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Tropical Infections in Pregnancy: Dengue Fever, Kala Azar and Leptospirosis

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Many of the tropical diseases have not remained confined to the endemic areas. The diseases have become widespread and can occur anywhere in the world because of people migration and international travels. As a result it becomes imperative that every clinician should be aware of such tropical diseases and principles of their management. In this chapter an attempt is be made to discuss on dengue fever, kala azar (leishmaniasis) and leptospirosis.

DENGUE FEVER

Dengue has been called the most important mosquito-transmitted viral disease in terms of morbidity and mortality. Dengue fever is a benign acute febrile syndrome occurring in tropical regions. In a small proportion of cases, the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation (DIC) known as dengue hemorrhagic fever (DHF). In 20 to 30 percent of DHF cases, the patient develops shock, known as the dengue shock syndrome (DSS).

Dengue virus infection is increasingly recognized as one of the world's major emerging infectious diseases.[9,15] Dengue is endemic in most tropical and subtropical countries. Health care providers in these areas and those attending to people returning from those areas need to understand the epidemiology, risk factors, clinical spectrum, diagnosis, management, and prevention of dengue.

The Virus, the Vector, and the Epidemiology of Dengue

Dengue virus belongs to the family Flaviviridae (single-stranded, nonsegmented RNA viruses) and has four serologically distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4).[9] Dengue virus serotypes are distinguishable by complement-fixation and neutralization tests.[24] Infection with one serotype confers long-term immunity only to that serotype, and therefore persons maybe infected up to four times.[12] Humans are the main reservoir for the dengue virus, although nonhuman primates in Asia and Africa may also be infected.[6]

Dengue virus is transmitted by mosquitoes of the genus aedes, such as *Aedes aegypti* and *A. albopictus*.[9] *A. aegypti*, found worldwide in the tropics and subtropics, is the principal vector. It is an efficient vector because it is highly susceptible to dengue virus, feeds preferentially on human blood, is a daytime feeder, has an almost imperceptible bite, and is capable of biting several people in a short period for one blood meal.[6] The mosquito is well-adapted to life in urban settings and typically breeds in clean, stagnant water in containers that collect rainwater, such as tires, tin cans, pots, and buckets.[9]

Dengue virus is now the most common cause of arboviral disease in the world, with an estimated annual occurrence of 100 million cases of dengue fever and 250,000 cases of dengue hemorrhagic fever and a mortality rate of 25,000 per year.[6,7] Dengue virus

infection has been reported in more than 100 countries, with 2.5 billion people living in areas where dengue is endemic.[2,12] Most cases of dengue hemorrhagic fever are reported from Asia, where it is a leading cause of hospitalization and death among children. In Latin America, dengue hemorrhagic fever was a rare disease before 1981.[10] The 1980s and 1990s saw a dramatic geographic expansion of epidemic dengue fever and dengue hemorrhagic fever from Southeast Asia to the South Pacific Islands, the Caribbean, and Latin America, with regions changing from nonendemic (no serotypes present) to hypoendemic (one serotype present) or hyperendemic (multiple serotypes present).[11] The World Health Organization (WHO) classifies dengue as a major international public health concern because of the expanding geographic distribution of both the virus and the mosquito vector, the increased frequency of epidemics, the cocirculation of multiple virus serotypes, and the emergence of dengue hemorrhagic fever in new areas.[6,9] The reasons for this resurgence are complex and include urbanization with substandard living conditions, lack of vector control, climatic change, virus evolution, and international travel.[12]

There is no known sex predilection; however, fewer cases of DHF/DSS have been reported in men than in women. And all ages are susceptible for the disease. But, in endemic areas, a high prevalence of immunity in adults may limit outbreaks to children

Clinical Aspects of Dengue Virus Infections

Pathogenesis

After an infected mosquito has bitten a person, the virus replicates in regional lymph nodes and is disseminated through the lymphatic system and blood to other tissues. Replication in the reticuloendothelial system and skin results in viremia.[26] The incubation period ranges from 3 to 14 days, but it is usually 4 to 7 days. Infection with dengue virus of any of the four serotypes causes a spectrum of illness, ranging from no symptoms or mild fever to severe and fatal hemorrhage, depending largely on the patient's age and immunologic condition.[6]

