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A Systematic Review of Randomized Controlled Trials of Antibiotic Use in Diabetic Foot Ulcer Infections: Focus on Clinical Cure

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ABSTRACT

Background: The use of antibiotics in diabetic foot ulcer infections (DFUI) is essential in reducing morbidity. Optimal administration of antibiotics can improve clinical outcomes and reduce the risk of antibiotic resistance. This study aims to review the efficacy, in terms of clinical cure, of various regimens and the duration of antibiotic administration in DFUI patients, based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The efficacy based on microbiological response is also reviewed as the secondary outcome.
Materials and Methods: We used three databases, namely PubMed, Scopus, and ScienceDirect, to search for randomized controlled trials (RCTs) in patients with DFUI who required antibiotics.
Results: A total of 16 studies were included in the systematic review. The study locations and bacterial patterns varied, with the most common pathogen being *Staphylococcus aureus*. Most studies did not demonstrate a significant difference in clinical cure and pathogen eradication, either in the comparison between systemic and topical antibiotics or in the duration of administration. Some studies had similar characteristics and were analyzed to conclude. These studies showed that ertapenem had comparable efficacy to piperacillin/tazobactam. Similar results were also conducted from studies of piperacillin-tazobactam+amoxicillin-clavulanic acid *vs.* moxifloxacin.
Conclusion: Most studies have heterogeneous characteristics, possibly due to differences in research location. Therefore, there is no strong evidence to recommend a specific antibiotic with the highest efficacy. However, since all included studies are RCTs, this review provides a good summary in considering antibiotic choices when treating DFUI patients.

Keywords: Antibiotics; Diabetic foot ulcer; Infection; Randomized controlled trial; Systematic review

INTRODUCTION

Diabetes mellitus (DM) is a serious long-term disease that has a major impact on the lives and well-being of individuals, families, and communities around the world. The global

prevalence of diabetes in 2019 was estimated at 463 million people, forecast to increase to 578 million (10.2%) by 2030 and 700 million (10.9%) by 2045 [1]. With this increasing prevalence rate, complications and hospitalization requirements associated with DM will also increase. Diabetic foot ulcer infection (DFUI), which is one of the complications of DM, poses a 56 fold higher risk of hospitalization compared to non-DFUI [2]. Recent studies have shown that the rate of DFUI patients experiencing lower extremity amputations is 17.0%, and the level of mortality within 1 year reached 15.0% [3].

In patients with DFUI, antibiotics are the main treatment, in addition to surgical intervention [4]. The route administration of antibiotic can be parenteral, oral, or topical. Inappropriate use of antibiotic can trigger the emergence of antibiotic resistance and increase the burden of treatment costs. In 2019, the International Working Group on the Diabetic Foot (IWGDF) recommended the administration of antibiotic based on the severity of the DFUI [4]. Empirical administration of antibiotic after diagnosis of DFUI, with the aim of identifying pathogens and adjusting the antibiotic regimen, is very important to improve clinical outcomes and prevent amputation [4, 5]. In addition to choosing the type of antibiotic, determining the most appropriate duration of administration is also important [6], and is an issue still being debated [7]. The optimal duration of antibiotic aims to produce the best clinical outcome for the patient, minimize the impact of adverse drug reactions and antibiotic resistance, and reduce treatment costs [8, 9].

To date, there have been four systematic reviews comparing the efficacy of antibiotic in patients with DFUI, with the last randomized controlled trial in 2018 [10-13]. Therefore, the purpose of this study is to review the efficacy of both various regimens and duration of antibiotic administration based on the updated randomized control trials, with a specific focus on the clinical cure aspects in patients with DFUI. In addition, we attempted to describe microbiological profiles and responses in each study. We also aim to make a qualitative synthesis and draw conclusions from studies with similar characteristics.

MATERIALS AND METHODS

1. Search strategy
The literature search was conducted using three electronic databases, namely PubMed, ScienceDirect, and Scopus, to identify relevant articles. The combination of keywords used included 'diabetic foot infection', 'diabetic foot ulcers', 'antibiotic', 'antimicrobial', 'antibacterial', and 'randomized'. The combination form used in each database is shown in **Supplementary Table 1**. The last search took place in October 2021.

2. Inclusion and exclusion criteria
The article search was based on the PICO formula, as detailed below.

1) Participants / Population
DFUI patients with diabetes mellitus type I or II, with or without osteomyelitis.

2) Intervention (s) / Exposure (s)
All antibiotic regimens (intravenous, oral, or topical) at various doses, frequency, or duration of administration.

3) Comparator (s) / Control
Other antibiotics include monotherapy or in combination, in a topical or systemic route of administration, or a placebo.

4) Outcome
Primary outcome: The efficacy as seen from the clinical cure outcome, which is assessed based on improvement in symptoms and signs of infection, as well as laboratory, radiological, and/or use of no additional antibiotics.

