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Comparison of The Sensitivity of Generic and Branded Ciprofloxacin Antibiotics Against Salmonella Typhi

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Abstract

Background. *Salmonella typhi* is the leading cause of typhoid fever, a gastrointestinal infection that resulted in about 9 million cases and 110,000 deaths globally in 2019. One of the drugs that is currently often used in the treatment of this disease is ciprofloxacin. Over time, more and more bacteria are experiencing drug resistance, including to these drugs. In addition, many patients also doubt the quality of generic ciprofloxacin drugs because they are cheaper than branded drugs. In fact, the Regulation of the Minister of Health No. HK.02.02/MENKES/068/I/2010 requires the use of generic drugs in government health facilities. **Primary Objective**: This study aimed to see and compare the sensitivity of generic and branded ciprofloxacin antibiotics in inhibiting *Salmonella typhi*. **Methodology**: This study was an antibiotic sensitivity test by the agar diffusion method (Kirby Bauer). **Results**: The results showed that one generic ciprofloxacin and seven branded classes still had sensitive inhibitory power and there was no significant difference between the generic and branded groups. **Conclusions**: There was no significant difference between generic and branded antibiotics between generic and branded antibiotics ciprofloxacin against *Salmonella typhi*.

Keywords: *Ciprofloxacin, Antibiotic sensitivity, Generic drug, Branded drug, Salmonella typhi.*

Introduction

Salmonella typhi (Salmonella enterica serovar typhi) is a rod-shaped, gram-negative bacterium and a facultative anaerobe belonging to the Enterobacteriaceae family. *Salmonella typhi* is the primary cause of gastrointestinal infections, commonly known as typhoid fever.

Salmonella typhi is typically transmitted through contaminated food or beverages that come into contact with human feces containing the bacterium. Once ingested, the bacteria can withstand the acidic pH of the stomach and then adhere to the small intestine. Depending on the body's defense mechanisms, an infectious dose ranging from 1,000 to 1 million organisms may be required to infect a healthy individual[1].

Contaminated food is the primary route by which Salmonella typhi enters the human body. The acidic pH of the stomach does not harm this bacterium, and it is able to proliferate in the intestine. The bacteria infiltrate the intestinal mucosal cells, particularly the M cells, and form plaques when the mucosal humoral immunity (IgA) is reduced. Salmonella typhi can proliferate and survive within macrophages before migrating to the mesenteric lymph nodes and distal ileum, forming Peyer's patches. The thoracic duct provides another route for the bacteria within macrophages to enter the bloodstream, initially causing asymptomatic bacteremia, which then spreads to reticuloendothelial organs such as the liver and spleen. Bacteria that evade phagocytosis in these organs proliferate extracellularly or in the sinus spaces before re-entering the bloodstream, leading to secondary bacteremia, followed by symptoms of systemic infection[1].

In the liver, the bacteria enter the gallbladder, multiply, and are periodically released into the intestinal lumen along with bile. Some of the bacteria are excreted in the stool, while others re-enter the bloodstream after reaching the intestines. This cycle repeats as activated macrophages become hyperactive. Many inflammatory mediators are produced during the phagocytosis of Salmonella typhi, leading to symptoms of systemic inflammatory response, including fever, malaise, headache, muscle pain, abdominal discomfort, vascular instability, mental disturbances, and coagulation[1,2].

Transmission typically occurs via the fecal-oral route, often through contaminated food and beverages[3,4]. Once ingested, the bacteria infect the gastrointestinal tract, with symptoms such as malaise, headache, high fever, bradycardia, constipation, myalgia, and hepatosplenomegaly manifesting after an incubation period of 10–14 days[1,2].

According to the World Health Organization (WHO), there were an estimated 9 million cases of typhoid fever globally in 2019, resulting in approximately 110,000 deaths. In Indonesia, the prevalence of typhoid fever is about 1.6%, or roughly 350–810 cases per 100,000 population. Specifically, in South Sulawesi Province, there were 23,271 reported cases in 2019[5].

First-line antibiotics for treating *Salmonella typhi* infections include chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. However, in recent decades, the emergence of multidrug-resistant (MDR) *Salmonella typhi* has necessitated the use of fluoroquinolone antibiotics, such as ciprofloxacin[6–8].

Antibiotics are generally categorized as generic or branded drugs. Generic drug names may derive from chemical or common names, international nomenclature (e.g., International Nonproprietary Names or INN), or abbreviations. Some generic drugs are marketed under specific trade names, referred to as branded generic medicines. Branded drugs are often sold at higher prices due to additional costs for packaging, branding, and promotion[9–11].

Research by Dyan R indicates that people tend to prefer branded drugs over generics, assuming that branded drugs contain higher doses or multiple active ingredients, thus making them more effective. Similarly, M. Alif's study found that patients have lower trust in generic drugs compared to branded ones, as branded drugs are perceived to offer superior quality due to habitual use and effective marketing campaigns[9,12].

