



Leptospirosis

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Abstract

Background: Leptospirosis disease has been recognized for decades, particularly in resource-poor, developing countries. Outbreaks have been associated with flooding and natural disasters. Leptospirosis is transmitted by direct or indirect contact with urine of infected animals. Other sources of exposure include blood, fluids, or tissues of parturition of infected animals. Diagnosis requires a high manifestation of suspicion based on clinical presentation associated with epidemiological exposure. Affected individuals can present with an extensive spectrum of clinical manifestations ranging from subclinical illness to renal and hepatic failure and pulmonary haemorrhages. Disease can be presented in two phases, the initial phase and the immune phase. Treatment of disease includes usage of antibiotics such as penicillin-G and Doxycycline along with supportive therapy. Alternative therapeutic agents include Cephalosporins and traditional medicines. Prevention and controls of Leptospirosis should be targeted at the source of infection, the route of transmission between infection sources and the human host; or infection of disease in the human host. Personal and environmental hygiene should be emphasised by the high risk groups where preventive measures should be taken.

Conclusion: The studies of etiology and epidemiology of Leptospirosis has led to the development of effective preventive strategies. Recent advances in the molecular biology of Leptospire offer the prospect of more rapid progress in the future.

Introduction

Leptospirosis is recognized as an emerging and re-emerging disease of public health problem in a number of countries of South-East Asia (SEA) region and it occurs regularly in tropical and subtropical areas with high rainfall. [1][2][6][12] Flash flooding is reported frequently from these countries which is responsible for Leptospirosis epidemics in past two decades. For instance, outbreaks of Leptospirosis have often been reported from coastal areas of India, Sri Lanka, Indonesia and Thailand. [6][7] As in Malaysia, Leptospirosis had been discovered in the year 1925 by a scientist named Fletcher W. Later on, numerous and continuous researches have been conducted in

Malaysia as to investigate the causes of infection and also to figure out the ways of treatments. [14]

The first description of Leptospiral infection in human was made by Landouzy' in 1883 but it remains until 1886 where Adolf Weil was to clearly separate Leptospiral jaundice from a heterogeneous group of infections associated with icterus. [4] Adolf Weil's name is still attached to a severe form of Leptospirosis called Weil's disease, conventionally attributed to rat transmitted infection caused by the serovars icterohaemorrhagiae and copenhageni. At present, it is preferable to refer to all Leptospire infections as Leptospirosis regardless of clinical symptoms and signs. [2][4]

Leptospirosis, commonly known as "rat-urine fever" in certain countries, is caused by infection with pathogenic spirochetes of the genus *Leptospira* and it is transmitted directly or indirectly from animals to humans. [1][2] The disease is found mainly when human come into contact with carrier animals or environment contaminated with Leptospire. Although rats and other rodents are the primary hosts, a wide range of other mammals including dogs, cattle, sheep, and pigs also carry and transmit the disease as secondary hosts. [3][6][7]

Humans get infected through skin contact with water or soil containing urine from infected animals or by consuming contaminated food or water. Human-to-human transmission is rare to occur. [3][7][12][14] Leptospirosis is usually a biphasic illness where the first phase is called the acute or septicaemia phase and the second phase as immune phase. [5][6]

Etiology And Microbiology

The classification of Leptospire is based on serological analysis of the antigens of Leptospire. [9][10] Each serovar has a characteristic antigenic make-up. Serovars having antigenic similarities are formed into serogroups, and over 200 pathogenic serovars divided into 25 serogroups have been verified. [2][7][8] Pathogenic serovars are now found in the species such as *Leptospira interrogans*, *L. noguchii*, *L. weilii*, *L. fainei* and *L. alexanderi*. The two classification systems based on the serovar and species can be confusing as a serogroup can have strains belongs to different species. [9]

Leptospirosis is caused by various species of

Leptospira (genus). Leptospire is an aerobic spirochete whose cells are flexuous, motile, tightly coiled and have axial flagella. [8][9][10] They differ from other spirochetes by the presence of end hooks. [2] In general, the bacteria are about 0.1µm in diameter and 10-20µm in length. They are gram negative and there is no visual difference between serovars. They appear as a chain of dots instead of a continual structure with their rapid rotation under visible light. They are propelled by two flagella as well. The capability of Leptospire to move fast through water is vital to their life cycle, as they need to spread out in order to maximise the chance of infecting a new host. [7][8][10] Several Leptospire are pathogenic, although others are harmless freshwater saprophytes. Pathogenic Leptospire are found in nature in the renal tubules of certain animals whereas Saprophytic Leptospire are found in settings of wet or humid environments. [2][7][8][12]