Secondary outcome: The efficacy based on microbiological response as seen from pathogen eradication after treatments.

The exclusion criteria for article selection were research articles published outside the period of 2005 – 2021, patients under 18 years old, publication not in English, articles that are not original research, and study designs that are not randomized controlled trials.

3. Data extraction
All the research studies identified from the database were processed using Zotero software (Corporation for Digital Scholarship, Vienna, VA, USA). Through this software, two reviewers screened the articles through their titles and abstracts. After screening, the reviewers examined the eligibility of the full-text articles based on the inclusion and exclusion criteria. Articles that met the requirements (eligibility) were included and reviewed systematically. The data extraction process was presented in the form of a flow chart based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

4. Quality assessment and risk of bias
Article screening and risk assessment were conducted using the Jadad criteria [14]. Two reviewers conducted independent assessments and disagreements were resolved by discussion.

5. Data synthesis and analysis
The included studies were summarized using the clusterization method and narrative description. The outcome that we focused on was a clinical cure, defined as the occurrence of resolution, which is assessed based on improvement in symptoms and signs of infection, as well as laboratory, radiological, and/or no additional antibiotics. The extent of the clinical cure effect is seen from the proportions and/or mean differences, with statistical significance indicated by the *P*-value or confidence interval (CI). We also analyzed the proportion of patients with pathogen eradication in each treatment. Besides describing the results of each study, we analyzed antibiotic comparisons that were studied in more than one RCTs. We attempted to conclude if it was possible to combine them according to their characteristics.

RESULTS

1. Literature search results
We identified 1,102 relevant studies (1,096 through database searches and four through other methods). Of these, we conducted a systematic review of 16 that met the inclusion and exclusion criteria. Thirteen studies compared the efficacy of antibiotics, both topical and systemic, and three specifically compared efficacy based on the duration of antibiotic administration. The searching flow schematic is shown in **Figure 1**.
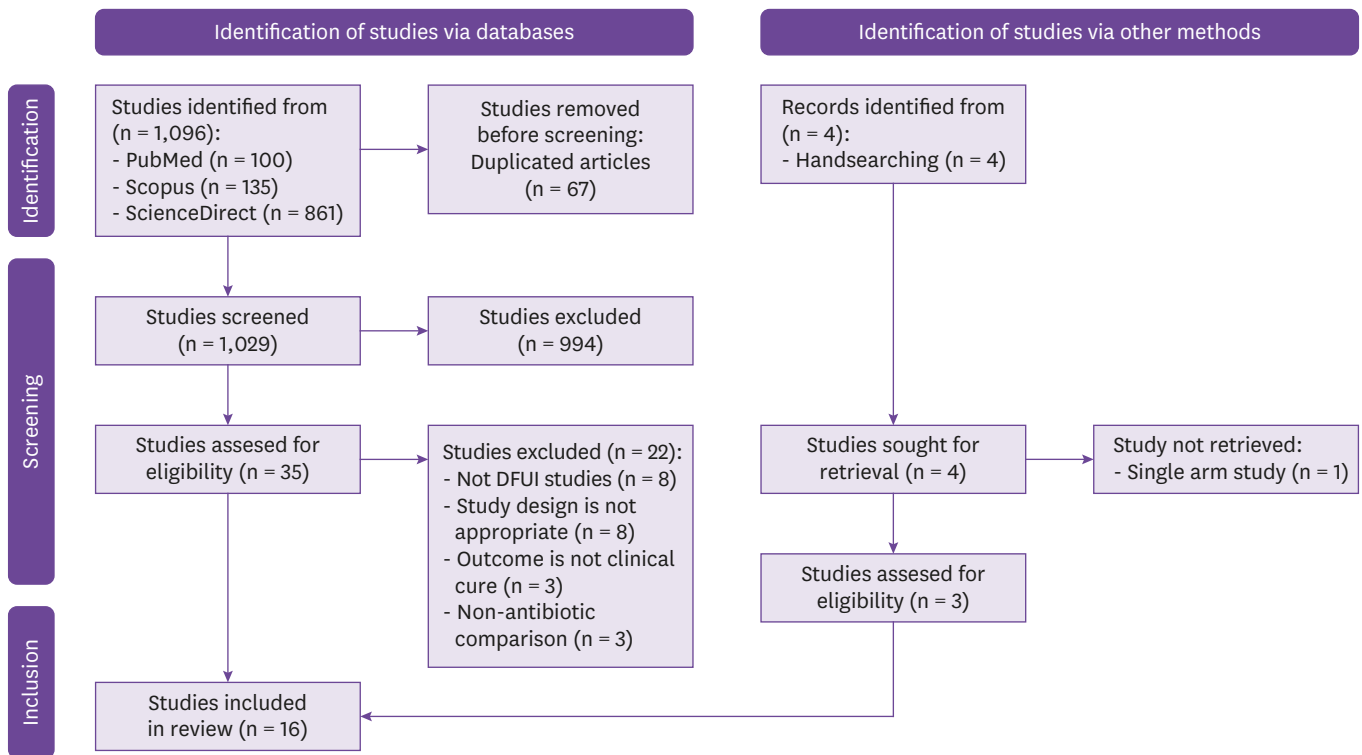
Figure 1. Research Flow Schematic.

