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Can We Stop Antibiotic Therapy When Signs and Symptoms Have Resolved in Diabetic Foot Infection Patients?

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Abstract

The study aimed to investigate whether we can stop antibiotic therapy when signs and symptoms have resolved in diabetic foot infection (DFI) patients with different grades of peripheral arterial disease (PAD) and those without PAD, and to determine whether the severity of PAD and infection has an effect on antibiotic therapy duration. A prospective randomized controlled trial of DFI patients was carried out. Patients were randomized into 2 groups when signs and symptoms had resolved: continuing antibiotics group (CAG) and discontinuing antibiotics group (DAG). The recurrence and clinical outcomes were recorded. The recurrence rate of mild infection with mild/moderate PAD was similar in the 2 groups. Compared with CAG, the recurrence rate of mild infection with severe PAD was higher in DAG ($P = .030$), also for moderate/severe infection with PAD (mild/moderate [$P = .032$]; severe [$P = .008$]). No difference was found in the 2 groups (either mild or moderate/severe) for those without PAD. The clinical outcomes of mild infection in patients were similar in the 2 groups. For moderate/severe infection, the healing rate was higher (73.3% vs 48.3%), and the rate of minor/major amputation and death was lower (23.8% vs 49.4%; 6.9% vs 20.7%; 2.0% vs 13.8%) in the CAG. When the clinical signs and symptoms of infection have resolved, it might be appropriate to stop antibiotics for DFI patients without PAD, and also for patients with mild infection with mild/moderate PAD. For patients with mild infection with severe PAD and moderate/severe infection with PAD, we should perhaps continue antibiotic treatment. Continuing antibiotic therapy could improve clinical outcomes for patients with moderate/severe infection.

Keywords

diabetic foot, infection, antibiotic therapy, clinical outcomes

Infections of the foot are common in persons with diabetes mellitus (DM).[1] Diabetic foot infection (DFI) is now the most frequent diabetic complication requiring hospitalization and is often the pivotal event leading to lower extremity amputation.[2,3] Most of these amputations are probably avoidable by appropriate care, including topical and/or systemic antimicrobials, restitution of skin perfusion, pressure offloading, appropriate debridement, surgical procedures, disinfection, and use of appropriate dressings.[4]

Antibiotic therapy is necessary for all clinically infected diabetic foot (DF) wounds, because antibiotic therapy is associated with frequent adverse effects, high financial costs, and increasing risk of antibiotic resistance.[5] Therefore, how to reasonable use antibiotics for DFI is a very crucial problem for clinicians. According to the 2012 Infectious Diseases Society of America (IDSA) clinical practice guideline for the diagnosis and treatment of DFI, duration of antibiotic therapy for a DFI should be based on the severity of the infection, the presence or absence of bone infection, and clinical response to therapy, and antibiotic therapy can generally be discontinued when signs and symptoms of infection have resolved.[6]

However, whether the degree of lower limb ischemia could influence the antibiotic therapy duration of DFI is unknown. And no study to our knowledge has investigated if stopping antibiotic therapy may increase wound infection

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recurrence and influence the clinical outcomes of patients when clinical symptoms and signs of infection have resolved. This study aimed to discuss whether there was a difference in continuing and discontinuing antibiotic therapy of DFI patients with different degrees of lower limb ischemia or without ischemia after clinical symptoms and signs of infection had resolved.

Methods

A prospective randomized controlled trial of patients with diabetic foot ulcer infection was carried out in the Metabolic Hospital of Tianjin Medical University from March 2010 to August 2012. Patients were evaluated for DFI by 2 experienced physicians. DFI diagnosis was performed according to IDSA guideline.[6] For those with multiple foot ulcer lesions, the higher infection grade was included.

