

Original Article

Effect of antibiotic therapy based on culture results on ulcer healing in chronic venous insufficiency

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Abstract

Aim: This study aims to evaluate the effect of antibiotic therapy based on wound culture results on wound healing in patients with stage C6 -Chronic Venous Insufficiency (CVI) who have resistant stasis ulcers that do not respond to standard CVI treatments.

Material and Methods: The study included 40 patients diagnosed with stage C6 -CVI at our clinic between 2020 and 2024. All stasis ulcers were located in the medial malleolus region. Swab cultures were obtained from all stasis ulcers, and antibiograms were performed on the cultures. Based on the antibiogram results, antibiotics to which the microorganisms were sensitive were administered concurrently with standard CVI treatment. Follow-up visits were scheduled at 30 and 45 days after treatment. Demographic data, history of Deep Vein Thrombosis (DVT), pre-treatment ulcer size, and wound healing times at follow-up were recorded.

Results: The most frequently isolated microorganisms from the stasis ulcer cultures were *Staphylococcus aureus* (70%), *Pseudomonas aeruginosa* (20%), *Escherichia coli* (7.5%), and *Klebsiella oxytoca* (2.5%). The average wound healing time for patients who received antibiotics based on the culture antibiogram and standard CVI treatment was 34.5 days. In patients with stage C6-CVI, administering antibiotics according to culture and antibiogram results may shorten the wound healing time in stasis ulcers.

Conclusion: In patients with stage C6-CVI, administering antibiotics according to culture and antibiogram results may shorten the wound healing time in stasis ulcers.

Keywords: Venous ulcers, wound healing, antibiotic therapy

INTRODUCTION

Chronic venous insufficiency (CVI) is a long-term condition of the venous system that predominantly affects the lower extremities, leading to significant impairment of venous return. The disease is common and affects up to 30% of the population, with advanced stages resulting in complications such as venous ulcers [1]. Stage C6-CVI is characterized by the presence of non-healing ulcers, typically located in the medial malleolus region, which are resistant to standard treatment methods. Venous ulcers are associated with substantial economic and social consequences, including lost work capacity, decreased quality of life, and increased healthcare costs. Approximately 1% to 3%

of the population in the U.S. develops venous ulcers, and these ulcers may persist for months or even years without effective healing [1-3].

In the treatment of stage C6-CVI, various approaches such as compression therapy, venotonic agents, and wound care are typically employed. However, despite these interventions, many patients experience slow or incomplete healing of ulcers, which often become complicated by bacterial infections. The presence of bacterial colonization or infection in these ulcers has been shown to significantly delay wound healing, making infection management an essential component of treatment. In some cases, systemic antibiotic therapy based on wound culture

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and antibiogram results may play a critical role in facilitating healing by targeting specific pathogens. While antibiotics are not routinely recommended for all CVI ulcers, studies suggest that they may be beneficial when there is a clear bacterial infection that impedes the healing process. This study aims to investigate the effect of antibiotic therapy, guided by wound culture results, on the healing time of stasis ulcers in patients with stage C6-CVI.

MATERIAL AND METHODS

This study is a single-center, retrospective observational study. Ethical approval was obtained from Kastamonu University ethics committee (2024-KAEK-66/26.09.2024). A total of 40 patients who presented to the Vascular Surgery outpatient clinic with stage C6-CVI between 2020 and 2024 were included in the study. Patients who met the following criteria were included in the study. Patients with Stage C6 Chronic Venous Insufficiency (CVI) and clinically diagnosed as Stage C6-CVI according to the Clinical, Etiological, Anatomical, Pathophysiologial (CEAP) classification system were included in the study. Only patients with stasis ulcers that did not respond to standard CVI treatments (such as compression therapy, venotonic agents, wound and care) were included. Patients aged 18 years and above were included, with no upper age limit. All patients had to have wound cultures taken from their ulcers before starting antibiotic treatment. Patients who had not received antibiotics for their ulcers before participating in the study were included to ensure that the results were not affected by previous antibiotic treatment.

These patients had previously been referred to our clinic multiple times with symptoms of C6-CVI and had non-healing stasis ulcers that were resistant to conventional CVI treatment. These patients had been receiving all known classical treatments for venous insufficiency for a long period, including venotonic agents, compression stockings, and topical wound care. However, in our study design, we hypothesized that antibiotic therapy based on wound culture results might offer an alternative treatment approach for wound healing. This is why the treatment plan was adjusted to include antibiotics based on the wound culture findings. It was confirmed that these patients had not received antibiotics for their ulcers before the study. Demographic data of the patients were recorded. Swab cultures were obtained from the stasis ulcers of all patients. The bacterial growth from the cultures was recorded according to the antibiogram results.

