Factors associated with the failure of conservative surgery of diabetic foot osteomyelitis

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Key words
- Conservative surgery
- Diabetic foot infection
- Diabetic foot osteomyelitis
- Internal pedal amputation.

Article points
1. Conservative surgery (CS) leaving the wound open to heal by secondary intention is a safe procedure to arrest bone infection in cases of diabetic foot osteomyelitis (DFO).
2. CS may fail, and the patient will require an amputation.
3. Soft tissue infection, and isolation of Pseudomonas in bone cultures were factors associated with failure of CS.
4. Patients with osteomyelitis without soft tissue infections had a low rate of failure of CS.

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Conservative surgery (CS) is a safe procedure to arrest the bone infection in cases of diabetic foot osteomyelitis (DFO). The authors conducted a case-control study of 83 patients with DFO who underwent CS as the first attempt to arrest the bone infection and presented with a failure of this surgical approach. CS failed in 21 patients (25.3%) and required amputations; 15 minors (18%) and six majors (7.3%). The factors associated with failure of conservative surgery and subsequent amputation were isolation of *Pseudomonadacea* in bone cultures, and soft tissue involvement. Just three out of 44 patients (6.8%) had a failure of CS, and none of them underwent a major amputation when patients with osteomyelitis without soft tissue infections were analysed separately.

Surgical treatment has been the treatment of choice of diabetic foot osteomyelitis (DFO) for many years. Nowadays, the trend is toward a more conservative approach using exclusively antibiotics to arrest the bone infection (Lazaro-Martinez et al, 2014; Aragon-Sanchez and Lipsky, 2018). However, surgery is necessary in cases in which there is no response to antibiotics, extensive soft tissue envelope involvement, or progressive bone damage (Lipsky et al, 2020). Modern surgeons have developed new surgical techniques with the aim of avoiding amputations (Ha Van et al, 1996; Aragon-Sanchez, 2010; Faglia et al, 2012). These techniques that are named ‘internal pedal amputation’ or conservative surgery (CS) could be cosmetically more acceptable to the patients and minimise the risk of recurrence. However, it is far from being demonstrated (Aragon-Sanchez et al, 2021a).

The feasibility of performing CS depends on the clinical presentation of DFO (Aragon-Sanchez et al, 2008; Aragon-Sanchez, 2012). The preferences and experiences of the surgeon are also factors that influence the type of surgery offered to patients. Even though the use of CS is increasing (Yammine et al, 2021), few studies have analysed the risk factors associated with the failure of CS for treating DFO. In cases of failure of CS, the patients might require a higher level of amputation.

Aim

It is the aim of the present retrospective cohort study to analyse the variables associated with the failure of CS in patients who underwent this type of surgical approach as the first attempt to treat DFO.

Methods

The authors conducted a retrospective cohort study of patients with DFO who underwent CS as the first attempt to arrest the bone infection and presented with a failure of this surgical approach. These patients were collected from a larger cohort of patients treated for diabetic foot infections (DFIs) from January 2017 to December 2018 in the Diabetic Foot Unit at San Juan de Dios Hospital, San José, Costa Rica. The collection process is shown in the flow chart shown in *Figure*

1. The cohort of patients was consecutively collected during the period of the study in a clinical database that is also used for research purposes. Medical background, diabetes-related complications, laboratory results and other variables of interest were collected in the database. The diagnosis of osteomyelitis was based on a combination of clinical signs, probe-to-bone test and X-ray in two views as previously reported (Aragon-Sanchez et al, 2011). The diagnosis was always confirmed by histopathological study of the resected specimen, which was also sent to the Microbiology Department. Severity of the infection was classified according to the International Working Group on Diabetic Foot guidelines (Lipsky et al, 2016).

Surgical techniques

CS is defined as a surgical procedure in which the infected bone is resected without performing any amputation of the foot. CS preserves more distal tissues, both soft tissue and bone. The types of CS performed in this study were distal phalanx resections, interphalangeal joint resections, metatarsal-phalangeal resections, metatarsal head resections and bone debridement in cases of calcaneal osteomyelitis. CS may be combined with soft tissue debridement when required.