Patients

Patients aged ≥18 years who were newly diagnosed with diabetic foot ulcer infection could potentially be enrolled if they had an infected wound below the ankle and the infection duration was less than 2 weeks. Patients were excluded if they had hepatic dysfunction (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or total bilirubin exceeds the upper limit value of the normal 3 times or more), heart dysfunction (NYHA 3 or 4 grade), requirement for renal dialysis, and other infectious diseases such as pneumonia and urinary tract infection. Patients with peripheral arterial disease (PAD) who needed vascular intervention or were intolerant of vascular intervention were also excluded according to the vascular surgery specialist consultation. The study received ethical approval of the independent ethics committee of our hospital on January 23, 2010. Informed consent was obtained from all the patients enrolled.

Data Collection

All the patients were evaluated by the multidisciplinary diabetic foot care team, which included physician, diabetes specialist, orthopedist, and diabetes nurses on admission. A standardized data collection form was used to record the following information: age, gender, height, weight, body mass index (BMI), diabetes duration, DF ulcer duration, duration of antibiotic therapy prior to hospitalization, DF ulcer duration, ulcer size, ulcer type, ulcer depth, infection grade, complications or concomitant disease including coronary heart disease (CHD), cerebrovascular disease, diabetic nephropathy (DN), diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), and PAD.

Laboratory Data Collection

The fasting venous blood sample was collected after admission. Blood urea nitrogen (BUN), creatinine (Cr), ALT, AST, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG) were measured using a biochemical analyzer (Abbott, Abbott Park, IL). Glycated hemoglobin A1c (HbA1c) was measured by a HLC-T OSOH 723 G7 automated glycated hemoglobin analyzer. Plasma concentrations of highly sensitive C-reactive protein (hs-CRP) was determined using commercially available kits (Finland Orion Diagnostica Company, Espoo, Finland). Fasting blood glucose (FBG) and 2-hour postprandial blood glucose (P_2BG) were measured by a glucometer (Johnson & Johnson).

Bacterial Isolates

At the first day of admission, before antibiotic therapy, specimens were obtained from the base of a debrided ulcer by curettage and taken to the microbiology laboratory in 30 minutes, transported by sterile containers. Bacteria were identified using the VITEK2 automatic bacterial analyzer (bioMérieux, Paris, France). Antimicrobial susceptibility testing was performed by the Kirby–Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute.[7] Bacteria culture and antimicrobial susceptibility testing were reviewed once a week or according to the clinical manifestation.

Study Definitions

PAD was diagnosed and classified into 3 grade according to the ankle brachial index (ABI): mild (0.60-0.89), moderate (0.40-0.59), severe (<0.4),[6] which was assessed by a Doppler ultrasound blood flow detector (Japanese Lin Electronics Co, Ltd). And we also assessed the lower limb blood supply with color ultrasound (General Electric, Fairfield, CT). For patients with ABI > 1.1, a reduction in lumen diameter of more than 75% with color ultrasound was considered as severe PAD and 25% to 75% was considered as mild/moderate PAD. DPN was diagnosed if the patient met the following criteria: absence of perception of the Semmes-Weinstein monofilament 5.07/10 g at 2 of 10 standardized plantar sites on either foot and vibration sense <5/8 grade of a 128-Hz tuning fork.[8,9] Diabetic foot osteomyelitis (DFO) was diagnosed if 2 of the 3 tests were positive: X-ray, probing to bone test, and the observation at surgery of purulence in bone.

The definitions of amputation were as follows[10]: a minor amputation was defined as any amputation distal to the ankle joint; a major amputation was defined as any amputation up to or proximal to the ankle joint. Healing was defined as the complete epithelialization of the ulcer and without reulceration during the follow-up.

Treatment

After admission, all the patients were given insulin therapy, and the insulin type or dosage was adjusted based on

