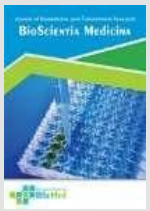
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Antibiotics Used in Leptospirosis: A Narrative Literature Review

Amelia F. Dewi[1*], Armen Ahmad[2,3], Fadrian[2,3]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Division of Tropical Medicine and Infectious Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[3]Division of Tropical Medicine and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Antibiotics
Leptospirosis
Zoonosis

***Corresponding author:**
Amelia F. Dewi

E-mail address:
ameliafdewi88@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i12.628

A B S T R A C T

Leptospirosis is an acute infectious disease that affects both humans and animals (zoonosis). This disease is caused by the *Leptospira* species, a bacterium with 250 serovar variations which thus detecting its cases is prominently challenging. In Indonesia, Leptospirosis is regarded as an iceberg phenomenon since such a challenge prevents this disease from being diagnosed in clinical practice, despite study data indicating that a significant percentage of reservoir rats in Indonesia are positive for *Leptospira* bacteria. As such, this disease has a high mortality of rats due to therapeutic delays. The usage of antibiotics is consequently considered an optimal therapy for leptospirosis. Antibiotics are chosen based on the clinical severity of the disease and should be administered as prophylaxis in high-risk groups in order to lower morbidity and mortality.

1. Introduction

Leptospirosis, a zoonotic infection caused by the bacterium *Leptospira*, is a worldwide health concern. In Indonesia, leptospirosis infection cases are still classified as 're-emerging disease', which emerge infrequently and yet can cause extraordinary events.[1,2] Leptospirosis is an endemic disease in many tropical and subtropical community groups living in slum regions, either in cities or in rural.[2] The global incidence of leptospirosis ranges between 0.1 and 1 per 100,000 people per year in temperate settings to 10-100 per 100,000 people per year in humid tropics.[3] In the event of outbreaks or high-risk groups, the number of incidences can exceed 100 per 100,000 people per year.[2] As a result, professionals desperately need to perform effective prevention, diagnosis, and therapy to reduce the disease's mortality. The majority of the patients were in stable health conditions, but there were those in critical conditions that required immediate and proper treatment. This medical state can be classified as an icteric or anicteric phase, depending on clinical signs. This review aimed to describe the usage of antibiotics in leptospirosis.

Epidemiology of leptospirosis

In Indonesia, 411 cases with 56 deaths (case fatality rate 13.63%) were reported from January to

October 2014.[2] The high mortality of rats was notably driven by epidemics in DKI Jakarta and Central Java Provinces because of floods caused by heavy rains.[2] Leptospirosis infections in Indonesia significantly increased in 2019 to 920 cases, with 122 deaths and an estimated comorbidity rate of 39.2 per 100,000 population. According to the International Leptospirosis Society, Indonesia has a high incidence of leptospirosis and ranks third in the world in terms of mortality. The findings of the Special Research on Disease Vectors and Reservoirs (Rikhus Vector) across 25 Indonesian provinces from 2015 to 2017 revealed that there was a presence of rats positive for Leptospirosis bacteria in the province.[2,4]

Leptospirosis is also known as mud fever, slime fever, swamp fever, autumnal fever, infectious jaundice, field fever, and cane fever. Based on etiology, spirochetes bacteria from the genus *Leptospira*, family Treponema, cause leptospirosis. This organism is convoluted, thin, and flexible, measuring 5-15 m long and 0.1-0.2 m wide, with one of the junks inflated to create a hook. These germs are aquatic bacteria with modest growth in rats. Leptospira can be observed with a dark field microscope and silver staining (Figure 1). Leptospira requires a particular medium to grow and takes weeks to establish a good culture. Fletcher's media allows obligatory aerobes to grow.[5]

