Jurnal Biologi Tropis

Original Research Paper

Incidence of Cefixime Resistance in Patients with Chronic Kidney Disease at Harapan Keluarga Hospital

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Article History
Received : February 08th, 2025
Revised : March 15th, 2025
Accepted : April 04th, 2025

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Abstract: Antibiotic resistance is an increasing global health challenge, especially in patients with advanced chronic kidney disease (CKD). This study aims to investigate cefixime resistance in patients with stage 4-5 CKD at Harapan Keluarga Hospital with a retrospective cohort design using medical record data. Chi-squared test analysis showed a significant association between cefixime resistance and advanced CKD ($\chi^2 = 34.714$, $p = 0.003$). The results showed a higher prevalence of cefixime resistance in male patients (60%), antibiotic use of more than 14 days (65%), and hospitalization of more than five days (80%). The mechanism of resistance involves beta-lactamase production and changes in the gut microbiota due to dysbiosis. Factors such as irrational antibiotic use, length of hospital stay, and catheter use contributed to higher resistance. This study highlights the need for evidence-based antibiotic stewardship strategies to reduce resistance, especially in vulnerable populations such as patients with advanced CKD. Scientific implications include the development of more effective infection management strategies, close monitoring of antibiotic use, dose adjustment according to CKD severity, and education of health care workers to increase awareness of antibiotic resistance. This study contributes to efforts to prevent antibiotic resistance in the advanced CKD population.

Keywords: antibiotics; cefixime resistance; chronic kidney disease (CKD); comorbidities.

Introduction

Antibiotic resistance is a growing global health problem, particularly among patients with chronic kidney disease (CKD). CKD itself is a significant public health problem with increasing prevalence worldwide, including in Indonesia. Recent data indicate that the prevalence of CKD in Indonesia is 0.38%, with the highest incidence reported in North Kalimantan (0.64%) and the lowest in West Sulawesi (0.18%) (Hidayangsih et al., 2023). Advanced stages of CKD, especially stages 4 and 5, are associated with a significantly increased risk of morbidity and mortality. It is estimated that people with end-stage CKD have a 50% risk of dying within five years. Globally, CKD affects more than 843 million people, and the number is steadily increasing due to the increasing burden of risk factors (Kovesdy, 2022). In Indonesia, the prevalence of CKD has increased from 0.2% in 2013 to 0.3% in 2018, with approximately 200 new cases per million population each year (Mills et al., 2015). This upward trend highlights the urgent need for improved management and prevention strategies, particularly in advanced stages of CKD, to mitigate the impact on healthcare systems and patients' quality of life. Second, antibiotic resistance is defined as the ability of bacteria to survive and proliferate despite exposure to antibiotics that would normally inhibit their growth or eradicate them (Wang et al., 2019). According to the World Health Organization (WHO), antibiotic resistance is responsible for approximately 1.27 million deaths per year worldwide, a figure that

could exceed 10 million deaths per year by 2050 if left unchecked. Patients with advanced CKD (stages 4-5) are particularly susceptible to bacterial colonisation due to frequent medical interventions such as haemodialysis and kidney transplantation. These procedures create potential entry points for antibiotic-resistant pathogens, increasing the risk of serious infections (Huemer et al., 2020).

CKD is characterised by irreversible structural or functional renal impairment, defined by a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² or albuminuria ≥30 mg per 24 hours that persists for more than three months (Ammirati, 2020). In CKD stages 4-5, renal function deteriorates significantly, with GFR falling below 30 mL/min, predisposing patients to complications, including infections, which can further accelerate disease progression. Infections are a major contributor to CKD progression, leading to increased mortality and reduced quality of life. Close monitoring and effective management strategies are therefore essential to prevent further deterioration.

A critical challenge in the management of infections in CKD patients is the increasing prevalence of antibiotic resistance, including resistance to cefixime, a widely used antibiotic for bacterial infections (Chen et al., 2019). Resistance to cefixime can lead to treatment failure, ultimately increasing morbidity and mortality in CKD patients. Poorly controlled infections not only accelerate the decline in kidney function, but also significantly reduce patients quality of life (Munita & Arias, 2016). Therefore, monitoring cefixime resistance in patients with CKD stage 4-5 is crucial to develop more effective treatment strategies and improve clinical outcomes.