the blood glucose monitoring results until the blood glucose reached the standard level (FBG = 6-8 mmol/L, P_2BG = 8-10 mmol/L). Patients with PAD were given medical treatment, including prostaglandin E1 (alprostadil) and/or Cilostazol (4 weeks). All patients were given low-molecular-weight heparin 5000 U once per day to prevent venous thrombosis of lower limbs for an average of 7 to 10 days. Empirical antibiotic therapy (intravenous and/or oral antibiotics) was initially started based on the DFI duration, previous antibiotic treatment, any available microbiological data, and the severity of the infection. For the patients with mild infection, and/or without antibiotic therapy history, infection duration less than 2 weeks was treated with agents that only covered aerobic Gram-positive cocci (GPC) for 1 to 2 weeks. For the patients with more extensive chronic moderate, severe infections, the agents that were against aerobic GPC, as well as common gram-negative, were given, and agents covering obligate anaerobic organisms were also given for patients with deep abscess and/or stench. Therapy was modified according to the antibiotic susceptibility results and the clinical response. The infected wound care was according to the IDSA guideline (2004). The wound was washed carefully by saline and covered with sterile saline gauze or Vaseline oil gauze once a day. Patients with deep abscess and necrotic soft tissue were treated with debridement in time. The patients with severe infection and good blood supply were treated with debridement in 24 hours after admission. For the patients with severe ischemia, debridement was given after the blood supply improved. For the patients with DFO, the infected bones were removed by the same experienced surgeon.

Group and Follow-up

All the patients were randomized into the following 2 groups in sequence: continuing antibiotics group (CAG) and discontinuing antibiotics group (DAG) when the signs and symptoms of infection had resolved after comprehensive treatment. We consider the infection of patients were effectively controlled when the following signs were observed: (*a*) no systemic inflammatory response signs (fever, chills) and local infection signs (erythema, swelling, warmth, and pain); (*b*) no purulent discharge and necrotic tissue, with the growth of granulation tissue; (*c*) bacterial culture negative 2 times in a row; (*d*) white blood cell (WBC) and hs-CRP levels returned to the normal range. Local treatment of the ulcer was the same for both the groups. The 2 groups were observed for 2 consecutive weeks. During the observation period, once the foot infection recurred, we added or replaced antibiotics immediately according to the results of an antibiogram or provided appropriate surgical intervention.

Patients were followed-up as outpatients after discharge at 1week, 1 month, and 3 months, and the clinical outcomes were recorded in detail. We defined infection recurrence by the presence of at least 2 of the following: (*a*) the appearance of erythema, swelling, warmth, pain with and without fever, chills; (*b*) the occurrence of purulent discharge or necrotic tissue, granulation tissue broken easily, bleeding, or from red to yellow, purple or edema; (*d*) positive bacterial culture; (*d*) an elevation of hs-CRP, WBC, and erythrocyte sedimentation rate.

Statistical Analysis

Quantitative variables of the 2 groups were expressed as means ± SD, and qualitative variables were expressed as percentages. *T* tests were used. The percentages of recurrence were compared using the χ^2 test. The correlation intensity of infection recurrence and clinical outcomes between the 2 groups were analyzed by relative risk analysis with odds ratio (OR) and 95% confidence interval (CI). A *P* value of <.5 was considered significant. All statistical analyses were performed by using the SPSS statistical software, version 19.0.

Results

A total of 405 patients were diagnosed with DFI in our center during the period of study. The main reasons for exclusion were the presence of acute myocardial infarction (n = 7), acute stroke (n = 7), acute cardiac failure (n = 5), urinary tract infection (n = 2), pneumonia (n = 2), and loss to follow-up (n = 7). A total of 375 patients met the inclusion criteria of the study. A total of 184 patients (49.1%) were randomized to the CAG and 191 (50.9%) to the DAG. The demographic and clinical characteristics of the study population are shown in Table 1. In both groups, the mean age was more than 60 years, and the duration of DM was more than 10 years. No differences were found in the DFI duration (CAG: 11.4 ± 9.2; DAG: 12.5 ± 8.3), previous antibiotic treatment duration (CAG: 5.6 ± 3.7 days; DAG: 4.8 ± 3.1 days), and the percentage of CHD (47.3% vs 50.8%, *P* = .498), cerebrovascular disease (28.3% vs 29.3%, *P* = .736), DR (54.9% vs 53.9%, *P* = .851), and DN (61.4% vs 63.4%, *P* = .699).