Although the mechanisms for the development of severe hemorrhagic disease are not fully understood, the main risk factor for the development of dengue hemorrhagic fever and dengue shock syndrome is thought to be secondary infection with another serotype.[7,12] Cross-reactive but non-neutralizing anti-dengue antibodies from the previous infection bind to the new infecting serotype and enhance viral uptake of monocytes and macrophages. This antibody-dependent enhancement results in an amplified cascade of cytokines and complement activation, causing endothelial dysfunction, platelet destruction, and consumption of coagulation factors leading to plasma leakage and hemorrhagic manifestations.[12-14,16] The severity of the disease also depends on the strain and serotype of the infecting virus, the age and genetic background of the patient,[8,12,23] and the degree of viremia.[27]

Asymptomatic Infection and Acute Febrile Illness

Most persons with dengue infections in areas where the disease is endemic are asymptomatic or they present with mild febrile illness.[6]

Classic Dengue Fever

Classic dengue fever is characterized by the sudden onset of fever, accompanied by a severe headache, retro-orbital pain, and fatigue, and it is often associated with severe myalgia and arthralgia ("breakbone fever").[26] The fever usually lasts five to seven days. A rash, typically macular or maculopapular and often confluent with the sparing of small islands of normal skin, has been reported in about half of infected persons. It usually appears near the time of defervescence, often lasts for two to four days, and maybe accompanied by scaling and pruritus. Other signs and symptoms include flushed facies (usually during the first 24 to 48 hours), lymphadenopathy, injected conjunctivae, an inflamed pharynx, and mild respiratory and gastrointestinal symptoms. Patients with dengue fever may have hemorrhagic manifestations, such as petechiae, purpura, or evidence of a positive tourniquet test for capillary fragility; the test is positive if 20 or more petechiae appear in a 1-inch^2 (6.25-cm^2) patch on the forearm after deflation of the blood pressure cuff. Gum bleeding, epistaxis, menorrhagia, and gastrointestinal hemorrhage are only occasionally seen. Very rare complications of dengue fever include myocarditis, hepatitis, and neurologic abnormalities, such as encephalopathy and neuropathies. Laboratory findings commonly associated with dengue fever

include thrombocytopenia, leukopenia with lymphopenia, mild-to-moderate-elevations of hepatic aminotransferases and lactate dehydrogenase, and hyponatremia.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

The hallmark of dengue hemorrhagic fever is capillary leakage, accompanied by hemorrhagic manifestations. The presentation of patients in the first days of the illness is similar to that seen in dengue fever, but plasma leakage develops four to seven days after the onset of the disease, at approximately the time of defervescence. Abdominal pain and vomiting, restlessness, a change in the level of consciousness, and a sudden change from fever to hypothermia maybe the first clinical warning signs and are often associated with a marked decrease in the platelet count.[6]

The diagnosis of dengue hemorrhagic fever is made on the basis of the following triad of symptoms and signs: hemorrhagic manifestations; a platelet count of less than 100,000 per cubic millimeter; and objective evidence of plasma leakage, shown either by fluctuation of packed-cell volume (greater than 20 percent during the course of the illness) or by clinical signs of plasma leakage, such as pleural effusion, ascites, or hypoproteinemia. Hemorrhagic manifestations without capillary leakage do not constitute dengue hemorrhagic fever. A positive tourniquet test is incorporated in the WHO clinical case definition of dengue hemorrhagic fever, but the definition differentiates poorly between dengue and dengue hemorrhagic fever and is not very specific.[19] Mortality rates from dengue hemorrhagic fever can range as high as 10 to 20 percent, but they are as low as 0.2 percent in hospitals with staff experienced in the management of the disease.[6,8,22]

Dengue shock syndrome is characterized by a rapid, weak pulse with a narrowing pulse pressure of less than 20 mm Hg, or profound hypotension (systolic pressure of less than 90 mm Hg among those five years of age or older). The duration of shock is short. Typically, patients either recover rapidly after appropriate volume-replacement therapy is administered or die within 12 to 24 hours; the mortality rate is up to 40 percent.[6] In contrast to classic dengue, DHF/DSS is predominantly a disease of children.

Diagnosis and Differential Diagnosis

A confirmed diagnosis is established by culture of the virus (from tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence, or ELISA), polymerase-chain-reaction (PCR) tests, or serologic assays for IgG and IgM antibody with enzyme-linked immunosorbent assay or hemagglutination inhibition test. All these tests have limitations. PCR testing is not available in many settings and is sensitive only in the very early stages of the disease. The test based on an increase in the IgG titer by a factor of four is difficult in routine clinical care because a second blood sample is required at the convalescent stage. Cross-reactions with other flaviviruses interfere with serologic testing, particularly the ELISA for IgG, and this affects the interpretation of test in such patients who were previously vaccinated against flavivirus infections, such as yellow fever and Japanese encephalitis. The most commonly used test for the diagnosis of dengue is the IgM capture ELISA, but this test is negative early in the course of the disease, should be performed only four to five days after the onset of symptoms, and gives only a probable diagnosis . Rheumatoid factor may lead to an IgM capture assay that is false positive for dengue, and so may other flavivirus infections (albeit less so than with dengue IgG assays).

