Essence of Scientific Medical Journal (2025), Volume 22, Number 2:1-6
P-ISSN.1979-0147, E-ISSN. 2655-6472

TINJAUAN PUSTAKA

ANALYZING ANTIBIOTIC USE IN LEPTOSPIROSIS TREATMENT TO OVERCOME RESISTANCE AND ENHANCE THERAPEUTIC SUCCESS

I Gede Yogi Lingga Pradipa,[1] Jerroll Septian Tammubua,[1] Putu Masayu Cahyaning Lestari,[1] Made Yudha Rindawan,[1] I Made Bagus Krishna Wiguna,[1]
[1]Program Studi Kedokteran, Fakultas Kedokteran, Universitas Pendidikan Ganesha, Buleleng

ABSTRAK

Pendahuluan: Leptospirosis adalah infeksi zoonosis luas di seluruh dunia yang disebabkan oleh bakteri "*Leptospira* spp.", umumnya di daerah tropis dan dapat menyebabkan epidemi skala besar setelah banjir atau hujan lebat. Penanganan utama leptospirosis adalah dengan menggunakan antibiotik seperti penisilin, ampisilin, amoksisilin, atau doksisiklin. Tata laksana pemberian antibiotik dengan dosis yang lebih tinggi pada pasien leptospirosis menciptakan kemungkinan resistensi antibiotik yang menyebabkan bakteri menjadi resistan terhadap efek antibiotik. Penelitian ini bertujuan untuk memastikan tingkat kesembuhan bagi pasien dan intervensi medis yang lebih efisien. Penelitian ini menggunakan metode kajian pustaka sistematis, yaitu menggunakan artikel-artikel penelitian yang berkaitan dengan topik yang dicari menggunakan metode PICO dengan kriteria inklusi yang digunakan adalah artikel yang diterbitkan dalam rentang tahun 2019-2024, bisa diakses lengkap, relevan dengan kata kunci dan ditulis dalam bahasa Indonesia dan bahasa Inggris.
Pembahasan: Dari hasil penelusuran artikel jurnal yang didapat, ditemukan bahwa artikel-artikel tersebut berisi temuan tentang resistensi dan perubahan f\ungsi beberapa antibiotik seperti *β-laktam*, sefalosporin, doksisiklin, siprofloksasin, fluorokuinolon, asam nalidiksat, penisilin, streptomisin, dan ampisilin pada leptospirosis. Studi-studi ini juga menyoroti hubungan resistensi antibiotik pada leptospirosis agar menekankan perlunya pemantauan berkelanjutan untuk mengurangi peningkatan resistensi antibiotik pada leptospirosis.
Simpulan: Penelitian ini menguatkan kekhawatiran mengenai resistansi antibiotik pada kasus leptospirosis, dengan hubungan faktor genetik dan mekanisme, seperti pompa *efflux* yang mempersulit tercapainya pengobatan dan menyoroti perlunya pengawasan berkelanjutan dan strategi pengobatan yang lebih efektif.

Kata kunci: Antibiotik, Leptospirosis, Resistensi

ABSTRACT

Introduction: *Leptospirosis is a globally widespread zoonotic infection caused by the bacterium "Leptospira spp.", particularly common in tropical regions and can cause large-scale epidemics following floods or heavy rains. Primarily, the management of leptospirosis will use antibiotics such as penicillins, ampicillin, amoxicillin, or doxycycline. The management of giving antibiotics with higher doses to leptospirosis patients also creates the possibility of antibiotic resistance which causes the bacteria to become resistant to the effects of antibiotics. This study aspires to ensure better patient outcomes and more efficient medical interventions. This research uses a systematic literature review method, which uses research articles related to the topic based on the PICO method with the inclusion criteria used were articles published between 2019-2024, were fully accessible, relevant to keywords and also written in Indonesian and English.*
Discussion: *From the search results for journal articles, it was found that it consists of brief descriptions of resistance and changes in function of several antibiotics like β-lactams, cephalosporins, doxycycline, ciprofloxacin, fluoroquinolones, nalidixic acid, penicillin, streptomycin, and ampicillin in leptospirosis. These studies also highlight the association with antibiotic resistance in leptospirosis and emphasize the need for continued monitoring to reduce the increase in antibiotic resistance in leptospirosis.*
Conclusion: *The research emphasizes the growing concern of antibiotic resistance in Leptospira species, with genetic factors and mechanisms like efflux pumps complicating treatment outcomes and highlighting the need for ongoing surveillance and more effective treatment strategies.*

