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INFECTION

What is the appropriate extended duration of antibiotic prophylaxis after two-stage revision for chronic PJI?

X. Fang,
Q. Wang,
X. Yang,
F. Zhang,
C. Huang,
Z. Huang,
H. Shen,
W. Zhang

From The First Affiliated Hospital of Fujian Medical University, Fuzhou,China

Aims

To explore the effect of different durations of antibiotics after stage II reimplantation on the prognosis of two-stage revision for chronic periprosthetic joint infection (PJI).

Methods

This study involved a retrospective collection of patients who underwent two-stage revision for chronic PJI and continued to use extended antibiotic prophylaxis in two regional medical centres from January 2010 to June 2018. The patients were divided into a short (≤ one month) or a long (> one month) course of treatment based on the duration of antibiotics following stage II reimplantation. The difference in the infection control rate between the two groups was compared, and prognostic factors for recurrence were analyzed.

Results

A total of 105 patients with chronic PJI were enrolled: 64 patients in the short course group and 41 patients in the long course group. For 99 of the patients, the infection was under control during a follow-up period of at least 24 months after two-stage revision. For the short course group, the mean duration of antibiotic prophylaxis after stage II reimplantation was 20.17 days (SD 5.30) and the infection control rate was 95.3%; for the long course group these were 45.02 days (SD 15.03) and 92.7%, respectively. There was no significant difference in infection control rates between the two groups (p = 0.676). Cox regression analysis found that methicillin-resistant staphylococcus infection (p = 0.015) was an independent prognostic factor for recurrence.

Conclusion

After stage II reimplantation surgery of two-stage revision for chronic PJI, extended antibiotic prophylaxis for less than one month can achieve good infection control rate.

Cite this article: *Bone Joint Res* 2021;10(12):790–796.

Keywords: Periprosthetic joint infection, Stage II reimplantation, Course of antibiotics

Article focus

- This study surveyed the effects of different durations of antibiotics after stage II reimplantation on the prognosis of two-stage revision for chronic periprosthetic joint infection (PJI).

Key messages

- The infection control rates of different courses of extended antibiotic prophylaxis after two-stage revision for chronic PJI were compared. We concluded that extended antibiotic prophylaxis for less than one month can achieve good infection control rate, and longer antibiotic treatment may not be necessary.

Strengths and limitations

- This study showed that the short course of antibiotics can also achieve good results after stage II reimplantation surgery of two-stage revision for chronic PJI.
- Retrospective bias in the data collection and analysis process was unavoidable, and the antibiotic duration after stage II reimplantation does not follow the random principle. Therefore, it may lead to a certain degree of selection bias.

Correspondence should be sent to Wenming Zhang; email: zhangwm0591@fjmu.edu.cn

doi: 10.1302/2046-3758.1012.BJR-2021-0225.R1

Bone Joint Res 2021;10(12):790–796.

Introduction

Periprosthetic joint infection (PJI) is a serious complication following hip and knee arthroplasty. Previous studies have reported approximate PJI incidences of 0.5% to 2% after primary arthroplasty.[1,2] PJI often leads to multiple operations, prolonged use of antibiotics, a heavy burden on patients, and major consumption of medical resources.

Several strategies are used to treat this complication. One such strategy is two-stage revision for chronic PJI, where antibiotic-impregnated spacers are placed in stage I resection surgery followed by stage II reimplantation surgery.[3] The success rate of two-stage revision varies greatly between different medical institutions.[4,5] In addition to surgical procedures, antibiotic treatment is also an important part that affects efficacy.[6]

One of the controversial points is whether extended antibiotic prophylaxis following reimplantation is required. Randomized controlled studies (RCTs) have shown that antibiotics for three months after stage II reimplantation surgery can help reduce the recurrence rate of infection.[7,8] However, there is also the view that if pathology and culture in reimplantation surgery confirm no infection, it should be considered aseptic surgery, and the extended use of antibiotics may render pathogens resistant to antibiotics and adversely affect the patient's intestinal flora, as well as liver and kidney function.[9-11] Focusing on whether antibiotics are needed after stage II surgery, all of the aforementioned studies were designed to compare standard antibiotic prophylaxis (two to three days) with long course antibiotics (six to 12 weeks) after reimplantation surgery.

In our view, although stage II reimplantation surgery can be equated with aseptic surgery, the patient's systemic immunity and local soft-tissue conditions are not comparable to those of primary arthroplasty. Extension of antibiotic treatment rather than primary arthroplasty is necessary. Therefore, we sought to establish the appropriate extended duration of antibiotic prophylaxis.

