%. As a zoonosis, leptospirosis affects almost all mammalian species and represents a significant veterinary burden. Rodents, especially rats, are the most important reservoir, although other wild mammals as well as domestic and farm animals may also harbor these microor ganisms. Leptospires establish a symbiotic relationship with their host and can persist in the urogenital tract for years. Some serovars are generally associated with specific animals—e.g., Icterohaemorrhagiae and Copenhageni with rats, Grippotyphosa with voles, Hardjo with cattle, Canicola with dogs, and Pomona with pigs—but may occur in other animals as well. Leptospirosis presents as both an endemic and an epidemic disease. Transmission of leptospires may follow direct contact with urine, blood, or tissue from an infected animal or, more commonly, exposure to environmental contamination. The dogma that human-to-human transmission is very rare is challenged by recent findings on household clustering, asymptomatic renal colonization, and prolonged excretion of leptospires. Both of the latter features could imply human infection sources that are not recognized. Because leptospires can survive in a humid environment for many months, water is an important vehicle in their transmission. Epidemics of leptospirosis are not well understood. Outbreaks may result from exposure to floodwaters contaminated by urine from infected animals, as has been reported from several coun tries. However, it is also true that outbreaks may occur without floods, and floods often occur without outbreaks. The vast majority of infections with Leptospira cause no or only mild disease in humans. A small percentage of

infections (~1%) lead to severe, potentially fatal complications. The proportion of leptospirosis cases that are mild is unknown because patients either do not seek or do not have access to medical care or because the nonspecific symp toms are interpreted as an influenza-like illness. Reported cases surely represent a significant underestimation of the total number. Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and

FIGURE 189-2 Transmission electron microscopic image of Leptospira interrogans invading equine conjunctival tissue. (Image kindly provided by Dr. JE Nally, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA.) Recreational exposure and domestic-animal contact are prominent sources of leptospirosis. Recreational freshwater activities, such as canoeing, windsurfing, swimming, and waterskiing, place persons at risk for infection. Also, several out breaks have followed sporting events. For example, an outbreak took place in 1998 among athletes after a triath lon in Springfield, Illinois. Ingestion of one or more swallows of lake water during the swimming leg of the tri athlon was a prominent risk factor for illness. Heavy rains that preceded the triathlon, with consequent agri cultural runoff, are likely to have increased the level of leptospiral contamination in the lake water. In another outbreak, 42% of partici pants contracted leptospirosis during the 2000 Eco-Challenge-Sabah mul tisport endurance race in Malaysian Borneo. Swimming in the Segama River was shown to be an indepen dent risk factor. Furthermore, out breaks among athletes participating in the recently popular mud-runs are increasingly reported. Approximate time scale Incubation period Incubation Leptospires present in Blood CSF Urine Antibody titers High Low “Negative” Laboratory investigations Culture/PCR PCR In addition, leptospirosis is a trav eler’s disease. Large proportions of patients acquire the infection while traveling in tropical countries, usually during adventurous activities such as whitewater rafting, jungle trekking, and caving or spelunking. Recent data from the GeoSentinel Global Surveil lance Network described in detail 180 returned travelers (mostly male; 74%) with leptospirosis from January 1997 Serology Phases FIGURE 189-3 Biphasic nature of leptospirosis and relevant investigations at different stages of disease. Specimens 1

and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup. CSF, cerebrospinal fluid. (Used with permission of [ASM], from Leptospirosis, PN Levett, 14:296, 2001; permission conveyed through Copyright Clearance Center, Inc. and Turner, Leptospirosis I, Transactions of the Royal Society of Tropical Medicine & Hygiene, 61:842, 1967. Permission is granted as per the terms of the STM Permissions Guidelines. Reproduced by permission of Oxford University Press on behalf of the Royal Society of Tropical Medicine & Hygiene.)

through December 2016. Infection was predominantly acquired in Southeast Asia (52% [n = 93]; mainly [n = 52] from Thailand); overall, 110 patients (59%) were hospitalized, and one patient died. Transmis sion via laboratory accidents has been reported but is rare. New data indicate that leptospirosis may develop after unanticipated immersion in contaminated water (e.g., in an automobile accident) more frequently than has generally been thought and can also result from an animal bite.

