

LEPTOSPIRAL INFECTION

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ABSTRACT

Leptospirosis is a zoonotic infection that occurs globally and the most widespread zoonosis in the world. Humans usually become ill after contact with infected urine, or through contact with water, soil or food that has been contaminated with leptospira organisms which come from rodents and domestic animals. Tropical countries such as Malaysia would provide a conducive environment for the survival and spread of leptospiral infection because of its climate is warm and wet throughout the year. There are no precise estimates of the human leptospirosis cases due to it is a challenging to diagnose. This is due to a) it is often presents as a non-specific presentations at the early phase such as fever, severe headache and myalgia, b) frequent cause of undifferentiated febrile illness in developing countries and c) misdiagnosis in regions where dengue and other infectious diseases with overlapping presentations are endemic. The illness may progress to kidney or liver failure, aseptic meningitis, life-threatening pulmonary haemorrhage and other syndromes. The mortality rate of leptospiral infection is dependent on many factors for example: old age, multiple underlying medical problems and nutritional status. In addition, inadequate laboratory test remains the major barrier for diagnosis and epidemiologic surveillance. Therefore, the Malaysian government should continue to work out measures to tackle this infection so that its incidence does not continue to rise. Furthermore, it is necessary to reinforce on step to be taken by general public to control of leptospirosis by practicing hygienic measures and rodent control around their own premises. The control of this disease is largely dependent on our action to prevent it since an effective human vaccine is still not available.

Keywords: leptospirosis, zoonotic, leptospiral infection

INTRODUCTION

Leptospirosis is a zoonotic infection that occurs globally and the most widespread zoonosis in the world. It is a bacterial infection caused by a species of pathogenic leptospira genus called Spirochaetes (Paul, 2001). Different serogroups predominate in different countries but icterohaemorrhagiae is encountered in the majority of countries. Generally there is a higher incidence of leptospirosis in tropical countries (Sarkar, Chopra, Katageri, Raj, & Goel, 2012) and Malaysia is one of it because of its climate is warm and wet throughout the year favours the growth of pathogenic Spirochaetes (Mohammad Jalii, 2000). According to (WHO, 2003) incidences range from approximately 0.1–1 per 100 000 per year in temperate climates to 10–100 per 100 000 in the humid tropics. Disease incidence may reach over 100 per 100000 during outbreaks and in high-exposure risk groups. Adolf Weil described leptospirosis as a disease entity in 1886. His name is still attached to a serious form of leptospirosis called Weil's disease, traditionally attributed to rat-transmitted infection caused by the serovars icterohaemorrhagiae and copenhageni (WHO, 2003).

In Malaysia, leptospirosis is an old disease as the very first case of human leptospirosis was discovered by Fletcher in the year 1925. According to the statistics from the Ministry of Health the number of cases continues to increase significantly from 2004 to 2009 with 263 cases and 20 deaths in the year of 2004, to 1418 cases and 62 deaths in the year 2009 (Lim, 2011) as shown in Table 1. Since flooding occur frequently especially at the end of each year, Malaysians are always at risk of exposure to water and soil contamination with the urine of rats (Lim, 2011). Mohamed el-Jalii (2000) in his research has identified that human leptospirosis is an endemic infection in Malaysia. Additional risk factors include occupational exposure, recreational activities, and residence especially in poor urban slum communities or travel in countries where the organisms are common in the environment. Organisms are shed in the urine of infected animals, including rodents and domesticated animals, which may not show signs of disease. Humans usually become ill after contact with infected urine, or through contact with water, soil or food that has been contaminated.

Table 1 showed an apparent increase in leptospirosis cases which could be due to several reasons such as an actual rise in the number of cases, increased awareness and diagnosis, reporting, and laboratory capacity.

CAUSAL AGENT

Leptospirosis is caused by various species of *Leptospira*, a spirochete in the family Leptospiraceae, order Spirochaetales. Some *Leptospira* are harmless saprophytes (free living and generally considered not to cause disease) that reside in the environment, while others are pathogenic (having the potential to cause disease in animals and humans). Pathogenic leptospire are maintained in nature in the renal tubules of certain animals.