Primary infections are characterized by an increase in dengue-specific IgM antibodies 4 to 5 days after the onset of fever and by an increase in IgG antibodies only after 7 to 10 days.[28] IgM antibodies are detectable for three to six months, whereas IgG antibodies remain detectable for life. In secondary infections, the level of IgM antibodies is lower than in primary infections and the antibodies are sometimes even absent, whereas levels of IgG antibodies rise rapidly in secondary infections, even during the acute phase.[12] Thus, the presence of high liters of IgG early in the course of the disease is a criterion for secondary infection.

Therefore, since a laboratory-based diagnosis of dengue is often unavailable at the time of care, a clinical diagnosis is initially made on the basis of clinical manifestations and laboratory features developing over a period of time and as other diseases, such as malaria, are ruled out. The relation in time between the drop in the platelet count and the rapid

increase in the hematocrit is unique to dengue hemorrhagic fever, and together with the clinical signs is sufficient to establish a clinical diagnosis of dengue hemorrhagic fever. However, the symptoms and signs of mild febrile illness or classic dengue fever are nonspecific and hard to distinguish from many other undifferentiated febrile syndromes. The differential diagnosis includes malaria, typhoid fever, leptospirosis, chikungunya, West Nile virus infection, measles, rubella, acute human immunodeficiency virus conversion disease, Epstein-Barr virus infection, viral hemorrhagic fevers, rickettsial diseases, early severe acute respiratory syndrome (SARS), and any other disease that can manifest in the acute phase as an undifferentiated febrile syndrome.[26] A combination of laboratory variables (low platelet or leukocyte count and increased liver aminotransferase levels) is highly predictive of the diagnosis of dengue and may help to differentiate dengue from typhus and early SARS. A positive tourniquet test or leukopenia (5000 cells per cubic millimeter) are the two tests with the highest sensitivity (about 90 percent) for the diagnosis of early dengue, since the platelet count may initially be normal and drop only on subsequent days. If the two tests are combined, the sensitivity decreases, but the positive predictive value increases.

Management

No specific therapeutic agents exist for dengue. Corticosteroids, carbazochrome (a drug that decreases capillary permeability), and antiviral agents have no proved role (although ribavirin, interferon alfa, and 6-azauridine have shown some antiviral activity *in vitro*).[4,6,25] Prompt and correct institution of fluid replacement is thought to reduce mortality rates due to dengue hemorrhagic fever and dengue shock syndrome.[5] Treatment is therefore based on symptoms and supportive, with the principal aim to prevent death. Mild or classic dengue is treated with antipyretic agents such as acetaminophen, bed rest, and fluid replacement (usually administered orally and only rarely parenterally); most cases can be managed on an outpatient basis. Aspirin and nonsteroidal anti-inflammatory drugs are best avoided because they can increase bleeding. Intramuscular injections should not be given because they may cause large hematomas. Platelet counts and hematocrit determinations should be repeated at least every 24 hours to allow prompt recognition of the development of dengue hemorrhagic fever and institution of fluid replacement.[5]

Patients with a platelet count of less than 100,000 per cubic millimeter are usually admitted to a hospital since they have the highest risk of the development of dengue hemorrhagic fever. The critical period is often on the day of defervescence, typically four to seven days after onset of the illness. A decrease in the platelet count, which usually precedes the rise in hematocrit, is of diagnostic and prognostic value in cases of dengue hemorrhagic fever. A rise in the hematocrit of 20 percent indicates considerable plasma loss, and patients with this condition require intensive care with intravenous replacement of fluids such as normal saline and Ringer's lactate.[5] In patients with worsening shock, colloid or crystalloid solutions should be added (10 to 20 ml per kilogram of body weight per hour), although some studies suggest that colloid solutions are superior to crystalloid solutions.[5,26] If there is evidence of bleeding or disseminated intravascular coagulation, fresh blood or fresh-frozen plasma should be administered. Once the capillary leakage stops and resorption of extravasated fluid begins, care must be taken not to cause fluid overload and pulmonary edema.[26] Therapy with parenterally administered fluids should be stopped or reduced when the hematocrit drops below 40 percent and is accompanied by improving clinical signs and urine output, which occur generally after 24 to 72 hours.[26] Guidelines concerning the rate of intravenous infusion and specific time periods for infusion have been published by the WHO.[29]