The pathophysiology of CKD involves progressive nephron damage resulting from various aetiological factors such as diabetes mellitus, hypertension and glomerulonephritis (Kovesdy, 2022). Renal Dysfunction disrupts filtration of metabolic waste, fluid balance and electrolyte homeostasis, predisposing patients to serious complications, including recurrent infections (Thomas et al., 2020). Uncontrolled infections accelerate renal deterioration and worsen overall prognosis (Versino & Piccoli, 2019). Antibiotic resistance, particularly to cefixime, further complicates the management of infections in CKD patients. Resistance mechanisms include bacterial adaptation strategies such as enzymatic degradation of antibiotics and alterations in membrane permeability to evade antimicrobial effects (Huemer et al, 2020). In addition, CKD-associated circulatory abnormalities and microbiota imbalances increase susceptibility to multidrug-resistant pathogens (Chen et al., 2021). Inappropriate or repeated antibiotic use in CKD patients further accelerates the development of resistance, increasing the likelihood of treatment failure and associated complications (Munita & Arias, 2016). Therefore, a comprehensive and integrated approach to infection management and antimicrobial resistance surveillance in advanced CKD patients is imperative.

This study aims to investigate the incidence of cefixime resistance in patients with CKD stage 4-5 at Rumah Sakit Harapan Keluarga. Given the global increase in antibiotic resistance, particularly in patients with impaired renal function, this research seeks to identify emerging resistance patterns and contributing factors. By elucidating the relationship between patient clinical status and cefixime resistance, the results of this study may contribute to the development of more precise and effective treatment strategies, while strengthening efforts to prevent antibiotic resistance in advanced CKD populations. Furthermore, this study may serve as a basis for the formulation of evidence-based antibiotic stewardship policies in healthcare facilities, particularly for infection management in patients with CKD stage 4-5.

Materials and Methods

This study was conducted at the Harapan Keluarga Hospital (RSHK) in June 2024, selected based on population characteristics that are in accordance with the research objectives. This study used a quantitative design with a retrospective cohort approach to analyze the relationship between cefixime antibiotic resistance and the incidence of stage 4-5 CKD. The study population is CKD patients who will be treated at RSHK in 2024, with a sample of 32 patients selected using random sampling techniques based on the inclusion and exclusion

criteria that have been set. The independent variable is CKD patients, while the dependent variable is CKD patients who show resistance to cefixime, which is identified through the results of bacterial resistance tests based on medical record data.

The research began after obtaining ethical approval and informed consent from the relatives. Data were collected from the patients' medical records, which included information on the diagnosis of CKD and the results of the bacterial resistance test to cefixime. All data were recorded and categorized according to a predetermined scale. Data analysis was performed using SPSS statistical software. Univariate analysis was performed to describe the characteristics of the sample based on gender, type of disease, duration of antibiotic use, and patient comorbidities. Bivariate analysis using the chi-squared test was performed to test the relationship between cefixime antibiotic resistance and the incidence of stage 4-5 CKD, with a significance criterion of p-value < 0.05.

Results and Discussion

In this study, the authors investigate cefixime resistance in patients with chronic kidney disease (CKD) stage 4-5. The tables presented provide important information on subject characteristics, resistance rates and relationships between the variables studied. Below is a detailed explanation.