Pathogenic leptospire belong to the genus *Leptospira* and the basic unit of *Leptospira* taxonomy is the serovar. It is a long corkscrew-shaped bacteria and too thin to be visible under the ordinary microscope. Therefore, a dark-field microscopy is required. Serovars consist of closely related isolates based on serological reactions to the organism's lipopolysaccharide. More than 250 pathogenic serovars, and at least 50 nonpathogenic serovars, have been identified (Levett, 2013). Pathogenic bacteria are generally from the leptospira interrogans genomospecies and there are eleven detected species of leptospira while thirty-seven serovars are found from wildlife and humans in Malaysia (The Leptospirosis Information Centre, 2010). According to Elisa & Case (2003) there is more than 240 pathogenic serovars still cannot be differentiated on the basis of morphology (Elisa & Case, 2003).

RISK OF INFECTION

There is a risk of infection when an individual have contact with infected animals or soil/water where the bacteria are present. It can be divided into three categories which are a) people who involve with handling animals or animal products such as farmers, veterinarians, animal caretakers, dairy farmer and slaughterhouse workers; b) people with frequent contact with contaminated environments such as sewer workers, coal miners, plumbers, workers in the fishing industry, members of the military; c) people who involve with outdoor water activities or recreational activities such as swimming, water sports, picnic, gardening at the infected area will expose an individual to a high risk of infection too. Several outbreaks have occurred in recent years among triathletes; and d) people who live in areas/premises where sanitation is poor and exposed through rat's urine.

Table 1: Cases of Leptospirosis in Ministry of Health Hospitals, Malaysia from Year 2004 to 2009

No	State	Year					
		2004	2005	2006	2007	2008	2009
1	Perak	29 (4)	71(4)	93 (9)	149 (3)	289 (16)	280 (19)
2	Selangor	16 (5)	20(3)	37	93	97 (2)	208 (7)
3	Pahang	29 (1)	24	51(3)	184 (3)	198 (7)	184 (5)
4	Kelantan	15 (1)	38 (1)	17 (1)	81(1)	180 (4)	138 (4)
5	Terengganu	7(1)	17	42(1)	55(3)	107 (4)	126 (9)
6	Kedah	15 (1)	27	31	28 (1)	52 (2)	106 (9)
7	N. Sembilan	27(1)	41	24	49	59	91
8	Sarawak	32 (2)	42 (2)	37 (3)	46 (1)	58 (5)	70 (4)
9	Johor	30 (1)	29 (6)	31 (2)	115 (2)	87 (3)	59 (3)
10	WP KL	31	20 (1)	27 (1)	31	45	54
11	Sabah	13 (1)	12 (1)	19	41 (2)	34 (2)	35 (1)
12	P. Pinang	9	25 (1)	28	37	25 (2)	32
13	Melaka	7 (1)	9 (1)	79 (2)	32 (1)	25	20 (1)
14	WP Putrajaya	1	1	7	3	1	14
15	Perlis	2(1)	2	4	5	6	1
16	WP Labuan	0	0	0	0	0	0
Total		263 (20)	378 (20)	527 (22)	949 (22)	1263 (47)	1418 (62)

() Death

Source:

Report of Morbidity and Mortality for Patients for The Year 2004 to 2009,
Health Management Information System, Medical Care Subsystem,
Health Informatics Centre, Planning and Development Division, Ministry of Health, Malaysia

MANIFESTATIONS

Most cases of leptospirosis are asymptomatic or mild. Usually an infected individual does not show any manifestation in less than 24 hours unless the volume of bacteria invading the body is higher than the usual volume (The Leptospirosis Information Center, 2011). The incubation period for leptospirosis is normally 5-14 days and within a range of 2-30 days (World Health Organization, 2003). The overall case fatality rate is estimated to be 1–5%, but varies with the form of the disease, the health and age group, the availability of medical care and other factors.

Human infections vary from asymptomatic to severe. Asymptomatic infections are common (up to 60-70%) in endemic areas. The infection normally systemic and infects the whole body. The usual presentation is an acute febrile illness with headache, and myalgia which typically affects the back, thighs or calves (often severe) that may not be recognized as leptospirosis. Other common manifestations include nausea, vomiting, abdominal pain, diarrhoea, and arthralgia. Due to this non-specific clinical presentation, leptospirosis remains a much underdiagnosed illness especially in developing countries (Sarkar et al., 2012). The infection also has been misdiagnosed as other infections including dengue, typhoid, hepatitis, influenza, meningoenzephalitis, yellow fever and malaria especially when these diseases are endemic at that point of time.