Keywords: *Antibiotic, Leptospirosis, Resistance*

[1]Program Studi Kedokteran, Fakultas Kedokteran, Universitas Pendidikan Ganesha, Buleleng

INTRODUCTION

Leptospirosis is a globally widespread zoonotic infection, particularly common in tropical regions and can cause large-scale epidemics following floods or heavy rains.[1,2] The disease is caused by the bacterium *"Leptospira* spp.*"* from a member of the gram-negative family *"Leptospira"*. The bacteria are helical in shape, motile, and use axial flagella for movement.[3] Despite being first identified over a century ago, leptospirosis continues to pose a significant public health risk with severe cases manifesting as Weil's disease-characterized by renal dysfunction, hepatomegaly, and altered consciousness.[4] Leptospirosis is prevalent in regions like East Sub-Saharan Africa, Oceania, and Southeast Asia, where it accounts for approximately 73% of cases globally.[1,5] In Indonesia, based on data from Pusdatin in 2019, total reported cases of leptospirosis are 920 cases with 122 cases of death that spread in 9 provinces, namely DKI Jakarta, West Java, Special Region of Yogyakarta (DIY), East Java, Banten, North Kalimantan, South Sulawesi, and Maluku. The infection primarily affects individuals in high-risk occupations, such as military personnel, farmers, and sewage workers, as well as populations living in poor urban conditions with low sanitation.[6] Globally, leptospirosis results in an estimated one million cases annually, with a mortality rate of 6.86%, leading to around 60,000 deaths each year.[7] The highest infection and mortality rates are seen in men aged 20 to 49 with regions like the Caribbean and Tropical Latin America experiencing the greatest disease burden.[5] In a study of leptospirosis cases in Colombia, 85.6% of patients were men with an average age of 36.7 years.[6] Similarly, research in South Africa reported 68.1% of cases were male with an average age of 37 years.[8] Infection occurs when mucous membranes come into contact with the urine of infected rodents, wolves, cattle, or sheep, with rodents serving as a primary reservoir, and cases in India peaking during the late monsoon season.[9]

Primarily, the management of leptospirosis will use antibiotics without waiting for diagnostic test results because the sooner treatment is given, the quicker it will be to reduce the severity.[10] Despite *Leptospira*'s cell wall resembling that of Gram-negative bacteria, antibiotics typically used for Gram-positive infections have been found effective, leading to ongoing testing of various antibiotics to evaluate their efficacy against *Leptospira*.[11] For patients with mild symptoms, ampicillin, amoxicillin, or doxycycline can be given orally, while patient with severe cases of leptospirosis should be given high-dose IV penicillin (benzylpenicillin IV 30 mg/kg) for 5-7 days.[12] WHO guidelines consistently recommend antibiotic treatment for leptospirosis at all stages and levels of severity, with sodium penicillin G commonly suggested as the first-line treatment for severe cases.[13]

