FIG. 237.12 Congenital syphilis. (A) Scaling annular rash of congenital syphilis. (B) Ulceration of perineal region in newborn with congenital syphilis. (C) Face of the same infant reveals perioral papules, ulcerous lesions, and labial fissures. (D) Dusky macular rash extending over the anterior trunk of a newborn infant with congenital syphilis. *(Courtesy Dr. Leon Chameides, Hartford, CT.)*

TABLE 237.3 Clinical Signs of Congenital Syphilis

Early Congenital Syphilis
Osteochondritis, periostitis
Snuffles, hemorrhagic rhinitis
Bullous lesions, palmar/plantar exanthem
Hemolytic anemia
Hepatosplenomegaly
Jaundice
Central nervous system involvement: elevated cell count or elevated protein in cerebrospinal fluid
Generalized lymphadenopathy
Pneumonitis
Nephrotic syndrome
Nonimmune hydrops fetalis
Intrauterine growth retardation
Late Congenital Syphilis
Frontal bosses
Short maxillas
Saddle nose
Protruding mandible
Interstitial keratitis
Eighth nerve deafness
High palatal arch
Hutchinson incisors
Mulberry molars
Sternoclavicular thickening (Higoumenaki sign)
Clutton joints (bilateral painless swelling of knees)
Saber shins
Flaring scapulas

Modified from Kampmeier RH. Essentials of Syphilology. *3rd ed. Philadelphia: JB Lippincott; 1943; Stokes JH, Beerman H, Ingraham NR.* Modern Clinical Syphilogy: Diagnosis, Treatment: Case Study. *3rd ed. Philadelphia: Saunders; 1945; and Patton ME, Su JR, Nelson R, et al; Centers for Disease Control and Prevention. Primary and secondary syphilis—United States, 2005–2013.* MMWR Morb Mortal Wkly Rep. *2014;63:402–406.*

neonates will manifest both direct and indirect hyperbilirubinemia, as well as elevated transaminases. The major hematologic features of CS are anemia, leukocytosis or leukopenia, in some cases monocytosis, and thrombocytopenia.[462,482] Renal involvement with an immune complex glomerulonephritis, evidenced by the appearance of nephrotic syndrome, may develop and usually occurs at about the fourth month of life.[483] A generalized osteochondritis and perichondritis or periostitis may affect the architecture of all bones of the skeletal system but are most prominent in the long bones and can be easily discerned on radiographs.[484,485] CNS involvement is common, occurring in at least 22% of infected neonates,[486] ranging from asymptomatic invasion by *T. pallidum* to acute syphilitic leptomeningitis. When untreated, neurosyphilis in the infant can lead to a chronic meningovascular process, which results in hydrocephalus, cranial nerve palsies, and even cerebral infarction. Asymptomatic CNS involvement is inferred from the presence of abnormal CSF studies, such as pleocytosis (defined as >25 white blood cells/μL for infants <1 month), high CSF protein levels (defined as >150 mg/dL in term infants <1 month of age and >170 mg/dL in preterm infants <1 month of age, although some experts use a threshold of >40 mg), a reactive CSF VDRL test, or a combination of these, in a healthy-appearing infant. Asymptomatic CNS syphilis occurs in approximately 40% of infants who have clinical, laboratory, or radiographic abnormalities of CS but is infrequent in infants without such manifestations. Because CSF studies are of low sensitivity to detect spread of spirochetes into the brain, in some cases asymptomatic disease can be diagnosed only by serum or CSF IgM immunoblotting or by PCR detection of spirochetal DNA.[486] Hypopituitarism manifesting with persistent neonatal hypoglycemia has been observed among some infants with CS.[487] Although rare, chorioretinitis, glaucoma, and uveitis have also been described in newborns with early CS.[60]

With a few exceptions, the untreated child who survives the first 6 to 12 months of life will develop manifestations of late CS.[60] The generalized osteochondritis, perichondritis, and periostitis may result in deformities of the nose (saddle nose)[488] and the metaphyses of the lower extremities (anterior bowing, or saber shin).[60] Cardiovascular syphilis is rare, whereas interstitial keratitis is common.[489] Photophobia, pain, circumcorneal inflammation, and superficial and deep vascularization of the cornea may occur at any time between the ages of 5 and 30 years.[489] Asymptomatic late congenital neurosyphilis occurs in up to one-third of perinatally infected children, whereas symptomatic disease is rare and fits the adult patterns of tabes dorsalis, syphilitic encephalitis, and local gummas. Eighth nerve compromise with resulting sensorineural deafness is particularly common.[484] Other late characteristic stigmata include recurrent arthropathy and bilateral knee effusions (Clutton joints)[425]; centrally notched, widely spread, peg-shaped upper central incisors (Hutchinson teeth)[490]; frontal bossing; and poorly developed maxillas.[491]

A complete evaluation of the neonate suspected of having CS should include a complete physical examination and DF microscopic examination or DFA staining of suspicious lesions or body fluids (e.g., nasal discharge). Conventional blood tests, including a complete blood count and liver and renal function tests, along with HIV testing and long bone radiographs, should be done in all infants. Nontreponemal tests (VDRL or RPR) and, if available, IgM immunoblotting are recommended on serum and CSF (VDRL only on CSF). The CDC no longer recommends obtaining umbilical cord blood because of the potential for contamination with maternal blood and because RPR testing of umbilical cord blood is prone to false positives owing to contamination with Wharton jelly.[492] The nontreponemal test that is performed on the infant should be the same as that done on the mother so that the maternal and infant titers can be directly compared. Other tests should be performed as clinically indicated (i.e., chest radiography, abdominal ultrasonography, ophthalmologic examination, auditory brainstem response, and neuroimaging studies). It is important to note that a diagnosis of acquired syphilis in an older child is suggestive of sexual abuse, although some cases might be attributable to progression of CS.[493]

To maximize treatment of children potentially infected with *T. pallidum,* including those who are asymptomatic at the time of initial presentation, in 1996 the CDC issued a revised case definition for CS (see Table 237.2).[494] The criteria include all infants with clinical evidence of active syphilis, as well as normal-appearing neonates and stillbirths delivered to women with untreated or inadequately treated syphilis. According to these guidelines, a confirmed diagnosis of CS requires laboratory demonstration of *T. pallidum* in tissues or lesions of infected infants (see Table 237.2). Amniotic fluid, placental tissue, cytobrushings or sections of umbilical cord, nasal fluid, scrapings from a rash, tissue impressions, and lymph node aspirates are examples of specimens that can be examined for spirochetes.[473,495–497] DF microscopy, DFA-TP, immunohistochemistry, and silver staining can all be used to visualize *T. pallidum.* PCR can reveal small amounts of *T. pallidum* DNA in lesion exudates or tissues but cannot be used to confirm the presence of living organisms.[497–499] Because most of these detection methods are difficult to perform in most clinical settings, a confirmed diagnosis is achieved only in a small proportion of newborns, with most affected children receiving a diagnosis of presumptive CS. CS is highly probable if the neonate has any of the following: abnormal physical examination findings consistent with CS; a serum quantitative nontreponemal serologic titer that is greater than or equal to fourfold (two dilutions) the corresponding maternal titer; a reactive serum VDRL/RPR test and abnormal CSF (see earlier); and reactive treponemal antibody test after 15 months of age.

As per Table 237.2, the diagnosis of presumptive CS is made on the basis of (1) identification of syphilis in the mother; (2) adequacy of maternal treatment; (3) presence of clinical, laboratory, or radiographic evidence of syphilis in the infant; and (4) comparison of maternal (at delivery) and infant nontreponemal serologic titers obtained using the same test and preferably performed in the same laboratory.[500] Infants younger than 1 month who have normal physical examination findings and serum VDRL or RPR titers less than fourfold the maternal titer are presumed to have CS if their mother was not treated or received inadequate or suboptimal therapy. Some experts would also presume infants to have CS if their mothers had contact with a person with primary or secondary syphilis within 90 days before delivery and were not treated or were inadequately treated, even if the mother had nonreactive serology. A diagnosis of CS is unlikely if the infant has normal physical examination findings and a nonreactive VDRL/RPR test and the mother was adequately treated during pregnancy and had an appropriate serologic response, or if the neonate has normal physical examination findings and serum VDRL or RPR titer the same or less than fourfold the maternal titer and the mother was adequately treated before pregnancy and her titers remained low (VDRL <1:2; RPR <1:4) and stable before and during pregnancy and at delivery. Because at least one-third of the mothers who give birth to syphilitic children have not had prenatal care, and about half have had a nonreactive serologic test during the first trimester of pregnancy, serologic testing of the mother is always warranted at delivery, especially in high-risk patients. No infant or mother should leave the hospital unless the maternal serologic status has been documented at least once during pregnancy, and at delivery in communities and populations in which the risk for CS is high.

Parenteral penicillin is the drug of choice for the treatment of CS (see Table 237.2).[60,501] Infants 4 weeks of age or younger who have confirmed or presumptive disease should be treated with either aqueous crystalline penicillin G, 50,000 units/kg IV every 12 hours for the first 7 days of life and every 8 hours beyond 1 week of age for a total of 10 days, or aqueous procaine penicillin G, 50,000 units/kg IM once daily for 10 days (see Table 237.2). The levels of penicillin that are achieved in the CSF after intramuscular administration of procaine penicillin are lower than those with intravenous administration of aqueous penicillin.[502] However, the clinical significance of this observation is unclear because there have been no treatment failures reported after treatment with procaine penicillin.[461] If more than 1 day of penicillin therapy is missed, the entire course should be restarted. Single-dose therapy with intramuscular injection of BPG (50,000 units/kg) can be considered in the infant with normal physical examination findings, normal CSF, and normal radiographic and laboratory studies and whose nontreponemal test titer is the same or less than the maternal titer, under the following circumstances: (1) The mother was treated with the appropriate regimen for 30 or fewer days before delivery; (2) the mother received her recommended penicillin therapy for the stage of infection during the pregnancy but the nontreponemal titer did not decrease fourfold at the time of delivery; and (3) the mother has untreated syphilis or her treatment status is undocumented. Children who are diagnosed with CS after 1 month of age (including those with late CS) and children with acquired syphilis should be treated with aqueous penicillin G (50,000 units/kg IV every 4 to 6 hours for 10 days). In addition, for children with CS or findings compatible with CNS involvement, some experts suggest that the 10-day course of aqueous penicillin be followed with a single dose of intramuscular BPG (50,000 units/kg).