Generally, there are two types of infection that portray different manifestations, which are anicteric leptospirosis and icteric leptospirosis (Center for Food Security and Public Health, 2005 & Centers for Disease Control and Prevention, 2011). Ninety percent of cases are anicteric leptospirosis, which means that jaundice does not occur in this infection. Patients who suffer from anicteric leptospirosis infection undergo stage 1 and stage 2 of the illness. (The Leptospirosis Information Centre, 2010; Centers for disease control and prevention, 2011). In anicteric form of leptospirosis, the illness is always related with aseptic meningitis. (Centre for food Security and Public Health, 2005). This syndrome is characterized by a severe headache, stiff neck and other meningeal symptoms, and typically lasts a few days (Center for Food Security and Public Health, 2005). This less severe type of leptospirosis is rarely fatal but is associated with pulmonary haemorrhage even without jaundice and may lead to death.

The first stage of infection is also known as acute or septicemic phase, flu-like symptoms such as severe headache, sudden fever of 39°C and above, eyes inflammation, muscle aches, diarrhea, fatigue, nausea and vomiting, chills, rigors and maculopapular rashes are seen (Saunders, 1979). This stage of infection usually lasts several days to approximately a week, and is followed by a brief remission, during which the temperature drops and the symptoms abate or disappear. If the manifestations last around 3-5 days, the patient is said to have recovered. At this point there are many individuals recover completely.

Individuals who do not recover enter the second stage or called as the immune phase because anti-Leptospiral antibodies develop at this time. At this stage anti-Leptospira antibodies starts to multiply such that organisms of leptospirosis can be found in the patient's urine excretion. Infected patients fall sick again lasting for up to 30 days or more (Center for Food Security and Public Health, 2005).

Ten percent of cases develop into icteric leptospirosis which is more severe and known as Weil's syndrome (Madhu et al., 2008; Center for Food Security and Public Health, 2005 & Centers for Disease Control and Prevention, 2011). It occurs in 5–10% of all patients, is often rapidly progressive, and may be associated with multiorgan failure. This fatal infection tends to prolong the period of severe fever, jaundice, azotemia, hypotension as well as haemorrhagic vasculitis (Madhu et al., 2009). There may be no period of improvement between the septicemic and immune phases. The most commonly involved organ systems are the liver, kidneys and central nervous system. Within 10 days, most of the important organ and system are harmed such as liver, kidneys, brain, heart and central nervous system.

MODES OF TRANSMISSION

Leptospira are excreted in the urine of both acutely and chronically infected animals. Many animals can spread leptospirosis including pets, farm or wildlife animals. The animals constitute the reservoir of the agent and commonly spread leptospirosis are rodents, raccoons, cattle, swine, dogs, horses, sheep, goats and buffaloes. Rodents are known as the main source of spirochetes that are transmitted to humans. In Leptospirosis, humans are known as “dead-end” hosts because the spreading of infectious bacteria between human and human or human and animal never happens (Mohammad Jalii et al., 2000; & Khairani et al., 2006).

Pathogenic Leptospira do not multiply outside the host. In the environment, they require high humidity for survival and are killed by dehydration or temperatures greater than 50°C (122°F). These organisms may remain viable in the environment for several months under optimal conditions, for example; in water or contaminated soil. They survive best in bodies of water that are slow-moving.

Leptospiral can be transmitted either directly or indirectly from hosts in the contaminated environment (Paul, 2001). Indirect transmission are by: a) excretion of urine from the animal host causes the soil and water to be contaminated; and b) contaminated water or food is ingested by humans who then later become infected (Ann Florence, 2009); c) it might also be able to penetrate intact skin that has been immersed for a long time in water, although this is controversial (Levett, 2013). The organisms usually enter the body through mucous membranes or abraded skin.

The direct transmission is when the Leptospire invade the body when in direct contact with Leptospire through cuts as well as wounds (Centres for Food Security and Public Health, 2005). It also enters the human body through nasal, oral and conjunctiva mucosa if humans are in contact with contaminated water for a long period of time (Centre for Food Security and Public Health, 2005). According to Adnan (2010) evaporation of urine containing Leptospire into air droplets can be inhaled by humans and thus cause infection too. After penetrating the human body, Leptospire then pass into the blood stream and from the blood stream the Leptospire attacks body tissues and organs. Colleen (2010) states that generally reasons related to the rising of infection are due to occupational exposure, poor sanitation, climate changes, recreational activities as well as management of wild animals.