2. Quality of included studies

The assessments of study quality are summarized in **Supplementary Table 2**. Nine studies employed an appropriate randomization method; while the seven other studies were randomized, but the method was not specified. Appropriate double-blinding, *i.e.* at least blinding of the subject and investigator [15], was performed in two studies. Furthermore, 4 studies mentioned double-blinds without describing who was blinded, or blinding was not performed on the patient and the investigator. Ten studies did not give double-blind information or were open-label studies. Thirteen studies gave the number and reasons for participants withdrawing or being excluded from the study, and the three other studies did not explain the reasons for withdrawal. Of the total of 16 studies included in our systematic review, only that of Lauf et al. [16] demonstrated appropriate randomization and double-blinding method, and also explained the number and reasons of withdrawals from studies.

3. Study characteristics

The study locations varied, covering the continents of Europe, America, Africa, Asia, and Australia. All patients involved in the studies were suffering from DM and had DFUI ranging from mild to severe degree, with or without osteomyelitis. The percentage of women included in the studies ranged from 17.0% to 40.4%. The mean age of the participants was in the range of 52 to 71 years old. All the studies provided data on the age and sex of the participants, except Lipsky et al. [17]. Only one study that did not provide criteria of DFUI [18]. All reported the degree of infection in the lower extremities, except Vick-Fragoso et al. [19]. In addition, all studies provided a similar definition of clinical cure. With regard to the study design, five studies used pilot study designs [17, 20-23]. More complete characteristics are shown in **Supplementary Table 3**.

Table 1. Microbiological profile of individual studies

Authors	Location	Most Frequent Pathogens
Harkless et al, 2005 [24]	United States	*Staphylococcus aureus* (48.3%), *Streptococcus agalactiae* (14.6%), *Enterococcus faecalis* (6.6%)
Lipsky et al, 2005 [25]	Unites States	*S. aureus* (42%), *Peptostreptococcus* spp. (28.3%), *Prevotella-Porphyromonas* (18.6%)
Lipsky et al, 2007 [26]	United States, Canada, Israel, Argentina, Chile, Peru	*S. aureus* (35.8%), *Streptococcus* spp. (21.0%), *E. faecalis* (15.8%)
Vick-Fragoso et al, 2009 [19]	Philippines, Taiwan, Germany, Hungary, Spain, Israel, Argentina, Chile, Colombia, Mexico, South Africa, Peru	*S. aureus* (40.4%), *Escherichia coli* (14.7%), *E. faecalis* (8.0%)
Saltoglu et al, 2010 [18]	Turkey	CNS (24.2%), *Pseudomonas aeruginosa* (20.9%), *Streptococcus* spp. (12.9%)
Schaper et al, 2013 [27]	Belgium, Bulgaria, Germany, Greece, Hungary, Israel, Latvia, Lithuania, Poland, Romania, Russia, South Africa, Spain, Ukraine and United Kingdom	MSSA (31.7%), *E. faecalis* (17.0%), MRSA (6.6%)
Lauf et al, 2014 [16]	Europe, United States, Canada, Latin America, Asia, India, Australia and South Africa	MSSA (31.1%), *E. faecalis* (16.5%), *S. agalactiae* (10.8%)
Xu et al, 2016 [28]	China	MSSA (24.5%), ESBL-positive pathogen (*E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Proteus vulgaris*) (9.17%), *P. aeruginosa* (7.8%)
Patil et al, 2016 [29]	India	*S. aureus* (56.9%), *E. coli* (32.7%), *P. aeruginosa* (29.3%)
Lipsky et al, 2008 [17]	United States	*S. aureus* (142 patients), *E. faecalis* (105 patients), *S. agalactiae* (59 patients)
Lipsky et al, 2012 [31]	United States and United Kingdom	*S. aureus* (58.3%), β-Hemolytic *Streptococcus* (19.4%), CNS spp. (19.4%)
Uckay et al, 2018 [20]	Switzerland	*S. aureus* (8 patients), *P. aeruginosa* (4 patients), and *Staphylococcus epidermidis* (3 patients)
Uckay et al, 2018 [21]	Switzerland and France	MSSA (46.6%), *Streptococci* (12.5%), *Escherichia coli* (10.2%)
Tone et al, 2015 [30]	France	*S. aureus* (34.5%), CNS (29.3%), *Enterococcus* spp. (10.3%)
Gariani et al, 2021 [23]	Switzerland	*S. aureus* (47.0%), Gram-negative pathogens (30.0%), Streptococci (11.0%)
Pham et al, 2021 [22]	Switzerland	*S. aureus* (32.0%), Gram-negative pathogens (26.0%), Streptococci (18.0%)

CNS, Coagulase negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL: Extended Spectrum β-Lactamase.