Minor amputation is defined as any resection of both whole soft tissue and bone distal to the osteotomy site. Minor amputations are defined as those amputations distal to the ankle joint. Amputations through or above the ankle joint are defined as major amputations. The decision of performing CS was made when the surgeon considered that, after removing both infected soft tissue and bone, the bone infection could be arrested, and the wound would heal by secondary intention from the remaining soft tissue.

Amputations were performed in cases in which soft tissue destruction precluded the success of CS. Just cases in which the index surgical procedure was finalised as a CS procedure have been included in this retrospective cohort study. The extent of bone resection was based on the preoperative radiological study and appearance of the bone during the surgical procedure. The osteotomy site was chosen in an apparently healthy bone/hard bone with cortex intact without purulent drainage when the bone was cut. During the surgical procedure of both CS and minor amputations, a piece of bone from the proximal margin was taken and sent for microbiological study. The procedure was performed after removing the infected bone and non-viable soft tissues. Then, lavage of the surgical wound was carried out with 1–2 litres of running saline. After that, the surgeon changed his/her surgical gloves and an additional piece of bone from the proximal margin was resected with a Rounger sterile instrument. The wounds after CS or minor amputations were left open to heal by secondary intention. Wounds were measured with the imitoMeasure® app (imito A.G., Zurich, Switzerland).

The management of the wound was as follows: wounds with a surface >5 cm^2 were packed with a sponge and negative pressure wound therapy delivered by the Vacuum Assisted Closure (VAC) Therapy System (KCI USA, San Antonio, TX, USA) was applied. Wounds with a surface <5 cm^2 were filled with PolyMem WIC® Silver Rope Wound Filler (Ferris Mfg. Corp., Fort Worth, TX, U.S.A). Major amputations were sutured.

Peripheral arterial disease (PAD) was diagnosed on the basis of the following: previous vascular surgery, absence of one or both foot pulses, and/or ankle-brachial index (ABI) <0.9 or ≥1.2. Patients diagnosed for PAD were evaluated by the vascular team, and revascularisations were carried out at the discretion of vascular surgeons after treating the infectious problem. Soft tissue infection (STI) accompanying osteomyelitis was defined as the presence of skin necrosis (in an amount not precluding CS), deep abscess, tendon infection or extensive cellulitis.

Postoperative antibiotics were just used in cases in which residual soft tissue infection was apparent after surgery and were stopped when soft tissue infection disappeared. In the case that the Microbiology Department reported that bone margins were positive and antibiotics had been stopped, they were not restarted. Antibiotic treatment was modified according to the results of the antibiogram in cases in which postoperative antibiotics were necessary for residual soft tissue infection.

Failure of CS was defined as the need for an amputation, minor or major, after the first attempt to arrest the bone infection due to worsening and/or recurrence of the infection whether in bone or soft

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tissues precluding the healing of CS. The wound healing course was assessed twice or three times a week until healing. Time to healing was calculated from the day surgery was carried out until healing, which was defined as the epithelialisation of both the surgical wound and ulcer that was the portal of entry to the infection without recurrence of osteomyelitis. Recurrence of osteomyelitis was defined as the appearance of bone infections at the same or an adjacent site after healing in the same toe/metatarsal bone that was operated on in the first attempt. Patients who underwent a major amputation were excluded for calculation of time to healing due to the surgical wounds being closed with stitches. Patients were followed up once a month after healing until the end of the study (February 28, 2021) or death.