In the two medical centres where this study was conducted, extended antibiotic treatment (more than two weeks) after standard intravenous prevention is a routine procedure for patients who finished the reimplantation surgery. These cases were divided into two groups according to the duration of antibiotic treatment (one month as the critical point) after prosthesis reimplantation. The purpose of this study was to evaluate the influence of different extended antibiotic durations after two-stage revision for chronic PJI on the prognosis of infection.

Methods

Patient selection and definition of the prognosis. This study retrospectively analyzed patients who were infected after primary hip and knee arthroplasty and completed a two-stage revision for chronic PJI from January 2010 to June 2018 in two medical centres. The inclusion criteria were as follows: 1) cases diagnosed with PJI according to the MusculoSkeletal Infection Society (MSIS) criteria,[12] and defined as type IV according to the Tsukayama classification criteria;[13,14] and 2) the standard two-stage revision was finished, extended antibiotics prophylaxis (at least two weeks) were used after surgery. The exclusion criteria were as follows: 1) infection by fungi or mycobacteria; 2) infection by multidrug-resistant bacteria without antibiotic sensitivity; 3) other diseases that may affect the outcome, such as immunodeficiency, liver and kidney dysfunction, and infectious disease in other parts of the body; and 4) positive specimen culture during stage II reimplantation. To observe follow-up results, the patients were divided into a short course group (antibiotic treatment ≤ one month) and a long course group (antibiotic treatment > one month) according to the duration of extended antibiotic prophylaxis. Antibiotic-related complications included myelosuppression and antibiotic-induced dysfunction of the liver or kidney. Infection control was defined as follows: 1) during a follow-up period of at least 24 months after surgery, the patient had no clinical symptoms, signs, biology (i.e. inflammatory markers), imaging, or other signs suggesting infection; and 2) there was no need to continue antibiotic suppression.

Therapy process. The surgery for all chronic PJI patients at each centre is performed by the same surgeons (WZ, HS) under general anaesthesia, epidural anaesthesia, or combined spinal and epidural anaesthesia. The standard procedure of two-stage revision is as follows: first stage involving thorough debridement; removal of the primary prosthesis; implantation of an antibiotic-containing bone cement spacer;[15,16] and antibiotic treatment, usually including at least six weeks of antibiotics (intravenous combined with oral). Prior to reimplantation, it is customary to implement an antibiotic-free interval of six weeks or longer. During the antibiotic holiday, CRP and ESR were evaluated several times to ensure effective infection control. A new prosthesis was implanted in stage II reimplantation surgery. Next, effective intravenous antibiotics, as indicated by the drug susceptibility results of the stage I resection surgery, were routinely used for one to two weeks, after which oral antibiotics were employed. For methicillin-sensitive gram-positive bacteria, cefuroxime or cefazolin is generally administered intravenously, followed by an oral regimen, including cephalosporins, fluoroquinolone, rifampin, etc. If the pathogen is a methicillin-resistant staphylococcus (MRS), intravenous vancomycin is generally given and later changed to oral linezolid or fluoroquinolone. For gram-negative bacteria, third-generation cephalosporins (such as ceftazidime) are administered intravenously, followed by oral third-generation cephalosporins or fluoroquinolone; if resistant bacteria are present, the medication is adjusted according to the results of drug sensitivity.

Demographic characteristics. After imposing the inclusion and exclusion criteria, 125 cases treated with extended antibiotics prophylaxis after two-stage revision were collected. A total of 20 patients were excluded: three died (due to cerebral haemorrhage and pneumonia), and 17

Table I. Demographic data of the two groups of patients and related indicators.