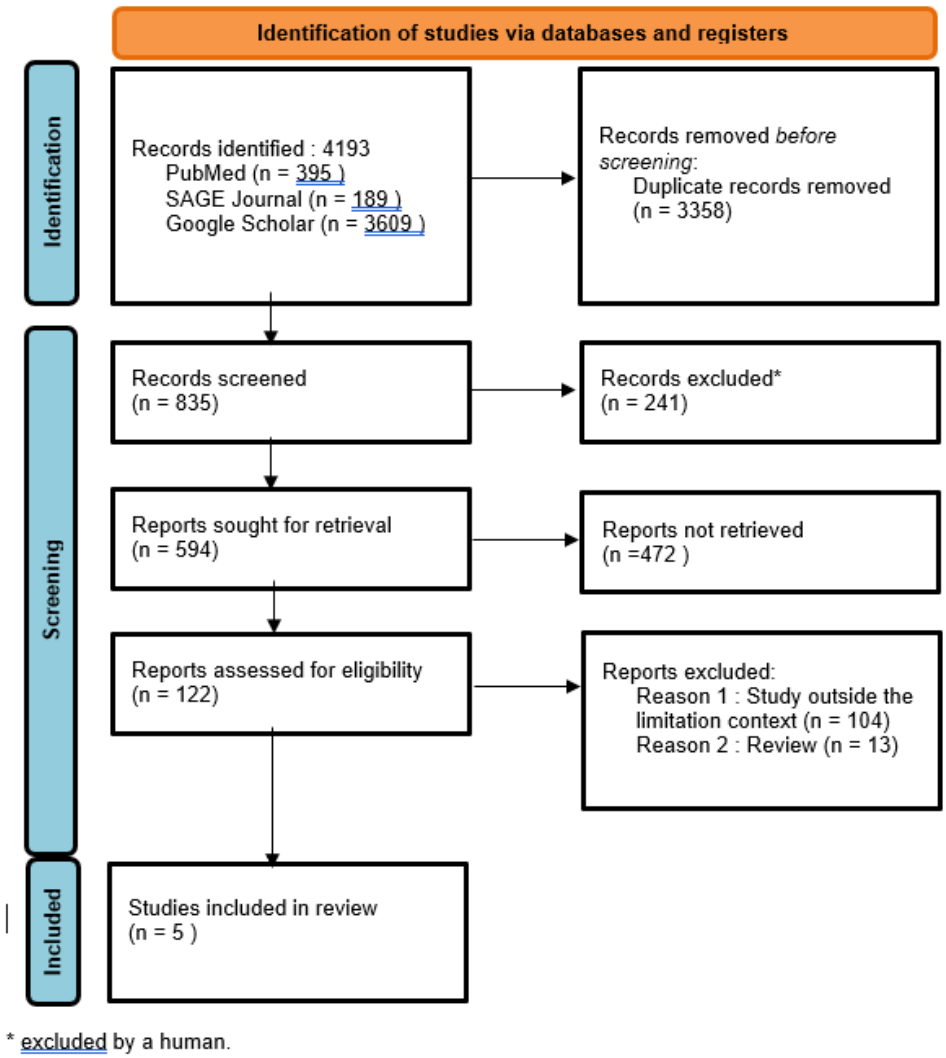
Other classes of antibiotics may offer alternatives, but they are unsuitable for pregnant women due to potential adverse effects on the fetus.[13] The management of giving antibiotics especially penicillin with higher dose to leptospirosis patients also creates the possibility of antibiotic resistance which causes the bacteria to become resistant to the effects of antibiotics.[14] There are three main mechanisms of antibiotic resistance, such as (i) modification of the antibiotic target, (ii) reduction of intracellular antibiotic concentrations, and (iii) inactivation of the antibiotics[15] Antibiotic-resistant bacteria have emerged as a serious challenge to contemporary health care due to the lack of new antimicrobial medications and the rising incidence of bacteria that are leading to treatment failures.[16]

This study aims to investigate the development of antibiotic resistance in individuals affected by leptospirosis. Through a comprehensive systematic review, we seek to assess the impact of antibiotic resistance on both the morbidity and mortality rates of these patients. Additionally, the research will explore the correlation between patients who have developed antibiotic resistance, with the ultimate goal of identifying more effective treatment options. This effort aims to contribute to the improvement of therapeutic approaches, enhancing the effectiveness of treatments for leptospirosis and addressing the growing challenge of antibiotic resistance in a more meaningful and impactful manner. By providing insights into resistance patterns and potential solutions, this study aspires to offer a valuable contribution to the ongoing battle against leptospirosis, ensuring better patient outcomes and more efficient medical interventions.