The Indonesian Ministry of Health Regulation Number HK.02.02/MENKES /068/I/2010 mandates the use of generic drugs in government health facilities to ensure affordable and accessible medications without compromising quality and safety[13]. Despite this, many individuals continue to opt for branded drugs, believing that higher prices equate to better quality, further reinforced by aggressive pharmaceutical marketing[14,15].

This study is of high urgency due to the increasing antibiotic resistance to various drugs, including ciprofloxacin, which is one of the primary treatment options for typhoid fever. This resistance poses a serious challenge in managing infections, particularly in developing countries such as Indonesia, where the prevalence of typhoid fever is high. Additionally, public perception that questions the quality of generic drugs compared to branded ones adds complexity to the issue, despite the fact that generic drugs are strictly regulated by the government and are used in healthcare facilities[9,16,17].

The novelty of this study lies in its approach, which directly compares the effectiveness of generic and branded ciprofloxacin against Salmonella typhi strain ATCC-14028. By using the disc diffusion method in accordance with CLSI standards, this research provides scientific evidence on the sensitivity of both drug groups, a study that has not been widely conducted in Indonesia. The results are expected to serve as an important reference for policymaking in antibiotic selection, particularly in supporting the use of generic drugs as an affordable solution without compromising therapeutic efficacy.

Materials and Methods

Study Design

This study employs a true experimental design with a post-test only approach to evaluate the sensitivity of generic and branded ciprofloxacin against Salmonella typhi strain ATCC-14028. The test is conducted using the disk diffusion method, also known as the Kirby-Bauer method, which was first developed in the 1940s and remains a standard technique in antimicrobial sensitivity testing (AST) within clinical microbiology laboratories. This method is particularly well-suited for laboratories with low to medium workloads due to its simplicity and reliability[18,19].

In this method, antibiotic-impregnated paper disks are placed on the surface of agar medium previously inoculated with the test bacteria. After incubation, the inhibition zones around the disks are observed and measured. The inhibition zone reflects the effectiveness of the antibiotic in preventing bacterial growth. Antibiotics are categorized as sensitive if a clear inhibition zone is present, and resistant if bacterial growth persists around the disk[18,19].

Sample

The study samples consisted of one type of generic ciprofloxacin and seven types of branded ciprofloxacin. Each type was tested three times, resulting in a sufficient number of trials to ensure the validity of the results.

Data Collection Techniques

Data were obtained by measuring the diameter of the inhibition zones (in millimeters) after 18–24 hours of incubation at 37°C. These measurements were conducted following the standards established by the Clinical and Laboratory Standards Institute (CLSI), which classifies the test results into three categories: sensitive, intermediate, or resistant.

Research Procedure

The tools used in this study included autoclaves, petri dishes, incubators, calipers, storage cabinets, inoculation loops, Erlenmeyer flasks, rulers, tweezers, L-glass, aluminum foil, cotton, micropipettes, and test tubes. The materials used comprised Mueller Hinton Agar (MHA), generic and branded antibiotics, and *Salmonella typhi* ATCC-14028[18,19].

The tools were cleaned, wrapped, and sterilized in an autoclave at 121°C and 1 atm for 15 minutes, followed by drying in an oven at 100°C for 1 hour. MHA was prepared by dissolving 38 grams of powder in 1 liter of distilled water, heating to a boil, and sterilizing in an autoclave[20,21].

The McFarland standard was used as a turbidity reference for the bacterial suspension. To prepare a 0.5 McFarland standard, 0.05 ml of 1% $BaCl_2$ solution was mixed with 9.95 ml of 1% H_2SO_4 solution and thoroughly homogenized using a vortex until the solution was completely mixed [20].

The test bacteria, *Salmonella typhi* ATCC-14028, were obtained from a pure culture provided by the Laboratory of the Faculty of Medicine, Universitas Muslim Indonesia. The 24-hour-old bacterial colonies grown on agar medium were suspended by transferring the inoculum with a sterile loop into a tube containing 2 ml of 0.9% NaCl solution. The suspension was adjusted to match the turbidity of the McFarland standard[21].

To prepare Mueller-Hinton Agar (MHA), 38 grams of MHA powder were dissolved in 1 liter of distilled water in an Erlenmeyer flask. The mixture was heated and stirred until boiling to ensure the powder was fully dissolved. The medium was then sterilized in an autoclave at 121°C under 2 atm of pressure for 15 minutes. After sterilization, the medium was poured into Petri dishes and left to solidify[22].