Table 1 shows the microbiological profile from each study. This data was extracted based on the three most frequent pathogens in DFUI that were isolated from patients. All studies reported that *Staphylococcus aureus* is the most common pathogen found in DFUI patients, except in Saltoglu et al. [18]. *Enterococcus faecalis*, *Streptococcus* spp, *Pseudomonas aeruginosa*, and *Escherichia coli* are the other most frequent pathogens. The order of most frequent pathogen after *S. aureus* are varied in each study. Some studies also found anaerobic bacterial [17, 19, 21, 24–30] and polymicrobial patterns [18, 20–27, 29, 30] infecting the patients.

4. Clinical cure or improvement

Table 2 provides the information of the included articles consisted of 13 comparative studies of antibiotic regimens [16-21, 24-29, 31] and three compared the duration of antibiotic administration [22, 23, 30]. We extracted 13 comparisons from the total of 16 studies included.

Table 2. Results of individual studies

Study	Diagnosis/Degree of Severity	Comparator A	Comparator B	Clinical cure (%)	Differences, 95% CI
Systemic therapy					
Harkless et al, 2005 [24]	Moderate to severe	TZP IV	SAM IV	TZP = 81.0% SAM = 83.1%	2.1%, 95% CI (-12.9 - 9.1)
Lipsky et al, 2005 [25]	Moderate to severe	ETP IV	TZP IV	DCIV day-5 ETP = 94.0% TZP = 92.0% FUA (10 days) ETP = 87.0% TZP = 83.0%	1.9%, 95% CI (-2.9 - 6.9)
Lipsky et al, 2007 [26]	Moderate to severe	MXF IV followed by MXF P.O	TZP IV followed by AMC acid P.O	MXF = 68.0% TZP - AMC = 61.0%	N/A

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Table 2. (Continued) Results of individual studies

Study	Diagnosis/Degree of Severity	Comparator A	Comparator B	Clinical cure (%)	Differences, 95% CI
Vick-Fragoso et al, 2009 [19]	N/A	MXF IV followed by MXF P.O	AMC IV, followed by AMC P.O	PP Population MXF = 51.0% AMC = 66.7%	PP Population 95% CI (-34.0 - 2.7)
				ITT Population MXF = 47.6% AMC = 60.6%	ITT Population 95% CI (-29.8 - 4.0)
Saltoglu et al, 2010 [18]	Moderate to severe	TZP IV	AMC IV	TZP = 46.7% IPM = 28.1%	N/A
Schaper et al, 2013 [27]	Mild to severe	MXF IV followed by MXF P.O	TZP IV followed by AMC P.O	PP Population MXF = 76.4% TZP - AMC = 78.1%	PP Population 95% CI (-14.5 - 9.0)
				ITT Population MXF = 69.9% TZP + AMC = 69.1%	ITT Population 95% CI (-12.4 - 12.1)
Lauf et al, 2014 [16]	Moderate to severe	TGC IV	ETP ± vancomycin IV	TGC = 77.5% ETP = 82.5%	-5.5%, 95% CI (-11.0 - 0.1)
	DFUI with osteomyelitis			TGC = 31.6% ETP = 54.2%	N/A
Xu et al, 2016 [28]	Moderate to severe	ETP IV	TZP IV	DCIV day-5 ETP = 93.6% TZP = 97.3%	-3.8%, 95% CI (-8.3 - 0.0)
				FUA (10 days) ETP = 92.2% TZP = 94.4%	-2.3%, 95% CI (-7.7 - 2.8)
Patil et al, 2016 [29]	Moderate	CRO IV	LVX P.O and MDZ P.O	CRO = 65.51% LVX + MDZ = 24.13%	N/A
Topical therapy					
Lipsky et al, 2008 [17]	Mild	Pexiganan cream	OFX P.O	303 and 304 EOT: Pexiganan = 86.8% OFX = 90.4%	-3.57%, 95% CI (-7.87 - 0.74)[a]
				Follow up: Pexiganan = 78.8% OFX = 83.9%	-5.05%, 95% CI (-10.41 - 0.31)[a]
Lipsky et al, 2012 [25]	Moderate	Gentamicin-collagen sponge + systemic antibiotic P.O/IV	Systemic antibiotic P.O/IV	TOC: Gentamicin-collagen Sponge = 100% Control = 70.0%	N/A
Uckay et al, 2018 [20]	Mild	Gentamicin-collagen sponge + local care	Local care	Gentamicin-collagen Sponge = 91.0% Control = 91.0%	N/A
Uckay et al, 2018 [21]	Moderate to severe	Gentamicin-collagen sponge + systemic antibiotic P.O/IV	Systemic antibiotic P.O/IV	Cure and improvement: Gentamicin-collagen Sponge = 88.0% Control = 87.0% Cure: Gentamicin-collagen Sponge = 94.0% Control = 79.0%	N/A
Duration of treatment					
Tone et al, 2015 [30]	DFUI with osteomyelitis	6 weeks duration	12 weeks duration	6 weeks = 60.0% 12 weeks = 70.0%	N/A
Gariani et al, 2021 [23]	DFUI with osteomyelitis	3 weeks after debridement	6 weeks after debridement	ITT 3 weeks = 84.0% 6 weeks = 73.0% PP 3 weeks = 85.0% 6 weeks = 74.0%	N/A
Pham et al, 2021 [22]	Moderate to severe	10 days after debridement	20 days after debridement	ITT 10 days = 77.0% 20 days = 71.0% PP 10 days = 78.0% 20 days = 67.0%	N/A

