Antibiotic treatment regimens for bone infection after debridement ： a study of 902 cases

Xiaohua Wang
Southwest Hospital
Li Fang
Southwest Hospital
Shulin Wang
Southwest Hospital
Yueqi Chen
Southwest Hospital
Huan Ma
Southwest Hospital
Hongwen Zhao
Southwest Hospital
Zhao Xie (xiezhao54981@163.com)

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Abstract

Purpose: Our aim was to investigate the clinical efficacy and complications of antibiotics treatment duration for the patients of bone infection. Methods: We retrospectively analyzed the patients with bone infection admitted to our hospital between March 2013 and October 2018. The surgical debridement was performed and the patients were divided into three groups: IV group (Intravenous antibiotics for 2 weeks); Oral group (Intravenous antibiotics for 2 weeks followed by oral antibiotics for 4 weeks); Rifampicin group (Intravenous antibiotics for 2 weeks followed by oral antibiotics plus rifampicin for 4 weeks). The infection control rate and complications were compared. Results A total of 902 patients were enrolled, the infection sites included 509 tibias, 228 femurs, 32 humeri, 23 radii and ulnae, 40 calcanei, 23 multiple-site infections and the other sites 47 cases. After at least 6 months of follow-up, 148 (16.4%) patients had recurrence of infection. The recurrence rate of IV group was 17.9%, which was no significant higher than that of Oral group (10.1%) or Rifampicin group (10.5%). The abnormal rate of Glutamic-pyruvic transaminase(ALT) in IV group was 15.1%, which was lower than that of Oral group (18.0%) and Rifampicin group (27.4%), P=0.026. The positive rates of proteinuria in the three groups were 3.2%, 4.5%, and 9.3%, respectively, P=0.020. Conclusion: After debridement of bone infection, the additional oral antibiotic treatment may increase the damage of liver and kidney, and can not significantly reduce the infection recurrence rate. Therefore, it is recommended to adopt short-term systemic antibiotic treatment after debridement.

Background

Bone infection is a common complication after bone fracture. Although modern medical advancements have brought treatment of bone infections to a new height, it is still a difficult disease for orthopaedic doctors to treat. The commonly used treatments include conservative debridement, continuous flushing, antibiotic carrier filling, and others. To achieve the desired results, clinicians frequently use parenteral antibiotic therapy at a high dose and for prolonged periods [1]. However, intravenous therapy carries with it substantial risks and it is inconvenient for patients [2]. In particular, long-term intravenous antibiotics therapy may bring the complication of catheter-related bloodstream infections and thrombosis[3]. Currently, the mainstream treatment method is debridement followed by systemic antibiotics therapy, which is commonly intravenous infusion for two weeks followed by oral antibiotics for 4-6 weeks [4, 5]. However, there is no evidence that antibiotics therapy for 4–6 weeks improves outcomes compared with shorter regimens [1]. Moreover, the long-term application of antibiotics may lead to adverse liver and kidney reactions [6]. The route and duration of antibiotics after debridement is important to eradication of infection, scholars are trying to reduce the use of antibiotics, but there is currently no accepted plan. In this study, we explored the use of 2 weeks IV antibiotics in the treatment of bone infection, the overall efficacy is adequate.

Patients And Methods

After receiving approval from our Institutional Review Board, we retrospectively analysed patients with bone infection admitted to our hospital between March 2013 and October 2018. Diagnosis of bone infection was made based on local bone pain and swellings during examination, imaging procedures, microbiological and histopathological examinations, and laboratory studies (such as the gold standard biopsy or deep tissue culture) [7]. The inclusion criteria were: patients with bone infection; treatment with debridement and subsequent filling with antibiotic cement; and use of postoperative systemic antibiotics. The exclusion criteria were: diabetic foot infection; patients without surgical treatment; patients with autoimmune disease and generalized vascular insufficiency; patients with incomplete follow-up data; patients with preoperative liver or kidney dysfunction; or a bone graft performed within six months after the debridement. The study flow chart is shown in Fig. 1.