Pregnancy and Dengue Fever

The risk of dengue virus infection during pregnancy has increased due to the current rush of frequent and severe dengue epidemics. The effects of dengue virus in the fetus and newborn children have been studied only superficially and with contradictory results .DF in pregnant women did not cause any infant abnormality, but it may have been responsible for fetal death. The rate of fetal death associated with DF (13.6%) was much higher than the mean rate for the gynecology unit at the hospital (1.9%).[1] The children from women with dengue during pregnancy present low weight, greater frequency of premature birth and increased fetal distress.[21]

Of interest, cases of neonatal infections were recorded and involved the transmission of the virus from mother to child at the end of the pregnancy.[3,17,18,20]

KALA AZAR

The current interest in leishmaniasis stems from the importance of this disease with respect to travel medicine, veterans of Operation Desert Storm, humanitarian concerns, and infection with human immunodeficiency virus. Since 1990, South Asia has experienced a resurgence of the lethal parasitic disease visceral leishmaniasis (VL). Protozoal infections occur throughout the world and are a major cause of morbidity and mortality in some regions. Immunocompromised patients are especially at risk. Primary immune deficiency is rare; whereas, secondary deficiency is more common. Immunosuppressive therapy, cancer and its treatment, HIV infection, and splenectomy all may increase vulnerability to infection. Infectious risk is proportional to duration of neutropenia and severity. Protozoal infections are typically more severe in immunocompromised patients than in immunocompetent patients.

India, Bangladesh, and Nepal account for an estimated 300,000 cases annually and 60 percent of the global burden (in terms of disability-adjusted life years lost) of VL.[4,9] Superimposed on this poorly controlled VL-endemic situation are outbreaks that affect hundreds of thousands of people, as in Bihar in the early 1990s.[2] The full-blown clinical syndrome caused by VL is characterized by fever, weight loss, splenomegaly, hepatomegaly, skin darkening, and anemia and is known as kala azar ("black fever" in Hindi). *Kala azar* is nearly always fatal if untreated.[5] Even with treatment, case-fatality rates often exceed 10 percent in VL-endemic areas of Asia and Africa.[1]

The Protozoan, the Vector, and the Epidemiology of Leishmaniasis

Protozoa of the *Leishmania* species cause leishmaniasis. Their life-cycle involves an insect vector (i.e., a different species of sandflies) and a vertebrate host. Different *Leishmania* species in many geographic regions cause disease. Infection maybe classified into the 3 clinical syndromes of cutaneous, mucocutaneous, and visceral leishmaniasis.

Cutaneous leishmaniasis (*Leishmania* tropical, *Leishmania* major, and *Leishmania* aethiopica) is caused by *Leishmania tropica mexicana*. The species for mucocutaneous leishmaniasis is *Leishmania braziliensis*. Depending on the geographical location, the species causing visceral leishmaniasis vary. In India it is *Leishmania donovani* , in South Europe and North Africa—*Leishmania infantum* and in Americas it is the *Leishmania chagasi*.

Visceral leishmaniasis could be classified as African, Mediterranean or Indian kala azar. African kala azar generally affects older children and young adults. Mediterranean kala azar also known as infantile kala azar, for which dogs, jackals, foxes, and rats are the potential reservoirs. While Indian kala azar is transmitted by sandflies and humans are the only known reservoir. Children are at greater risk than adults in endemic areas. Malnutrition has been shown to contribute to the development of disease. Persons with AIDS have an increased risk of developing leishmaniasis. Incomplete therapy of initial disease is a risk factor for recurrence of leishmaniasis. Incidence is highest in rural areas and areas where conditions are favorable for sandflies. Leishmaniasis occurs in Central America, South America, Africa, the Middle East, Mediterranean countries, and Asia. Subhimalayan India has higher prevalence.

In mucocutaneous leishmaniasis, death usually occurs from secondary infection. Visceral leishmaniasis is progressive. Mortality in untreated cases ranges from 75 to 95 percent. A highly fatal type of visceral leishmaniasis, which is found along the Mediterranean, specifically affects infants. Otherwise, occurrence is proportional to sandfly exposure.[4,13]

