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# Association of Antibiotic Rationality with Clinical Outcomes in Diabetic Foot Ulcer Patients in a Hospital in Badung, Bali

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**ABSTRACT:** Type II Diabetes Mellitus (T2DM) patients are at high risk of systemic infections, such as Diabetic Foot Ulcer (DFU). The rationality of antibiotic use in Indonesia has not yet reached 100%, which negatively impacts clinical outcomes. This study aims to analyze the relationship between the rationality of antibiotic use and clinical outcomes in T2DM patients with DFU at Badung Bali Hospital from July to September 2024. The study design was cross-sectional, involving 153 respondents with inclusion criteria (patients diagnosed with T2DM with DFU {January 2023-July 2024}, received antidiabetics and antibiotics) and exclusion (received antibiotics <24 hours {outpatient}, <72 hours {inpatient}, moved to another health facility). The rationality of antibiotic use was assessed using the Gyssens method supplemented by the latest therapeutic guidelines, and then the percentage was calculated. The analysis of the relationship between rationality and clinical outcomes was tested using Kendall's Tau-b. The results of the Gyssens evaluation showed that 96.92% and 98.13% were irrational in the outpatient and inpatient settings, respectively. Clinical outcomes were improved by more than 60%. There was a significant relationship (p = 0.009; r = -0.290) in inpatients, but not in outpatients (p = 0.493; r = -0.065). The low rationality of antibiotic use in this finding can serve as a basis for practitioners to evaluate and prevent resistance and worsening conditions.

**Keywords**: Antibiotics; clinical outcome; diabetic foot ulcer; rationality; type 2 diabetes mellitus

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## INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a common form of diabetes that accounts for 90% of cases worldwide (IDF, 2021). According to the Bali Provincial Health Profile Data (2021), Denpasar City has the highest number of T2DM sufferers, with 15,366 cases, while Badung Regency ranks third with 2,980 cases (Dinas Kesehatan Provinsi Bali, 2021). Individuals with this disease face a 4.4 times higher risk of developing systemic infections (Burekovic et al., 2014). Several studies have shown that one prevalent type of infection among T2DM patients is Diabetic Foot Ulcers (DFU), reported in over 50% of cases in Indonesia and 90% in Romania (Najihah & Paridah, 2021; Pemayun et al., 2015; Stancu et al., 2023).

DFU infection refers to a condition characterized by open wounds on the skin's surface caused by bacteria, leading to an inflammatory response and tissue damage. This condition is defined by a bacterial count of ≥ $10^5$, a body temperature higher than 37°C, and a leukocyte count exceeding 11,000 cells/µL (Agistia et al., 2017; Risnawati et al., 2018). Types of DFU include gangrene, diabetic ulcers, cellulitis, and osteomyelitis (Soelistijo, 2021). Management of DFU infection requires the use of antibiotics, which can be administered either empirically or definitively, according to aggressive therapy guidelines, to treat the infection and prevent further deterioration (Setyoningsih et al., 2022). The administration of antibiotics must be carried out rationally to prevent the development of antibiotic resistance (Sari et al., 2018). In Indonesia, the evaluation of antibiotic use rationality is conducted qualitatively using the Gyssens method (Permenkes RI, 2015).

Several studies in the Kudus (11.00%), Purwokerto (65.63%), and Surakarta (75.00%) areas showed that the rationality of antibiotic use had not reached 100% in DFU patients with gangrene and ulcers (Setyoningsih et al., 2022; Nafingah et al., 2022; Setiyanto & Suhesti, 2020). Irrational use of antibiotics in patients with T2DM hurts clinical outcomes such as antibiotic resistance, delayed wound healing to amputation, increased cost burden, worsening of the disease and death (Nafingah et al., 2022). Study by the Functional Medical Staff of Internal Medicine Riau and Sari (2018) at Dr. Soetomo General Hospital. M. Djamil Padang explained that the irrational use of antibiotics (ceftriaxone, ceftazidime, ampicillin sulbactam, meropenem, netilmicin; ceftriaxone, ciprofloxacin, cefotaxime) resulted in increased bacterial resistance (21.05%; 10.72%) in diabetic ulcer patients (Agistia et al., 2017; Sari et al., 2018).