Demographic	Short course group	Long course group	p-value
Mean age, yrs (SD)*	64.58 (9.48)	62.66 (11.04)	0.345†
Sex, n*			0.191‡
Male	38	19	
Female	26	22	
Mean BMI, kg/m^2 (SD)*	24.48 (2.78)	23.84 (2.29)	0.231†
Affected joint*			0.942‡
Knee	27	17	
Hip	37	24	
Diabetes*			0.963‡
Yes	8	5	
None	56	36	
Hypertension*			0.635‡
Yes	15	8	
None	49	33	
Before stage I resection surgery			
Sinus			0.963‡
Yes	8	5	
None	56	36	
Mean CRP, mg/l (SD)	37.80 (37.62)	38.57 (33.28)	0.915†
Mean ESR, mm/h (SD)	65.75 (30.80)	61.27 (33.74)	0.485†
Mean WBC, × 10^9/l (SD)	7.44 (2.89)	7.26 (2.91)	0.763†
Mean PMN, % (SD)	65.04 (17.44)	61.37 (17.20)	0.293†
Mean SF-WBC, × 10^6/l (SD)	41,221.39 (66,175.04)	41,918.48 (78,694.09)	0.965†
Mean SF-PMN, % (SD)	73.46 (17.69)	70.74 (20.62)	0.518†
Between stage I and stage II surgery			
Duration of antibiotic, wks (IQR)	6.0 (5.0 to 7.0)	6.0 (6.0 to 7.5)	0.125†
Antibiotic holiday, wks (IQR)	9.0 (6.0 to 16.0)	9.0 (6.5 to 15.0)	0.677†
Before stage II reimplantation surgery			
Mean CRP, mg/l (SD)	8.14 (2.32)	8.20 (1.89)	0.900†
Mean ESR, mm/h (SD)	11.58 (3.59)	10.34 (3.17)	0.074†
Mean WBC, × 10^9/l (SD)	5.8 (1.33)	6.09 (1.43)	0.297†
Mean PMN, % (SD)	59.52 (9.32)	56.83 (9.24)	0.152†
Mean SF-WBC, × 10^6/l (SD)	838.07 (276.55)	865.83 (266.29)	0.612†
Mean SF-PMN, % (SD)	46.78 (11.66)	42.8 (8.56)	0.065†

*This information was obtained before stage II reimplantation surgery.
†Independent-samples *t*-test.
‡Chi-squared test.
IQR, interquartile range; PMN, polymorphonuclear leucocyte; SD, standard deviation; SF, synovial fluid; WBC, white blood cell.

Table II. Comparison of the infection control between two groups.

Variable	Short course group	Long course group	p-value
Methicillin-resistant staphylococcus			0.243*
Yes	6	7	
No	58	34	
Culture-negative			0.754*
Yes	8	6	
No	56	35	
Multiple pathogen infections			1.000†
Yes	3	1	
No	61	40	
Mean follow-up time, mths (SD)	57.34 (28.590)	52.95 (22.77)	0.871‡
Infection control			0.676†
Yes	61	38	
No	3	3	

*Chi-squared test.
†Fisher's exact test.
‡Independent-samples *t*-test.
SD, standard deviation.

were lost to follow-up. Ultimately, 105 cases were included. There were 64 cases in the short course group with the mean follow-up time of 57.34 months (SD 28.59), and 41 cases in the long course group with the mean follow-up time of 52.95 months (SD 22.77). There was no significant difference between the two groups in terms of sex, age, BMI, surgical site, sinus condition, diabetes, hypertension, or infection-related indicators before the stage I resection surgery (Table I). There was no significant difference between the two groups in the proportion of MRS infection, culture negative, and multiple pathogen infection ($p = 0.243$, $p = 0.754$ (both chi-squared test), and $p = 1.000$ (Fisher's exact test), respectively) (Table II). Information about the pathogenic microorganisms detected in the 105 patients is shown in Table III.

The length of antibiotic treatment following stage I resection surgery and the exact antibiotic-free interval prior to reimplantation for the two groups were no significantly different ($p = 0.125$ and $p = 0.677$, respectively (independent-samples *t*-test)) (Table I). The mean time of antibiotic use after stage II reimplantation in the short course group was 20.17 days (SD 5.30) and 45.02 days (SD 15.03) in the long course group, with a significant difference ($p < 0.001$, independent-samples *t*-test). There was no significant difference between the two groups with regard to the defined antibiotic regimen after stage II reimplantation ($p = 0.431$, chi-squared test) (Table IV).

Statistical analysis. The Kolmogorov-Smirnov test was applied to evaluate the normality of the distribution of continuous variables. For continuous variables conforming to a normal distribution, the independent-samples *t*-test was used to compare differences between groups; if they did not conform to a normal distribution, the Mann-Whitney U test was used. For categorical variables,

Table III. Pathogenic microorganism information of 105 patients (at the time of the stage I resection surgery).