Clinical Aspects of Leishmaniasis

Pathophysiology

The parasites develop and multiply in the gut of the sandfly until they are introduced into the blood and tissues of the human host. They infect the reticuloendothelial system and then multiply. When the infected cells rupture, the infection spreads to other organs. Body temperature is an important factor that can be used to determine the localization of leishmanial lesions. Species causing cutaneous leishmaniasis cannot grow at core body temperature, while species causing visceral leishmaniasis are able

to grow at these temperatures. In cutaneous leishmaniasis, the hallmark of the disease is skin lesions, which can spontaneously heal in 2 to 10 months. In mucocutaneous leishmaniasis, mucosal ulcerations usually develop by metastasis rather than by local spread. Secondary infection plays a prominent role in the size and persistence of ulcers. Their progression is slow and steady. Typically, visceral leishmaniasis incubates for weeks to months. The disease can be subacute, acute, or chronic.[1]

Cutaneous Leishmaniasis

After the bite of an infected sandfly, the incubation period ranges from weeks to months. Systemic symptoms generally are absent. Skin trauma can result in activation of cutaneous infection long after the initial bite. The lesion usually evolves over time. Healed lesions leave an atrophic scar. Lesions can be pruritic or painful. Lesions caused by some species can heal without pharmacotherapy, but healing can take months. Systemic signs usually are absent.

Initially, the lesion is a small red papule up to 2 cm in size. The papule ultimately ulcerates. The ulcer has raised edges with surrounding dusky red skin. The ulcers can be moist or open with seropurulent exudate or dry with a crusted scab. Sores usually are found on exposed areas of skin, especially the extremities and face. Regional adenopathy, satellite lesions, and subcutaneous nodules can be present. Untreated sores can leave depigmented retracted scars.

Mucocutaneous Leishmaniasis

The incubation period is from 1 to 3 months. Mucosal lesions become painful gradually. Initial symptoms include nasal obstruction and bleeding. Cutaneous lesions can be single or multiple. Mucosal lesions often develop after the primary lesion has healed. Mucosal lesions can progress to involve the entire nasal mucosa and the hard and soft palates. Without treatment, the entire nasal mucosa and palates become deformed with ulceration and erosion of the nasal septum, lips, and palate. Signs include gingival edema to periodontitis, and adenopathy.

Visceral Leishmaniasis

Kala azar is the Indian name meaning "black disease." Many subclinical cases occur for each clinically recognized case. Malnutrition has been shown to contribute to the development of clinical disease. In endemic areas, kala azar maybe suspected in a patient with persistent, irregular, or remittent fever, leucopenia, and splenomegaly. Onset is insidious. Fever can be continuous, intermittent, or remittent, and it can recur at irregular intervals. Hepatosplenomegaly is seen secondary to compensatory production of phagocytic blood cells. Wasting and weakness are observed. Darkening of the skin is characteristic (thus, the name kala azar or black fever). Diarrhea may occur. Pancytopenia is common.

Complications of the disease include secondary bacterial infection, bleeding, splenic rupture, disfigurement of nose, lips, and palate. Edema, cachexia, and hyperpigmentation are seen in late stages. Metastatic lesions with tissue destruction will occur in the nasopharynx.[10]

Diagnosis and Differential Diagnosis

Diagnosis of the disease is important to initiate treatment. However, the disease does not require acute intervention.

Expanded differential diagnosis for cutaneous leishmaniasis includes bacterial tropical ulcers, such as sporotrichosis, atypical mycobacterioses, yaws, and syphilis. Leprosy and carcinoma need to be considered. Blastomycosis should be considered in the differential for mucocutaneous leishmaniasis. For visceral leishmaniasis, typhoid fever, tuberculosis, and lymphoma need be excluded.

Diagnosis of cutaneous leishmaniasis usually is based on the appearance of the lesion. Culture of the organisms is preferable but unreliable because organisms are difficult to isolate from the lesion, especially as the lesion becomes older. The organism grows on Schneider *Drosophila* medium (positive results in 1 week), and Novy-MacNeal-Nicolle (NNN) medium (media available from the Centers for Disease Control [CDC]). Cultures can produce positive results in 1 to 3 weeks. The leishmaniasis skin test produces positive results 3 months after the appearance of lesions. Serological tests are not well established.[3]

Mucocutaneous leishmaniasis is preferably diagnosed by culture of the organism, but organisms are often scant. On biopsy, a nonspecific granulomatous reaction often is observed. Giemsa's stain may show the organisms. Results from the leishmanin skin

test are positive after 2 to 3 months of infection. Serologic tests are available in some centers. Because the organisms often are scarce, the diagnosis often is epidemiologic (travel to endemic area, clinical picture coupled with lab data).