Previous studies have primarily focused on the rational use of antibiotics in DMT2 patients with gangrene and diabetic ulcer infections. However, they have not addressed DMT2 infections as a whole or their impact on patient clinical outcomes. Therefore, this study aims to analyze the relationship between the rationality of antibiotic use in DMT2 patients with various DMT2 infections and their clinical outcomes at a hospital in the Badung region of Bali.

## METHODS

### Research Design

This study employed a cross-sectional design, observing all variables—both independent and dependent—simultaneously at the Outpatient and Inpatient Installations of a regional hospital in Badung, Bali, from July to September 2024. The study received

approval from the Ethics Committee, as well as the necessary hospital permits (No: 070/6388/RSDM/2024).

**Research Sample**

The study included a total of 153 participants, comprising 103 outpatients and 50 inpatients. A purposive sampling technique was utilized, based on specific criteria established by the researcher. The inclusion criteria included patients diagnosed with Type 2 Diabetes Mellitus (T2DM) who had Diabetic Foot Ulcers (DFU) infections, such as ulcers, cellulitis, osteomyelitis, or gangrene, during their outpatient or inpatient care from January 2023 to July 2024. These participants could have either complications or comorbidities unrelated to the infection, must have been receiving antidiabetic medication and antibiotics, and needed to have complete medical records. Exclusion criteria included patients who had received antibiotics for less than 24 hours (outpatients) or less than 72 hours (inpatients), as well as those who transferred to another health facility.

**Data Collection and Analysis**

Data were collected using a standardized form to record information from the respondents' medical records. The rationality of antibiotic use was assessed according to the Gyssens method, categorizing usage into rational (category 0) and irrational (categories I, II, III, IV, V, or VI) (Setiyanto & Suhesti, 2020). Clinical outcomes were classified as either "improved" or "not improved." "Improved" was defined as a positive response to therapy in outpatients (as determined by a doctor's diagnosis) or in inpatients (indicated by one of the following improvements: a doctor's diagnosis, a decrease in leukocyte count to normal, reduced pain, or the resolution of fever). Conversely, an outcome was classified as "not improved" if there was no observed positive response to therapy after antibiotic administration.

Demographic data, disease descriptions, patterns of antidiabetic and antibiotic use, clinical outcomes, and evaluations of rationality were analyzed using Microsoft Excel. The relationship between rationality (treated as ordinal data) and clinical outcomes (also treated as ordinal data) was evaluated using Kendall's Tau-b.

## RESULT AND DISCUSSION

According to Table 1, both outpatients and inpatients predominantly consisted of males (53.40% for outpatients and 54.00% for inpatients), with a significant majority being aged 45 years or older (91.26% of outpatients and 88.00% of inpatients). This aligns with findings from several studies, which indicate that most patients with DFU are males aged 45 years or older (Agistia et al., 2017; Rachmawati et al., 2021; Moghaddam, 2023). This trend may be linked to reduced joint mobility and increased foot pressure in men (Beta et al., 2022).

At ages over 45, there is a decline in insulin secretion and an increase in insulin resistance due to the degenerative processes associated with ageing. This change significantly impacts the body's ability to regulate blood glucose levels (Detty et al., 2020; Nurhanifah, 2017). As shown in Table 2, the glycemic profiles of patients undergoing both treatments indicate levels above 126 mg/dL (74.76% and 76.00%) in individuals with Diabetes Mellitus (DM) for 1-5 years (57.28% and 60.00%). Several studies support the observation that a majority of patients with poorly controlled glycemic profiles have had diabetes for 1-5 years (Kalsum et al., 2024; Astuti et al., 2020; Moghaddam, 2023). Glycemic control is closely linked to the development of various complications and the overall severity of diabetes (Fitria et al., 2017; Mamurani et al., 2023). Furthermore, the average length of hospital stay for respondents was 3-6 days (76.00%). This duration of treatment

is associated with cases that have not shown improvement due to the seriousness of wound infections, necessitating an extended period of care (Sari et al., 2018).