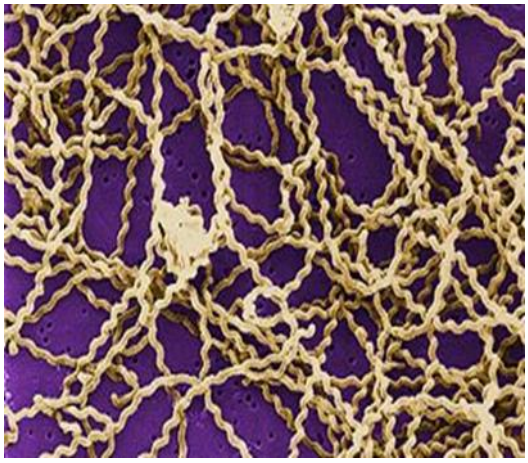


Figure 1. A *Leptospira* micrograph.[6]

The genus *Leptospira* is classified into two serovars: pathogenic *L. interrogate* and non-pathogenic *L. biflexa*.[6] Almost all mammals, including cattle, buffalo, horses, sheep, and rodents, can form the reservoir that serves as a source of infection transmission to humans. Rats are the first species identified as Leptospirosis reservoirs.

Risk factor

Individual conditions (age, gender, and family) and daily activities are more prevalent in persons with leptospirosis than in people without leptospirosis. Hence this group is more likely to contract the disease, as indicated in Table 1 below.

Table 1. Risk of transmission of leptospirosis.[5]

Workgroup	Activity group	Environmental group
Farmers and ranchers	Swimming in the river	Pet dog
Slaughterer	Canoeing	Cattle
Animal catcher/trapper	Camping	Rain puddles
Vet/Veterinarian	Hunting	Rats or mice environment
Woodcutter	Activities in the forest	Floods
Sewer workers		
Plantation workers		

Control of leptospirosis risk factor

Leptospirosis control consists of two events: primary prevention for healthy people to avoid leptospirosis and secondary prevention for people who are already sick to avoid complications that can lead to death. Control activities for leptospirosis risk factors are carried out at the source of infection, the transmission line between the source of infection and humans, and infection or disease in humans.

Pathophysiology of leptospirosis

Humans can be infected by *Leptospira* through direct contact (e.g., blood, urine, or body fluids) or indirectly through the urine of animals infected with *Leptospira* in puddles, rivers, lakes, sewers, or muck. *Leptospira* enter the human circulation through intact mucosa, and systemic vasculitis can be detected in both big and small blood vessels as well as other organs.[5]

The main organs affected by this disease are the kidneys, which have tubulointerstitial inflammation and tubular necrosis, as well as the lungs and heart. Clinical myocarditis, meningoencephalitis, uveitis, and hematology abnormalities can also appear in severe cases. Even after treatment, leptospirosis might be detected in the urine for several days.[5-7]

Clinical symptoms

The incubation time for leptospirosis ranges from 2 to 30 days, with an average of 7-10 days. The process of this infection activates the body's immune response, and leptospires release toxins that cause pathological damage to various organs.[7] Leptospirosis is divided into three phases: the leptospiremia phase, the immunological phase, and the healing phase. The leptospiremia phase is characterized by the presence of leptospires in the blood and cerebrospinal fluid, and on the third day, there may be conjunctivitis, skin lesions, organomegaly, and lymphadenopathy problems.[8] The immunological phase occurs when bacteria are no longer present yet antibodies can be discovered.[9] The clinical differences in the severity of leptospirosis are shown in Figure 2.