Bacterial isolates from both groups are shown in Table 2. The distribution of the bacterial isolates between the 2 groups was similar (Gram-positive bacteria: 48.6% vs 49.8%, *P* = .805; Gram-negative bacteria: 46.3% vs 46.7%, *P* = .932). A total of 439 were isolated from 375 patients, among which the top 3 were *Staphylococcus aureus* (including methicillin-resistant *S aureus*; 22.1%), *Staphylococcus epidermidis* (12.3%), and *Pseudomonas aeruginosa* (10.5%). Of the 375 patients, 64 DFIs which were polymicrobial, with *Staphylococcus* and anaerobic gram-negative bacilli, were moderate or severe infection.

Of all the 375 patients, 323 cases (86.1%) of foot infection were one site; 52 cases (13.9%) were multisite. The

Table 1. The Comparison of Clinical Baseline Data Between CAG and DAG.[a]

Variables	CAG (n = 184)	DAG (n = 191)	*P*
Age (years)	63.5 ± 9.9	62.9 ± 9.2	.571
Male sex (%)	131 (71.2)	141 (73.8)	.909
DFI duration	11.4 ± 9.2	12.5 ± 8.3	.823
Previous antibiotic treatment duration	5.6 ± 3.7	4.8 ± 3.1	.691
CHD (%)	87 (47.3)	97 (50.8)	.498
Cerebrovascular disease (%)	52 (28.3)	57 (29.8)	.736
DR (%)	101 (54.9)	103 (53.9)	.851
DN (%)	113 (61.4)	121 (63.4)	.699
Mild infection (%)	83 (45.1)	104 (54.5)	.711
With mild/moderate PAD	37 (44.6)	48 (46.1)	
With severe PAD	32 (38.6)	37 (35.6)	
Without PAD	14 (16.8)	19 (18.3)	
Moderate/severe infection (%)	101 (54.9)	87 (45.5)	.505
With mild/moderate PAD	43 (42.6)	40 (46.0)	
With severe PAD	46 (45.5)	33 (37.9)	
Without PAD	12 (11.9)	14 (16.1)	
HbA1c (%)	10.4 ± 2.1	9.4 ± 2.2	.962
FBG (mmol/L)	9.9 ± 2.2	10.22 ± 2.6	.353

Abbreviations: CAG, continuing antibiotics group; DAG, discontinuing antibiotics group; DFI, diabetic foot infection; CHD, coronary heart disease; DR, diabetic retinopathy; DN, diabetic nephropathy; PAD, peripheral arterial disease; FBG, fasting blood glucose.
[a]Data are presented as mean ± standard deviation or n (%).

Table 2. The Distribution of the Bacterial Isolates, n (%).

Microorganisms	CAG	DAG	Total
Gram-positive bacteria	104 (48.6)	112 (49.8)	216 (49.2)
Staphylococcus aureus	29 (27.9)	34 (30.4)	63
Methicillin-resistant *S aureus*	15 (14.4)	19 (17.0)	34
Staphylococcus epidermidis	24 (23.1)	30 (26.8)	54
Enterococcus faecalis	18 (17.3)	19 (17.0)	37
Streptococcus	14 (13.5)	8 (7.1)	22
Corynebacterium diphtheria	4 (3.8)	2 (1.7)	6
Gram-negative bacteria	99 (46.3)	105 (46.7)	204 (46.5)
Pseudomonas aeruginosa	28 (28.3)	23 (21.9)	51
Escherichia coli	21 (21.2)	25 (23.9)	46
Proteusbacillus vulgaris	20 (20.2)	22 (20.9)	42
Citrobacter	16 (16.2)	17 (16.2)	33
Klebsiella pneumoniae	14 (14.1)	18 (17.1)	32
Fungus	9 (4.2)	8 (3.5)	17 (3.9)
Others	2 (0.9)	0 (0.0)	2 (0.4)
Total	214	225	439

Abbreviations: CAG, continuing antibiotics group; DAG, discontinuing antibiotics group.