**Table 1.** Demographics of outpatients and inpatients

| Characteristics | Category | N (%) |
|---|---|---|
| **Outpatient** | | **103 (100%)** |
| Gender | Male | 55 (53.40%) |
| | Female | 48 (46.60%) |
| Age (years) | <45 | 9 (8.74%) |
| | 45-60 | 55 (53.40%) |
| | >60 | 39 (37.86%) |
| **Inpatient** | | **50 (100%)** |
| Gender | Male | 27 (54.00%) |
| | Female | 23 (46.00%) |
| Age (years) | <45 | 6 (12.00%) |
| | 45-60 | 22 (44.00%) |
| | >60 | 22 (44.00%) |

**Table II.** Glycemic profile and infection characteristics of DFU patients

| Characteristics | Category | N (%) |
|---|---|---|
| **Outpatient** | | **103 (100%)** |
| Glycemic profile (mg/dL) | <126 | 26 (25.24%) |
| | >126 | 77 (74.76%) |
| Duration of DM (years) | 1-5 | 59 (57.28%) |
| | 6-10 | 38 (36.89%) |
| | 11-15 | 6 (5.83%) |
| Degree of infection | Lightweight | 49 (47.57%) |
| | Medium | 54 (52.43%) |
| *Wagner* Classification | 0 | 9 (8.74%) |
| | 1 | 18 (17.48%) |
| | 2 | 24 (23.30%) |
| | 3 | 5 (4.85%) |
| | 4 | 47 (45.63%) |
| Symptoms experienced | Pain | 54 (51.92%) |
| | Swelling | 27 (25.96%) |
| | Tingling | 20 (19.23%) |
| | Stiff | 3 (2.88%) |
| Type of DFU | Gangrene | 49 (47.57%) |
| | Diabetic ulcer | 41 (39.81%) |
| | Cellulitis | 10 (9.71%) |
| | Osteomylitis | 3 (2.91%) |
| **Inpatient** | | **50 (100%)** |
| Glycemic profile (mg/dL) | <126 | 12 (24.00%) |
| | >126 | 38 (76.00%) |
| Duration of DM (years) | 1-5 | 30 (60.00%) |
| | 6-10 | 17 (34.00%) |
| | 11-15 | 3 (6.00%) |
| Length of hospitalization days | 3-6 | 38 (76.00%) |
| | 7-11 | 12 (24.00%) |
| Degree of infection | Medium | 28 (56.00%) |
| | Weight | 22 (44.00%) |

**Table 3.** Pattern of antidiabetic use

| Usage Pattern | Class (type) | N (%) |
|---|---|---|
| **Outpatient** | | |
| Single | Biguanid (metformin); mixed analog insulin (70% *protamine* aspart, 30% aspart); long-acting analog insulin (glargin); rapid-acting analog insulin (aspart) | 7 (6.80%); 6 (5.83%); 2 (1.94%); 1 (0.97%) |
| Combination of two | Fast-acting analog insulin, long-acting analog insulin (glulisin + glargin); long-acting analog insulin, fast-acting analog insulin (glargin + aspart); sulfonylurea, biguanid (glimepirid + metformin); long-acting analog insulin, biguanid (glargin + metformin); rapid-acting insulin analogs, long-acting insulin analogs (glulisin + detemir); rapid-acting insulin analogs, long-acting insulin analogs (aspart + detemir); sulfonylureas, long-acting insulin analogs (glikazid + glargin); long-acting insulin analogs (glargin + glargin) | 30 (29.13%); 25 (24.27%); 20 (19.42%); 1 (0.97%); 1 (0.97%); 1 (0.97%); 1 (0.97%); 1 (0.97%); 1 (0.97%) |
| Combination of three | Biguanids, sulfonylureas, long-acting analog insulins (metformin + glimepiride + glargin); rapid-acting analog insulins, mixed analog insulins (aspart + {a combination of 70% *degludec* + 30% aspart}) | 2 (1.94%); 1 (0.97%) |
| **Total** | | **103 (100%)** |
| **Inpatient** | | |
| Single | Biguanid (metformin); long-acting insulin analog (glargin); rapid-acting insulin analog (glulisin); sulfonylurea (glycazide); rapid-acting insulin analog (aspart) | 3 (6.00%); 2 (4.00%); 1 (2.00%); 1 (2.00%); 1 (2.00%) |
| **Inpatient** | | |
| Combination of two | Fast-acting insulin analogs, long-acting insulin analogs (glulisin + glargin); long-acting insulin analogs, fast-acting insulin analogs (glargin + aspart); sulfonylureas, biguanids (glimepiride + metformin); fast-acting insulin analogs, long-acting insulin analogs (glulisin + detemir); Sulfonylureas, biguanids (glibenclamide + metformin); long-acting insulin analogs, biguanids (glargin + metformin) | 23 (46.00%); 11 (22.00%); 3 (6.00%); 2 (4.00%); 1 (2.00%); 1 (2.00%) |
| Combination of three | Rapid-acting analog insulin, mixed analog insulin (aspart + {a combination of 70% *degludec* + 30% aspart}) | 1 (2.00%) |
| **Total** | | **50 (100%)** |