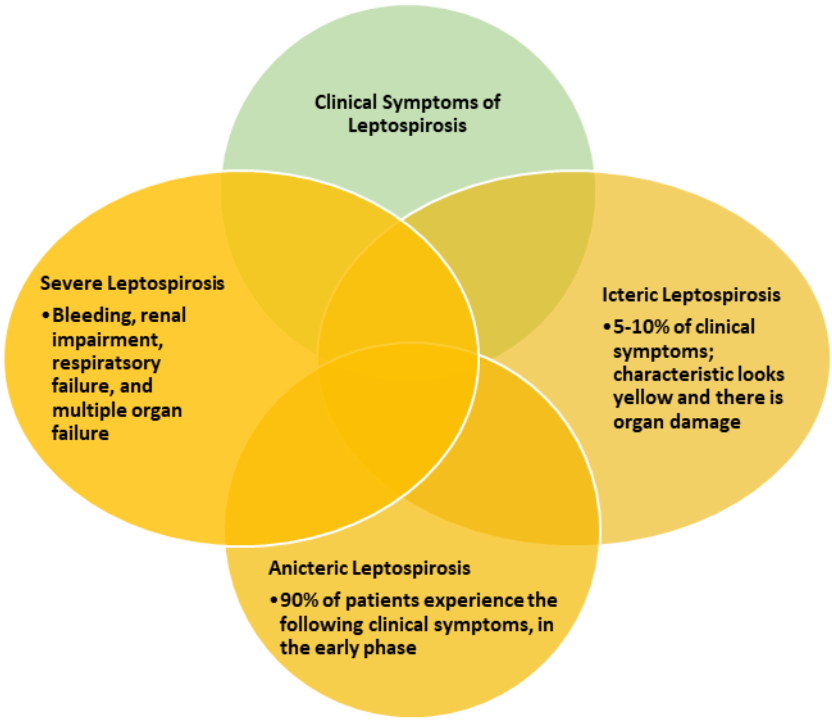


Figure 2. Clinical differences in degrees of leptospirosis.

Leptospirosis diagnosis

Leptospirosis cases are classified into three types: (1) suspicious cases, (2) likely cases, and (3) confirmed cases. Suspected cases have an acute fever (≥38.50C) or headache, muscle pain, weakness (malaise), conjunctival hyperemic, ciliary suffusion, and a history of exposure to a polluted environment or activity that is a risk factor for leptospirosis within 2 weeks. If the suspect case has two of the following clinical signs and symptoms, it is considered a probable case: calf pain, jaundice or jaundice, bleeding manifestations, shortness of breath, oliguria or anuria, cardiac arrhythmias, cough with or without hemoptysis, and skin rash.[10-12]

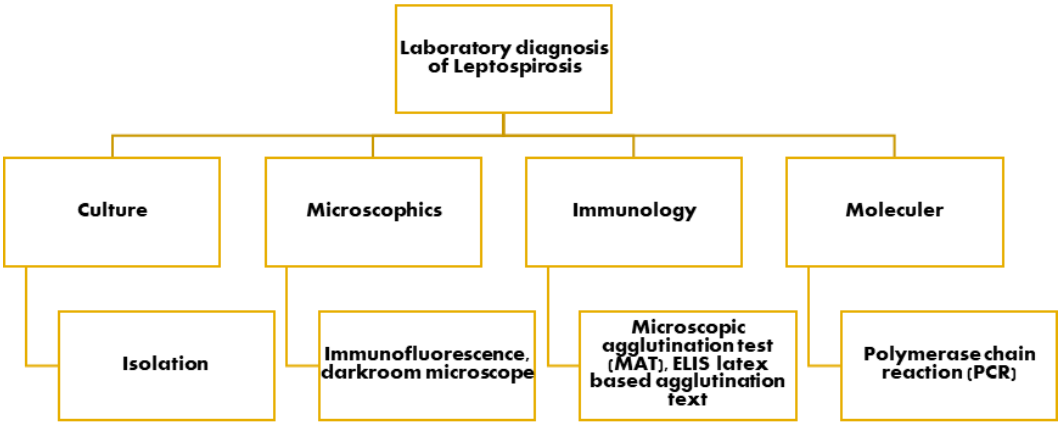


Figure 3. Leptospirosis diagnosis laboratory examination protocol.

