LEPTOSPIROSIS: A WORLDWIDE RESURGENT ZOONOSIS AND IMPORTANT CAUSE OF ACUTE RENAL FAILURE AND DEATH IN DEVELOPING NATIONS

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Leptospirosis, a spirochetal zoonosis, is a globally re-emerging infectious disease that has disseminated from its habitual rural base to become the cause of urban epidemics in poor communities of industrialized and developing nations. This review addresses the issues in the epidemiology, clinical features, and management of the disease, as well as progress made toward understanding the pathogenesis of leptospiral nephropathy. In developing nations, leptospirosis plays an important role as a potentially preventable cause of acute renal failure. The data indicate that in certain developing regions, such as the city of Salvador, Brazil, leptospirosis is misdiagnosed with other infectious disease such as dengue and the overall disease burden is likely underestimated partly because of the protean and nonspecific presentation. Severe forms of the disease are associated with high case-fatality rate. In urban Brazil, outbreaks of leptospirosis can be predicted by heavy rain and flooding and this may serve to indicate which resources should be allocated to prevent the disease. Advancements in the basic research and epidemiology of leptospirosis should contribute to the development of more accurate diagnostic tests and of an effective vaccine. Policy makers should be urged to address the underlying conditions of poverty as well as environmental issues, which have led to the emergence of leptospirosis. (*Ethn Dis*. 2009;19[suppl 1]:S1-37–S1-41)

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INTRODUCTION

The accelerated growth and impoverishment of urban populations and lack of basic sanitation in certain regions have produced conditions favoring rodent borne epidemic transmission of leptospirosis during periods of seasonal heavy rainfall and flooding. Urban epidemics of leptospirosis have emerged to become a major public health issue among impoverished populations in developing countries such as Nicaragua, Brazil, India and Korea.[1–6]

Although an infrequent cause of acute renal failure (ARF) in developed countries, leptospirosis is reported as one of the leading causes (24%–32%) of ARF in Thailand and Singapore.[7] In developed nations leptospirosis is also a public health problem related to recreational activities and occupational exposure.[8]

The following have been described as additional factors that have contributed to the re-emergence of this zoonosis: disturbances in natural ecological niches resulting from construction practices and paving; irrigation of formerly dry land; changes in climatic patterns perhaps due to global warming; increase in international travel and improvement in diagnostic facilities. [9,10]

This review highlights the epidemiology of leptospirosis, recent advances on the pathogenesis of leptospirosis renal disease, clinical features and treatment of this resurgent zoonosis.

EPIDEMIOLOGY

Leptospirosis is distributed worldwide, except for the polar regions. The highest prevalence rates remain in the tropics.[9] Rodents have been recognized to be the most important and widely distributed reservoirs of leptospiral infection.[11] The usual port of entry is through abrasions or cuts in the skin, intact mucous membranes and possibly also through waterlogged skin. Humans usually become infected through contact with urine-contaminated soil or water.[11,12]

Incidence rates are likely underestimated partly due to lack of awareness of the disease and the lack of accurate tests to permit the rapid diagnosis of the disease. In endemic regions, symptomless leptospirosis presenting as a flu-like illness or subclinical infection are common.[13]

Leptospirosis cases have been underrecognized and frequently misdiagnosed, especially in dengue endemic regions of the Caribbean, India, South Asia and South America.[3,14–16] Early phase leptospirosis and classic dengue fever have overlapping clinical presentations.[15] Rapid urbanization and a lack of basic sanitation in the context of seasonal rainfall and flooding have produced favorable conditions for transmission of both diseases.[2,3]

In 1996, an urban epidemic in Salvador, Brazil involving 326 cases of severe leptospirosis due to *L. interrogans* serovar *Copenhageni* was identified after heavy rainfall and flooding.[10] Individuals at highest risk were the urban poor living in the slums or city's periphery, which lack basic sanitation. A concurrent epidemic of dengue apparently has contributed to misdiagnosis and consequently to late referrals and the high mortality observed during the leptospirosis outbreak.