Mode Of Transmission

Leptospirosis is an infectious disease caused by pathogenic bacteria called Leptospire. [2] Both humans and animals can get infected with Leptospirosis. [12] Leptospirosis can be transmitted both directly between hosts and indirectly in the environment. Humans can be infected with Leptospirosis when they come into contact with the urine of infected animals or a urine-contaminated environment, such as soil and water. [12][2] Animals that can cause or transmit the disease are such as rodents, cattle, dogs and pigs. [12] There are also other possible modes of transmission of infection such as managing infected animal tissues and ingestion of contaminated food or water. [10][15][16]

Leptospire can invade into humans through cuts and abrasions in the skin, intact mucous membranes (nose, mouth, eyes) and conceivably through waterlogged skin. [2][7][8][9] Besides, for special cases, they may enter the human body via the inhalation of droplets of urine. [14][15][16] 30-50% of the cases are due to the occupational exposure.

Infection In Humans

In order to cause an infection, *Leptospire* have to gain entry into the bloodstream. [2][7][8] After entering the bloodstream, systemic infection can develop very rapidly. However, *Leptospire* grow very slow. [8] The incubation period can be between 2-30 days, typically ranging between 5 and 14 days. [2]

Incidences of human-to-human transmission are seldom to occur. They can be transmitted from human to human by sexual intercourse, the mother to the foetus through placenta and via breast milk to a child. There are also examples of human cases where transmission occurred as a result from rodent bites or after laboratory accidents. [2][7][9][16]

Clinical manifestations

Leptospirosis in human is a biphasic infection, meaning that the disease develops in two phases. [2][5][6] The first phase is known as the acute or septicaemia phase. This phase usually starts unexpectedly and lasts around a week. This phase is featured by nonspecific signs such as fever, chills, conjunctiva suffusion and headache. Besides, patients will also experience myalgia. Other symptoms such as mental confusion, nausea, abdominal pain, temporary skin rash, cough and minor haemoptysis may be observed as well. In some severe infections, even symptom like jaundice can be diagnosed. [5][6] All these symptoms last for around 4 to 9 days. Then, drop in temperature and fading away of the symptoms are typically observed in the following 1 to 3 days. [2][9][10][18]

The second phase of Leptospirosis is known as the immune phase. This phase is featured by the development of antibodies for *Leptospire* and the excretion of the bacteria in the urine. [5][6] This phase does not occur in all patients and can last up to 30 days. The patient becomes sick again during this phase. Those symptoms in the first phase, such as fever and myalgia, reoccur but with less severity. [9][10]

Leptospirosis is seen in two forms, icteric and anicteric. [9] To make it simple, it means Leptospirosis with jaundice (icteric) and without jaundice (anicteric). Most of the infections are of the anicteric form and the icteric form is more serious than the anicteric form. In general, deaths are rare in the anicteric form. The icteric form of disease occurs in 5-10% of all patients. This form progresses rapidly and is related with multi-organ failure (liver, kidneys and central nervous system). Kidney failure, cardiac involvement (congestive heart failure, myocarditis and pericarditis), pulmonary haemorrhage and other serious organ dysfunction can cause deaths. [2][8][9]

Infection In Animals

All mammals are subjected to Leptospirosis. [9] Rodents are the main reservoir hosts for most serovars while domestic animals such as cattle, dogs,

pigs and sheep are known to be the secondary hosts. The infections of Leptospire in animals are asymptomatic in most of the time. [2][7][9] They usually show unobvious effects after the infection with a particular serovar. However, disease may develop after infection with another serovar. [2] The clinical signs are usually associated to kidney disease, liver disease or reproductive dysfunction. Most dogs recover after two weeks if treatments are given. However, severe damage of kidney or liver can be fatal. [9]

Epidemiology

Internationally, there are up to 80% of individuals in tropical areas estimated to have positive seroconversion rates, indicating either past or present infection. [10] While in Malaysia, statistical data had shown that there are large numbers of cases of Leptospirosis infection during 1925. Table 1 showing the number of cases of Leptospirosis in Malaysia from year 2006 to 2009 was constructed as according to the investigations conducted by Ministry of Health of Malaysia.