■ ■PATHOGENESIS Transmission occurs through cuts, abraded skin, or mucous mem branes, especially the conjunctival and oral mucosa. After entry, the highly motile organisms proliferate, cross tissue barriers, and dis seminate hematogenously to all organs (leptospiremic phase). During this initial incubation period, leptospires can be isolated from the bloodstream (Fig. 189-3). Clearly, Leptospira can survive in the non immune host by evading parts of the innate immune response such as complement-mediated killing and phagocytosis; however, earlier stud ies have highlighted the relation between an exaggerated proinflamma tory immune response and mortality. During the immune phase, the appearance of antibodies coincides with the disappearance of lepto spires from the blood. However, the bacteria persist in various organs, including liver, lung, kidney, heart, and brain. Autopsy findings illus trate the involvement of multiple organ systems in severe disease. Renal pathology shows both acute tubular damage and interstitial nephritis. Acute tubular lesions progress in time to interstitial edema and acute tubular necrosis. Severe nephritis is observed in patients who survive long enough to develop it and seems to be a secondary response to acute epithelial damage. The reported deregulation of the expression of several transporters along the nephron contributes to impaired sodium absorption, tubular potassium wasting, and polyuria. Histopathology of the liver shows focal necrosis (widespread hepatocellular necrosis is usually not found), foci of inflammation, and plugging of bile cana liculi. Hepatocyte apoptosis has also been documented. Experimental work showed infiltration of Leptospira in Disse space (perisinusoidal space) and migration between hepatocytes with detachment of the CHAPTER 189 Leptospirosis Months-years

Years Week 1

Acute stage Convalescent stage Uveitis ? Interstitial nephritis 2-30 days Fever Reservoir host Convalescent shedder Normal response Titers decline at varying rates Delayed Early treatment Anamnestic Blood CSF Urine Urine

Leptospiremia Leptospiruria and immunity

FIGURE 189-4 Severe pulmonary hemorrhage in leptospirosis. Left panel: Chest x-ray. Right panel: Gross appearance of right lower lobes of lung at autopsy. This patient, a 15-year-old from the Peruvian Amazonian city of Iquitos, died several days after presentation with acute illness, jaundice, and hemoptysis. Blood culture yielded Leptospira interrogans serovar Copenhageni/Icterohaemorrhagiae. (Adapted with permission from E Segura et al: Clin Infect Dis 40:343, 2005. © 2005 by the Infectious Diseases Society of America.) intercellular junctions and disruption of bile canaliculi leading to bile leakage. Petechiae and hemorrhages are observed in the heart, lungs (Fig. 189-4), kidneys (and adrenals), pancreas, liver, gastrointesti nal tract (including retroperitoneal fat, mesentery, and omentum), muscles, prostate, testes, and brain (subarachnoid bleeding). Several studies show an association between hemorrhage and thrombocytope nia. Although the underlying mechanisms of thrombocytopenia have not been elucidated, it seems likely that platelet consumption plays an important role. A consumptive coagulopathy may occur, with elevated markers of coagulation activation (thrombin–antithrombin complexes, prothrombin fragments 1 and 2, D-dimer), diminished anticoagulant markers (antithrombin, protein C), and deregulated fibrinolytic activ ity. Overt disseminated intravascular coagulation (DIC) has been doc umented in several clinical studies. Elevated plasma levels of soluble E-selectin and von Willebrand factor in patients with leptospirosis reflect endothelial cell activation. More specifically, markers of