Antibiotic testing was conducted *in vitro* using the disc diffusion method with 6 mm paper discs. The bacterial suspension was applied to the MHA, and antibiotic discs were placed on the agar surface. The plates were incubated at 37°C for 18–24 hours[13]. The inhibition zones were measured in millimeters using the formula shown in Figure 1. Results were compared against sensitivity standards provided by the Clinical Laboratory Standard Institute (CLSI) 2020[23,24].

Post hoc analysis was performed to identify significant differences between generic and branded ciprofloxacin antibiotics. Data were analyzed using SPSS software[24].

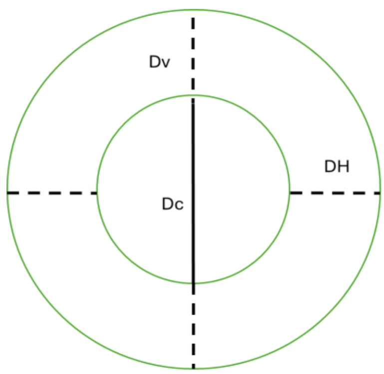


Figure 1. Calculation formula of the inhibition zone

Inhibition zone = [(DV - DC) + (DH - DC) / 2]
DV= Vertical Diameter; DC = Disc Diameter; DH=Horizontal Diameter

Data Analysis Techniques

The data analysis was conducted using ANOVA and Tukey Post-Hoc tests with SPSS, where a p-value < 0.05 was considered significant.

Ethical Consideration

This study adhered to ethical research principles. Approval for the study was granted by the Faculty of Medicine, Universitas Muslim Indonesia, and the relevant laboratory authorities. Additionally, the research received an ethics clearance number, UMI012406330, demonstrating compliance with applicable ethical standards

Result

In this study, researchers tested seven types of branded antibiotics and one generic antibiotic within the ciprofloxacin group, conducting three repetitions for each. The sensitivity results were then compared against the CLSI standard to classify the antibiotics as sensitive, intermediate, or resistant.

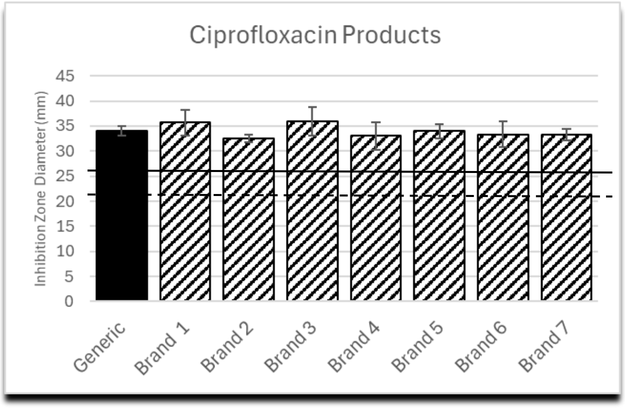
Table 1. Results of the average measurement of the diameter of the inhibitory zone of generic antibiotics and ciprofloxacin-branded antibiotics against *Salmonella typhi bacteria*

Cipro-floxacin	Diameter of the inhibition zone					
	R1	R2	R3	Average	STD	Information
Generic	34	35	33	34	1	Sensitive
Brand 1	33	38	36	35.6	2.52	Sensitive
Brand 2	32	33		32.5	0.71	Sensitive
			34.5			
Brand 3	34	38		36	2.83	Sensitive
			35.5			
Brand 4	31		35	33	2.83	Sensitive
		33.5				
Brand 5		33	35	34	1.41	Sensitive
	30.5					
Brand 6		34		33.3	2.57	Sensitive
	30.5		35.5			
Brand 7	32	34	34	33.3	1.15	Sensitive

R= inhibition zone diameter (mm); STD= standard deviation
***Source** : primary data*

Table 1 presents the results of the ciprofloxacin sensitivity test (5 µg), showing that the generic product exhibited an average inhibition zone diameter of 34 mm. The branded products (labeled 1 to 7) demonstrated inhibition zone diameters ranging from 32.5

mm to 35.6 mm, all exceeding the ciprofloxacin sensitivity threshold of 21 mm. Figure 2 provides a graphical comparison of the performance of generic and branded products.



Source : primary data
——— *= sensitive borderline*
------ *= resistance borderline*

Figure 2. Comparison of I nhibition Zones Between Generic and Branded Ciprofloxacin Products.

Table 2 presents the results of the ANOVA statistical test, indicating that all p-values for generic and branded antibiotics exceed 0.05.

Table 2 Results of the Tukey HSD post-hoc test for the diameter of the inhibitory zones of generic and branded ciprofloxacin antibiotics against *Salmonella typhi* bacteria

Types of antibiotics		Sig.
Generic	Brand 1	0.958
Generic	Brand 2	0.999
Generic	Brand 3	0.933
Generic	Brand 4	0.999
Generic	Brand 5	0.994
Generic	Brand 6	1.000
Generic	Brand 7	1.000

Source : Primary data.