Based on the culture results, the antibiotics to which the isolated bacteria were sensitive were determined. Each patient received appropriate antibiotic therapy orally and systemically simultaneously with standard CVI therapy. As part of standard CVI management, all patients were advised to use high-pressure compression stockings and take the same venotonic agent orally daily. No additional topical therapy was prescribed for wound care. All patients were scheduled for follow-up visits 30 and 45 days after the start of treatment. Wound healing rates were recorded during these follow-up visits.

Swab samples were taken from the stasis ulcers of our stage C6 CVI patients before initiating antibiotic therapy. After cleaning the wound with physiological saline, swab samples were collected using a sterile technique. The samples were transported to the microbiology laboratory in transport media under appropriate conditions. Cultures were inoculated onto 5% sheep blood agar (RTA, Türkiye) and Eosin Methylene Blue (EMB) agar (RTA, Türkiye). A smear was prepared for Gram staining. The cultures were incubated aerobically at 37°C for 18-24 hours, and plates that showed no growth were further incubated for up to 48 hours. Bacterial growth was assessed along with Gram staining characteristics. Pathogen identification and determination of antibiotic susceptibilities were performed using the VITEK 2 Compact automated system (BioMérieux, France), and the antibiotic susceptibility results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards.

Statistical Analysis

Statistical analysis was performed using descriptive statistics. Continuous variables were expressed as mean±standard deviation, while categorical variables were presented as frequency and percentage (%).

RESULTS

The 40 patients in the study ranged from 35 to 69 years, with a mean age of 59.55±6.57 years. Of the patients, 32 were male (80%) and eight were female (20%). Ten patients (25%) had a body mass index (BMI) >30 kg/m². Eleven patients (27.5%) had a history of previous DVT. The ulcer sizes before treatment ranged from 3 to 5 cm, with an average ulcer size of 3.52±0.9 cm in 40 patients. Among the important factors potentially affecting wound healing in venous ulcers, there was a history of diabetes in 3 patients with a rate of 7.5% and a history of smoking in 17.5% of 7 patients. None of our patients had peripheral arterial disease. Thus, only patients with venous ulcers were included in the study and ischemic etiology was excluded (Table 1).

Table 1. Demographic data		
Variable	Patients (n=40)	Mean/percentage
Age range (years)	35-69	59.55±6.57
Gender: male	32	80
Gender: female	8	20
BMI (kg/m²) >30	10	25
History of DVT	23	57.5
Ulcer size range (cm)	3-5	3.52±0.9
Peripheral arterial disease	0	0
Diabetes mellitus	3	7.5
Smoking history	7	17.5

All patients were evaluated as stage C6 according to clinical examination and the CEAP classification system and were diagnosed with active venous ulcer. After venous etiology was confirmed, venous Doppler ultrasonography (USG) and ankle-brachial index (ABI) measurements were performed to exclude ischemic ulcers. Patients with an ABI value less than 0.9 were excluded from the study because this is considered indicative of peripheral artery disease. Additionally, patients' medical histories were reviewed and those at risk of artery disease and patients prone to ischemic ulcers were excluded from the study.

Based on the wound culture results, the most commonly isolated microorganism was *Staphylococcus aureus*, identified in 28 patients (70%). The second most frequent pathogen was *Pseudomonas aeruginosa*, isolated in 8 patients (20%). *Escherichia coli* was identified in 3 patients (7.5%), and *Klebsiella oxytoca* was found in 1 patient (2.5%) (Table 2).

Table 2. Isolated bacteria from swab cultures		
Bacteria	Number	Percentage
Staphylococcus aureus	28	70%
Pseudomonas aeruginosa	8	20%
Escherichia coli	3	7.5%
Klebsiella oxytoca	1	2.5%

The antibiogram results of the wound cultures showing *Staphylococcus aureus* revealed these isolates were sensitive to Trimethoprim-Sulfamethoxazole. Similarly, *Pseudomonas aeruginosa* cultures were sensitive to Ciprofloxacin. Wound cultures positive for *Escherichia coli* were sensitive to Trimethoprim-Sulfamethoxazole. The single isolate of *Klebsiella oxytoca* was sensitive to Trimethoprim-Sulfamethoxazole (Table 3).