A retrospective study of 1016 cases of leptospirosis admitted to a state

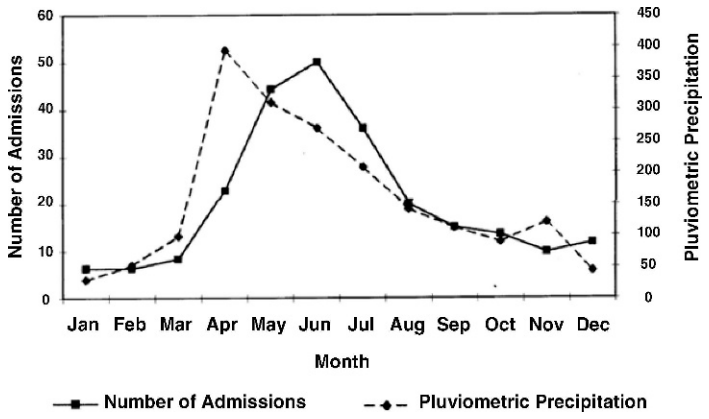

Fig 1. Monthly averages of hospital admissions due to leptospirosis and monthly averages of rainfall in the city of Salvador, from January 1993 to December 1996. Adapted, with permission from *Revista da Sociedade Brasileira de Medicina Tropical*. 2001;34(3):261–267 and the article's author.[17]

reference hospital for infectious diseases in Salvador, Brazil has shown that heavy rainfall and flooding antecede the outbreaks and that leptospirosis is associated with poverty (Figure 1).[17] Thus the presence of heavy rain and flooding indicate which resources should be allocated to prevent leptospirosis. In the study by Lopes et al, almost 94% of patients were Black or mixed race, the majority were male (81.1%) and among patients 18 years old or above, 92.7% had not graduated from high school. The majority (59.1%) had low paying jobs. Case fatality rate was 14.3% and acute renal failure was the attributed cause of death in 76.2%. Lopes et al have also demonstrated that in-hospital case fatality rate of leptospirosis is higher for adults than for children and adolescents and that among adults, older age was independently associated with higher risk of death.[18]

In the United States, leptospirosis is rarely reported.[19] The highest mean annual incidence rates has been detected in the state of Hawaii, Kauai island (7.9 cases per 100,000 population).[20] Seroepidemiological studies suggest that unrecognized urban cases of leptospirosis may represent a public health issue also in the United States. A study conducted in Detroit, Michigan, showed a high prevalence (≥30%) of leptospiral antibodies in inner-city children <6 years old.[21] A high seroprevalence (16%) of anti-leptospiral agglutinins has been described in the city of Baltimore.[22] Being aged <19 years and Black were independent risk factors associated with leptospiral antibody only in persons who did not own cats. Moreover, rodent-borne transmitted cases have been described in this Maryland inner city.[23]

Leptospirosis is a paradigm of an infectious disease for which globalization and worsening social inequalities have produced sharp contrasting epidemiological patterns for the poor and wealthy.[24] Cluster of cases have also been identified among the affluent who engage in recreational activities, sporting events, travel and adventure tourism.[8,13,19,25,26]

PATHOGENESIS OF LEPTOSPIROSIS RENAL DISEASE

Earlier experimental studies on vascular damage in guinea pigs inoculated with *L. icterohaemorrhagiae* have shown various degrees of capillary injury and necrosis of endothelial cells.[27,28] The proximal tubule is the location of leptospiral colonization and the renal involvement is characterized by an acute tubulo-interstitial nephritis.[29–32] Glomerular changes are usually not remarkable.[33]

The pathogenesis of the renal disease of leptospirosis is not completely understood. The data indicate, however, that inflammation plays an important role in the pathogenesis of leptospirosis nephropathy. In the acute phase of leptospirosis tumor necrosis factor-α (TNF-α) levels rise and are associated with the severity of the disease. A high IL10/TNF-α ratio is associated with a better prognosis, indicating that an anti-inflammatory response may be protective.[34]

The importance of the leptospira outer membrane (OM) antigenic and virulent components, especially the lipoprotein Lip 32 in the pathogenesis of tubulointerstitial nephritis has been recently described in experimental studies from Taiwan.[29,35,36] The addition of an OM protein preparation from *L. santarosai* serovar *Shermani* to cultured mice medullary thick ascending limb (mTAL) cells in vitro, induced an important nuclear DNA binding of the NF- κB transcription factor. A major increase in the mRNA expression of monocyte chemoattractant protein 1 (MCP-1), nitric oxide synthase (iNOS) and TNF-α, observed 48 hrs after the addition of the OM extract, has also been revealed by reverse transcription competitive polymerase chain reaction (RT-PCR).