Furthermore, having laboratory symptoms such as thrombocytopenia 100,000 cells/mm; leukocytosis with neutrophilia > 80%; an increase in total bilirubin >2gr% or an increase in SGOT/SGPT, amylase, lipase, and creatinine phosphokinase; and the use of quick diagnostic assays. While a porous case is considered confirmed when it is accompanied by one of the following outcomes: (a) isolation of leptospirosis bacteria from clinical specimens; (b) positive polymerase chain reaction (PCR) results and microscopic agglutination test (MAT) seroconversion from negative to positive; and (d) positive fast test results using different reagents, as shown in Figure 3.[9]

Leptospirosis cases are being misdiagnosed due to the difficulty in diagnosis due to clinical manifestations that are similar to other diseases and limited laboratory findings. The Faine criteria, which were modified in 2012, can be used as a scoring system, with a score between 20 and 25 indicating a possible diagnosis of leptospirosis but not confirmation (Table 2).

Table 2. Modified Faine criteria.

A. Clinical data	**Score**
Headache	2
Fever	2
Temperature >39°C	2
Bilateral conjunctival injection	4
Meningitis	4
Myalgia	4
Conjunctival injection, meningism, and myalgia	10
Jaundice	1
Albuminuria	2
Haemoptysis/respiratory failure	2
B. Epidemiological factors	**Score**
Flood	5
Contact with the contaminated environment	4
Farm animal contact	1
C. Bacteriology and laboratory	**Score**
Culture/culture of germs	25
PCR	15
IgM ELISA	15
Positive serology (positive slide agglutination test, Rapid positive test)	15
Increased MAT titer or seroconversion	25

Leptospirosis differential diagnosis

Malaria falciparum, dengue fever, dengue hemorrhagic fever, typhoid fever, and viral hepatitis all have symptoms similar to leptospirosis, but some of these conditions are also infected with this infectious disease.[10]

Antibiotics' role in leptospirosis

All leptospirosis patients, regardless of stage, are given antibiotics. Since the suspected case has been clinically established in endemic areas or outbreaks, the appropriate use of antibiotics is carried out. Meanwhile, in non-endemic areas and outbreaks, treatment begins once a probable case is identified.[10,13] Antibiotics are used to prevent pathogen growth and kill pathogens that cause infectious diseases. In general, antibiotics are selected empirically and definitively.[13,14] Therapeutic doses must be administered correctly to achieve the best treatment results by understanding the factors that influence drug action. As a result, it is important to understand that the factors that must be considered against the use of antibiotics are microorganism resistance to antibiotics, pharmacokinetics and pharmacodynamics, drug interaction factors, drug side effects, and cost factors for each type of antibiotic. In general, antibiotics are classified into two groups based on their pharmacokinetic properties: time-dependent killing and concentration-dependent killing. Time-dependent killing occurs when antibiotic levels in the blood exceed the minimum inhibitory level (MIC). This is critical in predicting clinical outcomes or cures. In this category, the level of antibiotics in the blood exceeds the MIC for at least 50% of the interval dose. Time-dependent killing antibiotics include penicillin, cephalosporins, and macrolides.[15]

Antibiotics are classified into two groups based on their pharmacokinetic properties: time-dependent killing and concentration-dependent killing. Time-dependent killing, which includes the number of times antibiotics remain in the blood at levels above the MIC, is critical for predicting clinical outcomes or cures. The antibiotic blood level in this group was above the MIC for at least 50% of the dosing interval. Penicillin, cephalosporins, and macrolides are examples of antibiotics with time-dependent killing. While concentration-dependent describes the higher the level of antibiotics in the blood beyond the MIC, the greater the bacterial killing power. A concentration/MIC ratio of approximately 10 is required for this group. This means that the chosen dose regimen must have serum or tissue levels that are 10 times higher than the MIC. Treatment will fail if these levels are not reached at the site of infection or tissue. This situation then becomes one of the sources of resistance.[16,17]