METHODS

The research design used in this study is to use the systematic literature review method which involves a search of major journal databases, namely PubMed, Google Scholar and SAGE Journal that was done in September, 2024. This study used the population, intervention, comparison, and outcome (PICO) approach. The population of this study was leptospirosis-infected patients. The intervention or issue of interest was antibiotic treatment. In the context of this study, the comparator was alternative leptospirosis treatments. The outcome of the study was incidence of antibiotic resistance. The keyword used in the search strategy was "leptospirosis AND antibiotic AND resistance AND effect".

The inclusion criteria used were articles published between 2019 and 2024. While the exclusion criteria used were studies that were inaccessible, not relevant to keywords and also used languages other than Indonesian and English. For the eligibility process, each author completed a critical appraisal on their own for the eligibility process before compiling the results.



Gambar 1. PRISMA Flowchart

DISCUSSION

The general characteristics of the studies included in this study are represented in Table 1. A total of 5 studies were include in the analysis. The information included are title, authors and country, research design, sample, result and finding.

Tabel 1. Result Finding

Title	Authors and Country	Research Design	Sample	Result and Finding
Detection of Genes Related to Antibiotic Resistance in *Leptospira*[11]	Pineda et al. (2024), Colombia	Quasi Experimental	Genome from 69 species of the genus *Leptospira* taken from the NCBI-Genome database	The mechanism of antibiotic resistance in the genus *Leptospira* is influenced by the genetic genes that make up each type

				of leptospirosis species.
Leptospirosis: A clinical review of evidence based diagnosis, treatment and prevention[17]	Lane & Dore (2016), United States	Clinical review	Leptospirosis Patients in United States	Growing antibiotic resistance in bacterial pathogens, the limited effectiveness against other tropical infections, and multiple studies reporting no clinical benefits including increased mortality with penicillin, have prompted the antibiotics use.
Association Between Antibiotic Treatment of Leptospirosis Infections and Reduced Risk of Dementia: A Nationwide, Cohort Study in Taiwan [18]	Chao et al. (2022), Taiwan	Retrospective cohort study	Leptospirosis Patients over 50 years old in Taiwan	Treatment of leptospirosis patients with antibiotics, such as β-lactams, cephalosporins, and doxycycline, for the first time, was associated with a reduced risk of dementia.
CARD 2023: expanded curation, support for machine learning, and resistome prediction at the Comprehensive Antibiotic Resistance Database[19]	Alcock et al. (2023), United Kingdom		180 new AMR gene families, 15 new drug classes, 1 new resistance mechanism, and two new ontological relationships	The Existence of Antibiotic Resistance to Streptomycin (ARO:0000040) with ARO Term Annotation with a total of 367 in *Leptospira* Bacteria Causes Modification of Resistance Mechanism and Modification of Cell Morphology
Detection of Antimicrobial Resistance Using Proteomics and the Comprehensive Antibiotic Resistance Database: A Case Study[20]	Chen et al. (2020), Canada	Case Study	Four isolates of Campylobacter jejuni	Phenotypic testing showed isolate 00-1597 resistant to ciprofloxacin, fluoroquinolones, and nalidixic acid, while isolates 00-0949 and 01-1512 were resistant to tetracycline. Isolate 01-1512 also had an ampicillin MIC 32 to 64 times higher than the other isolates.

According to the research findings, five key articles discuss the connection between antibiotic resistance and leptospirosis. Pineda et al. (2024) highlighted that antibiotic resistance in the *Leptospira* genus is influenced by genetic factors unique to each species.[11] The study identified five major genes associated with vancomycin resistance across 69 *Leptospira* species, with VanT from the VanG cluster being the most prevalent, followed by VanW and VanY. Additionally, resistance to beta-lactam antibiotics was observed in all species, with some carrying up to five copies of resistance-related genes.

Research by Lane & Dore (2016) highlighted that due to the rise of antibiotic-resistant bacteria, the limited effectiveness against tropical infections, and some studies showing no clinical benefits (including mortality reduction) from penicillin use, there is growing interest in evaluating alternative antibiotics.[17] In a study, 256 leptospirosis patients were randomly assigned to receive intravenous penicillin G, doxycycline, or cefotaxime, with no significant differences observed in mortality, fever duration, or hospital stay across the groups. Similarly, no significant difference in fever duration, renal impairment, or mortality when comparing ceftriaxone and penicillin G in 173 patients with severe leptospirosis. Notably, the overall role of antibiotics in treating leptospirosis remains unclear. Insufficient evidence to support the use of antibiotics in mild or severe leptospirosis cases, with no significant impact on mortality or the need for dialysis.