Table 3. Culture antibiogram results		
Sensitive antibiotic	Number	Percentage
Trimethoprim-sulfamethoxazole	32	80%
Ciprofloxacin	8	20%

Trimethoprim-sulfamethoxazole and Ciprofloxacin were administered orally twice daily for 15 days in addition to standard CVI therapy in patients susceptible to these antibiotics. No intravenous or inpatient treatment was administered. Patients were called for follow-up visits to our outpatient clinic after 30 and 45 days.

At 30-day follow-up, we observed 28 patients (70%) had complete or nearly complete healing of their ulcers. At 45-day follow-up, we observed that the remaining 12 patients (30%) had complete or almost complete healing of their ulcers (Table 4). In our study of 40 patients, the average wound healing time was calculated as 34.5 days.

Table 4. Wound healing progress at 30 and 45 days follow-up		
Follow-up day	Number of healed ulcers	Percentage
30 days	28	70%
45 days	12	30%

DISCUSSION

CVI is a venous system disease characterized by significant impairment of venous return in the lower extremities. In the United States, it has been reported that more than 2.5 million people live with CVI, with approximately 20% of them developing venous ulcers [4]. This condition is reported to affect 1% to 3% of the population in the U.S. [5]. As is the case worldwide, in our country, the development of venous ulcers in the advanced stages of CVI leads to several negative consequences. Chronic venous ulcers restrict participation in professional and social activities, leading to a decrease in quality of life and causing financial limitations. A study conducted in the U.S. found that over 12% of workers with venous ulcers had to retire early due to disability caused by chronic venous ulcers [6]. In addition to treatment costs and loss of workforce, many patients also suffer from psychological issues due to non-healing or frequently recurring ulcers [7].

CVI is a chronic condition characterized by impaired venous return, primarily affecting the lower extremities. CVI is classified according to the CEAP classification system, which evaluates the clinical, etiological, anatomical, and pathophysiological aspects of the disease. Specifically, stage C6 is characterized by the presence of non-healing ulcers, typically located in the medial malleolus region. In advanced stages of CVI, especially in stage C6, treatment-resistant ulcers are frequently observed, leading to significant social and economic consequences [1-3]. In the CEAP classification, stage C6 is defined as "non-healing ulcers" and represents a condition that significantly reduces patients' quality of life and requires prolonged treatment.

Several factors have been identified as risk factors for the development of ulcers in CVI, including age over 55, a family history of chronic venous insufficiency, high BMI, and a history of DVT [6]. In our study, the mean age was 59.55 years, with 25% of patients having a BMI>30 and 57.5% having a history of DVT, which is consistent with the findings in the literature. 57.5% of our patients had a history of DVT, so these patients were thought to have a stasis ulcer due to postthrombotic deep venous insufficiency. Among the 40 patients, the remaining 17 patients did not have a DVT, and therefore these patients were thought to have a stasis ulcer due to superficial venous insufficiency. Clinical data of patients with and without DVT were confirmed by venous Doppler USG. These patients were individuals with chronic venous ulcers who had been under

long-term follow-up due to stasis ulcers that either failed to heal for years or frequently recurred. They had previously presented to our clinic multiple times with similar complaints and had received treatment. Therefore, the duration of the venous ulcers, along with the patients' past treatment histories, highlight that recurrences have been a persistent, long-term issue.

Although many treatment options are available for managing stage C6 -CVI, standardized treatment has yet to be definitively established [8]. Numerous studies have described various interventions, including compression therapy, exercise, dressings, pentoxifylline, venotonic drugs, aspirin, and surgical treatments [9-11]. However, the use of antibiotics in treating C6-CVI has been debated in the literature [12]. Therefore, current clinical practice differs from antibiotic use for stage C6 CVI.

Vascular surgery was not performed on the patients in this study during the ulcer treatment process. The study focused on conservative treatment of venous ulcers, including compression therapy, venotonic agents, and antibiotic therapy based on culture results. The aim of the study was to evaluate the effect of antibiotic treatment on wound healing, so surgical interventions were not included.

In our study, all 40 patients had previously received most of the recommended treatments for CVI, excluding antibiotics, over several years. These patients had a history of ulcers that had persisted for months, as known from both their medical history and follow-up visits. Since our patients had chronic ulcers, all patients had wounds that had persisted for more than a year before the study. In all 40 patients, swab cultures were taken from the ulcers, and bacterial growth was recorded in every case. No patient had negative bacterial cultures. The most frequently isolated bacterium was *Staphylococcus aureus* (70%), followed by *Pseudomonas aeruginosa* (20%). These findings are consistent with the existing literature. Similar bacterial growth patterns were observed in a study by Halbert et al. [13].

