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INFECTION

Incidence and risk factors of recurrence in limb osteomyelitis patients after antibiotic-loaded cement spacer for definitive bone defect treatment

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Aims
This study was designed to characterize the recurrence incidence and risk factors of antibiotic-loaded cement spacer (ALCS) for definitive bone defect treatment in limb osteomyelitis.

Methods
We included adult patients with limb osteomyelitis who received debridement and ALCS insertion into the bone defect as definitive management between 2013 and 2020 in our clinical centre. The follow-up time was at least two years. Data on patients' demographics, clinical characteristics, and infection recurrence were retrospectively collected and analyzed.

Results
In total, 314 patients with a mean age of 52.1 years (SD 12.1) were enrolled. After a mean of 50 months' (24 to 96) follow-up, 53 (16.9%) patients had infection recurrence including 32 tibiae, ten femora, ten calcanea, and one humerus. Of all patients with recurrence, 30 (9.6%) occurred within one year and 39 (12.4%) within two years. Among them, 41 patients needed reoperation, five received antibiotics treatment only, and seven ultimately required amputations. Following multivariable analysis, we found that patients infected with Gram-negative bacilli were more likely to have a recurrence (odds ratio (OR) 2.38, 95% confidence interval (CI) 1.20 to 6.94; p = 0.046) compared to *Staphylococcus aureus*; segmental bone defects (OR 5.25, 95% CI 1.80 to 15.26; p = 0.002) and smoking (OR 3.00, 95% CI 1.39 to 6.50; p = 0.005) were also independent risk factors for recurrence after treatment.

Conclusion
Permanent ALCS might be an alternative strategy for definitive bone defect management in selected osteomyelitis cases. However, the overall high recurrence found suggests that it should be cautiously treated. Additionally, segmental defects, Gram-negative infections, and smoking were associated with an increased risk of infection recurrence.

Cite this article: *Bone Joint Res* 2023;12(8):467–475.

Keywords: Osteomyelitis, Risk factors, Recurrence, Definitive treatment, ALCS

Article focus
- Antibiotic-loaded cement spacer (ALCS) is commonly used but not always applied for permanent implantation in management of osteomyelitis, of which the overall recurrence and relative contraindications are unknown.
- This study focused on the incidence of recurrence and the associated risk factors of permanent ALCS in treating limb osteomyelitis.

Key messages
- The data show that ALCS can serve as an alternative method for definitive treatment in some limb osteomyelitis patients. However, the overall recurrence in this study suggests that it should be carefully treated.

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doi: 10.1302/2046-3758.128.BJR-2022-0413.R2

Bone Joint Res 2023;12(8):467–475.

- The study also demonstrated that segmental bone defect, smoking, and Gram-negative bacilli infection were independent risk factors and represent relative contraindications in osteomyelitis management.

Strengths and limitations

- The study enrolled a large series of limb osteomyelitis patients, and is the first to provide insights into their prognosis after permanent ALCS treatment and the risk factors associated with recurrence. The study's findings will help in counselling patients, preparing for treatment preoperatively, and improving outcomes.
- This was a retrospective study. Furthermore, not all risk factors could be considered within the confines of this study.

Introduction

The treatment of limb osteomyelitis is continuously challenging due to high recurrence, complex complications, and long-term processes. Antibiotic treatment and radical debridement of all dead and poorly vascularized tissues are essential to ensure success.[1-3] Debridement often creates dead spaces or bone defects, and placing an antibiotic-loaded cement spacer (ALCS)[4-6] has become the most common strategy. ALCS is broadly used to treat osteomyelitis based on high-dose local antibiotic delivery and good dead space management.[4,7] Moreover, ALCS can be an alternative method for definitive bone reconstruction after initial infection control.[1,8] Compared to common bone reconstruction options of bone graft[9] and bone transport technique,[10] the ALCS reconstruction is simple, highly reproducible, and may lead to satisfactory results in some cases.[8]

Nevertheless, ALCS is not always applied for permanent implantation and often needs removal. When ALCS is used for long-term implantation to treat osteomyelitis, researchers have recently raised great concern for possible exacerbation of infections from microbial colonization of the cement spacer, and promotion of drug resistance at subtherapeutic antibiotic levels, eventually resulting in higher recurrence.[11,12] In these cases, the recurrence and relative contraindications become the most concerning problems in osteomyelitis patients when ALCS is used for definitive treatment. However, reports have been published only for the long-term use of ALCS in periprosthetic joint infection (PJI) after joint arthroplasty. To our knowledge, few studies have indicated that ALCS is a definitive reconstruction method for limb osteomyelitis.[1,8] Furthermore, these studies were only case reports or small case series, and information on the incidence and risk factors of infection recurrence remains limited.