endo thelial cell activation correlate to disease severity in patients with severe leptospirosis. Experimental models show that pathogenic leptospires or leptospiral proteins are able to activate endothelial cells in vitro and to disrupt endothelial-cell barrier function, thus increasing permeability and promoting dissemination. Platelets have been shown to aggre gate on activated endothelium in the human lung, whereas histology reveals swelling of activated endothelial cells but no evident vasculitis or necrosis. Immunoglobulin and complement deposition have been demonstrated in lung tissue involved in pulmonary hemorrhage. PART 5 Infectious Diseases Leptospira species have a typical double-membrane cell wall struc ture harboring a variety of membrane-associated proteins, including an unusually high number of lipoproteins. The peptidoglycan layer is located close to the cytoplasmic membrane. The lipopolysaccharide (LPS) in the outer membrane has an unusual structure with relatively low endotoxic potency. However, host immunity depends on the pro duction of circulating antibodies to serovar-specific LPS. It is unclear whether other antigens play a significant role in protective humoral immunity. Pathogenic Leptospira contain a variety of genes coding for proteins involved in motility and in cell and tissue adhesion and invasion that represent (potential) virulence factors. Many of these are surfaceexposed outer-membrane proteins (OMPs). It is likely that several surface-exposed proteins mediate pathogen–host cell interactions, and these proteins may represent candidate vaccine components. Although animal-model studies have shown various degrees of vaccine efficacy for various putative virulence-associated OMPs, it is not yet clear whether such proteins elicit acceptable levels of sterilizing immunity. Ongoing breakthroughs in genetic manipulation of Leptospira and whole genome sequencing will undoubtedly provide more insight into the biology and virulence of this pathogen. ■ ■CLINICAL MANIFESTATIONS Although leptospirosis is a potentially fatal disease with bleeding and multiorgan failure as its clinical hallmarks, the majority of cases are

thought to be relatively mild, presenting as the sudden onset of a febrile illness. The incubation period is usually 1–2 weeks but ranges from 2 to 30 days. Leptospirosis is classically described as biphasic. The acute leptospiremic phase is char acterized by fever of 3–10 days’ duration, during which time the organism can be cultured from blood and detected by polymerase chain reaction (PCR). During the immune phase, resolution of symptoms may coincide with the appearance of antibodies, and leptospires can be cultured from the urine. The distinction between the first and second phases is not always clear: milder cases do not always include the second phase, and severe disease may be monophasic and fulminant. The idea that distinct clinical syndromes are associ ated with specific serogroups has been refuted, although some serovars tend to cause more severe disease than others. Mild Leptospirosis Most patients are asymptomatic or only mildly ill and do not seek medical attention. Serologic evidence of past inapparent infection is frequently found in persons who have been exposed but have not become ill. Mild symptomatic leptospirosis usually presents as a flulike illness of sudden onset, with fever, chills, headache, nausea, vomiting, abdominal pain, conjunctival suffusion (redness without exudate), and myalgia. Muscle pain is intense and especially affects the calves, back, and abdomen. The headache is intense, localized to the frontal or retroorbital region (resembling that occurring in dengue), and sometimes accompanied by photophobia. Aseptic meningitis may be present and is more common among children than among adults. Although Leptospira can be cultured from the cere brospinal fluid (CSF) in the early phase, the majority of cases follow a benign course with regard to the central nervous system; symptoms disappear within a few days but may persist for weeks. Physical examination may include any of the following findings, none of which is pathognomonic for

leptospirosis: fever, conjunctival suffusion, pharyngeal injection, muscle tenderness, lymphadenopathy, rash, meningismus, hepatomegaly, and splenomegaly. If present, the rash is often transient; may be macular, maculopapular, erythematous, or hemorrhagic (petechial or ecchymotic); and may be misdiagnosed as due to scrub typhus or viral infection. Lung auscultation may reveal crackles. Mild jaundice may be present. The natural course of mild leptospirosis usually involves spontane ous resolution within 7–10 days, but persistent symptoms have been documented. In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low. Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%. Higher mortality rates are associated with an age >40 years, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias. The classic presentation, often referred to as Weil’s syndrome, encompasses the triad of hemor rhage, jaundice, and acute kidney injury. Patients die of multiorgan failure after septic shock and/or severe bleeding complications that most commonly involve the lungs (pul monary hemorrhage), gastrointestinal tract (melena, hematemesis), urogenital tract (hematuria), and skin (petechiae, ecchymosis, and bleeding from venipuncture sites). Pulmonary hemorrhage (with or without jaundice) is now recognized as a widespread public health problem, presenting with cough, chest pain, respiratory distress, and hemoptysis that may not be apparent until patients are intubated. Jaundice occurs in 5–10% of all patients with leptospirosis; it can be profound and give an orange cast to the skin but usually is not associ ated with fulminant hepatic necrosis. Physical examination may reveal an enlarged and tender liver. Acute kidney injury is common in severe disease, presenting after several days of illness, and can be either nonoliguric or oliguric. Typical