A study by O'Meara et al. reported that bacteria that exhibit signs of infection colonize the majority of C6-CVI ulcers. The presence of disease has been suggested to delay ulcer healing in their study. This study proposed two main strategies for preventing and treating clinical infection in CVI ulcers: systemic antibiotics, topical antibiotics, or antiseptics. Furthermore, while there is no current evidence supporting the routine use of systemic antibiotics to accelerate healing in venous leg ulcers, the study recommends that systemic antibiotics should only be used for defined cases of infection rather than for bacterial colonization before drawing definitive conclusions about their efficacy in improving venous leg ulcer healing [14]. In our study, in this logic, appropriate and sensitive antibiotics were administered systemically

based on the results of wound swab cultures. In our study, patients received monotherapy with antibiotics based on the results of their wound culture and antibiogram. Each patient was prescribed an antibiotic that the isolated bacteria were sensitive to. For example, patients with *Staphylococcus aureus* infections were treated with Trimethoprim-Sulfamethoxazole, while those with *Pseudomonas aeruginosa* were treated with Ciprofloxacin. These antibiotics were administered orally in combination with standard CVI treatments, but no additional systemic or intravenous antibiotics were used. Thus, antibiotic therapy was tailored specifically to the individual bacterial sensitivities identified through the cultures, and no combination therapy was employed.

In our Cardiovascular Surgery outpatient clinic, 40 patients who received antibiotic therapy based on the results of wound swab cultures and antibiograms in addition to standard CVI treatment were followed up at 30 and 45 days. At the 30-day follow-up, 28 patients (70%) demonstrated complete or nearly complete healing of their ulcers. At the 45-day follow-up, 12 patients (30%) also demonstrated complete or almost complete healing of their ulcers. Based on these results, systemic antibiotics, administered orally according to the bacterial sensitivities found in the wound swab cultures, contributed significantly to wound healing, with notable improvements observed at the 30 and 45-day follow-ups.

Around 400 BC, Hippocrates wrote, "Standing is not appropriate in case of ulcers, especially when the ulcer is located on the leg." Hippocrates himself is known to have suffered from leg ulcers [15]. Indeed, the best treatment for leg ulcers associated with CVI depends on correct diagnosis and treatment of the underlying etiology. If all underlying causes are addressed, wound recurrence will likely be delayed. Various treatment methods, which are not standardized, are still used worldwide to manage ulcerative wounds [16]. There are many factors that can affect recovery time. These include the severity of the ulcer, comorbidities (e.g. diabetes), nutritional status and time to initiation of treatment for the ulcer. Additionally, factors such as ischemia, venous insufficiency, and bacterial colonization may also affect recovery time. The contribution of these factors to wound healing is evident. However, the primary aim of our study is to investigate the effect of targeted therapy based on culture and antibiogram results. Therefore, while these factors are considered, our main focus is on the direct impact of antibiotic therapy on wound healing.

According to our study, most bacteria identified in the wound cultures were 80% sensitive to trimethoprim-sulfamethoxazole. However, this does not necessarily imply that empirical antibiotic therapy should be initiated in C6-CVI or that Trimethoprim-Sulfamethoxazole should be the

first-line treatment. Nevertheless, a wound culture should be obtained in cases of C6-CVI that are unresponsive to or slow to heal despite all other medical and surgical treatments. If obtaining a culture is not possible, or in cases where infection is suspected, antibiotic therapy might be considered an adjunct to other recommended treatments, particularly in the first-line management of infected C6-CVI ulcers. Furthermore, studies have shown that bacterial colonization of venous ulcers is common, and this colonization can impede the natural healing process. In particular, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most frequently isolated pathogens in chronic venous ulcers, consistent with the findings of our study [13,14]. A survey by Harding et al. highlighted that bacterial infection in chronic wounds not only delays healing but also promotes chronic inflammation and tissue damage, which can further complicate the wound-healing process [17]. Although the routine use of systemic antibiotics in non-infected ulcers is not recommended, targeted antibiotic therapy based on culture results has improved healing rates in infected ulcers by eliminating pathogens that hinder the healing process [14]. This aligns with our findings, where administering appropriate antibiotics based on bacterial sensitivities significantly improved ulcer healing at both the 30 and 45-day follow-ups. However, as noted in other studies, it is crucial to balance antibiotic use to avoid the emergence of resistant bacteria, which remains a growing concern in wound care [18,19]. Thus, while antibiotics may play a role in managing infected CVI ulcers, their use should be carefully considered and based on microbiological evidence to ensure efficacy and safety. Our study shows that targeted antibiotic therapy shortens recovery time. By day 45, 30% of patients had made a full recovery and 70% had almost made a full recovery. Although not included in our empirical group study, the literature indicates that targeted therapy accelerates recovery due to more effective treatment of identified pathogens. Since our study is a retrospective study, there is no empirical cohort, but this would be an important direction for future research.