Herein, we retrospectively reported a large series of osteomyelitis patients who underwent an ALCS for definitive treatment after debridement and antimicrobial therapy. We aimed to identify the incidence of recurrence after ALCS for definitive bone defect treatment in limb osteomyelitis, and further assess the risk factors associated with infection recurrence. Our findings may help clinicians to appropriately select patients suitable for this treatment and the preoperative preparation to improve outcomes.

Methods

Study design. We performed an eight-year observational study by reviewing our clinical centre data. All adult patients treated for limb osteomyelitis between 2013 and 2020 were identified. The Department of Orthopaedics at Southwest Hospital is a tertiary, high-volume, level-one bone infection treatment centre, with approximately 300 osteomyelitis patients treated yearly. The inclusion criteria were: limb osteomyelitis (either haematogenous or post-traumatic);[9] remaining bone defects and ALCS insertion after debridement; patients over 18 years of age; medically unfit or refused revision surgery,[1,8] and selected ALCS for definitive bone reconstruction after infection control; and follow-up time ≥ 24 months. The exclusion criteria were: infections without curative treatment (palliative care); incomplete medical records and follow-up data; and patients with malignant disease. Patients included in the analysis were classified as either cured or had recurrence based on follow-up information. The medical ethics committee of Southwest Hospital approved this retrospective investigation.

Treatment protocol. Orthopaedic trauma and bone infection specialists were responsible for the treatment protocol. A multidisciplinary collaboration,[10] including plastic surgeons, microbiologists, pathologists, and clinical pharmacologists, was established in the Department of Orthopaedics at Southwest Hospital. All patients received debridement, standard antimicrobial treatment, and staged surgical protocol to treat the infection (Figure 1). First, a radical debridement was performed, and all dead and poorly vascularized tissues were operatively removed. Then, ALCS (500 mg gentamicin per 40 mg of poly(methyl methacrylate) (PMMA) powder mixed with 5 g vancomycin powder)[4,13] was used for dead space management. Cases with instability were reinforced with additional fixation,[14] and the plastic surgeon (JS) performed flap surgery when necessary. All patients were empirically treated with systemic broad-spectrum antibiotics when the microbial cultures were sent for analysis,[15] then tailored to the pathogen responsible once the culture results arrived. Sensitive antibiotics were intravenously administered for two weeks, then orally for four weeks after discharge.

At least six to eight weeks after debridement, when an initial clinical infection control was obtained, patients were considered for definitive bone reconstruction. The initial clinical infection control was defined as no clinical signs of infection, normalization of white blood cell (WBC) counts and CRP, and adequate healing of the soft-tissue.[1,6,16] If there were clinical signs of infection, a second debridement was performed. In the ALCS, PMMA first served as an antibiotic carrier and dead space management tool, and ultimately as a form of definitive bone

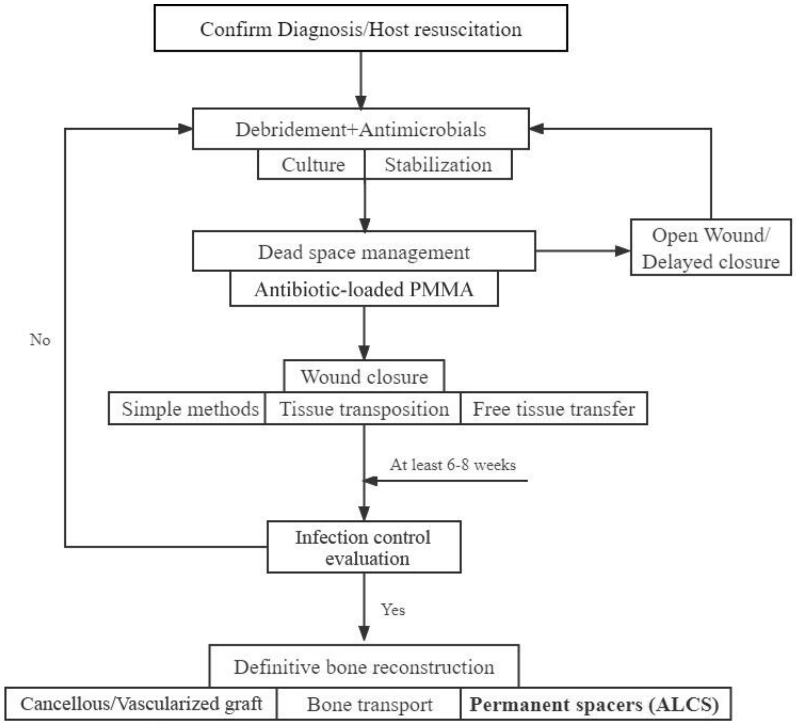

Fig. 1

Staged treatment protocol for limb osteomyelitis remaining bone defects. ALCS, antibiotic-loaded cement spacer; PMMA, poly(methyl methacrylate).