Pathogenic microorganisms	Short course group	Long course group
Staphylococcus epidermidis	11	10
Propionibacterium acnes	0	1
Escherichia coli	4	0
Staphylococcus aureus	1	1
Klebsiella pneumoniae	2	0
Staphylococcus warneri	1	0
Gram-positive bacilli	0	1
Staphylococcus lentus	1	0
Streptococcus lentus	1	0
Salmonella gallisepticum serotype	1	0
Multiple infections	3	1
MRCNS	0	3
Multiple infections	13	6
Helcococcus kunzii	0	1
Bacillus subtilis	1	0
Alcaligenes xylosoxidans	0	1
Coagulase-negative staphyloccocci	1	0
Culture-negative	8	6
Staphylococcus human	1	1
Staphylococcus haemolyticus	4	0
Staphylococcus caprae	1	0
Streptococcus lactis	0	1
Streptococcus dysgalactiae subsp. equine	1	0
Pseudomonas aeruginosa	1	1
Achromobacter	0	1
Staphylococcus intermedius	0	1
Methicillin-resistant *Staphylococcus epidermidis*	4	2
Mycobacterium gordonae	1	0
Methicillin-resistant *Staphylococcus aureus*	2	2
Staphylococcus cohnii	0	1

MRCNS, methicillin-resistant coagulase-negative staphylococci.

Table IV. Antibiotic treatment plan for the two groups of patients after stage II reimplantation.

Variable	Short course group	Long course group	p-value
Mean time of antibiotic use, days (SD)	20.17 (5.30)	45.02 (15.03)	< 0.001*
Antibiotic regimen			0.431†
Vancomycin + other	21	21	
Fluoroquinolone + other	20	10	
Cefuroxime + fluoroquinolone + others	10	4	
Cefuroxime + other	10	4	
Other	3	2	
Rifampin			0.860†
Yes	15	10	
No	49	31	

*Independent-samples *t*-test.
†Chi-squared test.
SD, standard deviation.

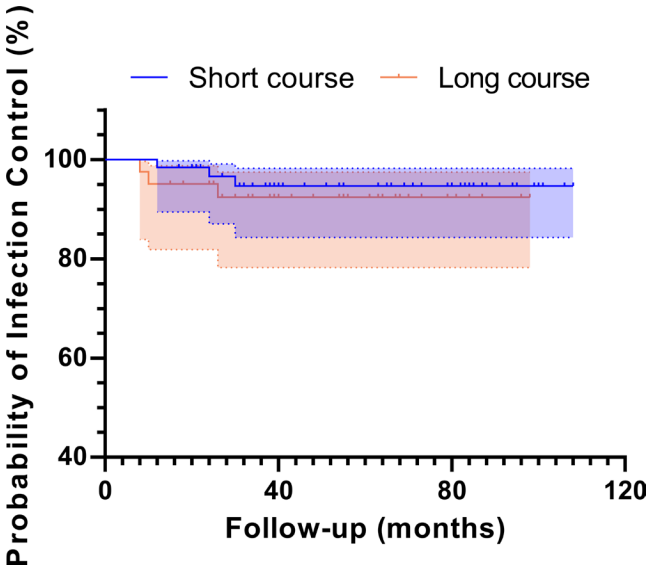

Fig. 1

Kaplan-Meier survival curve analysis results of two groups.

the chi-squared test or Fisher's exact probability test was used for comparison. Kaplan-Meier survivorship analysis and log rank method were used to identify possible factors affecting the prognosis of infection, and variables with significant differences were further analyzed by the Cox regression method. The difference was statistically significant at $p < 0.05$.

Results

Infection control rate and antibiotic-related complications. During the follow-up period of at least two years, according to the definition of the infection prognosis, the overall infection control rate was 94.3% (99/105). Six patients (5.7%) experienced infection recurrence after the stage II reimplantation, including three cases in each group (Table II). The infection control rates of the short course group and the long course group were 95.3% and 92.7%, respectively, without significant difference ($p = 0.676$, chi-squared test). The antibiotic-related complication rate of the long course group was higher (9.8%) than the short course group (7.8%), but without significant difference ($p = 0.734$, chi-squared test).

Kaplan-Meier survivorship analysis. Kaplan-Meier survival curves for the long course and short course groups were drawn and compared by the log rank method; the survival curves were the same (log rank, $p = 0.587$). In terms of infection control after stage II reimplantation, no obvious advantages for the use of long course antibiotics were found (Figure 1).

Cox regression analysis of prognostic factors for infection recurrence. Single-factor analysis (Kaplan-Meier survival

Table V. Six cases of recurrence infection.