Treatment methods

In all patients, debridement was performed, and antibiotic cement was implanted. After the cement was removed (following eradication of the infection), bone grafts were performed to repair the bone defects. In this study, only the infection control process was considered; the process of bone defect repair was not evaluated. During the operation, sequestrum and necrotic tissue were removed and bacteria were identified by drug susceptibility test. After debridement, bone defects were filled with antibiotic PMMA cement (Heraeus, Germany). The appropriate fixation method (plate internal fixation, plate external fixation, no fixation) was chosen considering the Cierny-Mader classification, and negative pressure drainage was allowed for 10 to 12 days.

The patients were divided into three groups according to whether oral antibiotics were taken after surgery: an IV group (Intravenous antibiotics for two weeks); an Oral group (Intravenous antibiotics for two weeks followed by oral antibiotics for four weeks); and a Rifampicin group (Intravenous antibiotics for two weeks followed by oral antibiotics plus rifampicin for four weeks). There was no significant statistical difference in any of the following general data: fixation method used; Cierny-Mader classification; or bacterial infection. The bacterial infection and the types and doses of antibiotics used are shown in Table 1.

Postoperative management and follow-up

All the patients were examined for the laboratory tests and urine protein levels on the 1st, 7th, and 14th days after surgery. Subsequently, the same examination was repeated weekly for the Oral group and Rifampicin group, and urine protein was repeatedly examined until the 6th week. Infection control and recurrence criteria [6] an apparent cure was defined as the absence of signs or symptoms of osteomyelitis for at least six months after cessation of antimicrobial therapy. A relapse was defined as an infection occurring at the same site from which it was apparently eliminated, requiring specific treatment with antibiotics or surgery. ALT and aspartic transaminase (AST) values greater than 40 U/L, and creatinine (Cr) values greater than 104 μmol/L were defined as abnormal.

Statistics

One-way analysis of variance (or the rank sum test where relevant) was used for comparisons of measurement data (recurrent time). A Pearson's chi-square test was used for comparison of enumeration data (abnormal rate of ALT, AST, and Cr, proteinuria, infection control rate). A P value below 0.05 was considered significant.

Results

A total of 902 patients were enrolled in this study. There were 717 males and 185 females with an average age of 40.25 (4-76) years. The mean duration of infection before admittance to the hospital was 70.7 months (14 days to 720 months). The infection sites included 509 tibias, 228 femurs, 32 humeri, 23 radii and ulnae, 40 calcanei, 23 multiple-site infections, and 47 miscellaneous sites. There were 666 cases of post-traumatic infection and 236 cases of haematogenous osteomyelitis. Bacteria were isolated from 640 (71%) patients. Of these, 307 (48.0%) were infected with *Staphylococcus aureus* (including 81 MRSA), 56 (8.8%) with *Pseudomonas aeruginosa*, 41(6.4%) with *Escherichia coli*, 33 (5.2%) with *Enterobacter cloaca*, 39 (6.0%) with *Staphylococcus epidermidis*, 25 (3.9%) with *Klebsiella pneumoniae,* 64 (10%) with other bacteria, 75 (11.7%) with more than one bacteria, and the remaining 262 cases were negative.

There were 148 (16.4%) recurrent infections within the six months follow-up period, with an average recurrence time of 63.0±4.8 (4-176) days. The recurrence rate of the IV group was 17.9% (130/727), which was not significantly higher than that of the Oral group 10.1% (9/89) and the Rifampicin group 10.5% (9/86); P=0.051. The recurrence time of the three groups was 62.37±6.93, 58.56±13.44, and 76.33±17.48 days, respectively; P=0.851. There were 727 patients in the IV group, of which 130 patients relapsed. The highest recurrence rate was observed with *P. aeruginosa*, which had a recurrence rate of 40.4% (19/47), while the recurrence rate of patients with no bacteria isolated was 8.1% (19/236); P<0.01.

The rate of ALT abnormality in the IV group was 15.1%, which was lower than that of the Oral group (18.0%) and Rifampicin group (27.4%); P=0.026. The rates of proteinuria in the three groups were 3.2%, 4.5%, and 9.3%, respectively; P=0.020. There was no significant statistical difference in the rate of AST abnormality (P=0.798) and Cr abnormality (P=0.620) among the three groups. The results are shown in Table 2.