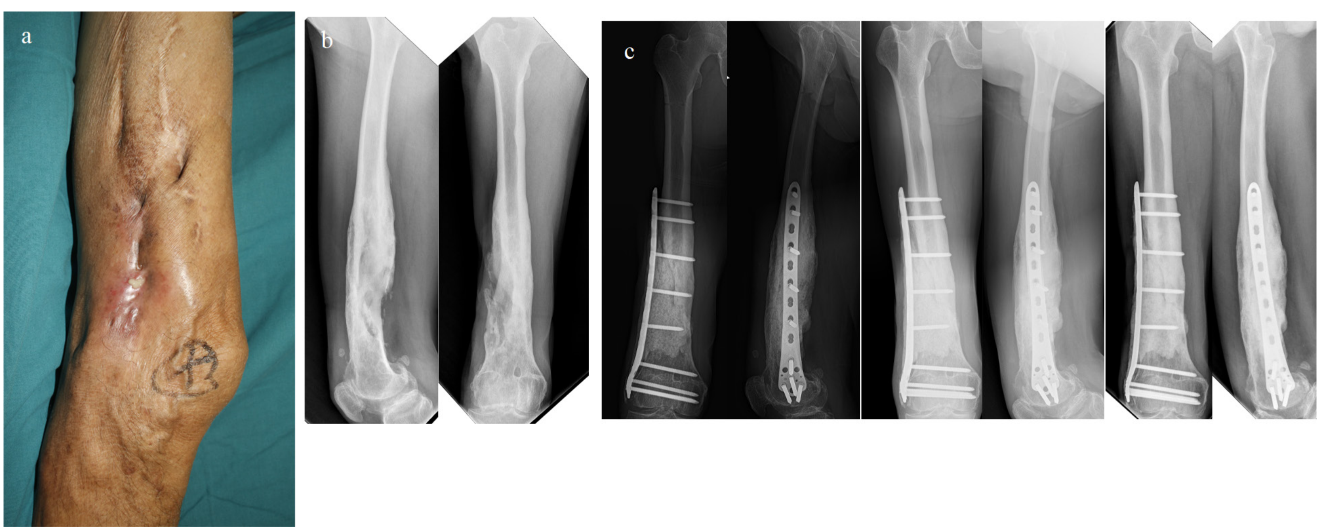

Fig. 2

Successful management of a 72-year-old male osteomyelitis patient in distal femur with an antibiotic-loaded cement spacer (ALCS) for definitive treatment. a) Photograph presenting a sinus in distal, lateral side of the thigh. b) Anteroposterior and lateral radiographs before debridement. c) Radiographs of three, 12, and 24 months after an ALCS for definitive treatment, where the implants and cement spacer were in place with no excessive bone loss.

reconstruction. ALCS was selected for definitive treatment based on the patient's willingness[8] and clinicians' experience.[1] These patients were followed up without any further treatment (Figures 2 and 3).

Definition and observation measures. The definition of osteomyelitis recurrence followed the consensus criteria on fracture-related infections (FRIs) of the European Bone and Joint Infection Society (EBJIS), confirmed by the presence of at least one of the following findings: 1) fistula, sinus, or wound breakdown; 2) purulent drainage from the wound or presence of pus during surgery; 3) pathogens identified by culture from at least two separate deep tissue/implant specimens; and 4) the presence of

