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 usually is available only in specialized laboratories and is used for determination 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 prevalent 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 commercially 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.

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 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, hantavirus infections (hemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome), and dengue share epidemiologic and clinical features with leptospirosis. Dual infections have been reported. In this light, it is advisable to conduct serologic testing for hantavirus, rickettsiae, and dengue virus when leptospirosis is suspected. When bleeding is detected, dengue hemorrhagic fever and other viral hemorrhagic 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 208-1) as soon as the diagnosis is considered. Leptospires are highly susceptible to a broad range of antibiotics, and early intervention may prevent the development of major organ system failure or lessen its severity. Although studies supporting antibiotic therapy have produced conflicting results, clinical trials are difficult to perform in settings where patients frequently present for medical care with late stages of disease. Antibiotics are less likely to benefit patients in whom organ damage has already occurred. Two open-label randomized studies comparing penicillin with parenteral cefotaxime, parenteral ceftriaxone, and doxycycline showed no significant differences among the antibiotics with regard to complications and mortality risk. Thus ceftriaxone, cefotaxime, or doxycycline is a satisfactory alternative to penicillin for the treatment of severe leptospirosis.

In mild cases, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are coendemic, doxycycline or azithromycin is the drug of choice. In rare instances, a Jarisch-Herxheimer reaction develops within hours after the initiation of antimicrobial therapy.

TABLE 208-1 TREATMENT AND CHEMOPROPHYLAXIS OF LEPTOSPIROSIS IN ADULTS[a]

Indication	Regimen
Treatment	
Mild leptospirosis	Doxycycline[b] (100 mg PO bid) *or*
	Amoxicillin (500 mg PO tid) *or*
	Ampicillin (500 mg PO tid)
Moderate/severe leptospirosis	Penicillin (1.5 million units IV or IM q6h) *or*
	Ceftriaxone (2 g/d IV) *or*
	Cefotaxime (1 g IV q6h) *or*
	Doxycycline (loading dose of 200 mg IV, then 100 mg IV q12h)
Chemoprophylaxis[c]	
	Doxycycline[b] (200 mg PO once a week) *or*
	Azithromycin (250 mg PO once or twice a week)

[a]All regimens are given for 7 days. [b]Doxycycline should not be given to pregnant women or children. [c]The efficacy of doxycycline prophylaxis in endemic or epidemic settings remains unclear. Experiments in animal models and a cost-effectiveness model indicate that azithromycin has a number of characteristics that may make it efficacious in treatment and prophylaxis.

Aggressive supportive care for leptospirosis is essential and can be life-saving. Patients with nonoliguric renal dysfunction require aggressive fluid and electrolyte resuscitation to prevent dehydration and precipitation of oliguric renal failure. Peritoneal dialysis or hemodialysis should be provided to patients with oliguric renal failure. Rapid initiation of hemodialysis has been shown to reduce mortality risk and typically is necessary only for short periods. Patients with pulmonary hemorrhage may have reduced pulmonary compliance (as seen in ARDS) and may benefit from mechanical ventilation with low tidal volumes to avoid high ventilation pressures. Evidence is contradictory for the use of glucocorticoids and desmopressin as adjunct therapy for pulmonary involvement associated with severe leptospirosis.

PROGNOSIS

Most patients with leptospirosis recover. However, post-leptospirosis symptoms, mainly of a depression-like nature, may occur and persist for years after the acute disease. Mortality rates are highest among patients who are elderly and those who have severe disease (pulmonary hemorrhage, Weil's syndrome). Leptospirosis during pregnancy is associated with high fetal mortality rates. Long-term follow-up of patients with renal failure and hepatic dysfunction has documented good recovery of renal and hepatic function.

PREVENTION

Individuals who may be exposed to *Leptospira* through their occupations or their involvement in recreational freshwater activities should be informed about the risks. Measures for controlling leptospirosis include avoidance of exposure to urine and tissues from infected animals through proper eyewear, footwear, and other protective equipment. Targeted rodent control strategies could be considered.

Vaccines for agricultural and companion animals are generally available, and their use should be encouraged. The veterinary vaccine used in a given area should contain the serovars known to be present in that area. Unfortunately, some vaccinated animals still excrete leptospires in their urine. Vaccination of humans against a specific serovar prevalent in an area has been undertaken in some European and Asian countries and has proved effective. Although a large-scale trial of vaccine in humans has been reported from Cuba, no conclusions can be drawn about efficacy and adverse reactions because of insufficient details on study design. The efficacy of chemoprophylaxis with doxycycline (200 mg once a week) or azithromycin (in pregnant women and children) is being disputed, but focused pre- and postexposure administration is indicated in instances of well-defined short-term exposure (Table 208-1).