Statistical methods

The normal distribution of the variables was tested using the Kolmogorov-Smirnov test for continuous variables. For descriptive purposes, we used the mean and standard deviation (SD) for normally distributed continuous variables and median and interquartile range (IQR) for non-normally distributed continuous variables. The authors used percentages for discrete variables. The independence between discrete variables by the 2 test and Fisher's exact test when indicated was analysed. Normally distributed quantitative variables were analysed using Student's t-test for two independent samples. Non-normally distributed quantitative variables were compared by using the non-parametric Mann-Whitney U-test for two independent samples. Variables with *P*<0.05 in univariate analysis were included in a Cox's proportional hazards model for failure of conservative surgery and hazard ratios (HRs) were estimated. The statistical analysis was performed with SPSS version 20 for macOS (SPSS Inc., Chicago, IL, USA), and a *P*-value <0.05 (two-tailed) was set as the threshold for statistical significance.

A post-hoc calculation of the sample size for cohort studies was done for the two variables which achieved statistical significance in the multivariate model. The calculation was based on the risk in exposed and non-exposed cases with a power of 80% and 95% confidence level. Samples size were 83 patients for *Pseudomonadaceae* and 39 patients for soft tissue involvement. Sample size calculation was performed with Epidat software. V.4.2, July 2016 (Consellería de Sanidade, Xunta de Galicia, España; Organización Panamericana de la salud [OPS-OMS]; Universidad CES, Colombia).

The present study was conducted following the Declaration of Helsinki guidelines as revised in 2013. Every patient gave verbal consent to enter their clinical information into the database and provided written informed consent regarding the surgical procedures. The database was anonymised and approved for research purposes by the ethical committee. This study was approved by the Ethical Committee of San Juan de Dios Hospital (Caja Costarricense de Seguro Social), San José, Costa Rica (HSJD-059-CEC-2020). STROBE guidelines for cohorts were met in the present study.

Results

A total of 83 patients, 60 men (72.3%) and 23 women (27.7%), with a mean age of 60.7 years (SD 10.4) underwent CS for DFO. Sixteen patients (19.3%) presented with a severe infection, and 67 patients (80.7%) presented with a moderate infection. CS failed in 21 patients (25.3%) and required a further amputation, 15 minors (18%) and six majors (7.3%), as shown in *Figure 1*. The median duration of the lesion that was the portal of entry for the infection was 22 days (IQR 38). In patients with successful CS, the median duration of the lesion was 25 days (IQR 38), while in patients with failed CS, it was 21.5 days (IQR 47.5) (*P*=0.56). PAD was diagnosed in 29 patients (34.9%), and revascularisation was required in 13 of them (44.8%). Postoperative antibiotics were used in 13 cases (15.7%), with a median of 7 days (IQR 3). Failure of CS and need for amputation was always due to soft tissue infection and/or necrosis unresponsive to antibiotics.

Univariate analysis of the variables according to the success or failure of CS is shown in *Table 1*. The factors associated with failure of conservative surgery and subsequent amputation following application of Cox's proportional hazards model were isolation of Pseudomonadacea in bone cultures (HR: 3.4, 95% CI: 1.3–9.0, *P*=0.01), and soft tissue involvement (HR: 8.0, 95% CI: 2.3–27.3, *P*<0.01).

The sequence of treatment of the patients regarding the presence of STI is shown in *Figure*

2. Just 3 out of 44 patients (6.8%) without STI had a failure of CS, and none of them underwent a major amputation.

Healing was achieved in 20.4 weeks (SD 10.9) in patients without and 27.5 weeks (SD 17.2) in those with failure of CS (P=0.03).

The mean follow-up time was 38 months (SD 7.7), with a minimal follow-up time of 8.8 months and maximal follow-up time of 50 months. Overall, 81 out of 83 patients (97.6%) were followed for more than 1 year. No recurrences of osteomyelitis were found after healing during follow-up.

Discussion

The rate of failure of CS in the present series is 25.3%, with a rate of limb loss of 7.3%. The authors have found two factors associated with failure of CS, which are easily identifiable and include soft tissue infection and isolation of *Pseudomonas* in bone cultures.