The degree of infection among outpatients and inpatients was found to be moderate, with 52.43% of outpatients and 56.00% of inpatients experiencing such infections. According to Wagner's classification, the severity was categorized as grade 4 in 45.63% of the outpatient cases and 38.00% of the inpatient cases. Moderate infections, as classified by the PEDIS system, are identified based on clinical examinations conducted upon admission to the hospital. These infections often result from factors such as uncontrolled blood sugar levels, which can weaken the body's immune response and lead to more severe infections. Additionally, delays in referring patients to the hospital can exacerbate their condition and elevate the severity of their infections (Jalilian et al., 2020;

Pratiwi & Barry, 2024) (Jalilian et al., 2020) (Pratiwi & Barry, 2024). Wagner's classification, which ranges from 0 to 5, is utilized to assess the level of lower extremity complications and to guide therapeutic management (Fitria et al., 2017; Nisak, 2021).

The symptoms observed in both outpatients and inpatients predominantly included pain, reported at rates of 51.92% and 82.46%, respectively. The types of DFU identified were gangrene, occurring in 47.57% of cases, and cellulitis, found in 40.00%. Consistent with previous studies, most patients with DFU experienced pain symptoms associated with these types of diseases (Nisak, 2021; Herdani et al., 2023; Lellu, 2021; Stancu et al., 2023; Krishnappa et al., 2020; Sirijatuphat et al., 2020). Pain is a significant indicator of tissue or skin damage, which can result from peripheral neuropathy (Herdani et al., 2023). Gangrene is an infection of soft tissue and skin that occurs when necrotic tissue is affected by emboli from large arterial blood vessels, resulting in a cessation of blood supply (Rosa et al., 2019; Soelistijo, 2021). In contrast, cellulitis is typically caused by bacterial infections of damaged skin, leading to acute inflammation in the subcutaneous tissue and muscles (Anggriani et al., 2015; Soelistijo, 2021).

The most common pattern of antidiabetic medication use, as shown in Table 3, is a combination of rapid-acting insulin (glulisine) and long-acting insulin (glargine), used by both outpatients (29.13%) and inpatients (46.00%), respectively. This finding is consistent with previous studies conducted in Bali (33.75%), Manado (8.33%), and Pekanbaru (7.90%), which also indicated that the combination of rapid-acting and long-acting insulin is the most prevalent treatment (Djahido et al., 2020; Gamayanti et al., 2018; Inayah et al., 2017). This insulin combination can provide a more effective reduction in blood glucose levels by addressing both basal and prandial insulin requirements (Soelistijo, 2021).

**Table 4.** Outpatient antibiotic use pattern

| Goals | Type | Usage rules | N (%) |
|---|---|---|---|
| **Single** | | | |
| 3rd generation cephalosporins | Cefixime | 200 mg, 2x1, 5 days, PO | 87 (84.46%) |
| Metronidazole | Metronidazole | 500 mg, 3x1, 7 days, PO | 2 (1.94%) |
| Macrolides | Azithromycin | 500 mg, 1x1, 7 days, PO | 1 (0.97%) |
| 3rd generation cephalosporins | Ceftriaxone | 1 g, 1x1, 3 days, IV | 1 (0.97%) |
| 1st generation cephalosporins | Cefadroxil | 500 mg, 2x1, 7 days, PO | 1 (0.97%) |
| Quinolones | Ciprofloxacin | 500 mg, 2x1, 7 days, PO | 1 (0.97%) |
| **Combination** | | | |
| 3rd generation cephalosporin + metronidazole | Cefixime + metronidazole | 100 mg (2x1), 500 mg (3x1), 5-7 days, PO | 9 (8.74) |
| | Ceftriaxone + metronidazole | 1g (2x1), 500 mg (3x1), 3 days, IV | 1 (0.97%) |
| **Total** | | | **103 (100%)** |