Pathogenic leptospires may trigger an innate immune response through toll-like receptors 2 (TLR2) dependent pathway in renal epithelial cells.[30] In cultured murine proximal tubule cells, nanogram concentrations of leptospiral membrane protein preparation (LMLP) extracted from pathogenic *L. santarosai shermani* stimulates mRNA expression of neutrophil-chemoattractant chemokine CXCL1/KC.[37] Disturbances in activity of a variety of sodium cotransporters, exchangers, water channels and ATPase pumps have been described with conflicting results. [31,38–41]

Body fluid loss due to vomiting, diminished intake of fluids, massive gastrointestinal hemorrhage, and decreased intravascular volume caused by a shift from the intra- to extra-vascular space as a result of leptospirosis endothelial injury, may all be responsible for the development of hypovolemia, hypotension and pre-renal ARF, which may progress to acute tubular necrosis (ATN), if not promptly treated. Hypotension may also enhance cytoadherence and leukocytes migration as a result of modulation of adhesion molecules by variations in shear stress, which in turn, may potentiate organ damage.[42] Severe rhabdomyolysis has been cited as a potential cause of development of intrinsic ARF in leptospirosis.[43,44]

CLINICAL FEATURES

Clinical manifestations of leptospirosis range from a mild influenza-like illness to severe life-threatening disease forms, characterized by jaundice, renal failure, bleeding and severe pulmonary hemorrhage.[17] The vast majority of infections caused by leptospires are either subclinical or of very mild severity and patients will not seek medical care.[9,13]

Classic descriptions include a biphasic illness, with the acute or septicemic phase lasting about a week, followed by defervescence at 1–3 days.[9,11–13,45,46] During leptospiremia, organisms can also be found in cerebral spinal fluid (CSF) and most tissues.[9] The second or immune phase lasts for 4 to 30 days and is characterized by disappearance of the leptospires from the bloodstream, leptospiruria and the emergence of antibodies.[11,12,45] Weil's syndrome, seen in only 5%–10% of cases, represents the most severe form of the illness and may develop during the immune phase or present as a single, progressive disease.[47] Fever, chills, headache, prostration, nausea, vomiting, muscle tenderness more prominent in lumbar areas and calf, and conjunctival suffusion are common findings in acute leptospirosis. The latter two are considered the most distinguished physical findings.[9,11–13,45,46]

Renal involvement, the most serious complication, varies from sub-clinical course to severe ARF and accounts for the large proportions of death from leptospirosis.[2,9,46,48] Leptospirosis is unique among infectious causes of ARF in that patients frequently develop hypokalemia, natriuresis, kaliuresis, non-oliguria and even polyuria.[9,13,39,40,49]

TREATMENT

The initiation of effective treatment is recommended as soon as the diagnosis of leptospirosis is suspected and preferably before the fifth day of illness.[9,11–13,50–52] The World Health Organization and International Leptospirosis Society recommend that clinicians not wait for the results of laboratory tests before starting treatment with antibiotics, when clinical findings and epidemiological exposure history suggest leptospirosis.[53] Severe cases of leptospirosis should be treated with high doses of intravenous penicillin.[9,11,13,33,50–52,54]

There are conflicting data and inconsistencies regarding the benefit of introducing penicillin at the late stages of disease.[50–52,54] A randomized clinical trial conducted in Salvador, Brazil has shown that the use of penicillin after four days of symptoms of severe leptospirosis did not reduce the probability of death and necessity for dialysis treatment.[51] The only randomized clinical trial that has reported benefit with penicillin treatment late in the course of illness was the study conducted by Watt et al.[54] In addressing this question, this placebo-controlled trial of intravenous penicillin for severe and late leptospirosis has shown that late treatment reduced fever, duration of elevated creatinine, shortened hospital stays and prevented leptospiruria.

The Centers for Disease Control and Prevention recommends that patients with mild cases be treated with doxycycline 100 mg orally twice daily for seven days, and those admitted to a hospital because of persistent fever, hepatic or renal failure or severe neurologic disturbance be treated intravenously with penicillin G, 1.5 million units every 6 hours for 7 days.[55] Jarisch-Herxheimer reactions following treatment with penicillin have been rarely described and has not been considered a reason to preclude prompt treatment.[9,11,12,45]

Supportive treatment for dehydration, hypotension, hemorrhage, ARF and respiratory failure are required. Short-term peritoneal dialysis (PD) has been widely employed in developing countries for the treatment of ARF due to its availability, ease of administration and technical simplicity in a resource-poor context.[12,50,56]

Chemoprophylaxis

When high-risk and short-term exposure to leptospira is anticipated, chemoprophylaxis is effective.[8,13,57] Doxycycline prophylaxis does not prevent leptospiral infection in endemic areas, but has a protective effect in reducing morbidity and mortality during outbreaks.[13]

CONCLUSION

It is of crucial importance that a high index of suspicion and increasing alertness of leptospirosis be maintained in endemic areas so that timely therapy can be administered to patients. The continued elucidation of pathogenetic mechanisms of the disease should lead to improved patient treatment and the development of efficient diagnostic tests and vaccines. Determinants of poverty, such as poor sanitation, as well as the issues of global warming, which may lead to climate changes, should be promptly addressed by policy makers around the globe.

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