Follow-up of children treated for CS after the newborn period should be conducted as is recommended for neonates. The risk of infection for the infant is minimal if the mother has received adequate penicillin treatment during pregnancy. Nevertheless, the child must be examined monthly after delivery and until the nontreponemal test or PCR assay result becomes negative. Penicillin treatment should never be withheld to prove the diagnosis, and every neonate born to a syphilitic mother should be promptly treated unless adequate, serologically proven effective treatment with penicillin can be documented more than 1 month before delivery. Because giving penicillin to the neonate is almost risk free, all neonates born to syphilitic mothers should be treated, regardless of whether the mother was treated during pregnancy. Adequate treatment of the mother usually but not always ensures that the fetus will not be infected. Infants born to mothers who are coinfected with syphilis and HIV should receive the same evaluation and treatment as those whose mothers do not have HIV infection.[501] There is insufficient evidence to determine whether such infants require different evaluation, treatment, or follow-up.

IMMUNITY

For nearly 200 years, syphilologists have intensely pondered and debated the existence, timing, and nature of protective immunity in acquired

syphilis.[169,503,504] In the 19th century, it was believed that individuals became immune to reinfection during primary syphilis, a notion referred to by the term "chancre immunity." This flawed concept was based largely on "autoinoculation" experiments in which material taken from presumptive chancres failed to cause lesions when inoculated elsewhere on the same patient. Using his primate model, Neisser concluded that chancre immunity is dependent on the presence of active infection and that cure of the disease leads to the disappearance of immunity.[169] Chesney,[505] in contrast, correctly concluded from data generated using the rabbit model that syphilitic infection does indeed elicit lasting immunity, provided the initial infection is of sufficient duration. Important to note, he found substantially less cross-immunity to challenge with heterologous strains of *T. pallidum,* findings confirmed years later, also in rabbits, by Turner and Hollander.[132,505] In a meticulously executed study involving nearly 300 rabbits, which took advantage of the recent availability of penicillin, Magnuson and Rosenau[506] showed definitively that immunity to homologous challenge in the animal model was dose and time dependent and could be achieved in the absence of concurrent infection. To a significant extent, Magnuson and coworkers[140] replicated these results in humans several years later in a remarkable (and unrepeatable) series of experiments conducted at Sing Sing Prison. Although these investigators went to great length to explain that all participants were volunteers, the authors of this chapter must state unequivocally that they do not condone experimentation in incarcerated populations even if it was considered acceptable in the era in which it was performed. In any event, the Magnuson group showed that patients with treated primary and secondary syphilis were susceptible to challenge with the Nichols strain of *T. pallidum,* whereas those with treated or untreated late latent disease were resistant. Interpretation of these experiments is clouded by the extraordinarily high challenge inoculum used (1×10^5), more than 2000-fold greater than the median infective dose (ID_{50}) determined in the same study, compounded by the likely heterologous challenge in the majority of "volunteers." However, there is also abundant clinical experience that patients successfully treated for primary and secondary syphilis can be reinfected.[508,509] It seems reasonable to conclude, therefore, that the immunity that develops during early syphilis is limited, even more so against heterologous infection, and that it dissipates rapidly after treatment. In a controversial paper, Grassly and coworkers[35] used mathematical models derived from epidemiologic data to argue that the oscillatory pattern of syphilis epidemics over an approximate 11-year cycle is due to the buildup of immunity in untreated populations, followed by the waning of immunity after large-scale treatment. Their hypothesis deserves reconsideration given recent technical advances in sequencing genomes of syphilis spirochetes in lesions[33,180] and our much improved knowledge of *T. pallidum*'s OMP repertoire,[34,73] the presumptive targets of protective antibodies.

The lack of an inbred animal model has greatly hindered efforts to dissect the components of the immune response that confer protection. Because *T. pallidum* is an extracellular pathogen, one would expect passive administration of antibodies from immune animals to protect against homologous challenge. Such experiments have repeatedly shown that administration of large amounts of serum or purified immunoglobulins yields only modest lesion attenuation in rabbits challenged intradermally and that dissemination of spirochetes is not prevented.[169] In other words, passive immunization is at best only partially protective. The paucity of antigenic targets on the surface of the syphilis spirochete, coupled with other mechanisms for antibody avoidance (e.g., limited production of antibodies against surface-exposed epitopes, antigenic variation, and differential expression of OMPs; see earlier), is an attractive explanation for these results.[73]

The inability of public health measures to curtail the explosive increase in syphilis cases worldwide, with particular concern for the global burden of maternal syphilis and CS, has called renewed attention to the need for an effective vaccine.[5,434,503,504,510] The feasibility of eliciting a protective immune response against *T. pallidum* was demonstrated nearly 50 years ago. In a hallmark study, Miller[507] reported complete and long-lasting (1 year) protection of rabbits immunized over a 37-week period with *T. pallidum* rendered noninfectious by gamma irradiation. Important to note, this regimen did not protect against challenge with the Haiti B strain, thought at the time to be subspecies *pertenue* but now known to be subspecies *pallidum.* Until recently, efforts to replicate this stunning result by immunization with recombinant *T. pallidum* proteins believed to contain surface-exposed epitopes yielded either no or only partial degrees of protection. In what appears to be a major advance, Lithgow and colleagues[511] showed that immunization of rabbits with TP0751 reduced spirochete dissemination. The high degree of conservation of TP0751 in *T. pallidum* strains suggests that a vaccine containing this lipoprotein could be useful on a global scale.

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238 Endemic Treponematoses

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SHORT VIEW SUMMARY

Definition
- The endemic treponematoses include yaws, endemic syphilis, and pinta. All are cutaneous diseases caused by treponemes closely related to *Treponema pallidum,* the causative agent of syphilis.

Microbiology
- The treponemal species that cause the endemic treponematoses cannot be easily cultured for diagnosis. Microbiologic diagnosis is most often based on nontreponemal and treponemal serologic reactivity in tests designed for syphilis diagnosis.

Epidemiology
- The endemic treponematoses are generally spread only from human to human by direct contact. After global eradication campaigns in the 1950s and 1960s, yaws rates have again increased worldwide. Endemic syphilis and pinta remain uncommon, but the prevalence is unknown because of the lack of surveillance data.

Clinical Manifestations
- Similar to syphilis, initial lesions of endemic treponematoses resolve spontaneously; recurrent secondary lesions are typically cutaneous or involve bone or cartilage.
- A latent (asymptomatic) stage may occur in individuals infected with yaws or endemic syphilis, and a minority of untreated patients progress to bone, soft tissue, and cartilaginous destruction.

Diagnosis
- Diagnosis of endemic treponematoses is based on clinical recognition of compatible skin lesions and confirmed by serologic testing.
- The development of a point-of-care immunochromatographic lateral flow assay that simultaneously tests for treponemal and nontreponemal antibodies facilitates rapid diagnosis and treatment.

Therapy
- Benzathine penicillin G was the mainstay of therapy of the endemic treponematoses. More recently, oral azithromycin has been proven to be an easy-to-administer alternative to penicillin injections for therapy of yaws.

Prevention
- Yaws appears to be amenable to mass treatment as a control and prevention measure.
- In 2012 the World Health Organization announced plans to embark on mass treatment initiatives designed to eradicate yaws by 2020.

The endemic treponematoses comprise yaws, endemic syphilis, and pinta and are caused by *Treponema pallidum* subsp. *pertenue, Treponema pallidum* subsp. *endemicum,* and *Treponema carateum*. Nearly eliminated in the 1960s by an eradication campaign led by the World Health Organization (WHO), these relatively uncommon diseases are now often seen among children living in low-income and middle-income countries. The bacteria that cause the endemic treponematoses are morphologically and serologically indistinguishable from *T. pallidum* subsp. *pallidum,* the causative agent of sexually transmitted syphilis, and important parallels are found between the natural history of these diseases and syphilis. Similarly, the tools for management are adapted almost entirely from tools historically used as part of syphilis control efforts. Nonetheless, the endemic treponematoses differ from syphilis in terms of epidemiology, clinical manifestations, and at the level of the bacterial genome.[1–3,4,5]

Disease rates have again increased more recently.[1,6] Based on the successful eradication of yaws in India and the potential for recently described oral azithromycin therapy to facilitate control and prevention, the WHO announced a new effort to eradicate yaws.[7,8]

MICROBIOLOGY

Within the genus *Treponema,* four bacteria are presently recognized as human pathogens: *T. pallidum* subsp. *pallidum, T. pallidum* subsp. *pertenue, T. pallidum* subsp. *endemicum,* and *T. carateum.* Much remains to be learned about these organisms. They cannot be cultured in vitro, and current understanding of their biology is based on the careful study of relatively few clinical isolates, most often propagated in laboratory animals (e.g., rabbits, hamsters, and guinea pigs).[4,5] Although sequencing of the *T. pallidum* genome showed more than 99% DNA homology,[3] several genetic loci have been identified that may permit differentiation of *T. pallidum* subsp. *pallidum* from the other subspecies (*T. pertenue* and *T. endemicum*).[4,5] *T. carateum* isolates are not available for study at the present time, and any molecular similarities and differences have yet to be compared with the *T. pallidum* subspecies.[9] In the future, application of evolving molecular diagnostic methods to the study of human treponemes promises to provide new insights into the biology of these organisms.

Morphology

T. pallidum and the treponemes causing endemic treponematoses are long, thin (8–13 × 0.15 μm), motile bacteria that cannot be seen with Gram stain and are best seen in specimens of a lesion exudate with a Warthin-Starry silver stain, darkfield microscopic examination, or fluorescent antibody techniques. Their regular, spiral morphology and characteristic corkscrew motility are helpful for recognition in clinical specimens.

Antibiotic Sensitivity

Based on clinical and serologic response to therapy as well as studies performed in experimental animals, these treponemes are sensitive to penicillins and tetracyclines. Because the organisms cannot be propagated in vitro, data on minimal inhibitory and bactericidal concentrations are unavailable. Sulfa drugs and fluoroquinolone antimicrobials have not been found to be active against *T. pallidum* subsp. *pallidum*.[10,11] Clinical and laboratory resistance (mutations of 23S ribosomal RNA gene) to erythromycin and other macrolide antibiotics has been shown for multiple isolates of *T. pallidum* subsp. *pallidum* from North America and Western Europe,[12] but similar resistance among the endemic treponematoses was not documented until 2018.[13] With the adoption by the WHO of azithromycin as the preferred treatment for yaws,[14] close monitoring for macrolide resistance will be important.