percentage of moderate/severe infection was higher in CAG than DAG (101/184 vs 87/191). In the CAG, the number of mild infection with mild/moderate PAD, severe PAD, and only DPN was 37 (44.6%), 32 (38.6%), and 14 (16.8%), respectively; the number of moderate/severe infection with mild/moderate PAD, severe PAD, and without PAD was 43 (42.6%), 46 (45.5%), and 12 (11.9%), respectively (Table 3). In the DAG, the number of mild infection with mild/moderate PAD, severe PAD, and without PAD was 48 (46.1%), 37 (35.6%), and 19 (18.3%), respectively; the number of moderate/severe infection with mild/moderate PAD, severe PAD, and without PAD was 40 (46.0%), 33 (37.9%), and 14 (16.1%), respectively. The distribution of mild infection patients with mild/moderate PAD, severe PAD, and without

Table 3. The Comparison of Recurrence Rate Between the 2 Groups.

	CAG (n = 184)		DAG (n = 191)				
	Case, n	Recurrence, n (%)	Case, n	Recurrence, n (%)	OR	95% CI	*P*
Mild infection	83	6 (7.2)	104	17 (16.3)	2.508	0.941-6.681	.059
With mild/moderate PAD	37	2 (5.4)	48	3 (6.3)	1.167	0.185-7.367	.870
With severe PAD	32	4 (12.5)	37	13 (35.1)	3.792	1.090-13.185	.030
Without PAD	14	0 (0.0)	19	1 (5.3)	1.056	0.949-1.174	.383
Moderate/severe infection	101	24 (23.8)	87	39 (44.8)	2.607	1.398-4.862	.002
With mild/moderate PAD	43	8 (18.6)	40	16 (40.0)	2.917	1.078-7.889	.032
With severe PAD	46	14 (30.4)	33	20 (60.6)	3.516	1.375-8.994	.008
Without PAD	12	2 (16.7)	14	3 (21.4)	1.364	0.188-9.912	.759
Total	184	30 (16.3)	191	56 (29.3)			

Abbreviations: CAG, continuing antibiotics group; DAG, discontinuing antibiotics group; OR, odds ratio; CI, confidence interval; PAD, peripheral arterial disease.

PAD was similar in the CAG and DAG (44.6% vs 46.1%, $P = .830$; 38.6% vs 35.6%, $P = .675$; 16.8% vs 18.3%, $P = .803$, respectively). The percentage of moderate/severe infection with mild/moderate PAD and without PAD was similar in the 2 groups (42.6% vs 46.0%, $P = .639$; (11.9% vs 16.1%, $P = .404$), while the percentage of moderate/severe infection with severe PAD was higher in CAG than DAG (45.5% vs 37.9%, $P = .049$).

During the 2-week observation period, 30 (16.3%) patients were found to have recurrence in CAG, of which 2 were mild infection with mild/moderate PAD and 4 were with severe PAD; 8 were moderate/severe infection with mild/moderate PAD, 14 were with severe PAD, and 2 were without PAD. Fifty-six (29.3%) patients were found to have recurrence in DAG, of which 3 were mild infection with mild/moderate PAD, 13 were with severe PAD, and 1 was without PAD; 16 were moderate/severe infection with mild/moderate PAD, 20 were with severe PAD, and 3 were without PAD. In most of the patients (67/86, 77.9%) infection recurrence occurred in the first week of the observation period (CAG: 22/30, 73.3%; DAG: 49/57, 85.9%).

The recurrence rates of the 2 groups are shown in Table 3. There was no statistical difference of mild infection recurrence rate between the 2 groups (7.2% vs 16.3%, OR = 2.508; 95% CI = 0.941-6.681; $P = .059$), while the recurrence rate of moderate/severe infection was significantly higher in DAG than CAG (44.8% vs 23.8%; OR = 2.607; 95% CI = 1.398-4.862; $P = .002$). The recurrence rate of mild infection with mild/moderate PAD was similar in the 2 groups (6.3% vs 5.4%; OR = 1.167; 95% CI = 0.185-7.367; $P = 0.870$), while compared with CAG, the recurrence rate of mild infection with severe PAD was higher in DAG (35.1% vs 12.5%; OR = 3.792; 95% CI = 1.090-13.185; $P = .030$). We also found that when moderate/severe infection with PAD (whether mild/moderate or severe grade), the recurrence rate was significantly higher in DAG than CAG ([40.0% vs 18.6%; OR = 2.917; 95% CI = 1.078-7.889; $P = .032$], [60.6% vs 30.4%; OR = 3.516; 95% CI = 1.375-8.994; $P = .008$]). However, when infection (whether mild or moderate/severe grade) without PAD, there was no difference of the recurrence rate in the 2 groups ([0.0% vs 5.3%; OR = 1.056; 95% CI = 0.949-1.174; $P = .383$], [16.7% vs 21.4%; OR = 1.364; 95% CI = 0.188-9.912; $P = .759$]).