*Description: PO = Per Oral, IV = Intra Venous

The data on empirical antibiotic use presented in Table 4 indicate that cefixime is the most frequently used antibiotic among outpatients, accounting for 84.46% of cases. According to the Permenkes RI (2021), the selection of antibiotics for outpatient patients with lower kidney disease (LKD) is tailored based on the type of infection. For osteomyelitis, oral clindamycin is recommended at a dosage of 300-450 mg every 8 hours. For cellulitis, cloxacillin is prescribed at a dose of 500 mg every 6 hours. In cases of

gangrene, a combination of oral amoxicillin-clavulanate (625 mg every 8 hours) and oral metronidazole (500 mg every 8 hours) is advised (Permenkes RI, 2021). Cefixime is a third-generation cephalosporin antibiotic that inhibits transpeptidation, a process crucial for peptidoglycan synthesis in bacterial cell walls, ultimately leading to bacterial cell death (Harahap, 2019). Although cefixime is not typically recommended as an oral treatment option for outpatients with DFU, it is still commonly used in Indonesia (31.00%) and India (5.00%) (Herdani et al., 2023; Rajesh et al., 2020). The advantages of cefixime include its broad spectrum of activity against both Gram-positive and Gram-negative bacteria, rapid intestinal absorption, and stability due to the presence of a vinyl group at position 3. Furthermore, it is readily available and cost-effective (Herdani et al., 2023).

The antibiotic usage patterns displayed in Table V indicate that inpatients primarily utilise a combination of ceftriaxone and metronidazole, accounting for 26.00% of cases. According to the Permenkes RI (2021), the antibiotic regimen for inpatient patients with DFU includes the following treatments for specific conditions: for osteomyelitis, ampicillin-sulbactam is administered intravenously at a dose of 3 grams every 6 hours. For cellulitis, cloxacillin is administered at a dose of 500 mg every 6 hours, oral amoxicillin-clavulanate at 625 mg every 8 hours, oral clindamycin at 300-450 mg every 6 hours, and cefuroxime is administered intravenously at 1.5 grams every 8 hours, followed by oral cefadroxil at 500 mg every 12 hours. For gangrene, a combination of intravenous ampicillin at 1 gram every 6 hours with intravenous metronidazole at 500-750 mg every 8 hours is recommended (Permenkes RI, 2021).

Table 5 illustrates that, among hospitalised patients, the most common combination of definitive antibiotics used is ceftriaxone and metronidazole, accounting for 26.00% of cases. According to the Permenkes RI (2021), the selection of antibiotics for hospitalized patients with DFU is tailored based on the type of infection and the results of microbiological testing (Permenkes RI, 2021). Metronidazole functions by inhibiting nucleic acid synthesis, which damages bacterial DNA (Beta et al., 2022). Consistent with previous studies conducted in Samarinda (81.00%), Riau (79.00%), and Purwokerto (58.82%), it has been demonstrated that the combination of ceftriaxone and metronidazole is frequently used in patients with diabetic ulcers and gangrene (Beta et al., 2022; Agistia et al., 2017; Nafingah et al., 2022). This antibiotic combination is recommended for treating moderate to severe infections caused by bacteria such as Staphylococcus aureus, Streptococcus spp., Enterobacteriaceae, Clostridium spp., and Bacteroides spp. (Beta et al., 2022). Some advantages of using this combination include achieving a synergistic effect against microorganisms and reducing the risk of antibiotic resistance. Additionally, it is effective in broadening the spectrum of antibacterial activity against gram-positive, gram-negative, anaerobic, and aerobic bacteria (Beta et al., 2022; Sari et al., 2018).

According to Table VI, category IV for both outpatients and inpatients featured more effective antibiotics, with rates of 31.69% and 22.76%, respectively. These antibiotics were found to be less toxic (1.85% for outpatients and 23.13% for inpatients), cheaper (28.41% for outpatients and 6.34% for inpatients), and had a narrower spectrum (31.69% for outpatients and 22.39% for inpatients). Permenkes RI (2021) Guidelines for the Use of Antibiotics recommend selecting antibiotics based on the specific type of infection. For osteomyelitis, IV ampicillin-sulbactam or oral clindamycin is advised. For cellulitis, options include cloxacillin, clindamycin, or cefadroxil. In cases of gangrene or diabetic ulcers, IV ampicillin combined with IV metronidazole is recommended (Permenkes RI, 2021). In category IVb, a reference search was conducted using the Drug Information Handbook, edition 24, which included additional antibiotics based on therapeutic guidelines that have lower toxicity (American Pharmacists Association, 2015). The cost of antibiotics should be

a consideration to avoid incurring excessive expenses (Setyoningsih et al., 2022). Additionally, it is important to use antibiotics with a narrower spectrum to minimize the risk of antibiotic resistance (Permenkes RI, 2021).