Similarly, Chao et al.'s research (2022) identified aminoglycoside adenylyltransferase resistance as the rarest mechanism, appearing in only 3% of *Leptospira* species[18]. The N6′ac gene linked to aminoglycoside resistance was detected exclusively in species from clades P1 and S1. Another mechanism noted was the presence of a multidrug efflux pump, which aids in expelling antibiotics from bacterial cells, though this mechanism was absent in clade P1. Resistance to β-lactams, cephalosporins, and doxycycline was highlighted as a significant concern for leptospirosis treatment. Antibiotic treatment, including the use of these drugs, was also linked to a reduced risk of dementia for the first time.

The same result was given by Alcock et al.'s research (2023) highlights the presence of antibiotic resistance to streptomycin (ARO:0000040) in *Leptospira* bacteria, revealing a significant impact on both the resistance mechanisms and bacterial cell morphology.[19] The study identified 367 instances where ARO term annotations were linked to resistance in *Leptospira* species. This resistance to streptomycin, a commonly used aminoglycoside antibiotic, has led to alterations in the bacteria's cellular structure, potentially as an adaptive mechanism to survive antibiotic exposure. Such modifications not only complicate treatment but also indicate the bacteria's ability to evolve in response to therapeutic interventions.

Chen et al.'s (2020) study revealed that phenotypic testing showed isolate 00-1597 was resistant to ciprofloxacin, fluoroquinolones, and nalidixic acid, while isolates 00-0949 and 01-1512 exhibited resistance to tetracycline. Notably, isolate 01-1512 had an ampicillin MIC (minimum inhibitory concentration) 32 to 64 times higher than the other isolates.[20] These findings underscore the critical role of antibiotic resistance in *Leptospira* and its impact on clinical treatment outcomes. Despite using antibiotics like penicillin G, doxycycline, or cefotaxime, no significant differences in patient mortality or hospitalization duration were observed, though resistance to antibiotics, particularly tetracycline and doxycycline, continues to be a concern. In terms of resistance mechanisms, some *Leptospira* strains demonstrated genetic variations influencing antibiotic resistance. For example, the catalase-peroxidase enzyme encoded by the katG gene and detoxification regulation by the oxyR gene were found in strains from serovars Pomona and Manilae. Additionally, other resistance mechanisms, such as efflux pumps, were identified in several strains of serovar Pomona, providing deeper insight into how *Leptospira* develops antibiotic resistance.

Overall, this study underscores the need for continuous research on antibiotic resistance in *Leptospira* bacteria, particularly across various geographic regions. The significant differences in resistance observed emphasize the importance of ongoing surveillance by researchers and clinicians, as both geographic location and species-specific factors can influence treatment effectiveness. Additionally, further investigation is essential to uncover the resistance mechanisms in different *Leptospira* strains. The study reveals that certain strains can acquire resistance through complex processes, such as efflux pumps and genetic modifications, indicating the need for more targeted and region-specific treatment strategies.

CONCLUSION

Based on the result of 5 articles, research highlights the growing concern of antibiotic resistance in *Leptospira* species, with significant genetic factors and mechanisms like efflux pumps contributing to resistance across various regions. Studies show that resistance to antibiotics such as vancomycin, beta-lactams, aminoglycosides, and doxycycline varies among species, and these resistance traits complicate treatment outcomes. Despite

the lack of significant differences in patient mortality or hospitalization duration when using antibiotics like penicillin G, doxycycline, and cefotaxime, resistance remains a pressing issue. To address this, ongoing research and surveillance are crucial, focusing on understanding regional and species-specific resistance patterns, while also developing more effective, adaptive treatment strategies for leptospirosis.