electrolyte abnormalities include hypokalemia and hyponatremia. Loss of magnesium in the urine is uniquely associated with leptospiral nephropathy. Hypotension is associated with acute tubular necrosis, oliguria, or anuria, requiring fluid resuscitation and sometimes vaso pressor therapy. Hemodialysis can be lifesaving, with renal function typically returning to normal in survivors. In severe leptospirosis, an altered mental status may reflect lepto spiral meningitis. The diagnosis of leptospirosis meningitis may be challenging since patients may be anicteric or lack other diagnostic hallmarks of severe leptospirosis. Without proper antibiotic treatment, a mortality rate of 13% has been reported; in contrast, among patients treated with antibiotics, the mortality rate is 2%. Neurologic sequelae are described until months after acute illness. Other syndromes include (necrotizing) pancreatitis, cholecystitis, skeletal muscle involvement, and rhabdomyolysis with moderately ele vated serum creatine kinase levels. Cardiac involvement is commonly reflected on the electrocardiogram as nonspecific ST- and T-wave changes. Repolarization abnormalities and arrhythmias are considered poor prognostic factors. Myocarditis has been described. Rare hemato logic complications include hemolysis, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome. Long-term symptoms following severe leptospirosis include fatigue, myalgia, malaise, and headache and may persist for years. Autoim mune-associated uveitis, a potentially chronic condition, is a recog nized sequela of leptospirosis. ■ ■DIAGNOSIS The clinical diagnosis of leptospirosis should be based on an appropri ate exposure history combined with any of the protean manifestations of the disease. Returning travelers from endemic areas usually have a history of recreational freshwater activities or other mucosal or per cutaneous contact with contaminated surface waters or soil. For non travelers, recreational or accidental water/soil contact and especially occupational hazards that involve direct or indirect animal contact should be

explored (see “Epidemiology,” above). Although biochemical, hematologic, and urinalysis findings in acute leptospirosis are nonspecific, certain patterns may suggest the diagnosis. Laboratory results usually show signs of a bacterial infec tion, including leukocytosis with a left shift and elevated markers of inflammation (C-reactive protein level, procalcitonin, and erythrocyte sedimentation rate). Thrombocytopenia (platelet count ≤100 × 109/L) is common and is associated with bleeding and renal failure. In severe disease, signs of coagulation activation may be present, varying from borderline abnormalities to a serious derangement compatible with DIC as defined by international criteria. The kidneys are invariably involved in leptospirosis. The absence of renal involvement does not rule out leptospirosis. However, when the kidneys are involved, related findings range from urinary sediment changes (leukocytes, erythro cytes, and hyaline or granular casts) and mild proteinuria in mild dis ease to renal failure and azotemia in severe leptospirosis. Nonoliguric hypokalemic renal insufficiency (see “Clinical Manifestations,” above) is characteristic of early leptospirosis. Serum bilirubin levels may be high, whereas rises in aminotransferase and alkaline phosphatase levels are usually moderate. Although clinical symptoms of pancreatitis are not a common finding, amylase levels are often elevated. When symp toms of meningitis develop, examination of the CSF shows pleocytosis that can range from a few cells to >1000 cells/μL, with a predominance of lymphocytes. Predominant polymorphonuclear pleocytosis has been reported. This phenomenon may be related to the timing of the lumbar puncture: polymorphonuclear cells are thought to be found in early disease and are later replaced by lymphocytes. Although protein and glucose levels in the CSF are usually normal, protein levels may be slightly elevated. In severe leptospirosis, pulmonary radiographic abnormalities are more common than would be expected based on physical examination (Fig. 189-4). The most common radiographic finding is a patchy bilat eral alveolar pattern that corresponds to scattered alveolar hemorrhage. These abnormalities predominantly affect the lower lobes. Other find ings include pleura-based densities (representing areas of hemorrhage)

and diffuse ground-glass attenuation typical of acute respiratory dis tress syndrome (ARDS).