[a]Equivalence in this study was demonstrated if the 95% CI included zero.
IV, intravenous; TZP, piperacillin-tazobactam; SAM, ampicillin-sulbactam; CI, confidence interval; DCIV, discontinuation of intravenous therapy; ETP, ertapenem; FUA, follow-up assessment; P.O, per oral; MXF, moxifloxacin; AMC, amoxicillin/clavulanic acid; N/A, not available; PP, per-protocol; ITT, intention-to-treat; IPM, imipenem-cilastatin; DFUI, diabetic foot ulcer infections; TGC, tigecycline; CRO, ceftriaxone; LVX, levofloxacin; MDZ, metronidazole; EOT, end of treatment; OFX, ofloxacin; TOC, test of cure.

1) Piperacillin-tazobactam (TZP) vs. ampicillin-sulbactam (SAM)
Research conducted by Harkless et al. compared TZP (4 g/0.5 g every 8 hours IV) and SAM (2 g/1 g every 6 hours IV) and showed statistically equivalent clinical efficacy in patients with moderate to severe DFUI in the test of cure (TOC) visit (P = 0.124). Similar results were shown on days 4 and 7, and at the end of treatment (EOT). Logistic regression with the test article, as well as age and sex covariates, also showed similar results between groups [24].

2) Ertapenem (ETP) vs. TZP
Two studies compared ETP with TZP. Lipsky et al. compared ETP (1 g/day IV) with TZP (3.375 g every 6 hours IV), with their results showing that the efficacy of ETP was equivalent to TZP in the treatment of moderate to severe DFUI [25]. Assessments of the discontinuation of intravenous therapy (DCIV) and follow-up assessment (FUA) 10 days after the last dose was given showed statistically equivalent efficacy of ETP against TZP. Another study by Xu et al. compared ETP (1 g/day IV) with TZP (4.5 g every 8 hours IV) in DFUI patients in China. The results indicated that ETP is not inferior compared to TZP in moderate DFUI. However, in patients with severe DFUI, ETP resulted in a lower clinical cure rate (91.5%) than TZP (97.2%) (95% CI [-12.1% to -0.3%], P = 0.04) [28].

3) Moxifloxacin (MXF) vs. TZP + amoxicillin-clavulanate (AMC)
Two studies compared MXF with TZP + AMC. Lipsky et al. compared MXF (400 mg/day IV followed by 400 mg/day P.O) *vs.* TZP (3.375 g every 6 hours IV followed by AMC 800 mg every 12 hours P.O) and showed similar efficacy in treating moderate to severe DFUI patients (P = 0.54) [26]. Similar results were also obtained by Schaper et al., who found that MXF IV/P.O monotherapy was clinically similar to TZP + AMC in patients with moderate to severe DFUI [27].

4) MXF vs. AMC
The study by Vick-Fragoso et al. compared the use of MXF (400 mg/day IV, followed by 400 mg P.O) with AMC (1,000 mg/200 mg IV every 8 hours, followed by 500 mg/125 mg 3 × 1 P.O); their results were not statistically different in patients with DFUI, both in the intention-to-treat (ITT) and per-protocol (PP) groups [19].

5) TZP vs. imipenem-cilastatin (IPM)
Research by Saltoglu et al. compared the use of TZP (3 × 4.5 g IV) with IPM (4 × 500 mg IV). Although TZP gave a better clinical response rate than IPM in patients with severe DFUI (46.7% *vs.* 28.1%), the study showed no statistically significant difference [relative risk 1.6; 95% CI (0.84 - 3.25), P = 0.130] [18].

6) Tigecycline (TGC) vs. ETP
The study of Lauf et al. compared the use of TGC (150 mg/day IV) with ETP (1 g/day IV) and showed that TGC was significantly inferior to ETP ± vancomycin in patients with DFUI in the clinically evaluable (CE) group. These results are shown in the crude absolute difference and adjusted absolute difference (severity of infection). Meanwhile, in patients with osteomyelitis, the cure rate in the TGC group was lower than in the ETP ± vancomycin (31.6% *vs.* 54.2%), but the study did not perform formal statistical analysis for the osteomyelitis patients [16].