EPIDEMIOLOGY

The endemic treponematoses are diseases of low-income and middle-income countries, with varied geographic distribution. However, the true scope of disease is unknown because endemic treponematoses are

not notifiable diseases in most countries. Yaws appears to have worldwide distribution (Central and South America, Asia, Africa, and Pacific Islands) and is found in warm, humid climates with heavy rainfall including tropical regions and rainforests. Of 13 endemic countries that reported to the WHO between 1990 and 2014, prevalence of active yaws disease ranged from 0.31% to 14.54%, and prevalence of latent yaws ranged from 2.45% to 31.05% with a higher burden of infection in the Pacific Islands.[15] Endemic syphilis is less common than yaws and occurs primarily in dry, arid areas among nomadic and seminomadic rural populations. The disease has been most common in North Africa, Southwest Asia, and the eastern Mediterranean region. In contrast to the global distribution of yaws and endemic syphilis, pinta is limited to the Western Hemisphere. The disease has been described in Mexico, Caribbean islands (including Cuba), and Central and South American countries.[6,9] The prevalence of pinta is unknown at the present time because of the lack of surveillance data. However, substantial numbers of cases including a case series of more than 200 patients have been described in rural Brazil.[16] Within these regions, each of the endemic treponematoses disproportionately impacts impoverished people living in remote areas. Limited access to hygienic facilities has been associated with increased infection rates.

Transmission

Similar to syphilis, the endemic treponematoses are acquired and spread through direct contact with infectious exudates from patients with active infection or who have relapsed after latent infection (infected but asymptomatic). In the case of endemic syphilis, transmission is possible via fomites (see "Endemic Syphilis [Bejel]"). However, in contrast to syphilis, little evidence exists that transmission of endemic treponematoses occurs via blood, blood products, or transplacentally from untreated pregnant women to unborn children. Protective immunity induced by infection has been shown only in rabbit experimental models conducted in the early 20th century; however, a later study in hamsters concluded that immunity was not absolute.[1]

CLINICAL MANIFESTATIONS

The endemic treponematoses can be characterized by several common clinical characteristics as well as characteristics that distinguish them from one another.[17] Although there are several important differences, there are numerous parallels between the well-described course of untreated syphilis (*T. pallidum* subsp. *pallidum* infection) and the natural history of the endemic treponematoses. Similar to syphilis, each is a chronic bacterial infection that progresses through a series of well-described clinical stages, predictably progressing from an early, localized stage to a later, more widespread stage. Early in the course of infection, even before primary lesions develop, the treponemes spread hematogenously throughout the body; without treatment, they subsequently give rise to secondary and late manifestations of infection. Once primary lesions develop, regional lymphadenopathy follows. As in the case of syphilis, primary lesions of yaws and pinta resolve spontaneously without treatment; then in the secondary stage, skin lesions may recur up to 5 years, with the frequency of these recurrences declining with time.[1,4] Recurrent secondary manifestations of early endemic treponematoses are primarily dermatologic; however, a substantial proportion of persons also develop osteitis or other bony or cartilaginous lesions. Primary and secondary lesions may resolve, and a patient's infection may become latent, where the patient harbors infection without exhibiting signs and symptoms.[13]

Late Complications and Sequelae

In a minority of untreated patients with yaws and endemic syphilis, late complications of infection occur. The lesions of late infections tend to be more destructive than the early lesions and most commonly manifest either as ulcerative or hyperkeratotic cutaneous lesions or as bone and joint involvement. A distinguishing element of the endemic treponematoses is that, in contrast to syphilis, little evidence exists of cardiovascular or neurologic sequelae in late or untreated infection.

Differential Diagnosis

The differential diagnosis varies between the endemic treponematoses and their stages. As the clinical presentation of endemic treponematoses can be mistaken for sexually transmitted syphilis, it is difficult to distinguish between the two diseases especially in countries where both are endemic. Early yaws may present similar to impetigo, scabies, molluscum contagiosum, lichen planus, and cutaneous leishmaniasis. The differential diagnosis for endemic syphilis includes orofacial herpes simplex and noninfectious aphthous ulcers. Early lesions of pinta may be confused with eczema, psoriasis, and leprosy.

Yaws

Yaws, one of the 20 neglected tropical diseases according to the WHO, is a chronic infection caused by *T. pallidum* subsp. *pertenue* and is the most common of the endemic treponematoses. After years of relatively low levels of prevalence (see "Prevention"), there has been a resurgence of disease.[1,6,7] Yaws is most common in children 2 to 15 years of age. Human-to-human transmission of yaws is thought to be facilitated by skin breaks (e.g., lacerations, insect bites), crowding, and a relative lack of hygiene. These circumstances are generally more common in children than in adults and may explain why most initial infections occur in children and adolescents. Notably, yaws-like strains have been identified from skin lesions of African monkeys, baboons, and gorillas suggesting that *T. pallidum* subsp. *pertenue* may also cause the same disease in nonhuman primates.[2] To date, there has been no evidence of transmission from nonhuman primates to humans, but it is possible that nonhuman primates may be a potential reservoir for the bacteria.

A primary papule forms at the site of inoculation (commonly the legs, feet, or buttocks) after an incubation period of 9 to 90 days (mean, 21 days). Over a period of 3 to 6 months, the primary papule of yaws may increase in size and then heal spontaneously. Primary lesions are typically pruritic, facilitating autoinoculation; tender regional lymphadenopathy, fever, and constitutional symptoms may also develop. At about the time the primary papule heals, secondary lesions near or distant from the initial lesion often occur. These lesions may also be papular and are thought to be a consequence of local (autoinoculation) and hematogenous or lymphatic spread of infection (Fig. 238.1). In the secondary stage, lesions of yaws predominately involve the skin near the nose and mouth and bones or cartilage of the extremities and, even if untreated, generally heal without scarring (Fig. 238.2). Similar to the primary lesions, lesions of secondary yaws resolve spontaneously without therapy, and patients enter a latent stage that, if untreated, may last a lifetime.[4] Occasionally, secondary infection or ulceration of cutaneous yaws lesions occurs and results in more pronounced lesions and scarring.

About 10% of untreated patients develop late lesions of yaws characterized by hyperkeratotic plaques, destructive bony lesions, or gummata. In the 1820s, Spaniards first coined the term *gangosa* (nasal voice) to describe these disfiguring chronic manifestations, as they destroy bone,

FIG. 238.1 Initial papillomatous yaws lesion on upper thigh (also called primary frambesioma, mother yaw, *chancre pia nique*). Initial lesion usually commences as a papule on lower extremities and slowly enlarges to form a raspberry-like lesion. *(From Ferine PL, Hopkins DR, Niemel PLA, et al.* Handbook of Endemic Treponematoses. *Geneva: World Health Organization; 1984.)*

FIG. 238.2 Early ulceropapillomatous yaws on the leg (also called *ulcère post-chancreux*). *(From Ferine PL, Hopkins DR, Niemel PLA, et al.* Handbook of Endemic Treponematoses. *Geneva: World Health Organization; 1984.)*

FIG. 238.3 Gangosa. *(From Ferine PL, Hopkins DR, Niemel PLA, et al.* Handbook of Endemic Treponematoses. *Geneva: World Health Organization; 1984.)*

cartilage, and soft tissue of the mouth and nose (Fig. 238.3). Bowing of the anterior tibiae (saber shins) may likewise be a late manifestation of yaws arising from infectious periostitis.

Healing is promoted with therapeutic administration of azithromycin or penicillin. Complete healing may occur without sequelae in patients receiving early treatment. Yaws infections may be prevented with prophylactic administration of azithromycin in exposed patients (see "Therapy" and "Prevention").

Endemic Syphilis (Bejel)

Endemic syphilis is caused by *T. pallidum* subsp. *endemicum*.[1,6] Similar to yaws, endemic syphilis is a disease of childhood and adolescence, with most cases occurring in individuals 2 to 15 years of age. Not only does transmission of endemic syphilis occur via direct contact, but transmission via fomites (i.e., on shared eating or drinking utensils) also may occur because early lesions are often mucosal. The primary lesions of endemic syphilis are typically mucous patches on oral pharyngeal mucosa or lesions at the angles of the lips (angular stomatitis) and may go unobserved. These painless lesions may resolve without therapy, but secondary lesions may appear 3 to 6 months later. Secondary lesions of endemic syphilis manifest as rashes, as mucosal lesions, or with bony and cartilaginous involvement. Similar to secondary syphilis, endemic syphilis rashes in the secondary stage may display a wide variety of morphologies including disseminated papular lesions and condylomata lata in moist areas of the skin accompanied by regional lymphadenopathy.

After a period of latency shorter than for yaws (6 months to several years), late complications of endemic syphilis are relatively common.[4] These complications may manifest as gummatous lesions or chronic ulcerative skin lesions in 25% to 50% of patients. In contrast to early lesions, late lesions tend to be destructive, chronic progressive lesions, some of which progress to deforming bony and cartilaginous facial lesions referred to as *gangosa* (see "Yaws"). In addition to the ulcerative lesions of endemic syphilis, bony involvement may occur and is manifested as osteoperiostitis of the long bones and hands causing disability and deformity.

Pinta

Pinta is the endemic treponematosis caused by a unique treponemal species, *T. carateum*.[6] The peak age prevalence for pinta is older than for yaws or endemic syphilis, with most individuals 15 to 30 years of age. Pinta is also thought to spread between individuals through direct lesion contact. An important difference between pinta and the other endemic treponematoses is that without treatment the lesions tend to persist. The classic initial lesion of pinta is a papule or erythematous epithelial plaque. These lesions tend to occur on parts of the body that are not typically clothed, most often the leg, foot, forearm, or back of the hands where skin to skin contact is common. These lesions gradually enlarge through local extension to form hyperkeratotic pigmented lesions. The lesions of pinta are also accompanied by regional lymphadenopathy. Disseminated, small lesions (pintids) may occur distal to the initial lesion 3 to 9 months after infection and slowly enlarge and coalesce. Over time, the lesions of pinta become pigmented taking on a darker color described as slate blue. Late pinta is characterized further by additional pigmentary cutaneous changes; lesions may include dyschromic treponeme-containing lesions and achromic treponeme-free lesions. The depigmentation process of pinta occurs at different rates in the same lesion, giving the lesions a mottled appearance. No other disability or late complications of pinta have been described.

Attenuated Disease

A mild presentation of both yaws and endemic syphilis has been described in regions of lower prevalence. In highly endemic areas the papillomatous stage of yaws tends to last months to years, but in areas of low endemicity the stage is shortened and characterized by fewer, dry crops of lesions in the intertriginous regions.[1,6] Similarly in areas of lower prevalence, endemic syphilis has been characterized by fewer early and late lesions lasting a shorter period of time. Multiple factors are thought to lead to attenuated disease including improved hygiene, nutrition, and access to treatment.[6]

DIAGNOSIS

Diagnosis of individual cases of the endemic treponematoses in large part depends on recognition of appropriate clinical findings and is confirmed with serologic testing with tests for syphilis.[6]

Direct Visualization

Although not widely available, demonstration of characteristic treponemes with silver staining or darkfield microscopy of lesion exudates or immunofluorescent antibody stains for treponemes can provide immediate and highly specific diagnosis of the endemic treponematoses. However, facilities capable of performing these methods are limited in low-income and middle-income countries where endemic treponematoses are common. Therefore these methods are rarely used for diagnosis.