However, due to the growing concerns over antibiotic resistance caused by overuse and inappropriate prescription, we believe that further large-scale studies are necessary to obtain conclusive evidence regarding the efficacy and safety of antibiotic therapy in these patients.

Although it is reported in the literature that factors such as obesity and deep vein thrombosis may have potential effects on wound healing, our main focus in this study was to investigate the effect of antibiotic treatment based on culture and antibiogram results for stasis wounds [20]. Without ignoring that these factors may affect wound healing, we believe that including such variables in future studies will provide a more comprehensive understanding of wound healing.

In our study, the follow-up period was limited to 30 and 45 days, and the effect of this period on long-term recovery and recurrence rates is undoubtedly an important issue. We could not evaluate these parameters in our study due to the lack of long-term follow-up data.

We also acknowledge that the limited sample size in our study may limit the statistical power and generalizability of our findings. However, we acknowledge that long-term follow-up will play a critical role in future studies in terms of permanence of wound healing and recurrence rates.

Addressing bacterial colonization and targeted antibiotic therapy has been the primary focus of our study. However, we are aware that the risks associated with antimicrobial resistance are also an extremely important issue. It is obvious that it is possible to minimize the problem of antimicrobial resistance with careful and limited use of antibiotics.

Due to the limited data in our study, we believe subgroup analyses, including patient characteristics, ulcer size, and bacterial strains, should be explored in larger studies for more comprehensive insights.

In our study, according to culture antibiogram results, the average wound healing in stasis ulcers treated with antibiotics was 34.5 days. In the meta-analysis study conducted by De Carvalho et al., the mean healing time in stasis ulcers treated with bandages alone was reported as 83.8 ± 24.89 [21]. In this sense, it can be said that antibiotic treatment given according to culture antibiogram results can shorten the average wound healing times reported in the literature.

In our study, wound duration before treatment was not specifically determined. However, it was known that the wounds were chronic. Wounds that do not heal for a long time may prolong the healing process due to factors such as complications or bacterial colonization. However, our study focused more on the effect of antibiotic treatment based on culture and antibiogram results on wound healing time, and it has been shown that the use of appropriate antibiotics significantly shortens the healing time. Future studies could examine the role of pre-treatment wound duration on healing outcomes in more detail.

In our study, the effect of targeted antibiotic treatment based on culture and antibiogram results on the healing time of venous ulcers was examined. Targeted antibiotic therapy is recommended in studies instead of empirical therapy due to both treatment efficacy and the presence of antibiotic resistance. Our study is consistent with the literature with this logic [19].

Wound healing time is affected by many factors, not only antibiotic treatment. As is known, venous ulcers are a serious

medical problem. The healing period varies from several months to several years. It is the most common chronic leg ulcer in the geriatric population, especially in people with DM, mainly due to age-related neuropathy and localized ischemia. Other risk factors include excess weight, history of previous injuries, and inactivity [22]. Factors such as comorbidities (e.g., type II diabetes, hypertension, cardiovascular diseases), nutritional status, ischemia, and venous insufficiency can significantly affect the healing process. In addition, the severity of the ulcer, the time to start treatment and the suitability of local wound care are other factors that affect the healing time. Although the focus of our study is targeted antibiotic therapy, it is thought that these other factors should also be considered in more detail in treatment planning.

CONCLUSION

As is well known, although there is currently no standardized treatment protocol for C6-CVI worldwide, various treatment methods are employed to heal these ulcers. Systemic antibiotic therapy is not generally considered a recommended treatment for wound healing in C6-CVI. However, in cases where ulcers persist for months and fail to respond to standard C6-CVI treatment, the detection of bacterial colonization in wound cultures may suggest that systemic antibiotic therapy could benefit wound healing.

Although the findings of this study provide valuable insights into the potential benefits of systemic antibiotic therapy in the treatment of persistent ulcers in C6-CVI, it is important to acknowledge that the sample size was relatively small. Therefore, further research with larger cohorts is needed to confirm these results and determine the generalizability of the findings.

Ethics Committee Approval: Ethical approval was obtained from Kastamonu University Faculty of Medicine Ethics Committee (2024-KAEK-66/26.09.2024).

Patient Consent for Publication: Not necessary for this manuscript.

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