7) Ceftriaxone (CRO) vs. levofloxacin + metronidazole (LVX + MDZ)
Research conducted by Patil et al. showed that both the inpatient group receiving CRO (1 g/

day IV) and the outpatient group receiving the combination of LVX + MDZ (500 mg/day P.O + 400 mg every 8 hours P.O) were similar in efficacy (P >0.05) [29].

8) Pexiganan topical vs. ofloxacin (OFX)
Research conducted by Lipsky et al. compared the daily use of pexiganan cream with OFX (200 mg every 12 hours P.O) and obtained no different results in study 304 (pexiganan 1%), but significantly different results in study 303 (pexiganan 2.0%). However, based on the results of the combination studies 303 and 304, the results were comparable in the two treatment groups both at the EOT and at follow-up. In this study, it was stated that topical pexiganan may be an effective alternative for patients with mild DFUI if accompanied by appropriate wound care [17].

9) Topical gentamicin-collagen sponge + systemic antibiotic vs. single systemic antibiotic
Research by Lipsky et al. compared a combination of topical gentamicin-collagen sponge + systemic antibiotics (levofloxacin 750 mg/day P.O/IV or other antibiotics) *vs.* a single systemic antibiotic. On day 7, the two groups showed significantly different results, but on days 10, 14, and 21, these were not significant. In TOC (2 weeks after discontinuation of the drug), the results showed significant differences. The study concluded that the use of a gentamicin-collagen sponge can improve the clinical outcome of patients with moderate DFUI when combined with standard treatment [31].

A recent study by Uckay et al. to patients with moderate or severe DFUI indicated that the gentamicin-collagen sponge, although tolerated very well, did not significantly affect healing and overall improvement (P >0.05). Logistic regression analysis also showed that the gentamicin-collagen sponge was not significantly associated with clinical cure [adjusted odds ratio 1.0 (0.1 – 15.8)] [21].

10) Topical gentamicin-collagen sponge + local care vs. local care alone
The study by Uckay et al. compared a gentamicin-collagen sponge + local care *vs.* local care alone. Their results showed that the addition of a gentamicin-collagen sponge, although very well tolerated, did not appear to improve treatment outcomes in mild DFUI patients (P = 1.00) [20].

11) 10-day antibiotic group vs. 20-day antibiotic group in DFUI
A study by Pham et al. compared a group of antibiotics given 10 days *vs.* 20 days after debridement in patients with moderate to severe DFUI. The results were similar in both the ITT population (P = 0.57) and the PP population (P = 0.32). In multivariate analysis, remission rates were not significantly different in the two duration groups, either the ITT [hazard ratio (HR) 0.6, 95% CI (0.3 - 1.1)] or the PP [HR 0.8, 95% CI (0.4 - 1.5)] [22].

12) 6-week antibiotic group vs. 12-week antibiotic group in diabetic foot osteomyelitis
The study of Tone et al. showed that a 6-week duration group produced equivalent results in diabetic foot osteomyelitis patients compared to a 12-week duration group (P = 0.50) [30].

13) 3-week antibiotic group vs. 6-week antibiotic group in diabetic foot osteomyelitis (DFO)
The research by Gariani et al. showed that clinical cure in a 3-week duration group was not significantly different to a 6-week duration group for diabetic foot osteomyelitis patients (P = 0.21 in the ITT population and P = 0.26 in the PP population) [23].

5. Microbiological response

Some studies provided microbiological data based on isolated pathogens [16, 17, 24–27]. In those studies, the proportion of patients that undergo pathogen eradication toward the most common pathogens of *S. aureus* and *Streptococcus* are more than 50.0%. Meanwhile, Lipsky et al. found a less than 50.0% of patients with MXF successfully eradicated *E.faecalis* [26].

In **Supplementary Table 4**, eradication of *P.aeruginosa* in Harkless et al. is 0% in SAM group due to exclusion criteria of patients with this pathogen [24]. Eradication of *E.coli* in the study of Lipsky et al. is 0% from the total of only 1 patient included [26]. Judging from the significance of all studies that included specific pathogen identifications, the difference in eradication between antibiotics was not significant (**Supplementary Table 4**).

Some studies presented eradication data only as an overall analysis without mentioning the specific pathogen [18, 20, 21, 29, 31]. These studies showed no significant results between treatments, except for the study of Lipsky et al. that reported benefit in favor of the combination of gentamicin-collagen sponge and systemic antibiotic (*P* <0.001) [31]. There is no available data regarding pathogen eradication in studies of treatment durations [22, 23, 31]

DISCUSSION

The studies included in this systematic review were very heterogeneous due to differences in the study sites and the types of antibiotics used, the latter possibly caused by different local bacterial patterns especially pathogen variations after *S. aureus*.