Serology

No serologic tests have been specifically developed for diagnosis of endemic treponematoses; however, because the humoral antibody response to these diseases is indistinguishable from the response to syphilis, serologic tests for syphilis are important for confirmation of clinically suspected infections. Serologic tests for syphilis and the endemic treponematoses are divided into nontreponemal and treponemal tests.[18] The nontreponemal assays are based on cross-reactivity of cardiolipin-cholesterol-lecithin antigens with antibodies to *T. pallidum* and include tests such as the rapid plasma reagin (RPR) card test and Venereal Disease Research Laboratory (VDRL) tube tests. These tests provide quantifiable results that are useful not only for screening for infection but also for evaluation of response to therapy after treatment. In contrast, the treponemal assays are based on the reactivity of antibodies to either recombinant *T. pallidum* antigens or antigens from *T. pallidum* propagated in laboratory animals. The treponemal tests are available in a variety of formats including fluorescent treponemal antibody absorption, *T. pallidum* hemagglutination, or several different commercial enzyme-linked immunosorbent assays. False-positive results sometimes occur with both nontreponemal and treponemal tests. Because treponemal and nontreponemal tests are unrelated, use of an unrelated test to confirm an initial test result (i.e., confirmatory testing of reactive RPR or VDRL test results with a treponemal test) greatly increases the specificity of test results.

Six months after effective treatment, most patients with active endemic treponematoses have a fourfold (two dilutions) or greater decline in RPR or VDRL titers. Reinfection or relapse may be indicated with a VDRL or RPR titer that increases two or more dilutions. Reversion of treponemal serologic test results to nonreactive is considerably less common than for nontreponemal tests. Early in the disease, patients may have negative serologic tests.[16] Patients with latent infections will have positive serologic tests. Patients with advanced disease may have nontreponemal tests that have low titers or become nonreactive.[2]

Point-of-Care Syphilis and Endemic Treponematosis Test

A simple, point-of-care test based on simultaneous detection of both treponemal and nontreponemal antibodies has been developed for rapid diagnosis and treatment of syphilis and endemic treponematoses.[19] This immunochromatographic lateral flow assay detects both immunoglobulins (IgM and IgG) against a recombinant *T. pallidum* antigen (T1) and a nontreponemal antigen (T2). This assay may be used for testing serum, plasma, or whole blood; has a 1-year shelf life at room temperature; distinguishes between past and active infection; confirms the diagnosis in real time for patients with skin lesions; and can be performed outside of clinics, providing remote communities access to diagnostic testing. In addition, the test is useful for estimation of population prevalence of endemic treponematoses and detection of continued transmission after control efforts (e.g., mass treatment programs). A meta-analysis of 7267 tests showed good performance, but sensitivity was higher in patients with high-titer (RPR ≥1 : 16) infection compared with low-titer (RPR <1 : 16) infection for both the T1 component (98.2% vs. 90.1%, $P < .0001$) and the T2 component (98.2% vs. 80.6%, $P < .0001$).[20] As the number of active cases declines after a mass treatment campaign, a diagnostic test with higher sensitivity or repeat testing may be needed to confirm that all cases have been identified and treated.

Polymerase Chain Reaction

The use of polymerase chain reaction (PCR) for surveillance has been proposed to improve diagnostic accuracy of skin ulcers, especially in settings where other causative pathogens may be coendemic and cause similar lesions.[21] Treponemal DNA is detected with use of a PCR assay alone, which applies a qualitative or quantitative amplification-based method to detect single genes or with reverse-transcriptase PCR followed by the use of labeled primers to target amplicons from *T. pallidum* subsp. *pallidum* 16S ribosomal RNA. Specific areas in the *T. pallidum* genome that distinguish it from other bacterial organisms have been identified including *tpf-1, bmp, tmpA,* 47-kDa lipoprotein, and *polA*.[4] However, PCR testing is expensive, requiring electricity and trained laboratorians at equipped laboratory facilities to perform the test (which may not be available in field conditions); access and delivery of specimens from remote areas may also be difficult. The only reliable method at the present time to distinguish *T. pallidum* subspecies (*pallidum, pertenue,* and *endemicum*) is the combined use of PCR and DNA sequencing, which identifies molecular differences between subspecies (e.g., *gpd, tprC, tprI, arp,* IGR19), but availability is limited to a few reference laboratories.[5]

THERAPY

Benzathine penicillin G had been the preferred drug for treatment of the endemic treponematoses.[1,2,6] The need for refrigerated storage of penicillin, the inconvenience of injections for patients, the potential for allergic reactions to β-lactam antibiotics, and the risk of needlestick injuries to health care providers are drawbacks for many countries. A randomized trial in 2012 demonstrated that a single oral dose of 30 mg/kg of azithromycin (up to a maximal dose of 2 g) was noninferior to benzathine penicillin G for treatment of early yaws. Cure rates are similar with recommended doses of azithromycin or benzathine penicillin G.[14] Based on these landmark findings, the WHO now recommends azithromycin as the preferred treatment for endemic treponematoses.[8]

Observational studies in the Pacific region where endemic treponematoses and trachoma occur concurrently suggest that lower doses of azithromycin (20 mg/kg, up to maximal dose of 1 g) typically used to treat trachoma may also be effective against endemic treponematoses.[22,23] Studies comparing efficacy of the two doses (30 mg/kg and 20 mg/kg) of azithromycin for treatment are ongoing. If the infected individual is intolerant to azithromycin, WHO recommends a single dose of benzathine penicillin G, 600,000 U for children younger than 10 years of age or 1.2 million U for individuals 10 years of age or older, may be administered for treatment. Despite the lack of formal studies, extrapolation from experience with sexually transmitted syphilis suggests that tetracycline or doxycycline given for 14 days may also be effective.

Response to therapy may be determined through resolution of early lesions or, in patients with late infection, arrest of progression. Serologic response to therapy may also be documented by declines in RPR or VDRL titers of two or more dilutions 6 months following treatment (as with sexually transmitted syphilis). After treatment, however, titers may not revert to seronegativity.

PREVENTION

In the 1950s it was estimated that more than 50 to 160 million people worldwide were infected with yaws, of which 40 million may have had permanent disfigurement of the face, joints, bones, and soft tissues. Because of the large geographic distribution and disease burden, the WHO led a global control program from 1952 to 1964 using active serologic screening and staged treatment in 46 countries.[6,7] In this effort, about 300 million examinations were performed, and more than 50 million people were treated. Prevalence of endemic treponematoses was reduced by more than 95%. However, as disease prevalence waned, so did resources and commitment for continued surveillance and control efforts.[2,24] Infection rates of yaws once again rebounded[6,7] with global prevalence of disease estimated at about 460,000 cases in the late 1990s; however, this is likely an underestimate.[1]

In the past decade, progress has been made to eliminate yaws. The potential effectiveness of community-based control efforts has been demonstrated in India, where reimplementation of the control measures reduced the number of reported new cases from 3571 in 1996 to 0 cases in 2004 followed by negative serologic surveys among children younger than 5 years old for 3 consecutive years. In 2006 yaws was eliminated from India and formally declared eradicated by the WHO in 2016.[24] Ecuador also reported elimination of yaws through a mass treatment program.[25]

Based on the confirmed success in India and the potential to simplify provision of therapy for entire communities, in 2012 the WHO announced a new, aggressive roadmap that targets global elimination of yaws by 2020.[7,8] In contrast to the staged treatment strategy of the 1950s, two new treatment strategies will simplify case detection and treatment of active and latent disease. Total community treatment is the treatment of an entire community regardless of active cases. This strategy first aims for 100% treatment coverage of a confirmed endemic village or

community followed by surveillance and, if necessary, incorporates mop ups with additional treatment of identified cases. Total targeted treatment, the treatment of all active clinical cases and contacts, is used every 3 to 6 months to detect and treat remaining active cases.[8] Pilot total community treatment programs with azithromycin in some endemic countries (Solomon Islands, Papua New Guinea, and Ghana) demonstrated the potential for eradication of endemic treponematoses.[22,26,27] A longitudinal study followed the 16,092 inhabitants of a Papua New Guinea island (Lihr Island) in which nearly 84% received a dose of azithromycin. Although prevalence of yaws initially declined, it began steadily increasing 2 years later, likely due to relapse of untreated latent infections and reintroduction of yaws through in-migration. This study is the first to identify a point mutation in a yaws strain that conferred resistance to macrolides, previously unreported among endemic treponematoses. For successful eradication, the WHO now recommends treatment coverage rates should exceed 90%, and if rates are less, another round of mass treatment should be considered along with close monitoring for macrolide resistance.[28]

Scientific advances including development of point-of-care and molecular diagnostics will aid in achieving the 2020 goal. However, further studies are needed to continually improve these eradication strategies. The future of endemic treponemal research lies in improving surveillance and geographic mapping, integrating point-of-care testing, determining etiology of nontreponematoses skin ulcers by using advanced molecular diagnostics, monitoring for macrolide resistance, and looking for *T. pallidum* infections in nonhuman primates.[25]

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239 *Leptospira* Species (Leptospirosis)

David A. Haake and Paul N. Levett

SHORT VIEW SUMMARY

Definition
- Leptospirosis is caused by infection with pathogenic spirochetes of the genus *Leptospira.*

Epidemiology
- Leptospirosis is a zoonosis of global distribution.
- Leptospirosis is maintained in nature by chronic renal infection of carrier animals, especially rodents.
- Infections typically occur after occupational or recreational exposure to water or soil contaminated with rodent urine.
- In developing countries with poor housing standards, leptospirosis outbreaks occur regularly in urban settings after heavy rainfall and flooding.

Microbiology
- Twenty-three named leptospiral species have been described, of which 10 are known to be pathogenic (see Table 239.1).

Diagnosis
- Clinical diagnosis requires a high index of suspicion based on epidemiologic exposure. The signs and symptoms of early leptospirosis are nonspecific.
- Serologic tests are helpful when positive but may have poor sensitivity during the first week of illness. Polymerase chain reaction assay of serum and urine appears to be a promising diagnostic technique. Culture can be done using blood early in the course and urine later on but requires special media.

Therapy
- Antibiotic therapy (see Table 239.4) should be initiated as early in the course of the disease as suspicion allows. For mild disease, doxycycline, amoxicillin, or oral ampicillin is recommended. For more severe disease, intravenous ceftriaxone, ampicillin, or penicillin is used.
- Patients with early renal disease with high-output renal dysfunction and hypokalemia should receive aggressive volume repletion and potassium supplementation.
- Patients who progress to oliguric renal failure should undergo rapid initiation of hemodialysis or peritoneal dialysis, which is typically required on only a short-term basis.