Descriptive Data of the Antibiotic Resistance Study Sample

This study aimed to evaluate the level of antibiotic resistance of cefixime in patients with chronic kidney disease (CKD) based on various factors, such as gender, type of disease, duration of antibiotic use, and comorbidities. Descriptive data showed that cefixime resistance was higher in male patients than in women, as well as in patients with a duration of antibiotic use of more than 14 days. In addition, the level of resistance to cefixime also varies based on the type of disease and comorbidities the patient suffers from. The following are the results of the study presented in the form of a Table 1:

Tabel 1. Descriptive Data of the Antibiotic Resistance Study Sample

No.	Subject Criteria	% Cefixime Resistance
	Gender	
1.	Female	40%
	Male	60%
	Disease Type	
2.	CKD	50%
	Prostate Cancer	25%
	BPH	25%
	Duration of Antibiotic Use	
3.	< 14 days	35%
	> 14 days	65%
	Comorbidities	
	Type II DM	30%
4.	Autoimmune Disease (SLE, RA)	10%
	Hiperlipidemia	40%
	Imunodeficiency	20%

The level of cefixime resistance in male patients was found to be higher (60%) than in women (40%). This can be explained by biological factors, such as the influence of the hormone testosterone which increases systemic inflammation, thus affecting the effectiveness of antibiotics. In addition, male patients with CKD tend to have more comorbidities such as type II diabetes mellitus and hypertension, which worsen kidney function and increase the risk of antibiotic resistance. This combination of biological variables and underlying medical conditions most likely explains the differences in resistance by sex, as well as noted in previous studies that showed that impaired renal excretion in men can lead to the retention of antibiotics such as cefixime, thus giving bacteria more time to develop resistance (Su et al., 2018; Sumon et al., 2023).

In terms of disease type, CKD patients had the highest levels of cefixime resistance (50%) compared to patients with prostate cancer (25%) and benign prostatic hyperplasia (BPH) (25%). The high rate of resistance in CKD patients can be explained by complex systemic disorders that affect drug metabolism. CKD not only causes decreased kidney function, but also contributes to changes in the gut microbiota, which can worsen kidney dysfunction while increasing antibiotic resistance. In addition, CKD patients often experience recurrent urinary tract infections (UTIs), which are caused by bacteria that have become resistant to various types of antibiotics. The repeated use of antibiotics to treat these infections exerts greater selection pressure on the bacteria, thereby accelerating the development of

resistance (Liabeuf et al., 2024; Sumon et al., 2023). Meanwhile, patients with prostate cancer and BPH had lower levels of resistance, although it was still significant Resistensi pada kelompok ini sebagian besar disebabkan oleh penggunaan antibiotik profilaksis selama prosedur medis seperti biopsi prostat, yang meskipun bermanfaat dalam mencegah infeksi, dapat meningkatkan risiko resistensi pada bakteri yang terpapar (Sumon et al., 2023). Resistance in this group is largely due to the use of prophylactic antibiotics during medical procedures such as prostate biopsies, which while beneficial in preventing infection, can increase the risk of resistance in exposed bacteria (Sumon et al., 2023).

The duration of antibiotic use is also an important factor that affects cefixime resistance. Patients who took antibiotics for more than 14 days had a much higher level of resistance (65%) than those who took antibiotics for less than 14 days (35%). Long-term antibiotic use is known to lead to the selection of resistant bacteria, especially in CKD patients who often need antibiotic therapy to overcome recurrent infections. Cefixime, as a broad-spectrum antibiotic, is often used to treat UTIs in CKD patients, but prolonged exposure to antibiotics can alter the gut microbiota, contributing to resistance. These changes in the microbiota not only increase antibiotic resistance, but can also worsen kidney dysfunction, creating a vicious cycle that worsens the patient's condition (Liabeuf et al., 2024; Sumon et al., 2023).

Patient comorbidity also has a significant effect on the level of cefixime resistance. Patients with hyperlipidemia had the highest levels of resistance (40%), followed by type II diabetes mellitus (30%), immunodeficiency (20%), and autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (10%). Hyperlipidemia is known to contribute to vascular damage that interferes with kidney filtration, while type II diabetes mellitus can lead to diabetic nephropathy, which accelerates the progression of CKD and increases the risk of antibiotic resistance. These two conditions often occur simultaneously in CKD patients, thereby worsening systemic kidney function disorders. Immunodeficiency patients are also more susceptible to antibiotic resistance due to the body's reduced ability to fight infections, which allows for the development of resistant strains of bacteria. Although patients with autoimmune diseases such as SLE and RA have lower levels of resistance, the use of immunomodulatory therapies in this group can affect the body's response to antibiotics, which still puts them at risk of resistance, especially if accompanied by an underlying impaired kidney function (Kusumawardani et al., 2025; Su et al., 2018).