**Table 5.** Inpatient antibiotic use pattern

| Goals | Type | Usage rules | Bacteria | N (%) |
|---|---|---|---|---|
| **Single** | | | | |
| 3rd generation cephalosporins | Ceftriaxone | 1 g, 2x1, 3 days, IV | *Klebsiella pneumonia, Staphylococus aureus* | 11 (22.00%) |
| | Cefixime | 200 mg, 2x1, 5 days, PO | *Staphylococus aureus, Pseudomonas aeruginosa, Staphylococus cohnii, Klebsiella pneumonia* | 7 (14.00%) |
| | Cefotaxime | 1 g, 3x1, 6 days, IV | *Staphylococus aureus* | 4 (8.00%) |
| 1st generation cephalosporins | Cefadroxil | 500 mg, 2x2, 2 days, PO | *Staphylococus aureus* | 1 (2.00%) |
| 3rd generation cephalosporin + metronidazole | Ceftriaxone + metronidazole | 1g (2x1), 500 mg (3x1), 5 days, IV | *Aeromonas hydrophil, Staphylococus aureus* | 13 (26.00%) |
| 3rd generation cephalosporin + metronidazole + 3rd generation cephalosporin | Ceftriaxone + metronidazole + cefixime | 1g (2x1, IV), 500 mg (3x1, IV), 200 mg (2x1, PO), 5 days | *Staphylococus aureus* | 4 (8.00%) |
| 3rd generation cephalosporin + metronidazole | Cefotaxime + metronidazole | 1 g, 500 mg, 3x1, 3 days, IV | *Staphylococus aureus* | 2 (4.00%) |
| 3rd generation cephalosporins | Ceftriaxone + cefixime | 1 g (IV), 200 mg (PO), 2x1, 5 days | *Pseudomonas aeruginosa, Staphylococus aureus* | 2 (4.00%) |
| 3rd generation cephalosporins + aminoglycosides | Ceftriaxone + gentamicin | 1 g, 80 mg, 2x1, 6 days, IV | *Staphylococus aureus* | 2 (4.00%) |
| Generation 3 cephalosporins + *protein synthesis inhibitors* | Ceftriaxone + clindamycin | 2 g (1x1, IV), 300 mg (3x3, PO), 5 days | *Staphylococus aureus* | 1 (2.00%) |
| Quinolones + 3rd generation cephalosporins | Ciprofloxacin + cefixime | 500 mg, 200 mg, 2x1, 3 days, PO | *Staphylococus aureus* | 1 (2.00%) |
| 3rd generation cephalosporin + metronidazole + quinolone | Ceftriaxone + metronidazole + moxifloxacin | 1 g (2x1), 500 mg (2x1), 400 mg (1x1), 6 days, IV | *Staphylococus aureus* | 1 (2.00%) |
| 3rd generation cephalosporins + quinolones | Ceftriaxone + levofloxacin | 1 g (2x1), 750 mg (1x1), 4 days, IV | *Staphylococus aureus* | 1 (2.00%) |
| **Total** | | | | **50 (100%)** |

*Description: PO = Per Oral, IV = Intra Venous

The evaluation results for category IIIa indicated that antibiotics were prescribed for too long in 0.37% of cases. Specifically, metronidazole was administered for 10 days during hospitalization, while the recommended duration is only 7 days (Permenkes RI,