Prevention
- The most effective preventive strategy is to reduce direct contact with potentially infected animals and indirect contact with urine-contaminated soil and water.
- Vaccination of agricultural and companion animals is practiced, and vaccines for humans are used in France, Cuba, and parts of Asia.

HISTORY

A syndrome of severe multisystem disease, presenting with profound jaundice and renal function impairment, was described by Weil in Heidelberg in 1886. Other descriptions of disease that probably represent leptospirosis were made earlier, but the etiology cannot be definitively ascribed to leptospiral infection.[2] Leptospires were first visualized in autopsy specimens from a patient thought to have had yellow fever[3] but were not isolated until several years later, almost simultaneously in Germany and Japan.[4] Diagnostic confusion between severe icteric leptospirosis and yellow fever continued, with prominent researchers such as Stokes and Noguchi dying in their attempts to discover the etiologic agent.[4] Several authoritative reviews have been published.[2,4,5,6,7,8]

ETIOLOGY

"Leptospira" derives from the Greek *leptos* (thin) and Latin *spira* (coiled). Aptly named, the leptospires are a mere 0.1 µm in diameter by 6 to 20 µm in length. The cells have pointed ends, one or both of which is usually bent into a characteristic hook (Fig. 239.1). Motility is conferred by the rotation of two axial flagella underlying the membrane sheath, which are inserted at opposite ends of the cell and extend toward the central region.[9] Because of their small diameter, leptospires are best visualized by darkfield microscopy, appearing as actively motile spirochetes (Fig. 239.2). Leptospires are readily cultured in polysorbate-albumin media if specimens are obtained before initiation of antibiotic therapy.[10]

Historically, the genus *Leptospira* was classified into two species, *L. interrogans* and *L. biflexa,* composed of pathogenic and nonpathogenic strains, respectively. Within each species, large numbers of serovars were differentiated using agglutinating antibodies. Serovar specificity is conferred by lipopolysaccharide (LPS) O-antigens.[11] More than 250 serovars of pathogenic leptospires have been described; because of the large number of serovars, antigenically related serovars were grouped into serogroups for convenience in serologic testing.

Leptospires are now classified into a number of species defined by their degree of genetic relatedness, determined by DNA reassociation.[12,13] There are currently 23 named species, including pathogens (e.g., *L. interrogans*), nonpathogenic saprophytes (e.g., *L. biflexa*), and species of indeterminate pathogenicity (e.g., *L. inadai*) (Table 239.1).[14] This classification is supported by 16S RNA gene sequencing (Fig. 239.3)[15] but is quite distinct from the former serologic classification.[5]

The system of serogroup nomenclature has no taxonomic standing but is retained because presumptive serogroup determination by serologic testing has some epidemiologic value. However, serologic responses may bear surprisingly little relationship to the infecting serovar in individual patients.[16]

The genome sequences of several *Leptospira* spp. and strains have been determined,[17,18,19,20,21] and sequencing of another 200 strains is under way through the *Leptospira* Genomics and Human Health Project. The availability of these genome sequences has already led to better understanding of leptospiral pathogenesis.[22]

EPIDEMIOLOGY AND TRANSMISSION

Globally, leptospirosis is a leading zoonotic cause of morbidity and mortality that disproportionately affects vulnerable populations, such as rural subsistence farmers and urban slum dwellers. Human infections

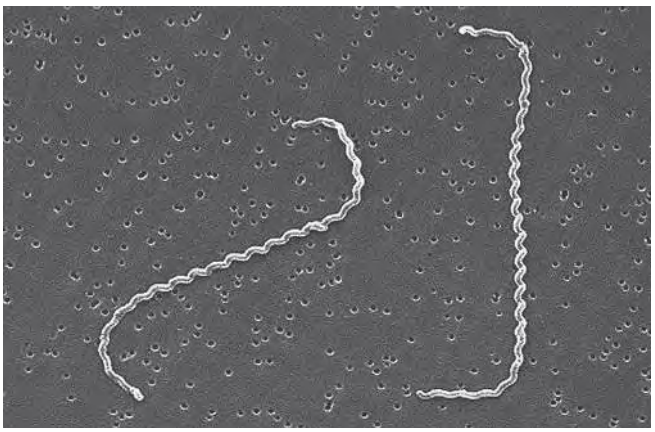

FIG. 239.1 Scanning electron micrograph of cells *leptospira interrogans* showing helical structure and curved (hooked) ends (original magnification ×60,000). *(Courtesy Rob Weyant, Centers for Disease Control and Prevention.)*

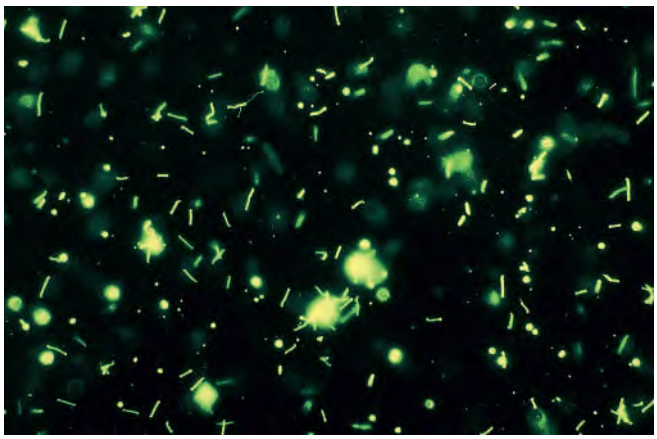

FIG. 239.2 Leptospires viewed by darkfield microscopy (original magnification ×100). *(Courtesy Mildred Galton, Public Health Image Library, Centers for Disease Control and Prevention.)*

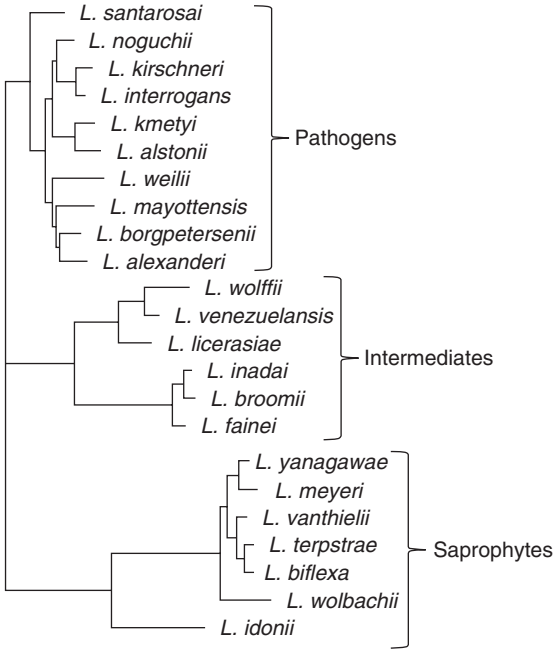

FIG. 239.3 Unrooted phylogenetic tree based on 16s RNA gene sequences of the leptospiraceae obtained from genbank. Species composed of pathogens (see Table 239.1) cluster separately from saprophytes (nonpathogenic species) and species whose pathogenicity is intermediate.

are endemic in most regions, and the peak incidence occurs in the rainy season in tropical regions and the late summer to early fall in temperate regions.[23] In developing countries with poor urban housing standards, leptospirosis outbreaks occur regularly after heavy rainfall and flooding.[24] In the United States the highest incidence is found in Hawaii; active surveillance in 1992 detected an annual incidence of approximately 128 per 100,000.[25] Based on a systematic review of 80 published studies and databases from 34 countries, it is estimated that there are 1.03 million cases and 58,900 deaths each year.[26] Morbidity and mortality are greatest in the poorest regions of the world and in areas where surveillance is not routinely performed. It is likely that these figures still underestimated the burden because leptospirosis patients are commonly misdiagnosed with dengue, malaria, and other infections. More important than incidence, estimates suggest that globally ~2.90 million of disability adjusted life-years (DALYs) are lost per annum from the approximately 1.03 million cases.[27] This estimate of DALYs from leptospirosis is more than four times greater than the ~0.83 million DALYs due to dengue.[28]

Leptospirosis is maintained in nature by chronic renal infection of carrier animals. The most important reservoirs are rodents and other small mammals, but livestock and companion animals are also significant sources of human infection. Infection of carrier animals usually occurs during infancy, and once infected, animals may shed leptospires in their urine intermittently or continuously throughout life.

Infection occurs through direct or indirect contact with urine or tissues of infected animals. Direct contact is important in transmission to veterinarians, workers in milking sheds on dairy farms, abattoir

TABLE 239.1 Species of *Leptospira* and Some Pathogenic Serovars

SPECIES	SELECTED PATHOGENIC SEROVARS
L. interrogans	Icterohaemorrhagiae, Copenhageni, Canicola, Pomona, Australis, Autumnalis, Pyrogenes, Bratislava, Lai
L. kirschneri	Bim, Bulgarica, Grippotyphosa, Cynopteri
L. borgpetersenii	Ballum, Hardjo, Javanica
L. mayottensis	Kenya, Mini
L. santarosai	Bataviae
L. noguchii	Panama, Pomona
L. weilii	Celledoni, Sarmin
L. alexanderi	Manhao 3
L. alstonii	Sichuan
L. kmetyi	Manilae
L. inadai	Intermediate
L. fainei	Intermediate
L. broomii	Intermediate
L. wolffii	Intermediate
L. licerasiae	Intermediate
L. venezuelensis	Intermediate
L. wolbachii	Nonpathogen
L. biflexa	Nonpathogen
L. vanthielii	Nonpathogen
L. meyeri	Nonpathogen
L. terpstrae	Nonpathogen
L. yanagawae	Nonpathogen
L. idonii	Nonpathogen

workers, butchers, hunters, and animal handlers; transmission to children handling puppies and to dog handlers has been reported. Males are predominantly affected, with approximately 80% of the total burden.[27] Indirect contact is more common and is responsible for disease after exposure to wet soil or water. The great majority of cases are acquired by this route in the tropics, either through occupational exposure to water, as in rice or taro farming, or through exposure to damp soil and water during avocational activities. Overseas operations place the US military, including military dogs, at risk of leptospirosis. This is particularly true of Special Operations Forces, who work closely with local military.[29]

Recreational exposures have become relatively more important, often in association with adventure tourism to tropical endemic areas. Several large point-source waterborne outbreaks involving attack rates as high as 42% have occurred recently after athletic events.[30,31] In recent years there has been an increase in leptospirosis cases among dogs in the eastern regions of North America and in the Midwest,[32] associated with a shift in the predominant serovars causing disease.[33,34] Veterinary vaccine manufacturers have responded to this problem by licensing new canine vaccines containing these emerging serovars.