Overall, the results of this study show that cefixime resistance is influenced by complex interactions between biological factors, disease type, duration of antibiotic use, and comorbidities. The highest levels of resistance were found in male patients, CKD patients, those on antibiotics for more than 14 days, as well as patients with hyperlipidemia. These findings are consistent with some previous studies, but make an additional contribution by showing a more specific relationship between each factor and cefixime resistance. However, this study has some limitations, such as the absence of a detailed analysis of the molecular mechanisms of resistance, which could provide more in-depth insights into the pathophysiology of cefixime resistance. In addition, the study was limited to a population of CKD patients at a single location, so the results may not be fully generalizable to a wider population (Liabeuf et al., 2024; Sumon et al., 2023).

Implications of this study include the need for stricter antibiotic management policies, including limiting the duration of antibiotic use, a gender-based approach in the management of CKD patients, as well as the management of comorbidities such as hyperlipidemia and type II diabetes mellitus to prevent antibiotic resistance. In addition, more closely monitoring is needed for patients with a history of long-term antibiotic use or with complex comorbidities. Further research is needed to explore the molecular mechanisms of cefixime resistance and its effect on clinical outcomes in CKD patients, as well as to develop more effective infection management strategies (Kusumawardani et al., 2025; Su et al., 2018).

Cefixime Resistance Data Based on Length of Patient Hospitalization

The results of this study evaluated the effect of the duration of hospitalization and catheter use on the level of cefixime resistance in

patients with chronic kidney disease (CKD). The data showed that CKD patients who were treated for more than five days had significantly higher levels of cefixime resistance compared to those who were treated for less than five days. In addition, the use of a urinary catheter for more than two days was also associated with increased cefixime resistance. These factors significantly affect the level of antibiotic resistance, mainly due to invasive medical procedures and hospital environments that favor the colonization of resistant bacteria.

Tabel 2. Cefixime Resistance Data Based on Length of Patient Hospitalization

No.	Subject Criteria	% Cefixime Resistance
1.	**Duration of Hospitalization for CKD Patients**	
	< 5 days	20%
	> 5 days	80%
2.	**Catheter Use**	
	< 2 days	25%
	> 2 days	75%

Based on the data in Table 2, the results showed that CKD patients who were treated for more than five days had a much higher level of cefixime resistance (80%) compared to those who were treated for less than five days (20%). In addition, catheter use for more than two days also increased cefixime resistance levels by up to 75%, compared to only 25% in patients with a catheter use duration of less than two days. Long duration of hospitalization is often associated with an increased risk of nosocomial infection due to exposure to resistant bacteria in a hospital setting. CKD patients who are treated for a long time tend to undergo more invasive medical procedures, such as urinary catheter insertion, which is the main entry point for pathogenic bacteria. This procedure facilitates the colonization of antibiotic-resistant bacteria, including cefixime, and increases the chances of biofilm formation, which is a microbial layer attached to the surface of a medical device. This biofilm protects bacteria from the effects of antibiotics, thereby increasing resistance. Bacteria such as Proteus mirabilis and Pseudomonas aeruginosa that are often found in catheter biofilms are known to produce beta-lactamase enzymes, which confer resistance to beta-lactam antibiotics, including cefixime (Feneley et al., 2015).

The use of urinary catheters, especially over a long period of time, is one of the main factors that affect antibiotic resistance in CKD patients. Urinary catheters, both urethral and suprapubic inserted, are often the breeding ground for pathogenic bacteria due to the formation of biofilms. Biofilm is a complex and organized layer of microbes, which attaches to the surface of the catheter and provides protection against bacteria from the body's immune response as well as the effects of antibiotics. This biofilm allows bacteria to survive in unfavorable conditions, including exposure to antibiotics, by creating a microenvironment that protects bacteria from drugs. In addition, biofilms also serve as a container for bacteria to exchange genetic material, including antibiotic resistance genes, thereby accelerating the spread of resistance among different strains of bacteria (Feneley et al., 2015).