2021). In category IIIb, it was observed that the duration of antibiotic administration was too short for both outpatient and inpatient care, with rates of 1.23% and 22.39% respectively. For instance, azithromycin and clindamycin were administered for only 3 days, whereas a course of 5 to 10 days is recommended, and metronidazole was administered for 3 days, whereas 7 days is suggested. The cephalosporin group included ceftriaxone and cefadroxil, which were used for 1 to 10 days but are recommended for 14 to 28 days, and cefixime, which was given for 3 days instead of the advised 5 to 10 days. Additionally, gentamicin, moxifloxacin, ciprofloxacin, and levofloxacin were prescribed for only 3 to 4 days, whereas the recommended duration is 7 to 14 days (American Pharmacists Association, 2015; Permenkes RI, 2021). Consistent with previous studies, it was found that antibiotic use among patients with ulcers and gangrene fell into category III, with rates of 2.80%, 12.31%, and 58.00% respectively (Nafingah et al., 2022; Setiyanto & Suhesti, 2020; Setyoningsih et al., 2022). According to the Permenkes RI (2021), inappropriate durations of antibiotic administration whether too long or too short can adversely affect treatment outcomes. Generally, the duration of antibiotic treatment is monitored and evaluated for at least 3 days to assess clinical improvement in patients (Permenkes RI, 2021).

According to Table 6, both outpatients and inpatients were classified under category II, with percentages of 0.31% and 0.75%, respectively. In category IIa, outpatients were prescribed azithromycin at a dose of 500 mg; however, it should have been administered as 500 mg on the first day and then 250 mg from the second to the fifth days. For inpatients, category IIb involved cefotaxime and metronidazole being given twice a day and once a day, respectively, whereas it should have been administered three times a day (Bergman & Shah, 2016). Previous studies have indicated the use of antibiotics categorised as II for patients with ulcers and gangrene at several hospitals, including Kudus Islamic Hospital (2.00%) and Margono Hospital (6.25%), as well as Dr Moewardi Surakarta, and Bagas Waras Klaten Hospital (22.20%) (Nafingah et al., 2022; Setiyanto & Suhesti, 2020; Setyoningsih et al., 2022). Inappropriate administration intervals are closely related to drug availability in the body. If the administration is not as required, microorganisms may regenerate and become stronger, leading to suboptimal effects and the triggering of antibiotic resistance (Herdani et al., 2023). Administering a dose that is too low can reduce drug bioavailability, shortening the drug's duration of action and complicating the selection of antibiotics for subsequent therapy (Cipolle et al., 2004). Optimal antibiotic efficacy is achieved when the timing of administration is appropriate (Herdani et al., 2023).

**Table 6.** *Gyssens* antibiotic rationality classification

| ***Gyssens* category** | ***Gyssens* Category Assessment** | **N (%)** |
|---|---|---|
| **Outpatient** | | |
| VI | Incomplete medical record data | 0 (0.00%) |
| V | No indication for antibiotic use | 0 (0.00%) |
| IVa | Other antibiotics are more effective | 103 (31.69%) |
| IVb | Other antibiotics are less toxic or safer | 6 (1.85%) |
| IVc | Other antibiotics are cheaper | 98 (28.41%) |
| IVd | Other antibiotics are narrower in spectrum | 103 (31.69%) |
| IIIa | Use of antibiotics for too long | 0 (0.00%) |
| IIIb | Antibiotic use is too short | 4 (1.23%) |
| IIa | Use of antibiotics not in the right dose | 1 (0.31%) |

Table 7 indicates that a significant majority of respondents, both outpatients and inpatients, experienced improved clinical outcomes, with rates of 61.17% and 98.00%, respectively. Clinical outcomes refer to the results observed in patients following therapy at the hospital. These outcomes are assessed based on several criteria: clinical improvement as determined by the physician, microbiological examination results (such as a decrease in leukocyte levels in the blood or normalization of these levels), a reduction in the severity of bacterial infections, typical vital signs (specifically a body temperature below 37.5°C), and the patient's reported level of pain.

**Table 7.** Clinical outcomes of patients

| Characteristics | Category | N (%) |
|---|---|---|
| **Outpatient** | | **103 (100%)** |
| Clinical outcomes | Improving | 63 (61.17%) |
| | Not improving | 40 (38.83) |
| **Inpatient** | | **50 (100%)** |
| Clinical outcomes | Improving | 49 (98.00%) |
| | Not improving | 1 (2.00%) |

Previous studies have reported that between 36.70% and 84.00% of patients with Diabetic Foot Ulcers (DFU) experienced improvements in their clinical outcomes (Agistia et al., 2017; Anggriani et al., 2015; Supriadi et al., 2020). Several factors contribute to these improvements, including controlled blood glucose levels in certain patients (25.24% and 24.00%), as well as comprehensive wound care treatments such as debridement and surgical interventions. These measures aim to accelerate the healing process, prevent amputations, and avoid further complications from the disease (Nisak, 2021; Sari et al., 2018).