PATHOGENESIS

Leptospires enter the body through cuts and abrasions, mucous membranes or conjunctivae, and aerosol inhalation of microscopic droplets. Swallowing contaminated lake water was the only behavioral risk factor identified in a case-control study of a large leptospirosis outbreak at the 1998 Springfield Triathlon.[30] However, the oral mucosae are probably a more important route of entry after ingestion than the intestinal tract. On entering the body there is widespread hematogenous dissemination, with levels as high as 10^6 leptospires per milliliter of blood documented by quantitative polymerase chain reaction (PCR).[35] Organisms readily penetrate tissue barriers, resulting in invasion of the central nervous system and aqueous humor of the eye. Transendothelial migration of spirochetes is facilitated by a systemic vasculitis, accounting for a broad spectrum of clinical illness. Severe vascular injury can ensue, leading to pulmonary hemorrhage, ischemia of the renal cortex and tubular-epithelial cell necrosis, and destruction of the hepatic architecture, resulting in jaundice and liver cell injury with or without necrosis.[36]

The mechanisms by which leptospires cause disease are not clearly understood. Potential virulence factors include immune mechanisms, toxin production, adhesins, and other surface proteins. Human susceptibility to leptospirosis may be related to poor recognition of leptospiral LPS by the innate immune system.[37,38] Human Toll-like receptor 4 (TLR4), which responds to extremely low concentrations of gram-negative LPS (endotoxin), appears to be unable to bind leptospiral LPS,[38,39] perhaps because of the unique methylated phosphate residue of its lipid A.[40] In contrast to human TLR4, mouse TLR4 can recognize leptospiral LPS and has been shown to play an important role in preventing fatal leptospirosis infection in mice.[39,41] Direct tissue damage may also be due to production of hemolytic toxins, which may act as sphingomyelinases, phospholipases, or pore-forming proteins, and collagenases.[42–44]

Immune-mediated mechanisms have been postulated as one factor influencing the severity of symptoms.[45] Investigation of the same triathlon outbreak mentioned earlier identified the human leukocyte antigen (HLA) DQ6 as an independent risk factor for leptospirosis.[46] The structural location of HLA-DQ6 polymorphisms associated with disease suggested that leptospires produce a superantigen that can cause nonspecific T-cell activation in susceptible individuals. Other immune mechanisms, including circulating immune complexes, anticardiolipin antibodies, and antiplatelet antibodies, have been proposed, but their significance is unproven. Although immune or autoimmune mechanisms may play a role in some cases of leptospiral uveitis,[47] a high percentage of such patients have leptospiral DNA in the aqueous humor by PCR.[48]

Much recent work has focused on the roles of surface lipoproteins in leptospiral pathogenesis.[49] The major outer membrane lipoprotein LipL32 is highly conserved among pathogenic serovars.[50] LipL32 is a major target of the human immune response[51] and appears to be involved in pathogenesis of tubulointerstitial nephritis.[52] Virulent leptospires respond to the increased osmolarity of host tissues by inducing expression of the multifunctional Lig surface proteins that mediate interactions with a variety of host proteins, including extracellular matrix factors.[53] The Lig proteins are early antigens; IgM antibodies to their immunoglobulin-like repeats develop early in infection, offering an approach to improved detection of acute infection.[54] The endostatin-like LenA protein binds the complement regulatory protein, factor H, and pathogenic strains exhibit proteolytic activity that cleaves complement, suggesting an important role in serum resistance.[55,56]

CLINICAL MANIFESTATIONS

Leptospiral infection is associated with a broad spectrum of severity, ranging from subclinical illness, followed by seroconversion to two clinically recognizable syndromes: a self-limited, systemic illness seen in roughly 90% of infections and a severe, potentially fatal illness accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis.[2,6,7] In some patients the disease has two distinct phases: an initial septicemic stage that is followed by a temporary decline in fever, followed by an immune phase in which the severe symptoms occur. However, in many severe cases the distinction between these two phases is not apparent; in addition, many patients present only with the onset of the second phase of the illness.

The mean incubation period is 10 days, ranging from 5 to 14 days; determination of precise exposures may be difficult, leading to significant imprecision in estimated incubation times. The acute, septicemic phase of illness begins abruptly with high, remittent fever (38°–40°C) and headache, chills, rigors, and myalgias; conjunctival suffusion (redness without exudate); abdominal pain; anorexia, nausea, and vomiting; diarrhea; and cough and pharyngitis. A pretibial maculopapular cutaneous eruption occurs rarely (Table 239.2). Conjunctival suffusion and muscle tenderness, most notable in the calf and lumbar areas, are the most characteristic physical findings but may occur in a minority of cases (see Table 239.2). Other less common signs include lymphadenopathy, splenomegaly, and hepatomegaly. The acute phase lasts from 5 to 7 days. Routine laboratory tests are nonspecific but indicative of a bacterial infection. Leptospires can be recovered from blood and cerebrospinal fluid (CSF) during the acute phase of illness, but meningeal signs are not prominent in this phase. Leptospires may also be recovered from urine, beginning about 5 to 7 days after the onset of symptoms (Fig. 239.4). Urinalysis reveals mild proteinuria and pyuria, with or without hematuria and hyaline or granular casts. Death is rare in the acute phase of illness.

The immune phase of illness generally lasts from 4 to 30 days (see Fig. 239.4). The disappearance of leptospires from the blood and CSF coincides with the appearance of immunoglobulin M (IgM) antibodies.[7,57] The organisms can be detected in almost all tissues and organs and in urine for several weeks, depending on the severity of the disease. In addition to the acute-phase symptoms described in the preceding paragraph, the immune phase may be characterized by any or all of the following signs and symptoms: jaundice, renal failure, cardiac arrhythmias, pulmonary symptoms, aseptic meningitis, conjunctival suffusion with or without hemorrhage; photophobia; eye pain; muscle tenderness; adenopathy; and hepatosplenomegaly (see Table 239.2). Abdominal pain is not uncommon and may be an indication of pancreatitis.

Aseptic meningitis, with or without symptoms, is characteristic of the immune phase of illness, occurring in up to 80% of cases. In endemic areas a significant proportion of all aseptic meningitis cases may be caused by leptospiral infection.[58] Symptomatic patients present with an intense, bitemporal and frontal throbbing headache with or without delirium. A lymphocytic pleocytosis occurs, with total cell counts generally less than 500/mm.^{3} CSF protein levels are modestly elevated, between 50 and 100 mg/mL; the CSF glucose concentration is normal. Severe neurologic complications, such as meningoencephalitis, hemiplegia, transverse myelitis, cerebral venous thrombosis, or Guillain-Barré syndrome, occur only rarely.[5,59] Uveitis is reported in horses and humans and is associated with the second phase of illness, perhaps accounting for underreporting.[60,61] An unusual case of chronic meningoencephalitis in an immunocompromised child was diagnosed only by next-generation sequencing.[62]

The most distinctive form of severe illness that may develop after the acute phase of illness is Weil disease, characterized by impaired hepatic and renal function. More severe cases may progress directly

TABLE 239.2 Signs and Symptoms on Admission in Patients With Leptospirosis in Large Case Series

PERCENT WITH:	PUERTO RICO, 1963[150] (*N* = 208)	CHINA, 1965[151] (*N* = 168)	VIETNAM, 1973[152] (*N* = 93)	KOREA, 1987[153] (*N* = 150)	BARBADOS, 1990[63] (*N* = 88)	SEYCHELLES, 1998[154] (*N* = 75)	BRAZIL, 1999[24] (*N* = 93)	HAWAII, 2001[155] (*N* = 353)	INDIA, 2002[156] (*N* = 74)
Jaundice	49	0	1.5	16	95	27	93	39	34
Anorexia	—	46	—	80	85	—	—	82	—
Headache	91	90	98	70	76	80	75	89	92
Conjunctival suffusion	99	57	42	58	54	—	28.5	28	35
Vomiting	69	18	33	32	50	40	—	73	—
Myalgia	97	64	79	40	49	63	94	91	68
Arthralgia	—	36	—	—	—	31	—	59	12
Abdominal pain	—	26	28	40	43	41	—	51	—
Nausea	75	29	41	46	37	—	—	77	—
Dehydration	—	—	—	—	37	—	—	—	—
Cough	24	57	20	45	32	39	—	—	—
Hemoptysis	9	51	—	40	—	13	20	—	35
Hepatomegaly	69	28	15	17	27	—	—	16	—
Lymphadenopathy	24	49	21	—	21	—	—	—	15
Diarrhea	27	20	29	36	14	11	—	53	—
Rash	6	—	7	—	2	—	—	8	12