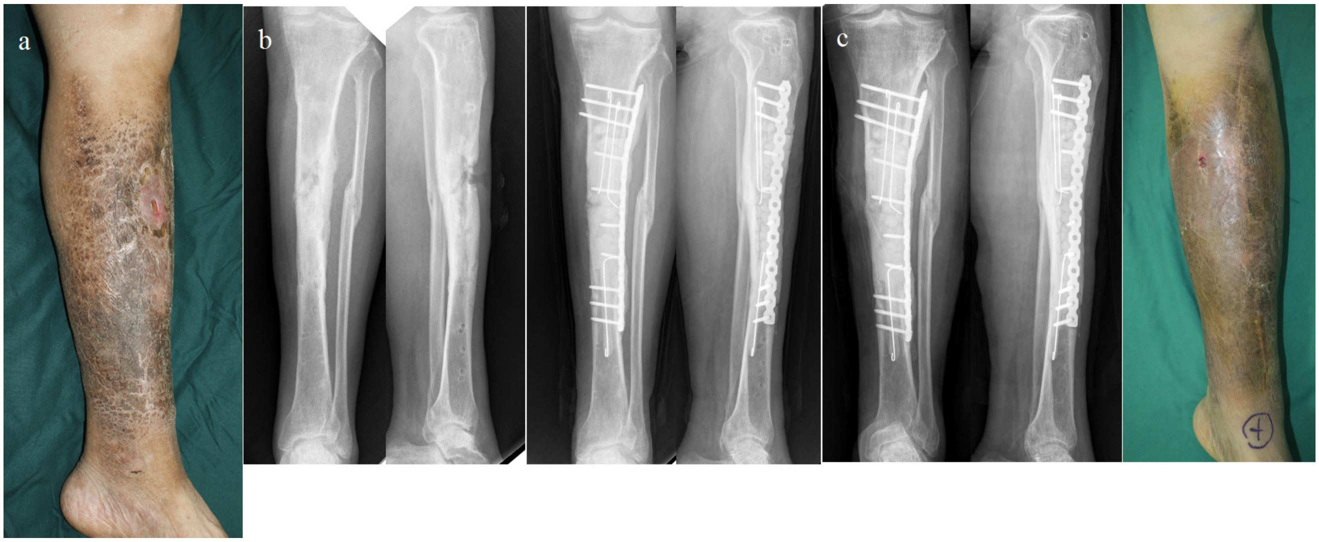

Fig. 3

Recurrent osteomyelitis patient (56 years old, male) with *Pseudomonas aeruginosa* infection in tibia shaft, who chose an antibiotic-loaded cement spacer (ALCS) for definitive treatment. a) Photograph presenting a sinus in midshaft, anterior side of the tibia. b) Anteroposterior (AP) and lateral radiographs before and after operation of debridement and placing an ALCS for dead space. c) Radiographs (AP and lateral) and photograph showing a sign of recurrence at 13 months, where the sinus occured in a previous site.

microorganisms in deep tissues during an operative intervention, confirmed by histopathological examination.[3,17]

The main outcome measure was infection recurrence after treatment. The time of recurrence and related complications were also collected. This information was finally converted into the population's recurrence and infection cure rates. Infection 'cure' was defined as infection-free after treatment in the two-year follow-up.[14] A special fellowship-trained clinical researcher (SW) prospectively conducted the follow-up after treatment, mainly via in-person outpatient visits. Patients' functional activities and complications were also recorded. Then, the follow-up information was retrospectively analyzed.

Patient demographic information was extracted from the electronic medical records, including sex, age, smoking history, comorbidities (e.g. coronary heart disease, hypertension, diabetes mellitus, and anaemia), Cierny-Mader (C-M) host type,[14] previous operation, infection aetiology, infection site, and infection duration. Other treatment-related variables, such as bone defect feature, identified microbiological results, fixation type, and additional flap coverage, were also collected. These variables were used as exposure factors for the risk factor analysis.

Statistical analysis. Data were analyzed using SPSS v22.0 (IBM, USA). The Kolmogorov-Smirnov test was used to verify normalization. Independent-samples *t*-tests (continuous variables) and Fisher's exact tests (categorical variables) were used to compare patient characteristics by osteomyelitis recurrence. Statistically significant variables ($p < 0.05$) in the single-factor analysis were used in the multivariable logistic regression model. Binary logistic regression analyses and the Cox regression model were used to assess the independent association between these potential factors and infection recurrence.

Results

Study sample and patient characteristics. From 2013 to 2020, 1,839 patients with a discharge diagnosis of osteomyelitis were identified in our initial search. Then, 1,253 osteomyelitis patients were excluded because they received bone grafts or bone transport techniques for reconstruction. A total of 246 patients were excluded because they were under 18 years of age or did not have limb involvement. Overall, 26 patients who had less than two years of follow-up were also excluded. Finally, 314 patients with limb osteomyelitis fulfilled our criteria and were included in this study. The demographics and clinical characteristics of the study sample are presented in Table I.

Among the study sample, 236 patients (75.2%) were male, and the mean age was 52.1 years (SD 12.1). The infection sites included 160 in tibia (48 proximal, 47 shaft, 65 distal), 89 in femur (14 proximal, 30 shaft, 45 distal), 17 in upper limbs (three ulna, five radius, and nine humerus), and 48 in the calcaneus. According to the C-M classification of osteomyelitis, only 37 (11.8%) patients were Host A, and the remaining were Host B due to local or systemic diseases, while the majority (92.1%) were C-M type III among all long bone infections (n = 266). Bacteria were initially isolated in 78.7% (247/314) of patients, while the remaining 21.3% (67/314) were culture-negative. *Staphylococcus aureus* was the main agent in 40.1% (126/314), methicillin-resistant *S. aureus* (MRSA) in 13% (13/314), Gram-negative bacilli were also common with 29.9% (94/314) (e.g. *Pseudomonas*

Table I. Characteristics in two cohorts with or without recurrence within two years of follow-up.