Yet, morbidity of Leptospirosis is not clear as Leptospirosis is thought to be under-diagnosed and underreported. This is because many cases are mild or asymptomatic. [9] Besides, Leptospirosis is easily confused with other diseases as its symptoms are nonspecific and diverse. [2] On the other hand, from all cases that have been reported, the mortality rate of Leptospirosis is observed to range from [2] In addition, the mortality rate varies with the form (icteric or anicteric), and elderly has higher mortality rate. [9][18] Risk groups are certain groups of humans in a population that are more likely to be exposed as a result of either occupational or recreational activities.[16] Since there are a large number of potential sources of infection and many different opportunities for transmission, risk groups may differ from one area to another. Occupations with a high risk of infection include sewer workers, coal miners, plumbers, farm workers, veterinarians, pet shop owners, abattoir workers, meat handlers, slaughterhouse workers, workers in the fishing industry, and the military.[2][9] Recreational activities that increase the risk of Leptospirosis include gardening and water sports such as canoeing, swimming and white-water rafting. Residents of some urban areas are exposed to Leptospirosis via rat urine. [2][8][9][16] The epidemiology of Leptospirosis is dynamic. [2] New risk groups may be formed as a result of changes in agricultural and social practices,

or in reservoir animal populations in an area. [2][9] Studies also revealed that males are having higher tendency to suffer from Leptospirosis than females because of greater occupational exposure to infected animals and contaminated environment. [18] Gender difference in susceptibility is not obvious under conditions where both men and women are at equal risk.[18] People in 20-30 years of age group are prone to Leptospire infections as compared to young children and infants, most probably, because of minimal exposure. [10][18]

Diagnosis Test

Generally, in most cases of human infection, diagnosis based on clinical symptoms is complicated and imprecise, thus the only assured diagnoses can be those based on serology tests such as MAT, ELISA and PCR. [1][2][8] Early diagnosis of Leptospirosis is crucial since antibiotic therapy provides greatest benefit when initiated early in the course of illness. In humans, the diagnosis of Leptospirosis starts by culturing the Leptospire from infected blood, spinal fluid, or urine and the detection of antigens or nucleic acids. Culture can be complicated and may require up to 13 to 26 weeks. [7][9][15]

Identification to the species' serogroup and serovar level is accomplished by reference laboratories, using genetic (DNA probes and polymerase chain reaction (PCR) techniques) and immunologic techniques. [2][7][8][9] Darkfield microscopy can be used but it is not specific. MAT is only performed in reference labs and requires acute and convalescent samples for diagnostic confirmation. [8][9] The test is serogroup but not serovar specific, and can be convoluted by cross-reactions. [9] Conversely, tests such as complement fixation, radioimmunoassay, immunofluorescence, counterimmunoelectrophoresis and thin layer immunoassay are less frequently used. [2][7]

Treatments

Modern medicinal treatment

Basically, treatments for acute or severe illness in humans can be categorized into two fractions- with the application of antibiotic to control the bacteria and general support of the patient's internal organs with close monitoring of serology, renal, hepatic and cardiac function in order to maintain their ability to recover while the bacteria are removed. [2][15]Leptospirosis can be treated by a broad range

of antibiotics consist of Doxycycline, Ampicillin, Amoxicillin, Penicillin and Erythromycin, therefore practitioners will decide on the most appropriate antibiotics based on availability, the patient's age and any other medications they might be consuming. [8] In mild cases, the medication will be given orally to the patient, however for severe infections; the antibiotics are administered intravenously and thus require patients to be hospitalized. [8][10][5] This is essential to monitor their health status as the infection progresses. [10][14][15][16]

Antibiotics

Treatment with proper antibiotics should be initiated as soon as the diagnosis of Leptospirosis is suspected and preferably before the fifth day after the onset of illness. Nevertheless, most clinicians treat the patients with antibiotics despite of the date of onset of the illness. [2][7] In most of the cases, penicillin is used. However, several alternatives are still accessible if the patient is allergic to it. [8] It is vital to take antibiotics as prescribed by finishing the full course of medication. Stopping a course of antibiotics before it ends can lead to arising of resistant bacteria and causing very severe illness. [8] Early antibiotic intervention is the major factor in recovery, and any delays while pending test results can be critical. [1][8][10]