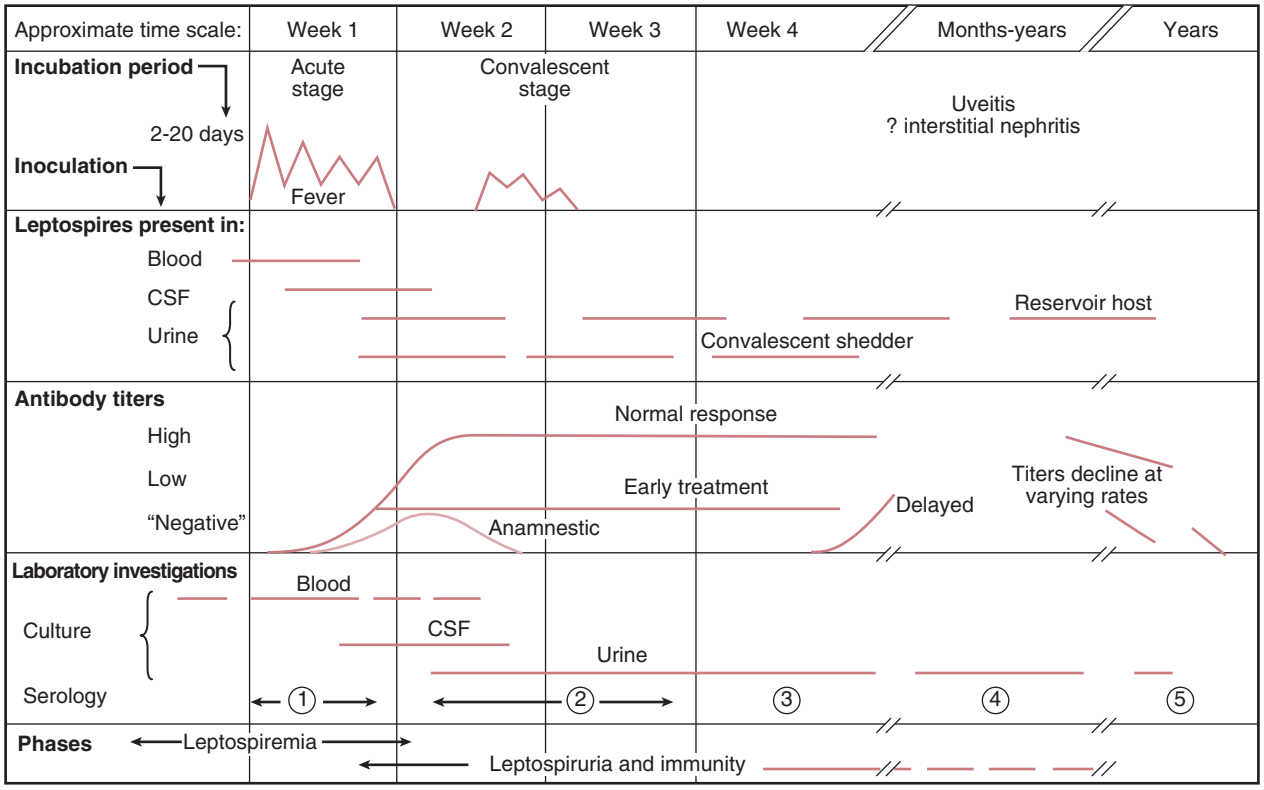

FIG. 239.4 Biphasic nature of leptospirosis and relevant investigations at different stages of disease. Specimens 1 and 2 for serology are acute-phase specimens; 3 is a convalescent-phase sample, which may facilitate detection of a delayed immune response; and 4 and 5 are follow-up samples that can provide epidemiologic information, such as the presumptive infecting serogroup. *CSF,* Cerebrospinal fluid. *(Modified from Turner LH. Leptospirosis.* Br Med J. *1969;1:231–235; and Levett PN. Leptospirosis.* Clin Microbiol Rev. *2001;14:296–326.)*

from the acute phase without the characteristic brief improvement in symptoms to a fulminant illness, with fever greater than 40°C and the rapid onset of liver failure, acute renal failure, hemorrhagic pneumonitis, cardiac arrhythmia, or circulatory collapse.[7] Mortality rates in patients developing severe disease have ranged from 5% to 40%.[2,5,6,63] In a study of 840 hospitalized patients with severe leptospirosis (14% case-fatality rate), risk of death was found to increase with age, especially in adults 40 years of age or older.[24,64] Altered mental status has been found to be the strongest predictor of death.[24,65] Other poor prognostic signs include acute renal failure (oliguria, hyperkalemia, serum creatinine >3 mg/

dL), respiratory insufficiency (dyspnea, pulmonary rales, chest radiograph infiltrates), hypotension, and arrhythmias.[24] In jaundiced patients disturbance of liver function is out of proportion to the rather mild and nonspecific pathologic findings. Conjugated serum bilirubin levels may rise to 80 mg/dL, accompanied by more modest elevations of serum aminotransferases, alanine aminotransferase and aspartate aminotransferase, which rarely exceed 200 IU/L.[66] This is in marked contrast to viral hepatitis. Jaundice is slow to resolve, but death due to liver failure almost never occurs in the absence of renal failure. At autopsy, degenerative changes are seen in hepatocytes, Kupffer cells may be hypertrophied, cholestasis is evident, and erythrophagocytosis and mononuclear cell infiltrates are observed.[67] Hepatocellular necrosis is absent.

Kidney involvement is initially characterized by a unique nonoliguric hypokalemic form of renal insufficiency. Hallmarks are impaired sodium reabsorption, increased distal sodium delivery, and potassium wasting. The impairment in sodium reabsorption appears to be due to selective loss of the epithelial sodium channel in the proximal tubular epithelium. The blood urea nitrogen level is usually less than 100 mg/dL, and the serum creatinine level is usually less than 2 to 8 mg/dL during the acute phase of illness.[68] Thrombocytopenia occurs in the absence of disseminated intravascular coagulation and may accompany progressive renal dysfunction.[69] Renal biopsy reveals acute interstitial nephritis; immune-complex glomerulonephritis may also be present.[70] If electrolyte and volume losses are not replaced, patients progress to oliguric renal failure. In fatal cases the kidneys are swollen and yellow, with prominent cortical blood vessels.[36] Histologic findings include a diffuse, mixed tubulointerstitial inflammatory cell infiltrate of lymphocytes, plasma cells, macrophages, and polymorphonuclear leukocytes, accompanied by focal areas of tubular necrosis.[67] Acute kidney injury in leptospirosis is associated with elevated markers of endothelial injury.[71]

Severe pulmonary hemorrhage syndrome (SPHS) can be a prominent manifestation of infection and may occur in the absence of hepatic and renal failure.[72] Frank hemoptysis can arise simultaneously with the onset of cough during the acute phase of illness.[73] However, hemorrhage is often inapparent until patients are intubated; clinicians should suspect SPHS in patients with signs of respiratory distress whether or not they have hemoptysis. With progressive pulmonary involvement, radiographic abnormalities seen most frequently in the lower lobes evolve from small nodular densities ("snowflake-like") to patchy alveolar infiltrates; confluent consolidation is uncommon but may occur.[74] The pathophysiology of SPHS is consistent with acute respiratory distress syndrome (ARDS) with diffuse lung injury, impaired gas exchange, and hemodynamic changes indicative of septic shock.[75] At autopsy, the lungs appear grossly congested and demonstrate focal areas of hemorrhage.[67] Histologically, damage to the capillary endothelium leads to congestion with foci of interstitial and intraalveolar hemorrhage, diffuse alveolar damage, and severe airspace disorganization.[76] Although inflammatory infiltrates are usually absent, a community-acquired pneumonia has been described in Indonesia, an area of high prevalence, from four patients who presented with fever, dry cough, dyspnea, and conjunctival suffusion or scleral icterus and crackles on physical examination. Infiltrates on chest radiograph were present in all cases, and the diagnosis of leptospiral pneumonia was supported by real-time PCR from multiple specimens and serologic confirmation.[77]

Congestive heart failure occurs rarely. However, nonspecific electrocardiographic changes are common.[78] In more than half of patients receiving continuous cardiac monitoring, cardiac arrhythmias may occur, including atrial fibrillation; flutter and tachycardia; and cardiac irritability, including premature ventricular contractions and ventricular tachycardia.[78] Atrial fibrillation is associated with more severe disease.[79] Cardiovascular collapse with shock can develop abruptly and in the absence of aggressive supportive care can be fatal. At autopsy, interstitial myocarditis with inflammatory involvement of the conduction system is seen[80]; acute coronary arteritis and aortitis are also common at postmortem examination.[81]

LABORATORY DIAGNOSIS

Direct Detection Methods

Direct visualization of leptospires in blood or urine by darkfield microscopic examination has been used for diagnosis (Table 239.3). However, artifacts are commonly mistaken for leptospires, and the method has both low sensitivity (40.2%) and specificity (61.5%).[82] A range of staining methods has been applied to direct detection, including immunofluorescence staining, immunoperoxidase staining, and silver staining. These methods are not widely used because of the lack of commercially available reagents and their relatively low sensitivity.

TABLE 239.3 Common Diagnostic Tests for Leptospirosis

TEST	SENSITIVITY[a,b]	SPECIFICITY[a,b]	COSTS[c]	ADVANTAGES	DISADVANTAGES[d]	REFERENCE
Culture	5%–50%	100%	++	Provides definitive evidence. Applicable to human and veterinary diagnosis.	Slow and requires significant expertise	Levett; WHO[113]
Darkfield microscopy (DFM)	10^4 bacteria/mL	Low; confusion with protein fibers	+	Quick and early diagnosis. Applicable to human and veterinary diagnosis.	Unreliable, requires confirmation	Levett, 2001[5]; WHO[113]
Microscopic agglutination test (MAT)	90%	>90%	+++	Gold standard.[e] Applicable to human and veterinary diagnosis.	Requires a panel of live antigens, difficult (expertise), laborious. Problems with seronegative carrier animals.	Levett, 2001[5]; WHO[113]
IgM–enzyme-linked immunosorbent assay (ELISA)	>90%	88%–95%	++	Cost effective and relatively rapid (1–2 h)	Serology, needs confirmation by MAT	WHO[113]
Latex agglutination test	82%	95%	++	Easy, quick (30 s), cost effective	Serology, needs confirmation by MAT	WHO[113]
Lateral flow test	81%	96%	++	Easy, quick (10 min), finger prick blood, cost effective	Serology, needs confirmation by MAT	WHO[113]
Real-time polymerase chain reaction (PCR)	100%	93%	+++	Early diagnosis. Applicable to human and veterinary diagnosis.	Few tests validated, sophisticated, expensive equipment, requires expertise	Ahmed et al, 2011[90]

[a]Sensitivity and specificity largely depend on a number of factors: stage of illness, type and producer of test, and panel of clinical materials used for testing.[5,157]
[b]Sensitivity of culture depends mainly on the route and transport time to the laboratory. MAT is the gold standard and should be 100%. However, when comparing with culture, this gold standard appears not optimal. Sensitivities of other serologic tests are compared with MAT.
[c]Excluding costs for equipment.
[d]Serology has the disadvantage that it detects antibodies 7–10 days after the onset of the disease. This is too late for antibiotic treatment, which should start within the first 4 days.
[e]Serologic confirmation requires testing of both acute and convalescent serum samples for seroconversion or significant titer rise.
Modified from Hartskeerl RA, Collares-Pereira M, Ellis WA. Emergence, control and re-emerging leptospirosis: dynamics of infection in the changing world. Clin Microbiol Infect. *2011;17:494–501.*

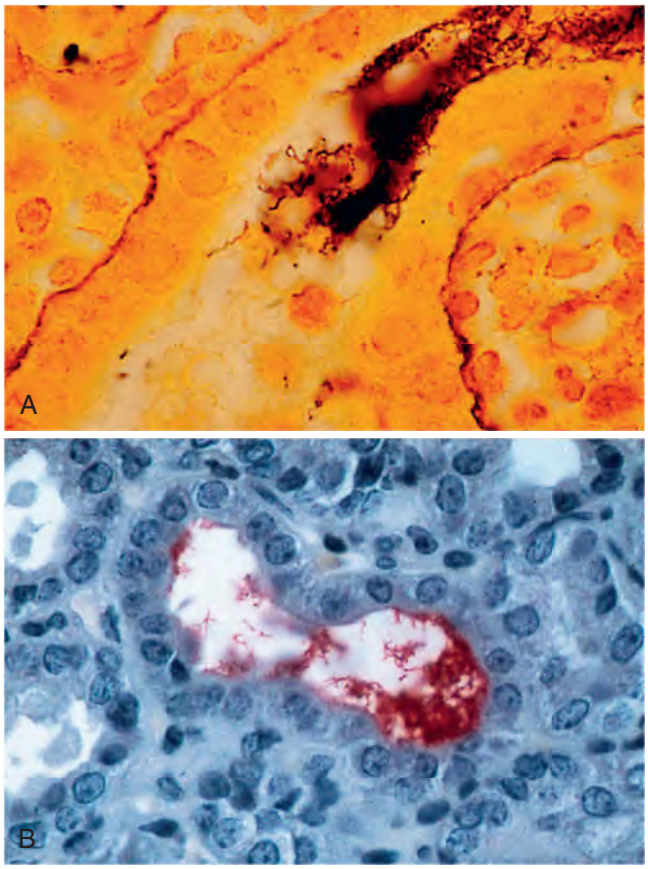

FIG. 239.5 Kidney sections stained by silver staining (A) and immunohistochemical staining (B), showing presence of multiple leptospires in tubules. *(A from Barnett JK, Barnett D, Bolin CA, et al.* Infect Immun. *1999;67:853–861.*[149] *B from Haake DA, Chao G, Zuerner RL, et al.* Infect Immun. *2000;68:2276–2285.)*