Definitive diagnosis of visceral leishmaniasis is made by observing the parasite on stained Giemsa's stain or by observing the culture of bone marrow, splenic, hepatic, or lymph node aspirates. Indirect fluorescent antibody test is now available but may cross react with other human leishmania and trypanosomes. Enzyme-linked immunosorbent assay (ELISA) test is available. Monoclonal antibodies (MoAb) or hybridization of tissue touch blots with labeled kinetoplast DMA probes are used for identification of different strains of *Leishmania*. An immunochromatographic strip test exists for rapid detection of antibodies to *Leishmania* antigen K39.[1]

These patients require a complete blood count. Leucopenia with a relative monocytosis and lymphocytosis, anemia, and thrombocytopenia result from bone marrow infiltration. Performing liver function tests and running a coagulation panel is important in management of the cases.

Management

Nonspecific measures, such as local heat and cleanliness, contribute to the spontaneous healing of the ulcers. Secondary infection of ulcers with skin flora can occur and must be treated. Transfusions are needed for patients with severe anemia. Antibacterial chemotherapy is needed for patients with bacterial superinfection.

Antiparasitic pentavalent antimonials are the mainstays of therapy. Sodium stibogluconate (Pentostam) is the recommended treatment. However, the procurement and prolonged intravenous or intramuscular administration of these drugs is procedurally difficult, especially in underdeveloped countries where the disease is most prevalent. Antimony resistance has been a problem in India and an amphotericin B regimen should be used. Other drugs that have been tried include ketoconazole, puromycin, interferon and antimony, and miltefosine.

New amphotericin B formulations have become major advances in treatment during the last decade. They are used in cases resistant to antimonials and are less toxic than they were in the past.

Prognosis depends on nutritional and overall immune status of the host and on the precise species of infection. With early treatment, the cure rate is higher than 90 percent. The mortality rate is 15 to 25 percent in untreated cases. If untreated, death occurs in 3 to 20 months.

Kala Azar in Pregnancy

Leishmaniasis during pregnancy is rare and deserves special attention since little information is available regarding the occurrence of visceral leishmaniasis during gestational period and the real possibility of vertical transmission of this disease. Because specific areas in the world are endemic for the disease and considering the continuous growth of the population, cases of pregnant women with visceral leishmaniasis are becoming more frequent.[15] Unfortunately, textbooks on infectious diseases do not include this specific group of patients, and studies in the literature on aspects related to pregnancy and visceral leishmaniasis are scarce. Only anecdotal cases of visceral leishmaniasis in pregnancy are reported in the literature, although the disease is life-threatening for both mothers and infants. Fever and hepatosplenomegaly are the main presenting symptoms. Untreated visceral leishmaniasis may result in consequences on the fetus or congenital visceral leishmaniasis.[11] Cases of stillbirths are reported.[7]

Kala azar in pregnant women is difficult to treat because for them the two commonly used drugs, sodium stibogluconate and pentamidine, are not considered safe. Amphotericin B cures kala azar during pregnancy with no harmful effects on the fetus.[14]

Vertical transmission of leishmaniasis is possible and the institution of treatment is imperative in cases of pregnant women with kala azar. Amphotericin B is strongly recommended as the first choice drug due to its fewer maternal-fetal adverse effects.[6]

LEPTOSPIROSIS

Leptospirosis, an acute anthropo zoonotic infection is considered the most common zoonosis in the world. Pregnant women face a high rate of fetal mortality. Increased awareness of the possibility of leptospirosis for pregnant women who live in areas where the disease is endemic is of utmost importance for early

detection and treatment of the disease and, thus, for the safety of the fetus.

The Organism and the Epidemiology of Leptospirosis

Caused by spirochete, it is a systemic infection usually producing fever with hepatorenal involvement, meningoencephalitis, and hemorrhage. *Leptospira interrogans* which has 23 serogroups and > 200 serovars. Various factors influencing the animal activity, suitability of the environment for the survival of the organism and behavioral and occupational habits of human beings can be the determinants of incidence and prevalence of the disease. The disease was considered inconsequential till recently, but it is emerging as an important public health problem during the last decade or so due to sudden upsurge in the number of reported cases and outbreaks. Since isolation rate of the microorganism from clinical specimens is low due to prior indiscriminate use of antibiotics, serological techniques remain the cornerstone of diagnosis.[15]

Leptospirosis is a worldwide zoonosis, usually transmitted to humans through contaminated water or direct exposure to the urine of infected animals. Such media include animal bedding, soil, mud, and aborted tissue. The organism enters the body via abraded skin or mucous membranes, such as the conjunctiva or alimentary tract. Occasionally, the organism may even enter the body through intact skin. Infection has occurred after animal and rodent bites, after contact with abortion products of infected animals, and after ingestion of contaminated food and water. The latter route of infection is believed to occur via the mucosa of the mouth and the esophagus because leptospires cannot survive in an acidic environment. Transmission between humans is rare. In infected animals the organisms is harbored in and excreted from renal tubules. It has also been detected in placenta and amniotic fluid.[21]