Characteristic	Total (n = 314)	No recurrence (n = 275)	Recurrence (n = 39)	p-value
Mean age, yrs (SD)	53.1 (12.1)	53.0 (12.3)	53.7 (10.7)	0.736*
Male, n (%)	236 (75.2)	204 (74.2)	32 (82.2)	0.329†
Smoker, n (%)	142 (45.2)	116 (42.2)	26 (66.7)	0.006†
Diabetes, n (%)	35 (11.1)	26 (9.5)	9 (23.1)	0.025†
Systemic disease, n (%)	90 (28.7)	74 (26.9)	16 (41.0)	0.088†
Aetiology of traumatic, n (%)	201 (64)	173 (62.9)	28 (71.8)	0.373†
Infection site, n (%)				
Femur (ref)	89 (28.3)	82 (29.8)	7 (17.9)	
Tibia	160 (51.0)	138 (50.2)	22 (56.4)	0.217†
Calcaneus	48 (15.3)	39 (14.2)	9 (23.1)	0.092†
Upper limb	17 (5.4)	16 (5.8)	1 (2.6)	0.777†
Sinus, n (%)	279 (88.9)	242 (88.0)	37 (94.9)	0.280†
Infection duration, n (%)				
≤ 3 mths (ref)	57 (18.2)	53 (19.3)	4 (10.3)	
3 to 24 mths	97 (30.9)	83 (30.5)	14 (33.3)	0.414†
≥ 24 mths	160 (51)	136 (50.0)	24 (57.1)	0.169†
Cierny-Mader host B, n (%)	276 (87.9)	238 (86.5)	38 (97.4)	0.064†
Prior debridement (≥ 2), n (%)	195 (62.1)	163 (59.3)	32 (82.1)	0.007†
Second debridement, n (%)	29 (9.2)	27 (9.8)	2 (5.1)	0.552†
Segmental bone defects, n (%)	21 (6.7)	12 (4.3)	9 (21.4)	0.001†
Polymicrobial, n (%)	79 (25.2)	67 (24.4)	12 (30.8)	0.431†
Staphylococcus aureus, n (%)	126 (40.1)	112 (40.7)	14 (35.9)	0.605†
Gram-negative bacilli, n (%)	94 (29.9)	72 (26.2)	22 (56.4)	< 0.001†
Flap coverage, n (%)	43 (13.7)	33 (12.0)	10 (25.6)	0.042†
Internal fixation, n (%)	139 (44.3)	119 (43.3)	20 (51.3)	0.391†

*Independent-samples *t*-test.
†Fisher's exact test.
ref, reference; SD, standard deviation.

aeruginosa, *Escherichia coli*, and *Enterobacter cloacae*), and 25.2% (79/314) were polymicrobial infections. Most (88.2%; 277/314) patients had debridement and antimicrobial therapy before being admitted to our clinic.

Furthermore, 285 (90.8%) patients received single-stage debridement and antimicrobial treatments, and the remaining 29 (9.2%) needed a second debridement due to incomplete initial infection control in the staged evaluation. Meanwhile, 43 (13.7%) patients performed additional flap coverage: 37 in the tibia (25 free and 12 rotational flaps) and six in the calcaneus (rotational flaps). All patients could walk independently after wound healing and were satisfied with the treatment. Most (210/314) patients were medically unfit for other bone reconstructions based on the clinician's experience. Some (75/314) patients had low physical demand, were satisfied with the current treatment, and refused further surgery, while the remaining (29/314) patients refused due to socioeconomic reasons. Thus, they chose ALCS for definitive bone reconstruction.

Characteristics of recurrence. The mean follow-up time was 50 months (24 to 96) and 53 (16.9%) patients had a recurrence, including 32 tibiae, ten femora, ten calcanea, and one humerus. The overall recurrence decreased over time; most recurrences (n = 30) occurred in the first year, and 39 within two years. The two-year infection cure rate was 87.6%. The recurrence rate for *S. aureus* was 19.0% (24/126), and for MRSA was 23.1% (3/13). Gram-negative bacilli were more common in patients with recurrence (22/94), in which the main pathogens were *P. aeruginosa, E. coli,* and *E. cloacae* with 21.2% (7/33), 25.0% (6/24), and 41.2% (7/17) recurrence rates, respectively. The recurrence of Gram-negative bacilli occurred mainly during early follow-up (Table II).

Among the 53 patients with recurrence, 41 accepted re-debridement and insertion of a new ALCS to achieve infection resolution. The mean number of procedures before infection resolution was 2.5 (2 to 5). Moreover, five recurrent femur patients had infection resolution by antibiotics treatment only. The remaining seven patients with infection recurrence ultimately required amputations: five in the tibia, one in the femur, and one in the calcaneus. These patients could not tolerate any treatment burden and finally chose an amputation after repeated failure. Except for those with amputation, patients had the cement spacer in place, and none had radiological evidence of excessive bone loss or suffered pain daily during the follow-up (Figures 2 and 3).

Risk factors of recurrence. The single-factor analysis was first conducted to evaluate the association between potential factors and infection recurrence. Since infection cure is generally defined as "an infection-free at the two-year follow-up", we mainly evaluated factors affecting the recurrence within this period. Segmental bone defects,

Table II. Initial microbiological characteristics in all patients (n = 314) and recurrence (n = 53).