The average follow-up duration was 4.6 months (3.6-6.8 months). In the CAG, the median time is 4.3 months (3.8-6.2 months); it was 4.8 months (3.6-6.8 months) for the DAG. At the end of follow-up, the healing rate was higher (OR = 3.569; 95% CI = 2.064-6.170; $P = .000$) and the rate of minor amputation, major amputation, and death was lower ([OR = 0.449; 95% CI = 0.266-0.759; $P = .004$], [OR = 0.229; 95% CI = 0.092-0.567; $P = .002$], [OR = 0.302; 95% CI = 0.092-0.567; $P = .034$]) in the CAG than DAG. Further analysis found that the percentage of healing, minor amputation, major amputation, and death of mild infection patients was similar in the 2 groups (90.4% vs 88.5%, $P = .676$; 7.2% vs 9.6%, $P = .562$; 0% vs 4.8%, $P = .067$; 1.2% vs 1.9%, $P = .584$). While for the moderate/severe infection patients, the healing rate was higher (73.3% vs 48.3%, $P = .000$) and the rate of minor amputation, major amputation, and death was lower (23.8% vs 49.4%, $P = .000$; 6.9% vs 20.7%, $P = .006$; 4.0% vs 13.8%, $P = .016$) in the CAG than DAG (Table 4).

Discussion

As we all know, the use of antibiotics is a "double-edged sword," which can cure infectious diseases when properly used; otherwise if increases financial costs and the risk of antibiotic resistance. A study about non-DM wounds found that reducing the "bioburden" of chronic skin wounds with antibiotics may improve healing is plausible, and some experimental animal data and studies with burn wounds and skin grafts support this theory.[11] To date, the optimal duration of antibiotic therapy for DFI has not been studied, and

Table 4. The Comparison of Clinical Outcomes Between the 2 Groups, n (%).

	CAG (n = 184)		DAG (n = 191)				
	Mild Infection	Moderate/ Severe Infection	Mild Infection	Moderate/ Severe Infection	OR	95% CI	*P*
Healing	75 (90.4)	74 (73.3)	92 (88.5)	42 (48.3)	3.569	2.064-6.170	.000
Minor amputation	6 (7.2)	24 (23.8)	10 (9.6)	43 (49.4)	0.449	0.266-0.759	.004
Major amputation	0 (0)	7 (6.9)	5 (4.8)	18 (20.7)	0.229	0.092-0.567	.002
Death	1 (1.2)	4 (4.0)	2 (1.9)	12 (13.8)	0.302	0.106-0.863	.034

Abbreviations: CAG, continuing antibiotics group; DAG, discontinuing antibiotics group; OR, odds ratio; CI, confidence interval.

the role of antibiotics for clinically uninfected wounds is a controversial issue.[12] To our knowledge, no studies have focused on whether continuing or discontinuing antibiotics has an effect on infection recurrence and clinical outcomes in DFI patients without PAD and/or PAD for whom the clinical signs and symptoms of infection have resolved.

In the present study, most of the diabetic foot patients with mild infection were treated in the hospital. This was not consistent with the IDSA guidelines, which showed that most patients with mild infections can be treated as outpatients. In our hospital, there was no outpatient treatment center. In addition, we found that most of the mild infection patients lacked understanding of glucose control and the severity of DFI, thus leading to severe DFI.