The progression of serum antibiotic levels is calculated using pharmacokinetic parameters. The three most important pharmacokinetic parameters for evaluating antibiotic efficacy are peak serum levels (C-max), minimum levels (C-min), and AUC on serum levels vs. time curves. Although these parameters quantify the progression of serum levels, they do not describe an antibiotic's bactericidal activity. Antibiotic activity can be measured by combining PK/PD and MIC parameters. These parameters are the peak level/MIC ratio, the time>MIC ratio, and the AUC-24 hour/MIC ratio.[17,18]

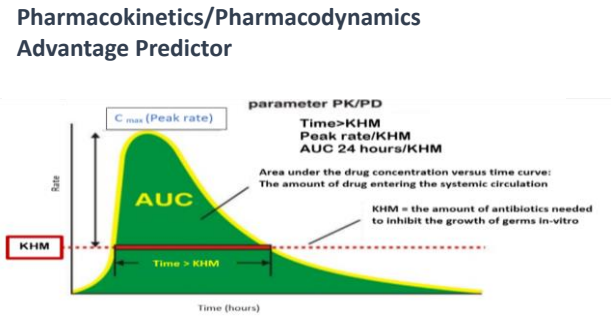


Figure 4. Pharmacokinetic/pharmacodynamic parameters.

The three pharmacodynamic properties of antibiotics that best describe their bactericidal activity are time dependence, concentration dependence, and persistent effect. The bactericidal rates are determined by the length of time required to kill bacteria (time dependence) or the effect of increasing drug levels (concentration dependence). The post-antibiotic effect is one of the persistent effects (PAE). PAE is the persistent inhibition of bacterial growth after antibiotic exposure (Table 3).

Table 3: Antibiotic activity pattern based on pharmacokinetic/pharmacodynamic parameters.

Activity Pattern	Antibiotics	Therapy goals	Parameter PK/PD
Activity Pattern Type I Bactericidal concentration dependence and persistent long-lasted effect	Aminoglycoside Fluoroquinolone	Maximizing doses	-Ratio AUC-24 hours/KHM - Peak ratio /KHM
Type II Bactericidal time-dependence and minimal persistent effect	Carbapenem Cephalosporin Erythromycin Linezolid Penicillin	Increasing the duration of exposure	Time>KHM
Type III bactericidal time-dependence and effect	Azithromycin Clindamycin Oxazolidinone Tetracycline Vancomycin	Maximizing the amount of drug that enters the systemic circulation	Ratio AUC-24 hours/KHM

The selection of antibiotics in cases of leptospirosis takes into account the drug's action as well as the factors that influence the drug's action. According to 2017 technical guidelines for controlling Leptospirosis in Indonesia, antibiotics are chosen based on the severity of the case. Doxycycline or other antibiotic alternatives, such as amoxicillin or azithromycin, are used in the treatment of mild leptospirosis.[17] Intravenous ceftriaxone, penicillin procaine, or intravenous ampicillin can be used for 7 days in cases of moderate to severe leptospirosis (Table 4).

Table 4. Drug administration regimens in leptospirosis.

Clinical	Regimen
Mild leptospirosis	Doxycycline 2 x 100 mg/oral, for 7 days, except in children, pregnant women, or when contraindications exist.
	Alternative;
	Adults: 3x500 mg amoxicillin/oral
	Or 10-20 mg/kg for 7 days in children.
	If you are allergic to amoxicillin, you can take 1x500 mg of azithromycin macrolide per day.
Moderate/severe leptospirosis	Ceftriaxone 1-2 g IV daily for 7 days
	Every 6 hours for 7 days, 1.5 million IM units of penicillin procaine were administered.
	4x1 gram IV ampicillin per day for 7 days
	If there are complications, such as kidney failure, organ bleeding, shock, or neurological disorders, supportive therapy is required.