The clinical spectrum of the disease ranges from an influenza-like syndrome to Weil's disease and multiple organ dysfunction syndromes. The causative agents of human leptospirosis belong to the genus *Leptospira*, which contains both saprophytic and pathogenic species.[17]There are several reports suggesting based on serologic testing that *L. fainei* might be pathogenic for humans[22] and *L. fainei* have been isolated from the urine and blood of patients.[18]

Occupational exposure probably accounts for 30 to 50 percent of human cases. The main occupational groups at risk include farm workers, veterinarians, pet shop owners, field agricultural workers, abattoir workers, plumbers, meat handlers and slaughterhouse workers, coal miners, workers in the fishing industry, military troops, milkers, and sewer workers. Leptospirosis maybe spread epidemically in large populations in conditions of widespread flooding.[12]

Urban dwellers are also at increased risk because these residents may become exposed sporadically to rat urine as inner cities deteriorate. The incidence is increasing in urban children. However, human disease remains mainly related to occupation. The prevalence is higher in males as they tend to be engaged in outdoor work more frequently than women.

Clinical Aspects of Leptospirosis

Pathophysiology

After it gains entry via intact skin or mucosa, the organism multiplies in blood and tissue. The resulting leptospiremia can spread to any part of the body but particularly affects the liver and kidney. In addition to interstitial nephritis and tubular necrosis, hypovolemia from dehydration and from altered capillary permeability also can contribute to renal failure. Liver involvement is seen as centrilobular necrosis with proliferation of Kupffer cells. Jaundice may occur as a result of hepatocellular dysfunction. Leptospires also may invade skeletal muscle, causing edema, vacuolization of myofibrils, and focal necrosis. In severe disease, a disseminated vasculitic syndrome may result from damage to the capillary endothelium. Leptospires may invade the aqueous humor of the eye, where they may persist for many months, occasionally leading to chronic or recurrent uveitis.[8]

The incubation period is usually 7 to 12 days and approximately 90 percent of patients manifest a mild anicteric form of the disease, and approximately 5 to 10 percent have the severe form with jaundice, otherwise known as Weil's disease. The natural course of leptospirosis falls into 2 distinct phases, septicemic and immune. During a brief period of 1 to 3 days between the 2 phases, the patient shows some improvement.[11]

Leptospiremic phase also called as septicemic phase since organism maybe isolated from blood cultures, cerebrospinal fluid (CSF), and most tissues and lasts for about 4 to 7 days, the patient develops abruptly a nonspecific flu like illness of varying severity. Period of improvement of couple of days follows only for fever to recur leading to clinical or subclinical meningitis.

Leptospiruric phase or immune stage since circulating antibodies maybe detected or the organism maybe isolated from urine; it may not be recoverable from blood or CSF. Disease referable to specific organs is seen. These organs include the meninges, liver, eyes, and kidney.

Anicteric disease Aseptic meningitis is the most important clinical syndrome observed in the immune anicteric stage. Meningeal symptoms develop in 50 percent of patients. Cranial nerve palsies, encephalitis, and changes in consciousness are less common. Mild delirium also maybe seen. Death is extremely rare in the anicteric cases.

Icteric disease Leptospires maybe isolated from the blood for 24 to 48 hours after jaundice appears. Abdominal pain with diarrhea or constipation (30%), hepatosplenomegaly, nausea, vomiting, and anorexia also are seen. Uveitis, iridocyclitis and chorioretinitis are late complications that may persist for years. Renal, pulmonary and adenopathy are other significant manifestations.

Clinical syndromes are not specific to the serotype, but often, the serovar helps to determine some of the more characteristic clinical manifestations. For example, jaundice is seen in 83 percent of patients with *L. icterohaemorrhagiae* infection and in 30 percent of patients infected with *L. pomona*. A characteristic pretibial erythematous rash is seen in patients with *L. autumnalis* infection. Similarly, GI symptoms predominate in patients infected with *L. grippotyphosa*. Aseptic meningitis commonly occurs in those infected with *L. pomona* or *L. canicola*.

Weil's Syndrome

It is a severe form of leptospirosis primarily manifesting with profound jaundice, renal dysfunction, hepatic necrosis, pulmonary dysfunction, and hemorrhagic diathesis. Weil's syndrome carries a mortality rate of 5 to 10 percent. The most severe cases of Weil's syndrome, with hepatorenal involvement and jaundice, carry a case-fatality rate of 20 to 40 percent. Mortality rate is usually higher for older patients.[15]

Diagnosis

Leptospirosis should be considered when a patient has a flulike disease with aseptic meningitis or disproportionately severe myalgia.