In terms of the recurrence rate, there was no significant difference between the 2 groups in the mild infection patients, but in the moderate or severe cases, it was significantly higher in the DAG than CAG (44.8% vs 23.8%, $P = .002$). Combining infection severity and PAD grade, we found that the infection recurrence rate of mild infection with severe PAD in DAG was higher than CAG (35.1% vs 12.5%, $P = .030$), and also in moderate/severe infection with mild/moderate PAD (40.0% vs 18.6%, $P = .032$) and severe PAD (60.6% vs 30.4%, $P = .008$). And the risk of infection recurrence was increased by 2.9 times and 3.5 times, respectively, in moderate/severe infection patients with mild/moderate PAD or severe PAD. It means that either infection severity or PAD grade has an influence on infection recurrence in DFI patients when the clinical signs and symptoms of infection have resolved. The 2 groups had similar clinical outcomes for patients with mild infection. However, for moderate/severe infection cases, healing rate (73.3% vs 48.3%, $P = .000$) in CAG was higher and the minor amputation rate (23.8% vs 49.4%, $P = .000$), major amputation rate (6.9% vs 20.7%, $P = .006$), and death rate (4.0% vs 13.8%, $P = .016$) were lower than DAG.

A previous study[13] reported a controlled trial about antibiotic treatment for purely neuropathic (without ischemia) forefoot ulcers in diabetes, and there was no difference in healing rate or ulcer size of the 2 groups after the 20-day follow-up. This was consistent with our study: no difference was found in recurrence rate and clinical outcomes of patients with infection (either mild or moderate/severe) and without PAD between CAG and DAG.

Foster et al[14] carried out a study on clinical uninfected diabetic foot patients with DPN and PAD. Patients were divided into antibiotics group and without antibiotics group. During the follow-up, 27 of 32 patients who were given antibiotic treatment healed completely and no cases had clinical infection and amputation. But in the other group, only 17 cases healing completely, 15 patients had clinical infection, and 3 patients required amputation. Compared with the other group, patients in the antibiotics group had higher healing rate, lower rate of amputation, and lower rate of clinical infection, especially in patients with PAD. Therefore, DM patients with PAD and "clean" ulcer should be given antibiotic treatment early.[15] However, the study did not analyze the influence of PAD severity on infection recurrence and clinical outcomes.

Edmonds and colleagues implied that DFI patients with ischemia and without antibiotics have a high risk of necrosis, which will then lead to major amputation.[15,16] This suggested that the clinical outcome of DFI with ischemia may be improved by antibiotic therapy.

Actually, it is common that diabetic foot patients are associated with ischemia and infection. Therefore, blood circulation may determine the duration of antibiotics, especially the degree of ischemia may have different strengths due to the influence of antibiotic treatment. We considered that clinical infection and outcomes were influenced by PAD and infection severity. Lipsky also holds the opinion that in some instances of extensive infection, large areas of gangrene or necrotic tissue, or poor vascular supply, more prolonged therapy may be needed.[12]

We found that for most of the patients both in CAG (73.3%, 22/30) and DAG (85.9%, 49/57), recurrence of infection occurred in the first week of observation. Thus, we speculated that patients with DFI, especially moderate/severe infection with PAD and mild infection with severe PAD after treatment whose signs and symptoms have reduced, may need to prolong the antibiotic treatment by 1 to 2 weeks. Further clinical studies are needed to prove this hypothesis.

The main limitations of the study are the following: this was a single-center randomized controlled study; the follow-up period was only 4.6 months on average; we could not analyze the mid- and long-term complications including late recurrences. In addition, the patients who required revascularization were excluded in the study, and further study should pay attention to this problem.

In spite of the aforementioned limitations, our study highlighted that when the clinical signs and symptoms of infection resolved, it might be appropriate to stop antibiotics for DFI patients without PAD, also for mild infection patients with mild or moderate PAD. For mild infection with severe PAD and moderate/severe infection with PAD patients, perhaps we should continue antibiotic treatment. Continuing antibiotic therapy could improve clinical outcomes for moderate/severe infection patients when signs and symptoms have resolved.

Declaration of Conflicting Interests

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