A previous study found no significant difference in clinical complaints between the intravenous penicillin group and the group that did not receive treatment.[17] Another study comparing clinical improvement between the IM penicillin group and the antibiotic user group (non-penicillin group) found no significant difference between the two treatment groups. There was no significant difference in the duration of fever, death, or complications like kidney failure, jaundice, or thrombocytopenia.

Previous studies compared the therapeutic effects of three antibiotics on various leptospirosis parameters (penicillin, cefotaxime, and doxycycline). The penicillin group received 1.5 million units every 6 hours (n = 87), the cefotaxime group received 1 gram every 6 hours IV (n = 88), and the doxycycline group received 200 mg intravenous doxycycline every 30 minutes, followed by a 12 hours infusion (n = 81). Parenteral therapy was administered until the patient's condition improved (afebrile), after which oral therapy was resumed. After 7 days of observation, there was no significant difference in mortality, time to differentiation, or hospitalization duration between the three groups.[19] Doxycycline is the recommended chemoprophylactic agent for post-exposure leptospirosis. The length of prophylaxis is determined by the level of exposure and the presence of sores. Individuals should continue to monitor themselves for fever and other flu-like symptoms and to wear personal protective equipment against exposure because antibiotic prophylaxis is not 100% effective.[13,17]

The decision to provide prophylaxis is based on an assessment of the risk of exposure. Individuals with low-risk exposure were those who had been exposed to flood or contaminated water but did not have cuts, sores, or open lesions on their skin. Doxycycline 200 mg in a single dose is administered prophylactically to low-risk exposure conditions within 24 to 72 hours of exposure. A moderate risk exposure was defined as an individual with a history of flooding or contaminated water, as well as the presence of cuts, sores, or open lesions on the skin or inadvertent ingestion of contaminated water. Doxycycline 200 mg once daily for 3-5 days should be started within 24 to 72 hours of exposure.

Individuals with high risks exposure are those who have had continuous exposure (those who have had more than one exposure or several days, such as those in flooded areas, rescue and relief workers) wading through flood or contaminated water with or without sores, sores, or open lesions on the skin. Swimming in flooded waters, particularly in urban areas infested with domestic rats/waste litter, and drinking contaminated water are also considered high-risk exposures. Doxycycline was given in doses of up to 200 mg once a week until the exposure ended. However, the Ministry of Health currently has no policy regarding prophylactic procedures, despite the fact that leptospirosis is easier to treat with antibiotics if detected early.

2. Conclusion

Leptospirosis is a zoonotic disease caused by the bacteria leptospira. Clinicians frequently encounter leptospirosis in their daily practice, but this disease is frequently diagnosed too late. Antibiotics are administered based on the severity of the disease in leptospirosis management. Antibiotics are used to prevent pathogen growth and to kill pathogens that cause an infectious process. The principle of antibiotic selection is demonstrated empirically and conclusively. As such, it is critical to understand and consider several factors before using antibiotics, such as antibiotic resistance in microorganisms, pharmacokinetics and pharmacodynamics, drug interaction factors, drug side effects, and cost factors for each type of antibiotic.

3. References

1. Noach SMC, Noach YR. Prevalence rate and causes of leptospirosis serovar on cattle at Giwangan's abattoir of Yogyakarta. J Trop Animal Sci Tech. 2020; 2(1).
2. Gasem MH, Hadi U, Alisjahbana B, Tjitra E, Hapsari MMDEAH, et al. Leptospirosis in Indonesia: diagnostic challenges associated with atypical clinical manifestations and limited laboratory capacity. BMC Infect Dis. 2020; 20:179.
3. Galan DI, Roess AA, Pereira SVC, Schneider MC. Epidemiology of human leptospirosis in urban and rural areas of Brazil, 2000-2015. PLoS One. 2021: 0247763.
4. Kurniawati RD, Nuryati S. The correlation between physical environmental factors and

the occurrence of leptospirosis. J Kesehatan Masyarakat. 2018; 14(2).