In mild to moderate cases, oral antibiotics such as Amoxicillin, Ampicillin, Doxycycline or Erythromycin can be used, with consideration of contraindications and age limits. [2][7][9] Oral Doxycycline has shown to decrease duration of fever and most symptoms of Leptospirosis. [10] Besides, a recent clinical trial reviewed that third-generation Cephalosporins such as Ceftriaxone and Cefotaxime are as effective as Doxycycline and penicillin in the treatment. [10] Cephalosporins are known to be rather effective but the primary drug of choice is always penicillin. [13][18]

Severe cases of Leptospirosis should be treated with high doses of intravenous penicillin G therapy. [7] Severe liver and kidney manifestations of the infection may occasionally involve intensive medical care and dialysis treatment. Adult dose is 5MU to 8MU per day for five days. In patients with penicillin allergy, a course of erythromycin can be used at 250mg QID for five days. [8] A Jarisch-Herxheimer reaction can sometimes triggered by penicillin therapy; but the risk balance is acceptable and should not provoke discontinuance. [8] Leptospire are usually resistant to Vancomycin, Chloramphenicol, Rifampicin and Metronidazole. [2][8][9][18]

Below is a Table 2 showing the summarization of treatment and prevention of Leptospirosis by

drugs.[6][17][18]

Traditional Treatment

The early stage of Leptospirosis follows a pattern described in the ancient text Shang Han Lun. The symptoms of Leptospirosis such as muscle ache, fever, chills, and headache match the Shang Han disease described in the ancient text. In the advanced stage of Leptospirosis, it can cause symptoms like meningitis and jaundice. These symptoms are similar to some cases of advanced Shang Han disease stated in Shang Han Lun. [24] The effectiveness of this 5000-year old medicinal system is proven when the prognosis according to Traditional Oriental Medicine (TOM) shows a much convincing outcome. The efficiency of TOM herbal approaches in treating Leptospirosis is ascertained by an immense amount of proofs. [25]

There is a list of herbs that have been found to be medically effective in preventing and treating Leptospirosis. Basically, the herbs have two types of action in preventing and treating the disease. Their ability to inhibit the growth of *Leptospira* has been validated through laboratory testing where the cultured bacteria are dead when the herb extract is applied. The other action of the herbs is that they result in the clearance of symptoms when administered to infected patients. This action is observed in clinical evaluation. [24] Examples of *Leptospira*-inhibiting herbs are *Isatis leaf* (da qing ye), *Isatis root* (ban lan gen), *Smilax Glabra* (tu fu ling), *Gardenia*, *Hu-chang*, *Coptis* (huang lian), *Scute* (huang qin), *Verbena*. [24][25]

The herb, *Smilax Glabra* is said to be the best among all the herbs listed above. This is because *Smilax* causes least damages to the body due to its gentle and neutral action. [26] *Smilax* is a popular Chinese traditional medicine which has potent effect in preventing and treating Leptospirosis. This profound effect of *Smilax* is seen in large clinical trials. [27][28] Apparently, *Smilax* is not really appreciated as a medical agent as there are only a few of *Smilax Glabra* in the market in spite of its profound efficacy. [24]

According to the book "Thousand Formulas and Thousand Herbs of Traditional Chinese Medicine", it is stated that there are five traditional formulas suggested for treating Leptospirosis. These formulas were formulated and divided based on the syndromes of the disease. [24]

Table 3 below shows the traditional formulas suggested for treating Leptospirosis. [24]

If the patient encounters a severe condition where the disease has already proceeded to the advanced stage, the traditional treatment is probably the best

approaches. [25]

Non-pharmacology treatments

Supportive treatment and haemodialysis

As severe cases of Leptospirosis can distress any of the organ system and subsequently lead to multi-organ failure, thus, admission to hospital for a few weeks is necessary. [2][18] Excellent supportive care and dialysis have reduced the mortality of this illness in recent years. [7] Immediate supportive cares with strict attention to fluid, electrolyte, painkillers and help with their breathing balance is therefore essential. [2][7] Patients should be managed in a monitored setting because their condition can rapidly progress to cardiovascular collapse and shock. [10][15] ECG monitoring is important as cardiac arrhythmias can eventually develop into fatal instabilities as the infection progresses. [8][9]