In a urinary catheter, a biofilm begins to form as soon as the catheter is inserted. This process begins with the attachment of proteins and organic molecules from the urine to the surface of the catheter, which creates a substrate for bacteria to attach to and multiply. Once the bacteria successfully attached, they began producing an extracellular matrix that protected microbial communities from the influence of the outside environment, including antibiotics. Bacteria such as *Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* are often found in biofilms formed on urine catheters. These three bacteria have the ability to produce the enzyme beta-lactamase, which directly breaks down the structure of beta-lactam antibiotics such as cefixime, thus making them ineffective in killing bacteria (Feneley et al., 2015).

In addition, urinary catheters used for a long period of time also increase the risk of recurrent urinary tract infections (UTIs). These infections are often caused by bacteria that have become resistant to different types of antibiotics, including cefixime, making treatment more difficult. In a clinical context, prolonged use of catheters not only increases the risk of bacterial colonization, but also worsens the condition of CKD patients because uncontrolled infections can lead to serious complications, such as sepsis or further kidney damage. Therefore, it is

important to limit the duration of use of the catheter and ensure that this device is only used when absolutely necessary. Another strategy that can be applied is the use of catheters with materials designed to prevent the formation of biofilms, such as silver-plated catheters or those containing antimicrobial agents, although its effectiveness still requires further research (Feneley et al., 2015).

These findings are in line with various previous studies that have shown that prolonged hospitalization and use of invasive medical devices increase the risk of resistant bacterial infections. A study reported that hospitalized CKD patients had a high risk of developing nosocomial infections due to multidrug-resistant bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*. The use of medical devices, such as urinary catheters, contributes to the formation of biofilms that protect bacteria from the effects of antibiotics (Santra et al., 2015). In addition, CKD patients are more susceptible to urinary tract infections due to colonization of resistant bacteria, especially in patients who undergo hospitalization for more than five days (Shankar et al., 2021). This study makes an additional contribution by showing a specific relationship between the duration of hospitalization, catheter use, and cefixime resistance in CKD patients, which has not been widely explored in previous studies.

This research has several advantages that are important to note. One of them is a specific focus on cefixime, which is one of the beta-lactam antibiotics often used to treat urinary tract infections in CKD patients. This focus provides deeper insights into patterns of resistance to cefixime, which can help in clinical decision-making regarding more effective antibiotic selection. In addition, the study successfully identified a significant relationship between the duration of hospitalization, catheter use, and cefixime resistance levels, which provides a solid basis for the development of infection prevention strategies in hospitals. These findings are also relevant for day-to-day clinical practice as they highlight the importance of invasive medical device management and duration of hospitalization to reduce the risk of antibiotic resistance in CKD patients.

Implications of this study include the need for policies to limit the duration of use of invasive medical devices, such as catheters, to reduce the risk of biofilm formation and antibiotic resistance. Closer monitoring of CKD patients who are hospitalized for a long time is essential to prevent nosocomial infections caused by resistant bacteria. In addition, the development of stricter antibiotic management protocols, including the use of antibiotics tailored to the results of bacterial sensitivity tests, is needed to reduce selection pressure on resistant bacteria. Further research is needed to explore the molecular mechanisms of cefixime resistance, including the role of biofilms and beta-lactamase enzymes, as well as to develop more effective prevention strategies. By understanding the factors that affect cefixime resistance, more effective measures can be developed to reduce the prevalence of antibiotic resistance in CKD patients.

Bacterial Resistance to Antibiotics

The study also showed a pattern of resistance of six bacterial species to various antibiotics, including cefixime. Bacteria such as *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* show high resistance to cefixime, while *Pseudomonas aeruginosa* and *Clostridium difficile* are comparatively more sensitive. Antibiotic resistance to these bacteria is a major challenge in the management of infections, especially in patients with chronic kidney disease (CKD), who have limitations in antibiotic choices. This study aims to analyze the resistance mechanisms and clinical implications of each bacterium to support more effective management of infections.

