Leptospirosis

Diagnosis

Clinical diagnosis is by isolation of leptospirosis from blood or cerebrospinal fluid during the first 7–10 days of acute illness, or from urine beginning in the second week of illness. Culture and isolation can be very difficult, requiring special media and incubation for up to 16 weeks, and the sensitivity of culture for diagnosis is low.

Diagnosis is most frequently confirmed by seroconversion demonstrated by fourfold or greater increase in serum agglutination titer of the microscopic agglutination test (MAT), the confirmatory serologic test, using acute and convalescent specimens obtained at least 10 days apart. Different serovars of leptospires can occur in different regions of the world, so MAT should use a panel of locally-occurring leptospire serovars. However, antibody titer increase might be delayed or absent in some patients, and seroconversion can occur asymptomatically, especially in endemic areas.

IgG assays, ELISA assays, and anti-Leptospira IgM detection kits in enzyme-linked immunosorbent assay or rapid formats are used to provide presumptive confirmation for leptospirosis. However, sensitivity is low (39%–72%) during the acute phase of illness (first 7 days). Immunofluorescence, immunohistochemical, and nucleic acid detection techniques are used for the detection of leptospires in clinical and autopsy specimens.

Polymerase chain reaction (PCR) assays for detection of leptospiral DNA have been developed for use on clinical samples, such as blood, and can be used for diagnosis during the first 7 days of infection. These tests are presently only available in reference and research laboratories. Direct examination of blood or urine using dark field microscopy has poor sensitivity and specificity. Inoculation of experimental animals such as golden hamsters, guinea pigs, or gerbils can also confirm diagnosis but is rarely used.

Treatment

Treatment with antimicrobial agents should be given as soon as possible. Penicillin G and doxycycline are effective in reducing morbidity. Penicillin G is recommended for the treatment of severe leptospirosis. Third-generation cephalosporins (ceftriaxone, cefotaxime) are an alternative to penicillin. Doxycycline, ampicillin, or amoxicillin can be used as oral regimens for the treatment of mild leptospirosis. Although their efficacy is not proven, quinolone agents, azithromycin, and clarithromycin are inhibitory in vitro and can be considered in patients with a history of adverse reactions to penicillin. Doxycycline should not be used in pregnant women or children younger than 8 years of age.

Jarisch-Herxheimer reactions can occur following initiation of antimicrobial therapy. Prompt triage of high-risk patients and aggressive treatment are required for hypotension, hemorrhage, and renal and respiratory distress associated with severe leptospirosis. Timely initiation of dialysis and mechanical ventilation are essential to preventing mortality from oliguric renal insufficiency and pulmonary hemorrhage syndrome, respectively.

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Malaria

Diagnosis

Dengue and malaria are very similar in terms of their initial clinical presentation. If malaria is a possibility based on the patient's travel history, then malaria blood smears should be done immediately. Malaria diagnosis is made by a history of travel to an endemic area, symptoms indicative of malaria, and positive blood smears. Thick and thin blood smears are the diagnostic test of choice. If the first smear is negative, the clinician should repeat blood smears every 12-24 hours for a total of 3 sets before deciding that the patient does not have malaria. If the blood smear is positive, the species of plasmodium must be identified and the level of parasitemia (the number of infected cells per 100 red cells) must be determined. Thick smears are best for detection of malaria parasites and thin smears are best for identifying species and determining parasitemia. Additional diagnostic tests include polymerase chain reaction assays (PCR) and antigen detection tests (commonly referred to as rapid diagnostic tests or RDTs). PCR for malaria is more useful for species confirmation and can be a bit more sensitive than microscopy, but PCR results might not be available in a timely manner to establish the diagnosis. RDTs can rapidly establish the diagnosis, but RDTs do not confirm species and they cannot quantify the level of parasitemia. Clinicians using RDTs need to confirm diagnosis with microscopy.

Treatment

There are many drugs available to treat malaria. These include chloroquine (Aralen®), hydroxychloroquine (Plaquenil®), primaquine, doxycycline, tetracycline, clindamycin, quinine sulfate (Qualaquin®), quinidine gluconate, mefloquine (Lariam®), atovaquone-proguanil (Malarone®), artemether-lumefantrine (Coartem®), and artesunate. The only FDA-approved IV treatment available for patients with severe malaria or who are unable to take medications orally is IV quinidine. This is used in conjunction with clindamycin, doxycycline, or tetracycline. However, quinidine is an old antiarrhythmic that might not be readily available in many hospitals. Recently, IV artesunate has been made available via investigational new drug (IND) protocol through CDC.

There are several factors that guide treatment of patients with malaria. The type of drug used for treatment will depend on the species of parasite and the risk that the person is infected with a drug-resistant species of plasmodium. Risk of drug resistance is based on where in the world the malaria infection was acquired. Parasite density and clinical status of the patient is used to determine the severity of disease and guide treatment and management decisions. Parasite density is monitored to determine response to treatment.

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Typhoid

Diagnosis

Typhoid fever can be difficult to diagnose clinically because typical signs and symptoms are similar to several other acute febrile illnesses, including dengue. Physicians must have a high index of suspicion based on travel to an endemic country, history of ingestion of potentially contaminated food or water, and clinical presentation consistent with typhoid fever. There are several commercially available rapid serologic tests available for the diagnosis of typhoid fever, but their sensitivity and specificity are not optimal and they should not replace bacterial culture. Culture of blood, stool, or bone marrow is the gold standard laboratory test for the identification of serovar Typhi and laboratory confirmation of typhoid fever. It is important to have the isolate from a culture so that antimicrobial susceptibility testing (and molecular subtyping, if necessary) can be performed.

Treatment

Antimicrobial treatment is recommended for patients with typhoid fever. *Salmonella enterica* serovar Typhi rapidly acquires resistance to antimicrobials, and treatment should be informed by the results of antimicrobial susceptibility testing whenever possible. If the resistance pattern is not known, empiric treatment for typhoid fever can include ciprofloxacin (500mg) twice daily for 10-14 days or ceftriaxone 1-2g per day IV for 10-14 days as an alternative. Other commonly used antibiotics include ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.

Patients treated with an appropriate antibiotic usually begin to feel better after 2–3 days of therapy. Patients who are not treated can continue to have intermittent fever for weeks or months, and as many as 20% can die from disease complications. Chronic carriage of serovar Typhi can be successfully eradicated in 90% of cases by treatment with ciprofloxacin (750 mg) or norfloxacin (400 mg) twice daily for 14–28 days.

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