STIs and necrosis have been previously reported as variables associated with the failure of CS (Aragon-Sanchez et al, 2008) and need for reoperation (Aragon-Sanchez et al, 2012). Even though in those series, the failure of CS was also defined as the impossibility to perform CS during the initial operation (Aragon-Sanchez et al, 2008).

In the present series, the authors have included just the patients who required reoperation after initial CS. It was reported more than 20 years ago that osteomyelitis associated with deep STIs had a worse prognosis than osteomyelitis alone (Eneroth et al, 1999). This finding was further confirmed by other authors (Aragon-Sanchez, 2012). The prognosis is worse when DFO is associated with necrosis compared to that in cases without necrosis (Aragon-Sanchez, 2012; 2021b). Necrosis has been shown to be a factor associated with amputation in many series dealing with DFIs (Sen et al, 2019). Even though the clinical presentation of osteomyelitis with STI is common, some series just include patients with chronic osteomyelitis without necrosis, abscess or severe infections (Faglia et al, 2012; Cecilia-Matilla et al, 2013; Tamir et al, 2016; Schoni et al, 2021). It reflects the differences regarding clinical presentation of DFO across different experiences and countries.

The authors wanted to show a series dealing with real-life in our country, and it is difficult to compare with other series that include just cases of chronic osteomyelitis with no or minimal STI. Most patients treated in the authors' department have advanced cases of DFO. For that reason, the rate of failure in the present experience is 25%, including 7.2% of major amputations. One similar experience in Spain reported an 18% failure rate with CS and a 5.4% failure rate with major amputations (Aragon-Sanchez et al, 2008). In the present series, just 3 out of 44 patients (6.8%) without STI had a failure of CS, and none of them underwent a major amputation when we excluded patients with STIs. One study dealing with CS versus antibiotic treatment reported a 13.6% failure rate of CS and

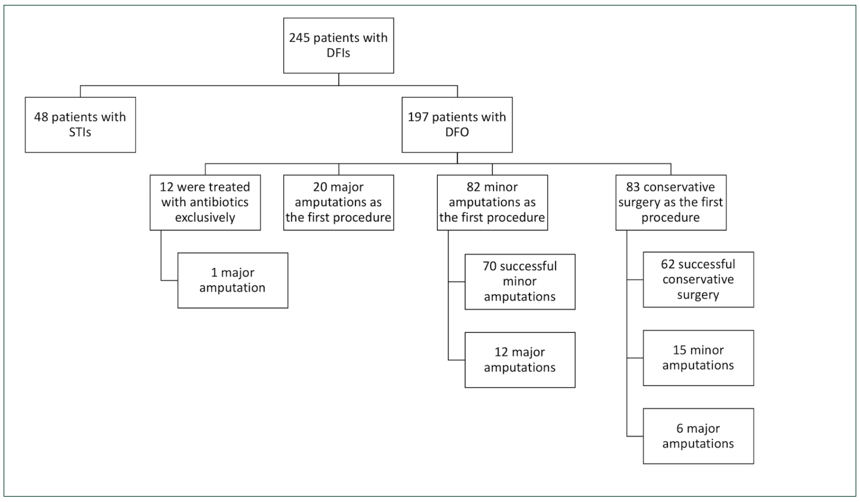

Figure 1: Sequence of collection of the case-control series.