5. Haake DA, Levett PN. Leptospirosis in humans. Curr Top Microbiol Immunol. 2015; 387:65-97.
6. Mgode GF, Machang'u RS, Mhampi GG, Katakweba A, Mulungu LS, et al. *Leptospira* serovars for diagnosis of leptospirosis in humans and animals in Africa: common *Leptospira* isolates and reservoir hosts. PLoS Negl Trop Dis. 2015; 9(12):e0004251.
7. Daher EF, Lima RSA, Silva Júnior GB, Silva EC, Karbage NNN, et al. Clinical presentation of leptospirosis: A retrospective study of 201 patients in a metropolitan city of Brazil. Brazilian J Infect Dis. 2010; 14(1):3–10.
8. Samrot AV, Sean TC, Bhavya KS, Sahithya CS, Chandrasekaran SC, et al. Leptospiral infection, pathogenesis, and its diagnosis-a review. Pathogens. 2021; 10(2).
9. Ko AI, Goarant C, Picardeau M. *Leptospira*: the dawn of the molecular genetics era for an emerging zoonotic pathogen. Nature Rev Microbiol. 2009; 736-47.
10. Jorge S, Schuch RA, de Oliveira NR, da Cunha CEP, Gomes CK, et al. Human and animal leptospirosis in Southern Brazil: A five-year retrospective study. Travel Med Infect Dis. 2017; 18:46-52.
11. Kurilung A, Chanchaithong P, Lugsomya K, Niyomtham W, Wuthiekanun V, et al. Molecular detection and isolation of pathogenic *Leptospira* from asymptomatic humans, domestic animals and water sources in Nan province, a rural area of Thailand. Res Vet Sci. 2017; 115:146-54.
12. Vitale M, Agnello S, Chetta M, Amato B, Vitale G, et al. Human leptospirosis cases in Palermo Italy. The role of rodents and climate. J Infect Public Health. 2018; 11:209-14.
13. Perez MG, Sancho JJB, Luque JCS, Rodriguez FM, Alfaro EM, et al. Current evidence on the antimicrobial treatment and chemoprophylaxis of human leptospirosis: a meta-analysis. Pathogens. 2021; 10(9):1125.
14. Illangasekera VL, Kularatne SA, Kumarasiri PV, Pussepitiya D, Premaratne MD. Is oral penicillin an effective chemoprophylaxis against leptospirosis? A placebo-controlled field study in the Kandy District, Sri Lanka. Southeast Asian J Trop Med Public Health. 2008; 39(5):882–4.
15. Shivaraj B, Ts R, Anithraj BY, Bayari R. A study on prophylactic doxycycline to reduce the incidence of leptospirosis among paddy field farmers in a coastal district of India. Int J Infect Dis. 2012; 16:E462.
16. Chusri S, McNeil EB, Hortiwakul T, Charernmak B, Sritrairatchai S, et al. Single dosage of doxycycline for prophylaxis against leptospiral infection and leptospirosis during urban flooding in southern Thailand: A non-randomized controlled trial. J Infect Chemother. 2014; 20:709–15.
17. Alikhani A, Salehifar E, Zameni F, Rafiei A, Yazdani-Charati J, et al. Comparison of azithromycin vs. doxycycline prophylaxis in leptospirosis, a randomized double-blind placebo-controlled trial. J Infect Dev Countries. 2018; 12:991–5.
18. Rodrigo C, de Silva NL, Goonaratne R, Samarasekara K, Wijesinghe I, et al. High dose corticosteroids in severe leptospirosis: A systematic review. Trans Res Soc Trop Med Hyg. 2014; 108(12):743–50.
19. Rahim MAA, Zaki AM, Atil A, Azme MH, Him NASN, et al. Effectiveness of antibiotic prophylaxis for leptospirosis among adults: a systematic review. Malaysian J App Sci. 2018; 3(2).