Bacteria type	All patients, n (%)	Recurrence		
		Within 1 yr, n (%)	Within 2 yrs, n (%)	Total, n (%)
Total, n (%)	314 (100)	30 (9.6)	39 (12.4)	53 (16.9)
Staphylococcus aureus, n (%)	126 (40.1)	11 (8.7)	14 (11.1)	24 (19.0)
MRSA, n (%)	13 (4.1)	1 (7.7)	2 (15.4)	3 (23.1)
GNB, n (%)				
Pseudomonas aeruginosa	33 (10.5)	5 (15.2)	5 (15.2)	7 (21.2)
Escherichia coli	24 (8.0)	5 (20.8)	5 (20.8)	6 (25.0)
Enterobacter cloacae	17 (5.4)	4 (23.5)	5 (29.4)	7 (41.2)
Other GNB*	28 (7.0)	5 (17.8)	8 (28.6)	9 (32.1)
Staphylococcus epidermidis, n (%)	25 (8.0)	2 (8.0)	2 (8.0)	2 (16.0)
Polymicrobial, n (%)	79 (25.2)	10 (12.7)	12 (15.2)	16 (20.3)
None, n (%)	67 (21.3)	2 (3.0)	3 (4.5)	5 (7.5)

*Other GNB: *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Proteus*, *Serratia marcescens*.
GNB, Gram-negative bacilli; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table III. Multivariable analysis for risk factors of recurrence (n = 39) within two years of follow-up.

Variable	OR	95% CI	p-value
Flap coverage	1.15	0.44 to 2.99	0.777
Diabetes: yes vs no (ref)	2.24	0.87 to 5.76	0.094
Prior debridement (n): ≥ 2 vs ≤ 1 (ref)	2.40	0.96 to 6.00	0.062
Bacterials: *Staphylococcus aureus* (ref)			
Gram-negative bacilli	2.38	1.20 to 6.94	0.046
Others	0.51	0.17 to 1.51	0.223
Smoker: yes vs no (ref)	3.00	1.39 to 6.50	0.005
Bone defects: segmental versus cavity (ref)	5.25	1.80 to 15.26	0.002

Model explained variance (R2) was 24.2%.
CI, confidence interval; OR, odds ratio; ref, reference.

smoking, diabetes, Gram-negative bacilli infections, previous multiple (two or more) debridements, and flap coverage were significantly related to recurrence (Table I) and were further included in the multivariable binary regression analysis (Table III). In the multivariable analysis, patients infected with Gram-negative bacilli were more likely to have a recurrence (odds ratio (OR) 2.38, 95% confidence interval (CI) 1.20 to 6.94; p = 0.046, logistic regression) compared to *S. aureus*, while segmental bone defects (OR 5.25, 95% CI 1.80 to 15.26; p = 0.002, logistic regression) and smoking (OR 3.00, 95% CI 1.39 to 6.50; p = 0.005, LR test) were also independent risk factors for recurrence after treatment. The overall infection-free survival time related to these risk factors significantly decreased as demonstrated by Cox regression model analysis, in considering the total follow-up period (Figure 4).

Discussion

One of the central principles of surgical treatment for osteomyelitis is to ensure that the dead space or bone defects are treated correctly after debridement. The staged procedure, also known as the Belfast technique, was first described by McNally et al[18] and has become the standard for osteomyelitis management. This two-stage protocol decreases surgical morbidity by separating infection treatment from restoring form and function. Applying an ALCS has become the most common strategy to eliminate dead space and delay bone reconstruction.[1,4,7,12] Previous studies have reported that a cement spacer is an alternative method for definitive bone reconstruction to treat limb osteomyelitis.[1,8] However, ALCS is not always suitable for permanent implantation, and the information is still limited.[1,8] Herein, we have supplemented the literature on this topic.

We found a 16.9% overall recurrence rate in osteomyelitis patients (n = 314) with an ALCS for definitive treatment. Previous studies have found more promising results but only included a few cases.[1,8] For example, Cierny and DiPasquale[1] first reported a case series of adult osteomyelitis patients (n = 22) treated with a permanent ALCS, and only a 12% recurrence rate occurred within two years of follow-up. Qiu et al[8] also reported eight cases of osteomyelitis treated with this method, and all patients achieved an infection cure. On the other hand, a recurrence rate of 0% to 12.26% has been reported for osteomyelitis patients treated with other, more advanced techniques.[3,6,19–21] Yalikun et al[19] reported 149 cases of tibial osteomyelitis treated with the bone transport