Case	Group	Age, yrs /sex	Diagnosis	BMI, kg/m²	CRP, mg/l	ESR, mm/h	Synovial fluid			Microorganisms (detected in stage I resection surgery)	Pathogenic microorganisms (recurrence)	Antibiotic regimen
							Traits	SF-WBC, × 10⁶ /l	SF-PMN, %			
1	Short course	64/male	Left hip PJI	32.8	90	120	Purulent	8,890	82	Methicillin-resistant *Staphylococcus epidermidis*	Methicillin-resistant *Staphylococcus epidermidis*	Vancomycin + Linezolid
2	Short course	63/male	Left knee PJI	29.6	66	112	Purulent	6,005	81	*Staphylococcus haemolyticus*	*Staphylococcus haemolyticus*	Cefuroxime
3	Short course	53/male	Right hip PJI	31.5	6	71	Purulent	6,766	71	Methicillin-resistant *Staphylococcus epidermidis*	Methicillin-resistant *Staphylococcus epidermidis*	Vancomycin + Levofloxacin
4	Long course	72/male	Right hip PJI	19.33	51	120	Purulent	143,270	91	*Staphylococcus aureus*	*Staphylococcus aureus*	Vancomycin + Moxifloxacin
5	Long course	63/female	Right knee PJI	26.5	9	45	Purulent	4,394	91	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	Meropenem + Cefuroxime Sodium
6	Long course	47/male	Left hip PJI	25.04	46	74	Purulent	160	63	Methicillin-resistant *Staphylococcus aureus*	Methicillin-resistant *Staphylococcus aureus*	Vancomycin + Cefuroxime

PJI, periprosthetic joint infection; PMN, polymorphonuclear leucocyte; SF, synovial fluid; WBC, white blood cell.

curve and log rank method) of the other possible factors affecting the prognosis of infection (including age, sex, surgical site, sinus, diabetes, hypertension, staphylococcal infection, MRS infection, culture-negative, multiple infections, antibiotic-related complications, and antibiotic duration after stage I surgery) was also conducted. According to the result of the log rank method, MRS infection was the prognostic factor for infection recurrence ($p = 0.002$). The MRS infection and the duration of antibiotic after stage II reimplantation were included in the Cox regression model for further analysis, which showed MRS infection ($p = 0.015$) to be a prognostic factor for infection recurrence after the stage II reimplantation.

Infection recurrence cases. Five of the six recurrent cases were staphylococci, including three cases of MRS. Information of the six patients with infection recurrence is shown in Table V.

For the cases 1 to 3 involved in the short course group, the pathogens at the time of primary infection were methicillin-resistant *Staphylococcus epidermidis* (MRSE), staphylococcus haemolyticus, and MRSE, and antibiotics were used for 21 days, 21 days, and 28 days after stage II reimplantation surgery, respectively. The recurrence occurred at 30 weeks, 24 weeks, and 12 weeks after stage II reimplantation, and the aetiological result was consistent with that of primary infection.

For the cases 4 to 6 involved in the long course group, the pathogens at the time of primary infection were *Staphylococcus aureus*, *Klebsiella pneumoniae*, and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively, and the antibiotics were used for 56 days, 42 days, and 60 days after stage II reimplantation surgery, respectively. The recurrence occurred at twenty-six weeks, eight weeks, and ten weeks after stage II reimplantation, and the aetiological result was consistent with that of primary infection.

Discussion

The common surgical approach for chronic PJI is two-stage revision,[17] although controversy remains with regard to the duration of antibiotic use after stage II reimplantation. Some studies have concluded that following stage II reimplantation, the use of two to three days of standard antibiotic prophylaxis can achieve infection control rates equivalent to four to six weeks of antibiotic use,[18-20] but studies with higher levels of evidence have found that extending antibiotic treatment to three months was beneficial for infection control.[7,8] The RCTs showed that extended antibiotics should be used, thus raising a new question: if antibiotics use needs to be extended, for how long should they be used? Therefore, our study divided patients into a short course of extended antibiotic treatment (mean 20.17 days (SD 5.30)) and a long course of extended antibiotic treatment (mean 45.02 days (SD 15.03)) and found infection control rates of 95.3% and 92.7% for the short course and long course groups, respectively, with no statistically significant difference ($p = 0.676$, Fisher's exact test). Further Cox regression analysis showed that the duration of systemic antibiotics after stage II reimplantation was not a prognostic factor for the recurrence of PJI. Hence, according to the results, extended antibiotic treatment after reimplantation can be shortened from three months to one month, which may reduce the side effects of antibiotics and the economic burden for patients with the same low recurrence rate.