The prevalence of DFUI-causing pathogens, including antibiotic sensitivity, varies by geographic, demographic, and clinical location. However, in the included studies, the results are quite homogeneous, which showed that *S. aureus* was the primary pathogen that causes DFUI. This is in accordance with recent meta-analysis [32]. The proportion of patients with *S. aureus* in the studies ranged between about 25.0 – 50.0%. In another study, the prevalence of *S. aureus* in Western countries such as the United States, Europe, and Australia, reached 40.0% of all identified pathogens [33]. We also noticed that most of the RCTs found polymicrobial and anaerobic bacterial in included patients. In the more severe infection, such as in a chronic state, aerobic Gram-negative are frequently found as co-pathogen. Meanwhile, obligate anaerobes are often involved as co-pathogen in patients with ischemic wounds or necrosis [34].

The highest prevalence of pathogens in Turkey in the study of Saltoglu et al. was coagulase-negative *Staphylococcus* (CNS) (24.2%) [18]. This contradicts the previous study that reported *S. aureus* as the most frequent pathogen in Turkey [35]. This difference may be caused by selection bias in Saltoglu et al. since the sample number is quite small.

In contrast to Western countries, Gram-negative bacteria, particularly *P. aeruginosa,* were among the three most common pathogens of DFUI in Asian countries, such as Turkey, China, and India [18, 28, 29]. This data align with Hawkin's review, stating that within Asia, *P. aeruginosa* is among the most frequent pathogen in DFUI patients [33]. The substantial differences in the microbiological profile of DFUI in Western countries compared to Asian countries may be due to several cultural, geographic, and climatic factors. It may also be related to the methods of obtaining and analyzing specimens, as well as differences in

the amount and type of antibiotics used. Each of these factors can potentially change the dominant flora that causes DFUI [35].

Most of the studies showed clinical cure that were similar between groups, except Lipsky et al., Xu et al. in severe category, and Lauf et al. Most studies also reported similar microbiological response except in Lipsky et al. Furthermore, the duration of administration did not differ, both in the studies of DFUI and DFO. The updated IWGDF recommends an antibiotic treatment duration of 1 - 2 weeks for most DFUI cases and up to 6 weeks for DFO cases [4]. Infectious Diseases Society of America (IDSA) recommends duration of 2 - 3 weeks for moderate to severe patients [34]. However, one pilot study to the same degree of severity reported that shorter duration (10 days) might be sufficient for clinical remission [22]. Another pilot study demonstrated shorter duration (3 weeks) was also adequate in treating DFO patients [23]. Larger RCT studies might be needed to increase the certainty and establish a robust antibiotic guideline.

Microbiological testing is a foundational tool needed in making clinical decisions regarding the appropriate use of antibiotics through eradication data of DFUI pathogens. In Lipsky et al., eradication of *E. faecalis* in the MXF group showed a yield of <50.0% [26]. In the study of Schaper et al., the results showed 63.3% for the same pathogen [27]. These proportions were relatively lower than other pathogens within the studies. Supported by other studies, the activity of fluoroquinolone antibiotics did give poor results against the *Enterococcus* sp. [36, 37]. In the study of Harkless et al., patients in the SAM group were excluded in the *P. aeruginosa* test. This is because SAM has no activity against *P. aeruginosa* [38]. In the treatment of empiric antibiotic selection, if the patients' ulcer is macerated or in a warm climate with suspected DFUI caused by *P. aeruginosa*, the use of SAM is not recommended [4].

Below are the qualitative analysis and conclusion for antibiotic comparisons that were analyzed in more than one RCTs within the determined period of review:

1. ETP *vs.* TZP

The studies of Lipsky et al. and Xu et al. demonstrated similar study characteristics: definition of DFUI, clinical cure, the observation period, and the proportions of sexes and mean ages. However, the antibiotic dosing regimen was slightly different, with the same total amount of dosages per day. Their studies illustrated that the use of ETP and TZP was not significantly different in the FUA group. However, Xu et al. study showed significantly different in the DCIV group, with a higher clinical cure rate with TZP. However, in Lipsky et al.'s study, the comparison in the DCIV group was not significantly different. This may have been due to the difference in the number of test participants in Xu et al.'s study, who were dominated by severe DFUI. This result was confirmed by a separate analysis in the moderate and severe infection groups. In severe DFUI, the results showed that TZP had better efficacy. In addition, this difference in results was also predicted to be due to differences in the region of the test participants in the two studies (Lipsky et al, United States; Xu et al, China). Although the moderate-to-severe DCIV group in Xu, et al showed a significant difference [95% CI (-8.3 - 0.0%)], the authors stated that the probability of superiority was lower than the non-inferiority margin of 15.0%, so ETP was still considered to be non-inferior to TZP. Furthermore, in terms of microbiological response, Lipsky et al. showed clinically similar for overall eradication between groups. A similar result was also shown in Xu et al. Based on the results of the two studies, ETP and TZP at moderate-severe DFUI have the same efficacy.