Tabel 3. Bacterial Resistance to Antibiotics

No	Bacterial Species	Antibiotic Names				
		Ampicillin	Trimethoprim	Ciprofloxacin	Metronidazol	Cefixime
1.	Escherichia coli	Yes	Yes	Yes	Yes	Yes
2.	Staphylococcus aureus	Yes	No	No	Yes	Yes
3.	Klebsiella pneumoniae	Yes	Yes	No	Yes	Yes

4.	Pseudo-monas aerugi-nosa	Yes	No	No	Yes	No
5.	Clostri-dium difficile	Yes	No	Yes	No	No
6.	Entero-bacter	Yes	No	Yes	No	Yes

Escherichia coli

Escherichia coli is one of the most resistant bacteria to cefixime. The main mechanism of resistance is the overproduction of AmpC β-lactamase, an enzyme capable of hydrolyzing beta-lactam antibiotics, including cefixime. AmpC β-lactamase significantly reduces the effectiveness of cefixime in treating urinary tract infections, especially in CKD patients. In addition, the spread of resistant strains such as ST12 in the community further exacerbates the situation. The combination of cefixime with β-lactamase inhibitors, such as amoxicillin/clavulanate, has been shown to increase therapeutic effectiveness against infections caused by E. coli (Zaragoza et al., 2024; Al-Tamimi et al., 2022). The clinical implication is the need for close monitoring of cefixime use to prevent the spread of resistance.

Staphylococcus aureus

In *Staphylococcus aureus*, resistance to cefixime is caused by the production of β-lactamase and changes in the target enzyme in the bacterial cell wall. Although resistance to cefixime is lower compared to ampicillin, this remains a challenge, especially in CKD patients who have limited therapeutic options. Antibiotic dosage adjustment is an important step to prevent the side effects of kidney toxicity while reducing the risk of further development of resistance (Vacaroiu et al., 2022). The study also suggests that resistance to S. *aureus* requires a more cautious approach to therapy, including the selection of alternative antibiotics that are safer for the kidneys.

Klebsiella pneumoniae

Klebsiella pneumoniae exhibit high resistance to cefixime, which is caused by the production of ESBL and AmpC enzymes β-lactamase. This resistance has significant clinical impacts, including increased mortality rates, longer duration of hospitalization, and higher health costs. Research shows that selection pressure due to uncontrolled use of antibiotics in hospitals is a major factor in the spread of resistance (Zhen et al., 2020). Therefore, a stricter antibiotic use policy is urgently needed to reduce the prevalence of resistance in K. *pneumoniae*.

Pseudomonas aeruginosa

In contrast to other bacteria, *Pseudomonas aeruginosa* shows a higher sensitivity to cefixime. However, resistance to other antibiotics such as ampicillin and metronidazole remains a major concern. The mechanism of resistance in *P. aeruginosa* involves the loss of outer membrane porines and the activity of the efflux pump, which reduces the concentration of antibiotics inside the bacterial cells. Strict monitoring of antibiotic doses in CKD patients is essential to prevent drug toxicity while inhibiting the development of broad-spectrum resistance (Chahine, 2022). The relative sensitivity of *P. aeruginosa* to cefixime indicates the potential of this antibiotic in the management of infections caused by the bacteria.

Clostridium difficile

Clostridium difficile tends to be more sensitive to cefixime compared to other antibiotics such as ampicillin and ciprofloxacin. However, resistance to these bacteria is often associated with irrational use of antibiotics, which disrupt the normal gut microbiota and facilitate the colonization of resistant strains. Strict antibiotic control policies in healthcare facilities are essential to prevent further resistance to *C. difficile* (Vacaroiu et al., 2022). Additionally, more selective use of antibiotics can help maintain the balance of the gut microbiota and reduce the risk of reinfection.