Liver function should be carefully evaluated and dialysis is indicated to patients in cases of renal failure. [7][15] In most of the conditions, the renal damage is reversible if the patient survives the acute illness. [10] Access to mechanical ventilation and airway protection should be available in the event of respiratory compromise. [7][10] In very rare cases patients can become psychologically disturbed and may need sedation for their own safety. [8][9] The infection is not particularly contagious where these symptoms are temporary and would not require specific treatment. Yet, symptoms such as longer-term depression and fatigue are to be expected, often lasting for several years. [8][18]

Other medications, Activities, Diets and Consultations

Regularly, patients will experience severe headaches, fever and nausea during the first or two week, and these can be overcome by usual non-prescription medicines. In some cases medical staff may prescribe additional programs of medication to help with liver or kidney function, or to support deficiencies in diet. A few cases have reviewed that plasma exchange, corticosteroids, and intravenous immunoglobulin may be beneficial in selected patients in whom conventional therapy does not elicit a response. [8][10] Maintaining a healthy diet with all the proper vitamins and minerals is vital during recovery and patients that feel fatigued should rest as much as they need to. [10] In mild cases, patients are encouraged to maintain adequate fluid intake as to avoid volume depletion.

Patients with hypotension or clinical shock should not be fed enterally until adequate perfusion is restored. [8][10]

In severe cases of Leptospirosis, several specialty consultations may aid in proper patient management. [10] An infectious disease specialist may assist in differentiating Leptospirosis from diseases with similar presentations but with significantly different treatments. Nephrologists should be prepared early in the course as the need for dialysis may present rapidly. [10] Besides, critical care specialists might be needed to manage patients with affected multiple systems. Last but not least, the CDC or the World Health Organization (WHO) can assist the clinician with laboratory diagnosis. [9][10][18]

Prognoses

Immediate therapy or treatment can reduce the mortality rate to a very low level. Most of the patients recover within one or two months. If the infection is persistent, there is a considerable number that shows medium-term health issues. Patients who undergo acute or subclinical infection will not suffer from any significant deficiency. Patients usually will be subjected to supervision and management for several years after the infection as long-term issues are very common in Leptospirosis. Symptoms such as headaches and depression are expected to occur again. [7]

Prevention And Controls

The control of Leptospirosis is complicated and is highly depend on the local conditions. This is due to the presence of large number of serovars and infection sources plus the wide differences in transmission conditions. [2][7] Hence, preventive measures must be conducted based on knowledge of the risk groups and the local epidemiological factors. [2][7] Prevention and control should be targeted at the infection source, the route of transmission between the infection source and the human host; or infection of disease in the human host. [2][6][8] There are several ways that can be implemented to prevent Leptospirosis.

Control of infection source

As we know, human can be infected if they are in contact with the animal urine or faces. Therefore, public should avoid themselves from consuming contaminated food or water. [2][6] It must be ensured that all the food and drinking water to be consumed

are cleaned. All drinking water should also be boiled unless it is known to be absolutely safe as physical filtration through ceramic or charcoal filters is not adequate for preventing Leptospirosis. [7][8][9][11] The food must be covered from the rat. In addition, fresh vegetables and fruit should be washed using clean water and then cooked or peeled before eating. [9][19] Another approach to prevent Leptospirosis is to practice personal hygiene. At home, one should wash their hands with soap before and after eating or use hand sanitizer after using the toilet. [19] If anyone had any cuts on their body, one should clean and cover it properly so that the germs cannot enter the wounds. [18]

Rodent control

This can be achieved by controlling or reducing infection in animal reservoir populations such as dogs or livestock. [9][18] Domestic animals should not be allowed to urinate in water as most of the residents in the rural area routinely depend on river as their main water sources. Thus, animal reservoirs should be separated from human habitations by means of fences and screens. [7] Besides, dogs and livestock should also be brought for immunization. [18][19][20][22]

Interruption of transmission

Workers from agriculture field like rice and cane farming area, construction workers, pest controller and water or sewer engineers have a higher tendency to be affected. [8] If working with materials that could potentially be contaminated, one should wear protective clothing that covers the skin, including waterproof boots or waders. [2][6][8][9] Farmer workers should habitually clean their hand after completing their work. By doing so, they can avoid or reduce their exposures to Leptospirosis infection.