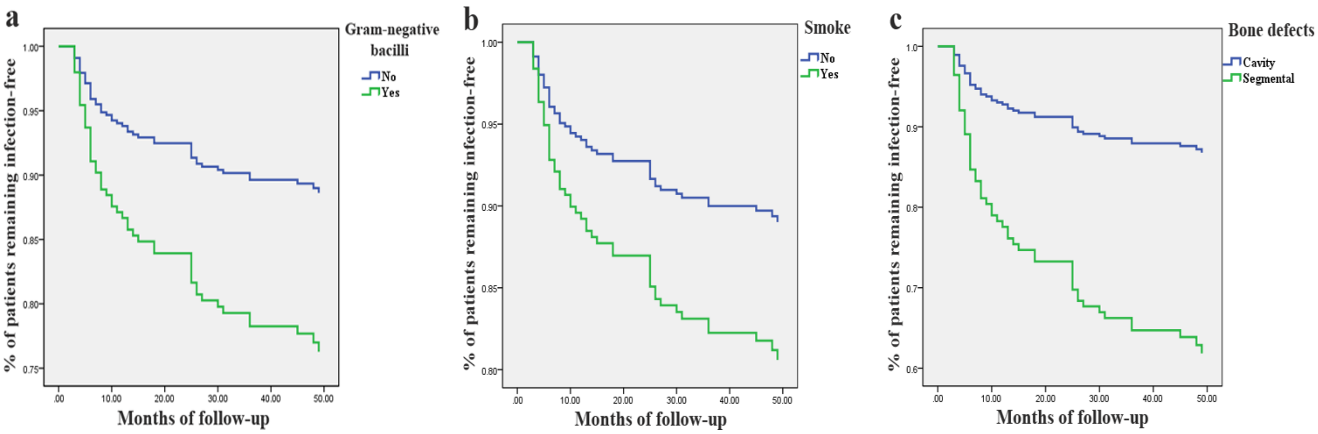

Fig. 4

Survival function curves using a Cox regression model for risk factors of: a) Gram-negative bacilli (risk ratio (RR) 2.24; $p < 0.004$); b) smoking (RR 1.85; $p < 0.031$); and c) segmental bone defect types (RR 3.39; $p = 0.001$).

technique, and an 11.4% recurrence rate was achieved with a mean follow-up of 37.5 months. Similarly, Wang et al[21] recently showed that the recurrence rate of osteomyelitis (n = 424) was 12.26%. These patients were treated with the induced membrane technique and the mean follow-up time was 31.6 months. Given the likelihood of recurrence rate (16.9%) in this large series, ALCS should be cautiously considered as a definitive treatment in limb osteomyelitis.

Moreover, specific indications for a permanent ALCS treatment in limb osteomyelitis are not established and generally depend on clinicians' experience and patients' willingness, as in our current research. In 2006, Cierny and DiPasquale[1] first introduced the ALCS for definitive treatment (also called 'permanent spacers') of limb osteomyelitis based on the clinician's experience. Qiu et al[8] also reported that patients who chose ALCS for definitive treatment were either medically unfit (n = 2) or refused further revision (n = 6) in stage management of osteomyelitis. In this study, most patients were medically unfit for other bone reconstructions, mainly because appropriate bone graft materials were unavailable in most situations or patients were unsuitable to perform a revision surgery with high-risk factors (e.g. old age) based on clinicians' experience. Additionally, some patients had low physical demand, were satisfied with a permanent spacer treatment, and refused further surgery. The remaining patients could not afford the subsequent treatment due to the high economic burden.[22] A cost of $17,000 to $150,000 per patient has been reported,[23,24] which is much worse in countries with limited resources.

Besides the above clinical setting, we found possible contraindications of this method based on the risk factor analysis. We identified several independent risk factors for osteomyelitis recurrence after ALCS for definitive treatment. As a successful infection cure is generally defined as "an infection-free at the two-year follow-up",[17] we mainly evaluated the recurrence of patients within this period. Segmental defects, smoking, and Gram-negative infections were independent risk factors for long-term success. First, smoking has been reported as an important risk factor for various bone infections,[25,26] affecting patients' prognosis by damaging their immune status. Thus, educating patients to quit smoking is crucial. Furthermore, other host-related factors, including multiple (two or more) previous debridements, diabetes, and flap coverage, were included in our multivariable analysis, all known complicating factors for osteomyelitis.[14,21]

Additionally, segmental bone defects due to osteomyelitis (often due to C-M type IV lesions)[16,27] are generally more complex, and the treatment is challenging. Previously, Cierny[14] reported permanent spacers with additional fixation in 8% (25/314) of segmental osseous defect patients due to osteomyelitis; however, no treatment result was available. When ALCS was applied for definitive treatment in this study, a high recurrence rate (42%) was detected in segmental bone defects, comprising an independent risk factor. The cement may not have integrated well with the bone, which would explain these poor results. There are inevitable frequent interactions between bone cement and bone under segmental defects, similar to prosthesis,[25] in which micro-friction between the prosthesis and bone surface is considered a risk factor for joint infection. Similarly, Belay et al[28] also reported a high recurrence rate (20.7%) with a permanent articulating spacer to manage chronic PJI. Based on these results, segmental bone defects due to osteomyelitis seem to be a relative contraindication for using ALCS as the definitive treatment, which requires further investigation.