Enterobacter

Enterobacter exhibits significant resistance to cefixime, which is largely due to the acquisition of the enzyme beta-lactamase through horizontal gene transfer. This resistance is a major challenge in CKD patients, as the choice of antibiotics that are safe for the kidneys is very limited. Research emphasizes the importance of a multidisciplinary approach in the management of infections caused by *Enterobacter*, including the use of combination therapy and strict monitoring of renal function

(Aloy et al., 2020). The clinical implication is the need to develop more effective therapeutic strategies to overcome resistance in these bacteria.

This study shows that resistance to cefixime in *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae,* and *Enterobacter* is a significant problem, especially in CKD patients. Resistance mechanisms such as the production of AmpC β-lactamase and ESBL are the main factors affecting the effectiveness of cefixime. In contrast, *Pseudomonas aeruginosa* and *Clostridium difficile* show higher sensitivity to cefixime, although resistance to other antibiotics remains a concern. The implications of this study include the need for stricter antibiotic use policies, especially in hospitals, to reduce the selection pressures that drive resistance. Careful monitoring of antibiotic doses in CKD patients is essential to prevent drug toxicity while inhibiting the development of broad-spectrum resistance. In addition, ongoing education for medical personnel regarding the rational use of antibiotics should be a priority to ensure adherence to clinical guidelines and prevent the spread of resistance in the community.

The Relationship Between Cefixime Resistance and CKD Stage 4-5 Patients

Antibiotic resistance not only worsens patients' clinical outcomes, but also creates serious public health problems. This study aims to explore the relationship between cefixime resistance and advanced CKD, as well as identify the main mechanisms that contribute to this resistance. By understanding this relationship, it is hoped that more effective intervention strategies can be found to overcome antibiotic resistance in CKD patients.

Tabel 4. The Relationship Between Cefixime Resistance and CKD Stage 4-5 Patients

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	34.714[a]	15	.003
Likelihood Ratio	40.029	15	.000
Linear-by-Linear Association	1.311	1	.252
N of Valid Cases	30		

The results showed a significant correlation between cefixime resistance and patients with chronic kidney disease (CKD), especially at stages 4-5. Pearson's chi-square assay [$\chi^2 = 34.714$] with significance level [$p = 0.003$] showed that advanced CKD significantly affected the development of antibiotic resistance. In addition, the probability ratio test ([$p = 0.000$]) further strengthens these findings. This correlation suggests that the clinical conditions of advanced CKD patients may create an environment conducive to antibiotic resistance, especially resistance to cefixime.

This relationship can be explained by several interrelated mechanisms, including gut microbiome alterations, selective pressure due to irrational antibiotic use, bacterial molecular resistance mechanisms, and specific clinical conditions in CKD patients. Alterations in the gut microbiome, or dysbiosis, in CKD patients are among the major contributors to antibiotic resistance. Dysbiosis results from the accumulation of uremic toxins, dietary changes and repeated antibiotic exposure, leading to increased colonisation of resistant pathogenic bacteria. Studies have shown that this dysbiosis weakens the body's ability to fight infection and creates an environment conducive to the growth of resistant uropathogens, including cefixime resistant strains. This condition is further exacerbated by reduced production of protective metabolites, such as short-chain fatty acids, that normally help maintain the balance of the gut microbiome (Wehedy et al., 2022).

Selective pressure from irrational antibiotic use is another key factor in the emergence of cefixime resistance. Studies in Indonesia have shown that overuse of cefixime, particularly in CKD patients, has led to an increase in resistance among uropathogenic bacteria such as *Escherichia coli* and *Klebsiella pneumoniae.* This selective pressure results from repeated exposure to antibiotics and favours the proliferation of resistant bacterial strains. These findings highlight the urgent need for evidence-based antibiotic stewardship policies to prevent the spread of resistance, especially in vulnerable populations such as patients with advanced CKD (Ramdhani et al., 2021).

At the molecular level, cefixime resistance in uropathogens is primarily mediated by the production of extended-spectrum beta-

lactamases (ESBLs), which degrade beta-lactam antibiotics. In addition, efflux pump activity in resistant bacteria further contributes to resistance by actively expelling antibiotics from bacterial cells, thereby reducing their efficacy. Research has shown that uropathogenic bacteria in CKD patients often harbor genes encoding these resistance mechanisms, making antibiotic therapy less effective, especially in advanced stages of CKD (Ahmed et al., 2022).