BIBLIOGRAPHY

1. Rajapakse S. Leptospirosis: clinical aspects. Clinical Medicine. 2022 Jan;22(1):14–7.
2. Petakh P, Oksenych V, Kamyshna I, Boisak I, Lyubomirskaya K, Kamyshnyi O. Exploring the complex interplay: gut microbiome, stress, and leptospirosis. Front Microbiol. 2024 Feb 27;15.
3. Cilia G, Bertelloni F, Albini S, Fratini F. Insight into the Epidemiology of Leptospirosis: A Review of Leptospira Isolations from “Unconventional” Hosts. Animals. 2021 Jan 14;11(1):191.
4. Jamal Khan S, Bilal khattak M, Khan A. Leptospirosis: A disease with global prevalence. J Microbiol Exp. 2018 Nov 28;6(5).
5. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, et al. Global Morbidity and Mortality of Leptospirosis: A Systematic Review. PLoS Negl Trop Dis. 2015 Sep 17;9(9):e0003898.
6. Parra Barrera EL, Bello Piruccini S, Rodríguez K, Duarte C, Torres M, Undurraga EA. Demographic and clinical risk factors associated with severity of lab-confirmed human leptospirosis in Colombia, 2015–2020. PLoS Negl Trop Dis. 2023 Jul 5;17(7):e0011454.
7. Bradley EA, Lockaby G. Leptospirosis and the Environment: A Review and Future Directions. Pathogens. 2023 Sep 16;12(9):1167.
8. Gizamba JM, Paul L, Dlamini SK, Odayar J. Incidence and distribution of human leptospirosis in the Western Cape Province, South Africa (2010-2019): a retrospective study. Pan African Medical Journal. 2023;44.
9. Karnik ND, Patankar AS. Leptospirosis in Intensive Care Unit. Indian Journal of Critical Care Medicine. 2021 May 1;25(S2):S134–7.
10. Nemhauser JB, editor. CDC Yellow Book 2024. Oxford University PressNew York; 2023.
11. Pineda S, Martínez Garro JM, Salazar Flórez JE, Agudelo-Pérez S, Monroy FP, Peláez Sánchez RG. Detection of Genes Related to Antibiotic Resistance in Leptospira. Trop Med Infect Dis. 2024 Sep 6;9(9):203.
12. S S, I A, AW S, B S, AF S. Buku Ajar Ilmu Penyakit Dalam Jilid III. IV. Jakarta: Interna Publishing; 2014. 3197.
13. Naing C, Reid SA, Aung K. Comparing antibiotic treatment for leptospirosis using network meta-analysis: a tutorial. BMC Infect Dis. 2017 Dec 5;17(1):29.
14. Huemer M, Mairpady Shambat S, Brugger SD, Zinkernagel AS. Antibiotic resistance and persistence—Implications for human health and treatment perspectives. EMBO Rep. 2020 Dec 3;21(12).
15. Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ V. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015 Jan 1;13(1):42–51.
16. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr. 2016 Mar 25;4(2).
17. Lane AB, Dore MM. Leptospirosis: A clinical review of evidence based diagnosis, treatment and prevention. World J Clin Infect Dis. 2016;6(4):61.
18. Chao PC, Chien WC, Chung CH, Huang CK, Li HM, Tzeng NS. Association Between Antibiotic Treatment of Leptospirosis Infections and Reduced Risk of Dementia: A Nationwide, Cohort Study in Taiwan. Front Aging Neurosci. 2022 Mar 23;14.
19. Alcock BP, Huynh W, Chalil R, Smith KW, Raphenya AR, Wlodarski MA, et al. CARD 2023: expanded curation, support for machine learning, and resistome prediction at the Comprehensive Antibiotic Resistance Database. Nucleic Acids Res. 2023 Jan 6;51(D1):D690–9.
20. Chen C, Clark CG, Langner S, Boyd DA, Bharat A, McCorrister SJ, et al. Detection of Antimicrobial Resistance Using Proteomics and the Comprehensive Antibiotic Resistance Database: A Case Study. Proteomics Clin Appl. 2020 Jul 28;14(4).