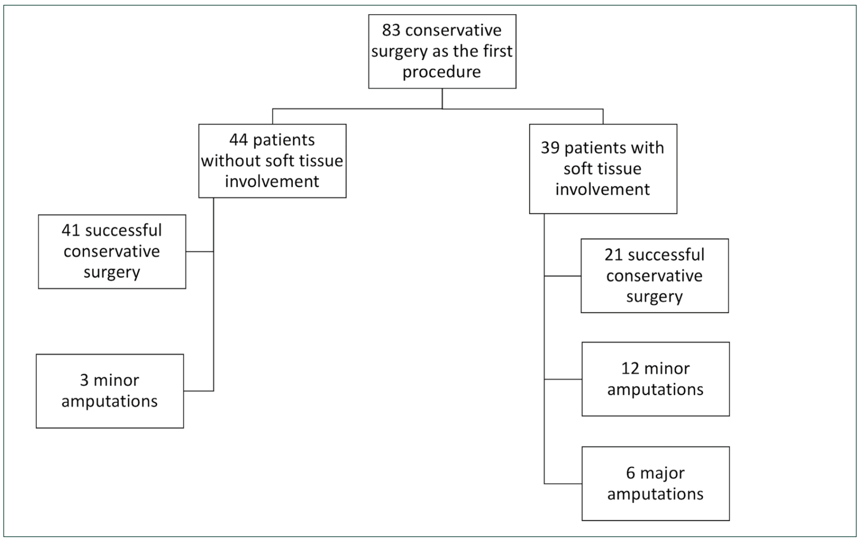

Figure 2: Sequence of surgical treatment according to the presence of soft tissue involvement.

Table 1. Demographic characteristics of participants (*n*=50). Univariate analysis of the series.				
	Series (*n* =83)	**Conservative surgery successful (*n*=62)**	**Failure of conservative surgery (*n*=21)**	***P*-value**
Foot ulcer history, *n* (%)	29 (34.9)	26 (41.9)	*3 (14.3)*	0.02
PAD, *n* (%)	29 (34.9)	22 (35.5)	7 (33.3)	0.85
Severe infection, *n* (%)	16 (19.3)	11 (17.7)	*5 (23.8)*	0.54
Soft tissue involvement, *n* (%)	39 (47)	21 (33.9)	18 (85.7)	<0.01
BLEE isolation, *n* (%)	5 (6)	1 (1.6)	4 (19)	0.01
Pseudomonadaceae isolation (8 *P. aeruginosa*, 1 *P. putida*) , *n* (%)	9 (10.9)	3 (4.8)	6 (28.6)	<0.01
Positive culture of bone margins, *n* (%)	62 (74.7)	47 (75.8)	15 (71.4)	0.69
Glucose (mg/dl) at admission, median (IQR)	175 (106)	171 (96)	179 (150)	0.64
Glucose (mmol/L) at admission, median (IQR)	9.71 (5.88)	9.49 (5.33)	9.93 (8.32)	0.64
BUN (mg/dl), median (IQR)	18 (12)	18 (10)	21 (14)	0.97
Creatinine (mg/dl), median (IQR)	1.1 (0.7)	1 (0.7)	1.1 (1)	0.42
eGFR (mL/min/1.73m^2), mean (SD)	68.1 (33.5)	67.9 (31.0)	68.6 (40.7)	0.93
Sodium (mmol/L), mean (SD)	134.0 (3.3)	134.2 (3.4)	133.4 (3.2)	0.38
Albumin (g/dL), median (IQR)	2.9 (0.3)	2.9 (0.3)	2.9 (0.6)	0.10
CRP (mg/dL), mean (SD)	18.4 (14.7)	17 (14.7)	22.5 (14.1)	0.14
Glycated haemoglobin (%), mean (SD)	9.0 (2.0)	8.7 (2.1)	9.7 (1.7)	0.06
Haemoglobin level (g/dL), mean (SD)	11.8 (1.9)	11.9 (1.8)	11.4 (2.1)	0.35
WBC (Cells/mm^3) count, mean (SD)	13526.0 (4945.0)	13613.8 (5287.8)	13266.6 (3858.0)	0.78
Platelets (109/L) count, mean (SD)	387.4 (162.6)	391.8 (163.1)	375.1 (164.6)	0.68
Lymphocytes (109/L) mean (SD)	2.4 (1.0)	2.4 (1.0)	2.1 (1.1)	0.20
Neutrophils (109/L), mean (SD)	7.3 (3.8)	7.1 (3.8)	7.9 (3.9)	0.46
Monocytes (109/L), median (IQR)	0.795 (0.551)	0.800 (0.459)	0.773 (1.204)	0.95
Mean platelet volume (fL), median (IQR)	9.7 (1)	9.8 (1)	9.4 (1.1)	0.44
ESR (mm/h), mean (SD)	80.7 (32.0)	77.0 (30.3)	91.6 (34.9)	0.07
Platelets to lymphocyte rate, mean (SD)	190.8 (109.1)	186.2 (116.2)	203.6 (87.3)	0.53
Neutrophil to Lymphocyte rate, median (IQR)	2.9 (3.2)	2.7 (2.3)	3.6 (3.5)	0.16
Lymphocyte to monocyte rate, median (IQR)	2.7 (2.1)	2.8 (2.1)	2.2 (2)	0.33
MPV to platelets rate, median (IQR)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.81
MPV to Lymphocyte rate, median (IQR)	4 (2.6)	4 (2.5)	4.7 (2.4)	0.28
CRP/albumin ratio, mean (SD)	6.5 (5.4)	5.8 (5.1)	8.6 (5.7)	0.03