DIAGNOSTIC TEST

A patient is suspected to acquire leptospirosis when experiencing symptoms for about 1-2 weeks after exposure to the urine of the carrier animals (Lim J K, Murugaiyah V A, Ramli A, Abdul Rahman H, Mohamed N, Shamsudin N, 2011). In humans, Leptospira may be found in the blood, cerebrospinal fluid, urine or tissue samples. Leptospira bacteria can be isolated from blood, urine or cerebrospinal fluid (CSF) during the first phase of the illness. The tests used are similar to those employed in animals, and include immunofluorescence and immunohistochemical staining, polymerase chain reaction (PCR), culture and microscopy (Levett, 2013).

This disease can be confirmed through blood tests to detect the presence of leptospira bacteria. In many cases, leptospirosis is diagnosed by serology, especially the microscopic agglutination test (MAT) or immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) (Washington State Department of Health, 2011). Presumptive diagnosis can be made when a positive result of a rapid screening test such as IgM ELISA, latex agglutination test, lateral flow, dipstick etc.

However, the diagnosis is confirmed when a positive PCR result using a validated method (primarily for blood and serum in the early stages of infection). Fourfold or greater rise in titre or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart (Washington State Department of Health, 2011). Microscopic agglutination test is a *gold standard* of serodiagnosis – unsurpassed diagnostic (serovar/serogroup) specificity in comparison with other available tests due to its sensitivity is 92% and specificity 95%. However, it unable to differentiate between agglutinating antibodies due to current, recent or past infections.

Other than that, urine analysis is also reliable. If a urine test gives a positive result during the second week of illness and continues on up to 30 days, the patient is confirmed to have leptospirosis. According to WHO (2003), the samples that are useful and most commonly collected are:

- a) Blood for culture in the first 10 days with heparin to avoid clotting. After 10 days leptospire have mostly disappeared from the blood and antibodies will have become detectable in the serum allowing serodiagnosis.
- b) Clotted blood or serum for serology. These should preferably have collected twice at an interval of several days based on the date of onset of disease.
- c) Urine for culture. Leptospire die quickly in urine. The use of urine for culture may be of value only when a clean sample can be obtained and inoculated into an appropriate culture medium not more than 2 hours after voiding. Survival of leptospire in acid urine may be increased by making it neutral.
- d) Postmortem samples. It is important to collect specimens from as many organs as possible, including the brain, cerebrospinal fluid, aqueous humour, lungs, kidney, liver, pancreas and heart, as well as heart blood, if possible, for serology.
- e) Cerebrospinal fluid and dialysate for culture.

Despite there are many laboratory tests that can be done to confirm leptospiral infection, the major challenge to diagnose it is when the laboratory tests is not always available especially in developing countries (WHO, 2003).

TREATMENT

Leptospirosis can be treated only if it is diagnosed early to avoid complication. Untreated patient can lead to a more severe and potentially fatal stage. Usually it is treated by primarily using antimicrobial therapy. Treatment with antibiotics is started before confirming if a patient has leptospirosis. This is because test and diagnosis may take a long time to process and the condition of the patient can become more serious if they continue to wait. Doxycycline is an excellent choice of initial antimicrobial treatment for an individual (Phimada, 2007). Sandara (2011) reinforced that it is important for patients to be managed in a monitored setting because their condition can rapidly progress to cardiovascular collapse and shock.

PREVENTION AND CONTROL MEASURES

Leptospirosis is a disease an unlikely candidate for eradication due to the large number of serovars, infection sources and the wide difference in transmission conditions. Due to that preventive measures must be taken seriously. Preventive measures should be based on

knowledge of those groups at higher risk of infection and of local epidemiological factors. According to (Elisa & Case, 2003) it includes:

- a) Identifying and controlling the source of infection for example open sewers and contaminated wells.
- b) Defined animal populations such as dog and rodent control due to control of wild reservoirs is often complicated and not feasible.
- c) Interrupting transmission to prevent infection or disease in the human host by: a) wearing protective clothes and equipment such as glove, face shield and rubber boots; b) disinfecting contaminated surfaces such as table and abattoir floors; c) placing warning signs at the areas with increased risk exposure; d) avoid contact with animal urine or body fluids especially there is a cuts or abrasion on the skin; and e) do not swim in, walk in or swallow water that may contain animal urine (CDC, 2011).
- d) Preventing infection or disease in human hosts includes: a) starts on antibiotic prophylaxis such as doxycyclin 200mg in one weekly dose) of exposed persons in areas of high exposures may be effective, example, for soldiers and b) raising awareness of the disease and it's of modes of transmission.
- e) Practicing good sanitation. As rats are the major hosts of these bacteria, one of the steps to control this disease is by controlling the rat population. Therefore, practicing good sanitation can control the rat (CDC, 2011). Improvements in sanitation reduce the risk of leptospirosis in urban slums. Environmental modifications such as draining wet areas may decrease the incidence of disease.
- f) Practicing good personal hygiene such as thoroughly wash hands and arms in soapy water before eating, after handling animals or carcasses, or after coming into contact with liquids that may be contaminated and shower thoroughly after contact with potentially contaminated water or soil.
- g) Provide vaccination to high risk individuals. However, human vaccines are available in a limited number of countries. In addition, immunization protects only against the serovar in the vaccine or closely related serovars, and regular boosting is required.