Hepatitis, meningitis, typhoid fevers are the diagnosis to be excluded at different phases of the disease. Malaria, Rickettsial infection and infectious mononucleosis are the conditions to be considered.

Definitive diagnosis is suggested by isolation of the organism by culture or a positive result on the microscopic agglutination test (MAT).

Blood cultures maybe negative if drawn too early or too late. Urine and cerebrospinal fluid may also be the sources to yield the spirochetes. Leptospires remain viable in anticoagulated blood for up to 11 days; hence, specimens can be mailed to a reference laboratory for culture. The infecting serovar can be isolated only by culture.

A 4-fold rise in convalescent titers on microscopic agglutination test is considered a positive result. A presumptive diagnosis can be made by observing an antibody titer of greater than or equal to 1:100 in the MAT in conjunction with symptoms consistent with the disease. Macroscopic slide agglutination test also allows presumptive diagnosis to be made. Only specialized labs carry out serologic tests; hence, the decision to treat should not be delayed while awaiting the results of testing.

Other tests include an indirect hemagglutination test, a microcapsule agglutination test, an immunoglobulin M (IgM) enzyme-linked immunoabsorbent assay (ELISA), and a dark-field examination of blood or urine. More recently, rapid commercial tests have been made available, such as the Dip-S-Ticks (PanBio, Inc, Baltimore, Maryland), which detects leptospira antibodies.[1]

Management

Treatment should be started as soon as possible. Antimicrobial therapy is indicated for the severe form of leptospirosis. Mild leptospirosis is treated with

doxycycline, ampicillin, or amoxicillin. For severe leptospirosis, the primary therapy is penicillin G, which is used widely in clinical practice. Alternative regimens are ampicillin, amoxicillin, or erythromycin. Several other antibiotics, including cephalosporins, maybe useful, but clinical experience with these is more limited. However, use of antimicrobials for the mild form of leptospirosis is controversial. Evidence from randomized clinical trials is insufficient to provide clear guidelines for the treatment of leptospirosis. The trials suggest that antibiotics could be useful. Patients with renal failure may require dialysis.[14] Those with Weil's syndrome may need transfusions of whole blood and/or platelets. Supportive therapy and careful management of renal, hepatic, hematologic, and CNS complications are important.

Vaccines are offered to high-risk workers in some European and Asian countries (e.g., farm workers). They are serovar specific and must be repeated yearly. They are associated with painful swelling, especially after revaccination.[8,9] Domestic livestock should also be vaccinated in areas where the disease is prevalent and help prevent infection in animals.

Doxycycline, in the dose of 200 mg every week, has demonstrated efficacy of 95 percent against leptospirosis and maybe given to help prevent the disease in those exposed. This regimen is recommended for those with short-term exposure and is not for repeated exposure over protracted periods of time.

Most patients with leptospirosis recover. The highest mortality rates are in elderly patients and in those with Weil's syndrome. Patients with hepatic dysfunction and renal failure have a good chance of recovering renal and hepatic dysfunction in the long term.

Pregnancy and Leptospirosis

Cases of leptospirosis in pregnant women have been reported.[3,5,19] Various perinatal outcomes are possible[10] and include intrauterine fetal death,[7] abortions, healthy newborns or newborn showing signs of active leptospirosis.[19]

Pregnant women also face a high rate of fetal mortality, as infected women have a higher-than-normal incidence of spontaneous abortion if the infection is acquired in the early months of pregnancy.[19] Since congenital infection is rare, leptospirosis should not necessarily be considered an indication to terminate pregnancy.[13] Increased awareness of the possibility of leptospirosis for pregnant women who live in areas where the disease is endemic is of utmost importance or early detection and treatment of the disease and, thus, for the safety of the fetus.

The diagnosis is based on urine tests, serological tests and cerebrospinal fluid.[16] Placental antigens have been detected in pregnancy with leptospirosis.[20]

Management consists of treatment with antibiotics and appropriate support measures.[16] To implement an effective treatment, management of leptospirosis must be based on accurate and early diagnosis. Doxycycline has been used for leptospirosis but is contraindicated in pregnancy. One may need to chose though less effective but safer antimicrobials.

Though the transmission between humans is rare, human-to-human transmission of Leptospira interrogans by milk is documented.[2] This fact needs to be kept in mind and breast feeding should be temporarily withheld.

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