2. MXF *vs.* TZP + AMC

The characteristics of the studies of Lipsky et al. and Schaper et al. are similar in the definition of clinical cure, inclusion and exclusion criteria, and the proportion of sexes and mean ages. However, the doses of AMC administered were slightly different (800 mg in Lipsky et al. and 1,000 mg in Schaper et al.), as was the severity of DFUI (moderate-severe in Lipsky et al. and mild-severe in Schaper et al.). The clinical cure results in the two studies in the two treatment groups were not significantly different, but caution should be exercised in interpretation, as Schaper et al.'s study involved patients with mild symptoms. However, these results are still reliable, considering that antibiotic coverage at moderate-severe degrees can generally cover mild degrees. In addition, the number of mild degree patients included in the study also tended to be small. For microbiological response, the proportions of patients with pathogen eradication in the studies were not significantly different between groups.

3. Gentamicin-collagen sponge + systemic antibiotics *vs.* systemic antibiotics

The clinical cure results in the two studies are different, with research by Lipsky et al. showing a significant difference (better in the case of gentamicin), but Uckay et al. showing an insignificant difference. The results are in line with the microbiological eradication response. This may be due to differences in patient characteristics, particularly in terms of severity and age. In Uckay et al., the mean age of the patients was 71 and severe infections were included. The possible explanation might be related to the collagenase activity. Gentamicin-collagen works through degradation by collagenase, so it can be absorbed systemically [39]. However, elderly patients have increased collagenase activity, meaning that the rate of degradation is faster, which weakens the wound healing process [40]. Therefore, the addition of gentamicin-collagen in the study of Uckay et al. was not significant. Although the use of topical antibiotics gave significant results in Lipsky et al's study, both in clinical cure and microbiological eradication, further studies need to be conducted to give more strong evidence in supporting the use of topical antibiotics for DFUIs.

NEW FINDINGS

We are able to create a quite comprehensive and updated systematic review that covers some of the knowledge gaps from previous reviews. Our systematic review updated previous reviews by adding more recent RCTs with the last research on 2021. Compare to Dumville et al. [10] and Peters et al. [12], we focus on antibiotic-only instead of antimicrobials. Two reviews did not analyze the comparison of treatment durations [10, 13], while another two [11, 12] included older RCTs compared to ours. In addition, compared to previous reviews, we have described and analyzed the characteristics similarity of studies of Lipsky et al. and Xu et al.; Lipsky et al. and Schaper et al.; and Lipsky et al. and Uckay et al. to create more robust analysis. We also reported pathogen profiles and eradications that were not reported in previous reviews and are essential in helping choices of proper antibiotics in DFUI patients. Based on the differences, there are generally two new findings from this study. First, most studies showed analogous significance between clinical cure and pathogen eradication, with most studies showing no significant difference between treatment groups. Second, recent RCTs of comparison of treatment durations demonstrated similar efficacy between groups; although we cannot determine the optimal duration of antibiotic treatments, there is an indication from the pilot studies [22, 23] that shorter duration may bring similar benefit compared to longer duration both in DFUI and DFO without surgery.

Our systematic review has several limitations. First, there are several studies with incomplete or unreported randomization information, however, more than 50.0% of the studies demonstrated an appropriate randomization method. Second, most studies were open-label designs, so there is a possibility of information bias [15]. Third, there is heterogeneity in the types and regimens of antibiotics, so that conclusions can only be drawn from a few comparative studies.

IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

Our evidence-based is not strong enough to recommend a specific choice of antibiotics due to heterogeneous characteristics; however, we summarized data about clinical cure, most common pathogen and its eradication in each study that can provide an overview of the regional pathogen prevalence and antibiotic efficacy. This information is expected to improve knowledge, optimize efficacy, and reduce the risk of antibiotic resistance due to inappropriate antibiotic consumption. Overall, this systematic review could assist healthcare professionals in considering the appropriate type and duration of antibiotics in patients with DFUI. Future research should be done with an adequate sample size and a good study design to minimize bias. Given the insignificant differences between drugs, the cost of treatment and the therapeutic regimen can be alternative considerations in the selection of antibiotics; for example, the administration of ertapenem is simpler than that of TZP [25] and the LVX + MDZ combination has a lower cost than ceftriaxone [29]. Therefore, study of cost-effectiveness related to the use of antibiotics in patients with DFUI also need to be performed to ensure a more rational and optimal use of antibiotics.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Keywords in databases searching

Click here to view

Supplementary Table 2
The Jadad scale

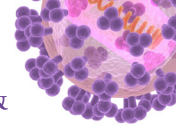**Click here to view**

Supplementary Table 3
Study characteristics

Click here to view

Supplementary Table 4
Microbiological responses

Click here to view

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