Guidelines for the Diagnosis, Management, Prevention and Control of Leptospirosis in Malaysia (2011) by Ministry of Health reinforced the prevention and control should be targeted at 3 different sources, which are: a) the infection source; b) routes of transmission between the infection source and human host; and c) prompt and proper treatment of infection.

The Malaysian government has taken the first step in order to create awareness and health education activities among the healthcare personnel and public regarding the leptospirosis disease and its prevention which includes in service training, guidelines, seminar, media, articles etc. Besides, strengthening laboratory capacity is important for early and accurate diagnosis. Therefore, prompt treatment can be given to the patient. Surveillance for leptospiral infection is important and by sharing the finding it is easy to strategized control & preventive measures such as *e-Notifikasi*. Today, with the *One Health* approach its facilitate to bridge the medical, veterinary professionals and related agencies in the control and prevention of

leptospirosis, for example early & prompt treatment, livestock's farms, garbage disposal, institutional hygiene, recreational areas sanitation and research.

Prevention and control measures by Ministry of Health in relation with leptospiral infection can be referred to these examples of guidelines and circular: a) Ministry of Health. Guidelines for The Diagnosis, Management, Prevention and Control of Leptospirosis in Malaysia. 2011; b) Ministry of Health. *Garispanduan Pemeriksaan Kesehatan Persekitaran Kem PLKN Jabatan Latihan Khidmat Negara*. 2008 and c) *Surat Pekeliling Ketua Pengarah Kesihatan Malaysia Bil. 33/2010: Pemberitahuan Pewartaan Penyakit Leptospirosis Sebagai Penyakit Yang Perlu Dinotifikasi Di Bawah Akta 342, Pencegahan Dan Pengawalan Penyakit Berjangkit 1988*.

CONCLUSION

Leptospirosis is a zoonotic infection that occurs globally and the most widespread zoonosis in the world. It is caused by various species of *Leptospira*, a spirochete in the family Leptospiraceae. Some *Leptospira* are harmless saprophytes while others are pathogenic. Humans usually become ill after contact with infected urine, or through contact with water, soil or food that has been contaminated with leptospira organisms which come from rodents and domestic animals. Leptospiral can be transmitted either directly or indirectly from hosts in the contaminated environment (Paul, 2001).

Most cases of leptospirosis are asymptomatic or mild. The incubation period for leptospirosis is normally 5-14 days and within a range of 2-30 days. Asymptomatic infections are common and up to 60-70% in endemic areas. The infection normally systemic and infects the whole body. Due to that, the infection also has been misdiagnosed as other infections including dengue, typhoid, hepatitis, influenza, meningoencephalitis, yellow fever and malaria especially when these diseases are endemic at that point of time. Generally, there are two types of infection that portray different manifestations, which are anicteric leptospirosis and icteric leptospirosis.

Leptospirosis can be treated only if it is diagnosed early to avoid complication. Early detection can reduce the morbidity & mortality risks too. Untreated patient can lead to a more severe and potentially fatal stage. Usually it is treated by primarily using antimicrobial therapy. In humans, *Leptospira* may be found in the blood, cerebrospinal fluid, urine or tissue samples and the laboratory test involved are such as MAT, PCR and ELISA's. Human infections vary from asymptomatic to severe.

Even though there are antibiotics that can be used to treat the disease, taking steps to prevent and control the infection is still the best option. The actions are such as identifying and controlling the source of infection, interrupting transmission to prevent infection or disease in the human host, and practicing good sanitation and good hygiene. Perhaps with the step that have been taken by the Malaysian Government may reduce the number of cases and death due to leptospiral infection. Besides, the prevention and control of this disease is also largely dependent on the community to prevent it especially practicing good hygiene at their residents or premises. Prevention is the best since an effective human vaccine is still not available. After all, prevention is better than cure.

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