**Table 8.** Relationship between rationality and clinical outcomes of patients

| Rationality | Clinical outcomes | | Total | P-value | Value of r |
|---|---|---|---|---|---|
| | Improved N (%) | Not improving N (%) | | | |
| **Outpatient** | | | | | |
| **Rational** | 5 (50.00%) | 5 (50.00%) | 10 (100%) | 0.493 | -0.065 |
| **Irrational** | 195 (61.91%) | 120 (38.09%) | 315 (100%) | | |
| **Inpatient** | | | | | |
| **Rational** | 4 (80.00%) | 1 (20.00%) | 5 (100%) | 0.009 | -0.290 |
| **Irrational** | 259 (98.48%) | 4 (1.52%) | 263 (100%) | | |

According to the statistical analysis presented in Table 8, there is an insignificant relationship (p = 0.493) with a very weak negative correlation (-0.065) between the rational use of antibiotics and clinical outcomes in outpatient settings. This negative correlation suggests that as the rationality of antibiotic use increases, the improvement in clinical outcomes diminishes. In contrast, among inpatients, a significant relationship was observed (p = 0.009) with a weak negative correlation (r =-0.290) between the rationality of treatment and clinical outcomes. Again, the negative direction indicates that higher

rationality in antibiotic use corresponds to lesser improvement in clinical outcomes. This finding aligns with the results of Setiyanto and Suhesti (2020), who reported a significant relationship (p = 0.041) with a moderate correlation between the rational use of antibiotics and therapeutic outcomes. Specifically, this study noted that the number of leukocytes was within normal limits in patients with type 2 diabetes mellitus (DMT2) who had ulcers and gangrene.

Findings from outpatient care showed insignificant results, potentially due to several factors, including age, duration of Diabetes Mellitus (DM), and the complications experienced by patients. Age can significantly impact wound healing; as individuals age, there is often a decline in physiological functions, which can slow down the wound healing process (Wahyuni, 2017). Additionally, research by Astuti et al. (2020) indicated a significant relationship between the duration of DM and the risk of complications, particularly microvascular complications such as neuropathy, which is a key factor contributing to the development of diabetic ulcers (Astuti et al., 2020).

In outpatient settings, the use of antibiotics is often irrational, yet patients tend to experience improved clinical outcomes. This improvement may be attributed to the broad-spectrum antibiotics prescribed, which effectively target both gram-positive and gram-negative bacteria. However, the irrational selection of antibiotics can contribute to the development of antibiotic resistance (Sari et al., 2018). It is important to note that this study has its limitations, as data collection was conducted retrospectively, relying on medical records without direct observation of the patients' clinical conditions.

## CONCLUSION

The results of the study indicated that most antibiotic use was irrational, despite improved clinical outcomes for patients, ranging from 60.00% to 98.00%. There was no significant relationship between the rationality of treatment and clinical outcomes in outpatients (p = 0.493; r = -0.065). However, a significant relationship was observed in another category (p=0.009; r=-0.290). This underscores the importance of using antibiotics rationally, adhering to aggressive therapy guidelines to cure patients, prevent worsening conditions, and combat antibiotic resistance. The low level of rational antibiotic use identified in this study serves as critical feedback for practitioners, highlighting the need to prevent antibiotic resistance and avoid deteriorating patient conditions, particularly in patients with DFU.

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## AUTHOR CONTRIBUTION

IPYP, NPDRWD, PMDR: Conduct literature reviews pertinent to the research, survey research sites, assist in preparing research proposals, take minutes of meetings and maintain archives and documentation related to research activities, prepare administration materials for managing research ethics reviews, create data collection sheets for gathering research data, guide research assistants in the data collection process, analyze research data, assist in compiling final research reports, and prepare manuscripts for research publications.

DWA: Manage research permits and ethics review submissions, assist in collecting and grouping research data.

## ETHICS APPROVAL

This study has obtained authorization from the Ethics Committee and permission from Mangusada Regional Hospital with the number 070/6388/RSDM/2024.

## CONFLICT OF INTEREST

None to declare.

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