A definitive diagnosis of leptospirosis is based on isolation of the organism from the patient, on a positive result in the PCR, or on seroconversion or a rise in antibody titer. In cases with strong clinical evidence of infection, a single antibody titer of 1:200–1:800 (depend ing on whether the case occurs in a low- or high-endemic area) in the microscopic agglutination test (MAT) is required. Preferably, a fourfold or greater rise in titer is detected between acute- and convalescentphase serum specimens. Antibodies generally do not reach detectable levels until the second week of illness. The antibody response can be affected by early treatment with antibiotics. The MAT, which uses a battery of live leptospiral strains, and the enzyme-linked immunosorbent assay (ELISA), which uses a broadly reacting antigen, are the standard serologic procedures. The MAT usu ally is available only in specialized laboratories and is used for deter mination of the antibody titer and for tentative identification of the involved leptospiral serogroup—and, when epidemiologic background information is available, the putative serovar. This point underscores the importance of testing antigens representative of the serovars preva lent in the particular geographic area. However, cross-reactions occur frequently, and thus definitive identification of the infecting serovar or serogroup is not possible without isolation of the causative organism. Because serologic testing lacks sensitivity in the early acute phase of the disease (up to day 5), it cannot be used as the basis for a timely decision about whether to start treatment. In addition to the MAT and the ELISA, various rapid tests with diagnostic value have been developed, and some of these are com mercially available. These rapid tests mainly apply lateral flow, (latex) agglutination, or ELISA

methodology and are reasonably sensitive and specific, although results reported in the literature vary, probably as a consequence of differences in test interpretation, (re)exposure risks, serovar distribution, and the use of biased serum panels. These methods do not require culture or MAT facilities and are useful in settings that lack a strong medical infrastructure. PCR methodologies, notably real-time PCR, have become increasingly widely implemented. Compared with serology, PCR offers a great advantage: the capacity to confirm the diagnosis of leptospirosis with a high degree of accuracy during the first 5 days of illness. CHAPTER 189 Leptospirosis ■ ■DIFFERENTIAL DIAGNOSIS The differential diagnosis of leptospirosis is broad, reflecting the diverse clinical presentations of the disease. Although leptospirosis transmission is more common in tropical and subtropical regions, the absence of a travel history does not exclude the diagnosis. When fever, headache, and myalgia predominate, influenza, SARS-CoV-2, and other common and less common (e.g., dengue and chikungunya) viral infections should be considered. Malaria, typhoid fever, ehrlichiosis, viral hepatitis, and acute HIV infection may mimic the early stages of leptospirosis and are important to recognize. Rickettsial diseases, den gue, and hantavirus infections (hemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome) share epidemiologic and clinical features with leptospirosis. Dual infections have been reported. In this light, it is advisable to conduct serologic testing for rickettsiae, dengue virus, and hantavirus when leptospirosis is suspected. When bleeding is detected, dengue hemorrhagic fever and other viral hemor rhagic fevers, including hantavirus infection, yellow fever, Rift Valley fever, filovirus infections, and Lassa fever, should be considered. TREATMENT Leptospirosis Severe leptospirosis should be treated with IV penicillin (Table 189-1) as soon as the diagnosis is considered. Leptospira are highly susceptible to a broad range of antibiotics, including the β-lactam antibiotics, cephalosporins, aminoglycosides, and macrolides, but are not susceptible to vancomycin, rifampicin, metronidazole, and chloramphenicol. Early intervention may prevent the development

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