Detection of leptospiral antigen in blood or urine has been attempted but without significant success. Many PCR assays[83–85] and several loop-mediated isothermal amplification assays[86–88] have been developed for the detection of leptospires, but relatively few have been evaluated in prospective clinical studies,[88,89] and there have been no multicenter studies of multiple molecular diagnostic methods. The chief advantage of PCR is the prospect of confirming the diagnosis during the early acute (leptospiremic) stage of the illness, before the appearance of IgM antibodies, when treatment is likely to have the greatest benefit.[90] For early diagnosis, serum or plasma might be the optimal specimen, but urine has been often positive, even early in the course.[91] In fulminating cases, in which death occurs before seroconversion, PCR may be of great diagnostic value.[83,92] Histologic diagnosis (Fig. 239.5) traditionally relied on silver impregnation staining,[3] but immunohistochemical staining offers greater sensitivity and specificity.[93,94]

Isolation and Identification

Leptospires can be isolated from blood, CSF, and peritoneal dialysate fluids during the first 10 days of illness. Specimens should be collected while the patient is febrile and before antibiotic therapy is initiated. One or two drops of blood should be inoculated directly into culture medium at the bedside. Survival of leptospires in commercial blood culture media or refrigerated blood samples for several days has been reported.[95,96] Urine can be cultured after the first week of illness. Specimens should be collected aseptically into sterile containers without preservatives and must be processed within a short time of collection; best results are obtained when the delay is less than 1 hour because leptospires do not survive well in acidic environments.[10]

Cultures are performed in albumin-polysorbate media such as EMJH (Ellinghausen-McCullough-Johnson-Harris),[97] which is available commercially. Primary cultures are performed in semisolid (0.2% agar) medium, to which 5-fluorouracil is usually added as a selective agent. Cultures are incubated at 30°C for several weeks because initial growth may be slow.

Isolated leptospires are identified to serovar level by traditional serologic methods.[98,99] These techniques are limited in availability to a few reference laboratories. However, molecular methods such as pulsed-field gel electrophoresis show promise for rapid identification of most isolates.[100] Identification to species level is accomplished by sequencing the 16S ribosomal RNA gene of isolates[15] or by sequencing the products of PCR directly.[90,101] Powerful molecular techniques, such as multiple locus sequence typing and multilocus variable-number tandem-repeat analysis, are being applied to the epidemiologic analysis of leptospirosis.[102–105] As more genomic data become available, these approaches are becoming more standardized.[106–109] In addition to molecular typing, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been investigated for identification of *Leptospira* isolates.[110]

Indirect Detection Methods

The majority of leptospirosis cases are diagnosed by serology. The reference standard assay is the microscopic agglutination test (MAT), in which live antigens representing different serogroups of leptospires are reacted with serum samples and then examined by darkfield microscopy for agglutination.[10] Due to regional variations in infecting strains, it has been considered important to include local serovars in a laboratory's MAT panel. Recently, this view has been challenged.[111] The MAT is a complex test to maintain, perform, and interpret, and participation of the laboratory in a proficiency testing program is essential to maintaining accuracy.[112] Use of the MAT is restricted to a few reference laboratories.

A serologically confirmed case of leptospirosis is defined by a fourfold rise in MAT titer to one or more serovars between acute-phase and convalescent serum specimens run in parallel.[113] A single titer of at least 1:800 in the presence of compatible symptoms is strong evidence of recent or current infection.[114] Suggestive evidence for recent or current infection includes a single titer of at least 1:200 obtained after the onset of symptoms.[115] Delayed seroconversions are common, with up to 10% of patients failing to seroconvert within 30 days of the clinical onset. Cross-reactive antibodies may be associated with syphilis, relapsing fever, Lyme disease, viral hepatitis, human immunodeficiency virus infection, legionellosis, and autoimmune diseases.[116]

The interpretation of the MAT is complicated by cross-reaction between different serogroups, especially in acute-phase samples.[5] Cross-reactivity in acute samples is attributable to IgM antibodies, which may persist for several years.[117] The MAT is a serogroup-specific assay and should not be used to infer the identity of the infecting serovar.[16] However, knowledge of the presumptive serogroup may be of epidemiologic value in determining potential exposures to animal reservoirs.

Diagnostic application of the MAT is limited by the relatively low sensitivity when acute serum samples are tested.[118] Other agglutination assays that detect total immunoglobulins, such as the indirect hemagglutination assay, suffer from similarly low sensitivities on acute specimens but have high case sensitivities when acute and convalescent specimens are tested.[119] IgM antibodies are detectable after about the fifth day of illness, and IgM-detection assays are available in several formats.[119–122] Use of these assays as screening tests offers the potential to enhance the diagnostic capacity of many laboratories, particularly in developing countries, where most cases of leptospirosis occur.[123] The modified Faine criteria scoring system, which combines serologic results with clinical history and epidemiologic factors, may be useful in some settings.[124] The persistently unsatisfactory state of diagnostics, especially in early disease, is summarized in a recent study and a recent review, which highlight the general problem of lacking a gold-standard diagnostic assay by which to assess the utility of tests that are affordable and require less extensive laboratory capacity.[125,126]

THERAPY

Antibiotic therapy should be initiated as early in the course of the disease as suspicion allows. There have been few randomized or placebo-controlled trials,[127,128,129,130] and these have produced conflicting results.

TABLE 239.4 Antimicrobial Agents Recommended for Treatment and Chemoprophylaxis of Leptospirosis

INDICATION	COMPOUND	DOSAGE
Chemoprophylaxis	Doxycycline	200 mg PO orally once per week
Treatment of mild leptospirosis	Doxycycline Ampicillin Amoxicillin	100 mg bid PO 500–750 mg q6h PO 500 mg q6h PO
Treatment of moderate-to-severe leptospirosis	Penicillin Ceftriaxone Ampicillin	1.5 MU IV q6h 1 g IV q24h 0.5–1 g IV q6h

bid, Twice daily; *IV,* intravenously; *MU,* million units; *PO,* orally.

Therapeutic benefits of antibiotics may be difficult to demonstrate in populations where patients present for medical care with late or severe disease, or both. Nevertheless, severe disease is usually treated with intravenous penicillin and mild disease with oral doxycycline (Table 239.4). Once-daily ceftriaxone has been shown to be as effective as penicillin.[131] Jarisch-Herxheimer reactions have been reported in patients treated with penicillin.[132] Patients receiving penicillin should be monitored because of the increased morbidity and mortality of such reactions.

Supportive therapy is essential for hospitalized patients. Patients with early renal disease with high-output renal dysfunction and hypokalemia should receive aggressive volume repletion and potassium supplementation to avoid severe dehydration and acute tubular necrosis.[68] In patients who progress to oliguric renal failure, rapid initiation of daily hemodialysis reduces mortality, particularly in critically ill patients, and is typically required on only a short-term basis. Renal dysfunction caused by leptospirosis is typically completely reversible.[133,134] Patients requiring intubation for SPHS have decreased pulmonary compliance and should be managed as cases of ARDS. Protective ventilation strategies involving low tidal volumes (<6 mL/kg) to avoid alveolar injury due to high ventilation pressures have been shown to dramatically improve survival rates.[135]

PREVENTION

Prevention of leptospirosis may be achieved by avoidance of high-risk exposures, adoption of protective measures, immunization, and use of chemoprophylaxis, in varying combinations depending on the environmental circumstances and the degree of human activity.

High-risk exposures include immersion in fresh water, as in swimming, and contact with animals and their body fluids.[2] Removal of leptospires from the environment is impractical, but reducing direct contact with potentially infected animals and indirect contact with urine-contaminated soil and water remains the most effective preventive strategy available. Consistent application of rodent control measures is important in limiting the extent of contamination. Appropriate protective measures depend on the activity but include wearing boots, goggles, overalls, and rubber gloves. In tropical environments walking barefoot is a common risk factor.[136] In an urban area of Thailand with high environmental contamination and unavoidable exposure to flood waters, a single dose of doxycycline, 200 g, was considered to have protective efficacy, particularly for flood victims with lacerations, in whom efficacy was estimated to have been 92%.[137]

Immunization of agricultural and companion animals with killed vaccines is widely practiced both to prevent disease and to reduce human exposure. Vaccination of animals at an early age before exposure is crucial in achieving optimum reduction of shedding.[138] Periodic (usually annual) boosters are required to maintain immunity.[139] Current bovine and porcine vaccines used in the United States contain serovars Icterohaemorrhagiae, Canicola, Grippotyphosa, Pomona, and Hardjo, whereas canine vaccines contain all except serovar Hardjo. New vaccines for bovine use stimulate a type 1 cell-mediated immune response against serovar Hardjo[140,141] and appear to protect against renal colonization and urinary shedding.[142]

Human immunization is not widely practiced. A vaccine containing serovar Icterohaemorrhagiae is available in France for workers in high-risk occupations,[143] and a vaccine has been developed for human use in Cuba.[144] Immunization has been more widely used in Asian countries to prevent large-scale epidemics in agricultural laborers.

For individuals who will be unavoidably exposed to leptospires in endemic environments, chemoprophylaxis is recommended (see Table 239.4). Weekly doxycycline (200 mg) has been shown to be effective in military personnel without previous exposure who underwent jungle training.[145] The use of doxycycline prophylaxis after excess rainfall in local populations in endemic areas has been studied.[146,147] Symptomatic disease was significantly reduced in one study, but serologic evidence of infection was found equally in subjects and controls.[146] Limitations of doxycycline are its photosensitivity, high frequency of gastrointestinal side effects, dietary calcium restrictions, and contraindication in pregnant women and children. In vitro susceptibility of leptospires to azithromycin[148] and its longer serum half-life suggest that this agent would be a reasonable alternative to doxycycline; however, clinical trials are necessary to validate this approach.

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The complete reference list is available online at Expert Consult.

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