CKD patients undergoing haemodialysis are at increased risk of antibiotic resistance due to recurrent infections, particularly catheter-related bloodstream infections (CRBSIs). On average, haemodialysis patients experience up to six times more infections than the general population, often requiring aggressive antibiotic therapy such as cefixime. The combination of advanced CKD, intensive antibiotic therapy and haemodialysis-associated infections creates an environment conducive to the proliferation of resistant bacteria (Chhakchhuak et al., 2023).

In addition to resistance concerns, the use of cefixime in CKD patients may also lead to adverse effects such as cognitive impairment due to impaired drug elimination. Declining kidney function in CKD patients hampers antibiotic excretion, leading to increased accumulation of the drug in the body. Over time, this not only exacerbates antibiotic resistance but also worsens the quality of life of CKD patients. Adjusting antibiotic doses according to CKD severity is therefore essential to minimise these risks (Liabeuf et al., 2024).

Cefixime-induced nephrotoxicity is a major concern in CKD patients, especially those in advanced stages with severely impaired renal function. This antibiotic can directly contribute to kidney damage, creating a vicious cycle in which declining renal function increases the risk of resistance due to prolonged antibiotic exposure (Dicu-Andreescu et al., 2023). The problem of resistance is exacerbated by deviations from clinical guidelines in antibiotic prescribing. Many CKD patients receive antibiotic therapy without consideration of disease severity, leading to inappropriate dosing. Subtherapeutic doses render treatment ineffective, while excessive doses increase the risk of adverse effects and resistance. These findings highlight the need for strict antibiotic monitoring in CKD patients to reduce the development of resistance (Valladales-Restrepo et al., 2024).

The results of this study have important implications in clinical management and health policies related to the use of antibiotics in patients with advanced chronic kidney disease (CKD). The finding of a significant association between cefixime resistance and stage 4–5 CKD confirms the need for individual antibiotic dose adjustments based on the severity of kidney disease to prevent drug accumulation, neurocognitive side effects, and nephrotoxicity. In addition, these findings highlight the importance of implementing stricter antibiotic stewardship policies to limit the irrational use of cefixime, especially in vulnerable populations such as haemodialysis patients who are at high risk of recurrent infections and recurrent antibiotic therapy. Intestinal microbiome dysbiosis that is common in CKD patients is also an important factor that needs to be considered, as it contributes to the colonization of resistant bacteria and decreased immune system effectiveness. Therefore, a multidisciplinary approach that involves monitoring the use of antibiotics, dietary modifications, and the development of alternative therapies is indispensable. These implications call for further research on the molecular mechanisms of resistance, long-term evaluation of antibiotic use patterns, and innovations in safer and more effective therapies for patients with kidney disorders to inhibit the systemic rate of antibiotic resistance.

Conclusion

This study reveals a significant association between cefixime resistance and patients with chronic kidney disease (CKD) stage 4-5 at Harapan Keluarga Hospital, with factors such as gender, duration of antibiotic use, comorbidities, length of hospital stay and catheter use influencing resistance rates. Male patients, those using antibiotics for more than 14 days and those with comorbidities such as type II diabetes and hyperlipidaemia had higher levels of resistance. In addition, *Escherichia coli* and *Klebsiella pneumoniae* showed significant resistance, while Pseudomonas aeruginosa was more susceptible. These findings underscore the need for strict antibiotic stewardship, dose

adjustment based on CKD stage and improved medical education to mitigate resistance and improve clinical outcomes in CKD patients.

Acknowledgment

We would like to express our sincere gratitude to Dr. dr. Anak Agung Ayu Niti Wedayani, M.Sc., as the Head of Degenerative and Primary Neoplasm Research, for overseeing this study. Our appreciation also goes to dr. Maz Isa Ansyori, spBTKV, dr. Akhada Maulana, Sp.U, as well as for their invaluable support. Furthermore, we extend our deepest gratitude to all parties who have provided assistance throughout the process of completing this journal.

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