subsequent minor amputation (Lazaro-Martinez et al, 2014). Another group reported an 11.5% failure rate of toe-sparing surgery in neuropathic toe ulcers requiring amputation (Tamir et al, 2016). Another group reported a 13.6% wound dehiscence rate in a series of 110 patients who underwent internal pedal amputation (Faglia et al, 2012). None of these patients required amputation (Faglia et al, 2012).

The isolation of *Pseudomonas* (eight cases of *P. aeruginosa* and one case of *P. putida*) in the bone biopsy was a variable associated with the failure of CS in our experience. The isolation of *P. aeruginosa* from DFO depends on the country in which the research was conducted. It has been reported to be 1.3% in the USA (Parks and Nguyen, 2019), 6.5% in Greece (Andrianaki et al, 2020), 15.4% in Spain (Aragon-Sanchez et al, 2013), 19% in Turkey (Saltoglu et al, 2018) and 42% in a series from the UK (Arias et al, 2019). The isolation of *P. aeruginosa* in polymicrobial cultures was a factor for higher mortality in a large cohort of patients with diabetes and skin and soft tissue infections (Lipsky et al, 2010). Infection with Gram-negative rods was a predictor of limb loss in a multicentre study conducted in Turkey (Saltoglu et al, 2015). Gram-negative isolation was associated with more severe infections in cases of DFO (Aragon-Sanchez, Lipsky et al, 2013). Barshes et al (2016), in their series, reported a 28.8% failure rate of surgical treatment for DFO, and the isolation of *P. aeruginosa* or *Escherichia coli* from bone biopsies was a risk factor for failure. The authors included the isolation of E. coli in the statistical study, which was not associated with the failure of CS (but the isolation of *Pseudomonadaceae* was).

Our study has limitations. First, it has retrospective nature. Second, even though every patient with PAD underwent evaluation by the vascular team and revascularisations were performed at discretion, non-invasive vascular tests were not collected in our research database. Third, healing without recurrence is a common endpoint after surgery for DFO, but it would have been desirable having inflammatory markers and imaging studies during the follow-up. Fourth, reoperations after failure of CS were indicated by soft tissue destruction after clinical evaluation. Although the bone seemed to be healthy, an additional bone sample during the second procedure could have assured that the bone was not the cause of the persistence of the infection.

The strengths of the present study are that osteomyelitis was always confirmed by pathological study. It ensured that every patient included in this study had osteomyelitis. Follow-up after complete healing of the wounds was long enough to detect late recurrences. Finally, the surgical decisions were made by the team, minimising the risk of bias.

Conclusion

CS leaving the wound open to heal by secondary intention is a safe procedure to arrest bone infection in cases of DFO. The failure rate of CS was 25.3%, with a rate of limb loss of 7.3%. The variables associated with the failure of CS were STI, and isolation of *Pseudomonas* in bone cultures. Patients with osteomyelitis without STIs had a low rate of failure of CS and did not undergo major amputations. ■

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