The overall infection control rate was 94.3% (99/105) in this study, which was at a high level compared to previous studies.[8,17,21,22] This may be related to the comprehensive use of tissue culture technology,[23] ultrasonic lysis technology, and metagenomic next-generation sequencing[24,25] to improve pathogen identification. The high detection rate of pathogens and clear drug susceptibility in the involved cases made the application of antibiotics more appropriate.[26] In addition, antibiotics were applied for at least six weeks after stage I resection surgery based on drug susceptibility results, followed by a minimum six-week antibiotic-free interval. Therefore, the interval between stage I and stage II was usually more than three months, and some patients even underwent stage II reimplantation one to two years after stage

I resection in our cohort. Although previous studies have pointed out that longer intervals will not bring better results,[27] we believe that extending the interval helps mitigate antibiotic-induced intestinal flora disorder and immunosuppression,[9] providing a chance for immune recovery to reduce the risk of infection after stage II reimplantation.

In contrast to Yang et al's[8] result that new pathogens account for the majority of cases of "re-infections" after reimplantation surgery, all cases of "recurrence" in this study were caused by original pathogens, of which MRS accounted for the majority. Of the 13 cases of infection with MRS, recurrence occurred in three patients, at a rate of 23.08%. Further analysis found that MRS was a prognostic factor for recurrence after stage II reimplantation. We believe that our more cautious strategy of a long antibiotic holiday has prevented some "reinfection" cases and that the recurrence cases were due to the host and pathogen's own factors. In terms of pathogens, for example, *S. aureus* evading host immunity and antibiotics through intracellular infection was considered as an important reason for recurrence in recent research.[28,29]

This study also has some limitations. Firstly, although this was a multicentre study, the sample size was still relatively small, which was related to the low incidence of PJI. Retrospective bias in the data collection and analysis process was unavoidable, and the antibiotic duration after stage II reimplantation does not follow the random principle, it may lead to a certain degree of selection bias. Secondly, the PJI patients in this study were from two medical centres, and the differences in the detailed process of two-stage revision will inevitably cause more confounding factors. Indeed, the two groups of patients can only be simply matched in terms of antibiotic regimen (such as deciding whether to use vancomycin). Finally, patients who were culture-positive during stage II reimplantation were excluded from our cohort, and such an approach will elevate the infection control rate of the included patient population.

In summary, after stage II reimplantation of PJI, the use of a short course of antibiotics did not increase the recurrence rate. Therefore, the use of long-term antibiotics may not be necessary. Certain pathogens, such as MRS infection, may be a prognostic factor for recurrence after stage II reimplantation. Patients with such a prognostic factor may need prolonged antibiotic use, although this conclusion needs to be verified by further research. This study provides useful information that the 'appropriate extension' strategy for prolonged use of antibiotics after stage II reimplantation surgery may be a more eclectic and effective approach.

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Author information:
- X. Fang, MD, PhD, Associate Chief Physician
- C. Huang, MD, Resident Physician
- Z. Huang, MD, PhD, Attending Physician
- W. Zhang, MD, PhD, Head of Department, Professor
  Department of Orthopaedic Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China.
- Q. Wang, MD, PhD, Attending Physician
- F. Zhang, MD, Resident Physician
- H. Shen, MD, PhD, Chief Physician
  Department of Orthopaedic Surgery, Shanghai Sixth People's Hospital, Shanghai, China.
- X. Yang, MD, Attending Physician, Department of Orthopaedic Surgery, Jiangle County General Hospital, Sanming, China.

Author contributions:
- X. Fang: Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.
- Q. Wang: Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.
- X. Yang: Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.
- F. Zhang: Investigation, Formal analysis, Writing – review & editing.
- C. Huang: Formal analysis, Writing – review & editing.
- Z. Huang: Methodology, Writing – review & editing.
- H. Shen: Methodology, Formal analysis, Writing – review & editing.
- W. Zhang: Methodology, Formal analysis, Writing – review & editing.

- X. Fang, Q. Wang, and X. Yang contributed equally to this work.

- X. Fang, Q. Wang, and X. Yang are joint first authors.

Funding statement:
- No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Acknowledgements:
- We thank Lixiong Nie, Yang Chen and Yuanqing Cai for their contribution in data collection and data processing, thank Dr. Wenbo Li and Dr. Bin Yang for their contribution to the ideas of the article and microbial culture.

Ethical review statement:
- Ethical approval was obtained from the First Affiliated Hospital of Fujian Medical University Ethics Committee (Approval No: MRCTA, ECFAH of FMU (2019) 296).

Open access funding
- The authors confirm that the open access fee for this study was self-funded.