Discussion

Ciprofloxacin is an antibiotic from the fluoroquinolone class that exerts its bactericidal effect by inhibiting the activity of DNA gyrase and topoisomerase IV enzymes in bacteria. These enzymes are crucial for bacterial DNA replication, transcription, and repair processes. By disrupting their function, ciprofloxacin induces bacterial DNA damage, ultimately leading to cell death. Its ability to penetrate the cell walls of gram-negative bacteria, including Salmonella typhi, makes it highly effective in treating systemic bacterial infections[25].

Ciprofloxacin has a broad spectrum of activity, particularly against gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae, and Salmonella spp. It also exhibits activity against certain gram-positive bacteria, though it is generally less effective than other antibiotics for gram-positive infections. In the context of Salmonella typhi infections, ciprofloxacin is frequently used to treat typhoid fever, especially in regions where resistance to other antibiotics, such as chloramphenicol and ampicillin, is prevalent. Its advantage lies in its ability to achieve high tissue concentrations, making it suitable for treating severe and systemic infections[25].

Ciprofloxacin's pharmacokinetic profile supports its use in managing various bacterial infections. It has good oral bioavailability (approximately 70–80%), allowing for administration as either tablets or intravenous infusions. The drug is widely distributed throughout the body, reaching tissues such as the kidneys, liver, bones, and cerebrospinal fluid. It is primarily excreted through the urine, with an average elimination half-life of 4–6 hours in individuals with normal renal function. However, dosage adjustments are necessary for patients with impaired renal function to prevent toxicity. Its ability to reach high concentrations in infected tissues, such as the urinary and gastrointestinal tracts, makes it a preferred choice for infections in these areas[25,26].

Despite its efficacy, ciprofloxacin faces significant challenges from bacterial resistance. Resistance in Salmonella typhi often arises from mutations in the gyrA and gyrB genes, which encode subunits of DNA gyrase. Additionally, bacterial efflux pump mechanisms can reduce intracellular ciprofloxacin concentrations, diminishing its effectiveness. Environmental factors, such as irrational antibiotic use and unregulated drug distribution, exacerbate the emergence of resistance. Routine surveillance of local resistance patterns is therefore critical for effective management of typhoid infections[27–29].

The results of the ciprofloxacin sensitivity test, shown in Table 1 and Figure 2, indicate that both generic and branded ciprofloxacin antibiotics demonstrate high effectiveness against *Salmonella typhi*, as evidenced by the inhibition zone diameters in all samples falling within the sensitive category. The sensitivity threshold for ciprofloxacin is 21 mm. The generic ciprofloxacin produced an average inhibition zone diameter of 34 mm with a standard deviation of 1 mm, indicating strong inhibition of bacterial growth.

Branded ciprofloxacin antibiotics exhibited similar effectiveness, with inhibition zone diameters ranging from 32.5 mm to 36 mm. This range reflects the consistent antimicrobial potency of ciprofloxacin, regardless of the brand. Statistical analysis revealed no significant difference between the generic ciprofloxacin and the branded products (p-value > 0.05 for all comparisons), suggesting that all types of ciprofloxacin tested were similarly effective.

Table 3 Prices of generic and branded ciprofloxacin antibiotics (2024)

Antibiotic Name	Price per tablet
Generic	IDR 600
Brand 1	IDR 1,100
Brand 2	IDR 2,000
Brand 3	IDR 14,860
Brand 4	IDR 18,648
Brand 5	IDR 16,319
Brand 6	IDR 2,000
Brand 7	IDR 16,000

Source : Primary data

Although resistance to ciprofloxacin has become an increasing challenge, this study demonstrates that the antibiotic remains significantly effective against *Salmonella typhi* ATCC-14028, which was isolated in Indonesia. However, it is important to note that various strains of *Salmonella typhi* cause typhoid fever across Indonesia. Conducting similar sensitivity tests on these strains is essential to assess the extent of ciprofloxacin resistance among *Salmonella typhi* populations throughout the country.

As previously mentioned, public trust in cheaper generic antibiotics tends to be lower than in branded antibiotics, which are perceived as more expensive. Table 3 displays the price differences of the antibiotics used in this study. While a price disparity is evident, this study found no significant difference in quality between generic and branded antibiotics. Therefore, the belief that branded drugs are superior to generic drugs, particularly regarding inhibition zones, is unfounded based on the results of this study.

Conclusion

Based on the study of ciprofloxacin sensitivity against *Salmonella typhi* ATCC-14028, it can be concluded that both generic and branded ciprofloxacin exhibit good sensitivity. No significant difference was found in the effectiveness of the two groups in inhibiting bacterial growth. As a recommendation, further research, including similar studies and clinical trials, should be conducted on various strains of *Salmonella typhi* found across Indonesia to evaluate the broader resistance properties of ciprofloxacin.

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