Furthermore, we hypothesized that microbiological aspects may have specific prognostic implications in limb osteomyelitis patients after ALCS treatment. Within the two-year follow-up period, Gram-negative bacilli (e.g. *P. aeruginosa, E. coli,* and *E. cloacae*) had a higher recurrence rate than other bacteria (23.4 vs 7.7%). Specifically, *E. cloacae* had the highest recurrence rate (29.4%). Osteomyelitis caused by Gram-negative bacilli was associated with more than a twofold increase in recurrence (OR 4.06; p = 0.046, multivariable logistic regression) compared to *S. aureus*. However, the relationship between treatment outcomes in osteomyelitis and bacterial type is contradictory. Cierny and DiPasquale[1] stated that there is no relationship between them by reviewing a large treatment cohort (n = 1,966). Other reported series have indicated that Gram-negative osteomyelitis is a therapeutic challenge,[29] especially infection caused by *P. aeruginosa* showing a marker for poor prognosis in its management.[20,21] Here, insufficient debridement and inadequate antimicrobial therapy against Gram-negative bacteria may be responsible for the poor outcomes. Since most patients had an early-stage recurrence (within one year), the added high-dose vancomycin was mainly used for Gram-positive bacteria. These bacteria might also secrete special virulence factors,[29,30] compromise host immunity, and increase the resistance to local gentamicin. Besides, 67 (21.3%) patients in this series were culture-negative, possibly due to antibiotic exposure before sampling, because 277 (88.2%) patients had received antimicrobial therapy before being admitted to our clinic. Notably, negative cultures were not associated with the patient's prognosis in previous studies.[31] These results suggest that ALCS as a definitive treatment may not be suitable for some refractory bacteria, while radical debridement, more prolonged courses, and/or intense regimens (or combinations of antibiotic agents) are recommended.

Although ALCS is most commonly used to manage dead space and provide high-dose local antibiotic treatment, many researchers have raised concerns about its long-term implantation.[11,12] The likelihood of infection recurrence in the current study might support these concerns. First, the long-term presence of cement can promote the adherence of microbes and biofilm formation.[29,32] In this study, the higher late recurrence rate occurred in series caused by *S. aureus* over time, the most common biofilm bacteria, which might offer some evidence. Second, ALCS can only maintain an effective bactericidal concentration within a few weeks after implantation, which raises concerns about promoting bacterial resistance at subtherapeutic antibiotic levels. Some in vitro studies[33,34] have found drug-resistant *S. aureus* and *Staphylococcus epidermidis* on the surface of bone cement containing gentamicin, tobramycin, and vancomycin. Despite not being addressed here, the total recurrence rate indicated the potential risk of promoting microbe adherence and drug resistance, which need further investigation. Some scholars recommend that the ALCS should be removed, if possible, within a few weeks after local treatment.[11,12,33]

However, our current study also has some limitations. First, since this was a retrospective study, randomization was impossible, and the treatment of osteomyelitis heavily relied on the surgeon's clinical experience. Additionally, not all risk factors could be considered. Nevertheless, there are also several strengths to this study: we provided many patients treated with standard techniques from a high-volume, level-one bone infection treatment centre. In addition, because this series of patients were treated by the same team of specialists, we decreased the impact of subjective variables (e.g. debridement) that may confound the outcomes. In the multivariable analysis, adjustments were made for diabetes, host type, and multiple prior debridements, all known complicating factors for osteomyelitis. Furthermore, the length of patient follow-up demonstrated that the probability of recurrence decreases over time. We supplemented the information in the literature; more evidence-based studies with longer follow-up durations are needed on this topic.

In conclusion, we enrolled a large series of limb osteomyelitis patients and provided insights into their prognosis after ALCS for definitive treatment and the risk factors associated with recurrence. The likelihood of recurrence suggests that ALCS should be cautiously considered as a definitive treatment, although it can be an alternative option in some selected osteomyelitis cases. The data also indicate that segmental defects, Gram-negative infections, and smoking were associated with an increased risk of infection recurrence. These patients need to be carefully treated to achieve long-term success.

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Funding statement:
- The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this work was supported by the Chongqing Natural Science Foundation Program (cstc2021jcyj-msxmX0541), the National Natural Science Foundation Program (No. 82202707, No. 82272515), Major Military Logistics Research Projects (AWS17J004-02), and the Technical Innovation Program (CX2019LC121) in Major Clinical Fields of Army Military Medical University.

ICMJE COI statement:
- All the authors declare that there are no conflicts of interest.

Data sharing:
- The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Acknowledgements:
- We thank the patients and all staff who participated in treatment of these patients.

Ethical review statement:
- This study was approved by the ethics committee of Southwest Hospital Chongqing, China (No. KY201878).

Open access funding:
- The authors report that they received open access funding for their manuscript from the Chongqing Natural Science Foundation Program (cstc2021jcyj-msxmX0541), the National Natural Science Foundation Program (No. 82202707, No. 82272515), Major Military Logistics Research Projects (AWS17J004-02), and the Technical Innovation Program (CX2019LC121) in Major Clinical Fields of Army Military Medical University. The financial support had no impact on the outcomes of this study.