On top of that, public should avoid visiting recreation areas or having vacation at the place where the disease is spreading especially the one that have tropical and subtropical climate with the high rainfall. [2][6][8][23] During flood season, workers in flooded fields should be cautioned against direct contact with contaminated water or mud. [11] Anyone that works in flood area is advised to put on waterproof dressings which include rubber shoes and gloves. [2][6][8][9][19] People should also avoid activities such as swimming or canoeing at the contaminated area as the disease can be easily transmitted from the water sources. [19][20][22]

The mapping of water bodies and human activities in water logged areas should be implemented. This will help to identify the high risk population. Farmers may

be educated to drain out the urine from the cattle shed into a pit, instead of letting it flow and mix with water bodies (rivers, ponds etc.) [8][18]

Human Protection

The key preventive measure for Leptospirosis is to build awareness regarding the disease and its prevention. [2] This has to be carried out continuously by various intensive educational campaigns so as to rise cautious among people against Leptospirosis disease, especially to the high-risk groups. [18] With these efforts, people can understand better and get to know well on every aspects of Leptospirosis. In addition, the disclosure of the risks and dangers of Leptospirosis can also motivate people to sustain our natural environment. Therefore, latest and updated news or information about Leptospirosis should be conveyed to the public through print and electronic media. [23]

One should not be hesitate to consult a physician for early medication if he or she experiences any of the signs and symptoms. [7] Children and pregnant women need to be aware of this disease as they are more susceptible to be affected by Leptospirosis. It is always advisable for pregnant mothers to stay away from the animal and its environment. Meanwhile, parents are advised to pay more attentions on their younger children' personal hygiene. [23]

In addition, Leptospirosis should be made a reportable disease in all endemic states. [2][7][18] During the peak transmission season, Doxycycline 200 mg may be prescribed to agricultural workers (eg paddy field workers, canal cleaning workers in endemic areas) once a week. [20][23] The chemoprophylaxis should not be extended for more than six weeks. [2][7][18] Health impact assessment should also be made oblige for all developmental projects along with environmental assessment. [2][8][9][18][19][20]

Vaccination of animals

Leptospire vaccines offer a limited period of immunity. [8] Boosters are needed every one to two years. [2][8][9][11] Vaccination should yet be very selective and used only in endemic situations having high incidence of Leptospirosis. [23] The vaccine must contain the dominant local serovars. Although this will help in preventing illness, however, it does not guarantee immunization from infection and renal shedding. [18][19][20][22]

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Illustrations

Illustration 1

Table 1: Number of cases of Leptospirosis

Years	No of cases
2006	527
2007	949
2008	1,263
2009	1,418

Illustration 2

Table 2: Summarization of Treatment and Prevention of Leptospirosis by drugs [6][17][18]

Purposes of Medications	Methods of medication
Indications	
Mild illness (suspect case)	Doxycycline, 100 mg orally administered twice daily for 7 days OR Ampicillin, 500- 750 mg orally 4 times daily OR Amoxicillin, 500 mg orally 4 times daily
Mild illness (Probable case)/ Severe case	Penicillin G, 1.5 thousand units intravenously 4 times daily OR Ampicillin, 1 g intravenously 4 times daily OR Amoxicillin, 1 g intravenously 4 times daily OR Ceftriaxone, 1 g intravenously 4 times daily OR Cefotaxime, 1 g intravenously 4 times daily OR Erythromycin, 500 mg intravenously 4 times daily
Prevention by drugs	Doxycycline, 200 mg orally administered once a week

]

Illustration 3

Table 3: Traditional formulas suggested for treating Leptospirosis[24]

Formula	Treatment of / Syndrome
<i>Yin Qiao San</i>	Initial symptoms (flu-like pattern)
<i>Sanshi San</i>	Skin manifestations of the disease (rashes) (<i>applied tropically</i>)
<i>Ermiao San</i>	Manifestations of the disease as liver disease (acute jaundice)
<i>Xin Jia Xiangru Yin</i>	Summer heat injuring the lung
<i>Zhengan Xifeng Tang plus Angong Niu Huang Wan</i>	Manifestations of the disease such as meningitis

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