Discussions

Treatment of bone infection is a difficult procedure. At present, the overall treatment strategy includes conservative treatment, palliative debridement, En-block resection, and amputation, but there is a lack of uniform treatment standards. A surgical operation is the usual method chosen by clinicians, but not all cases require surgical debridement [1], and many infections can be effectively treated with oral therapy [8-10]. Hamed [11] reported that intravenous antibiotics (six weeks) and oral suppression therapy were administered for cases of PJI infection, with reliable clinical efficacy. Research showed that drug therapy alone had an average success rate of 71.1%, while surgical treatment alone had an average success rate of 88.9% [12]. Systemic intravenous antibiotics after debridement can achieve a rapid reduction of the bacterial load at the site of infection [13]. Therefore, clinicians are more inclined to use surgical treatment combined with antibiotic treatment to arrest the infection.

According to previous studies, optimal treatment of acute hematogenous osteomyelitis involves intravenous antibiotics for several weeks, and then oral antibiotics until the symptoms and signs are alleviated [14, 15]. However, for chronic bone infection, debridement is often the first choice. Although research has shown that oral and parenteral therapies achieve similar success rates [1], clinicians are accustomed to considering the use of intravenous antibiotics during hospital stay [16, 17], followed by oral antibiotics for several weeks. It has been reported that intravenous antibiotics for less than one week have no significant effect on prognosis [18-20]. However, only limited data is available comparing intravenous antibiotics and oral antibiotics or concerning proper treatment durations. We applied debridement plus systemic antibiotic treatment. Most patients (80.6%) were treated with intravenous antibiotics for only two weeks, although long-term antibiotic use has achieved good results in previous reports. Our results showed the recurrence rate of the IV group was not significantly different from the other two groups and the overall infection control rate was 83.6%. The infection control rate is comparable to that of previous reports, providing support for the treatment of these patients with short-term systemic antibiotic regimens following debridement.

Multiple and refractory bacteria are common in bone infections, especially for chronic infections, so combined antibiotic treatments are commonly applied in the clinics. The most common oral combination drug is rifampicin, which has a bactericidal effect on multiple gram-positive and gram-negative bacteria [17]. Rifampicin can achieve high intracellular levels and is capable of penetrating bacterial biofilm [21, 22]. However, it is not advisable to only apply rifampicin for anti-infection treatment, because it can quickly lead to resistance [5]. Thus, rifampicin should be started after bacterial load reduction by surgery and when the wound is dry [23, 24]. In this study, 307 (48.0%) patients were infected with *Staphylococcus aureus* and 56 (8.8%) with *Pseudomonas aeruginosa,* accounting for more than 50% of the isolated bacteria, and so levofloxacin was applied more often in our clinic. Levofloxacin alone was unable to eradicate methicillin-susceptible *S. aureus* [25, 26]. The classic antibiotic combination for bone infections caused by *Staphylococcus aureus* and *P. aeruginosa* is levofloxacin plus rifampicin.

It is difficult to assess how long it will take for an infection to clear the following treatment of bone infection. Urania Rappo [27] evaluated the efficacy of infection after six weeks of treatment. Daver NG [6] indicated that the infection is apparently cured if it does not recur within six months. We evaluated infection control at six months after the operation. Although this may miss some cases of recurrence, our statistical analysis shows that recurrence occurs within two months in most cases.

Although rifampicin is rarely used alone in the treatment of bone infections, when used in combination with other antibiotics, rifampicin can increase the treatment outcomes of other antibiotics. Rifampicin diffuses very well within bone tissue and bacterial biofilms [28] and is a valuable treatment option. However, rifampicin often elicits a hepatotoxic response and gastroenteropathy. Our results indicated that the ALT abnormality rate of the Rifampicin group is significantly higher, suggesting that postoperative combinations including rifampicin may lead to liver damage. In addition, Sahoko [29] reported that rifampicin can cause acute renal damage. Our results show that the overall complication was acceptable in the three groups. The recurrence rate of the IV group was not significantly different from that of the other two groups. Meanwhile, the Oral group and Rifampicin group had higher ALT and proteinuria rates, and the abnormality was probably caused by the additional oral therapies. Although proteinuria the Rifampicin group was the highest, the creatinine positive rate was not statistically significantly different, suggesting that the additional rifampicin therapies may cause early or mild renal damage.

There are many highlights in this article including the large sample size and its use of standard techniques. However, there are several drawbacks. First, although our result showed that there was no significant statistical difference in the general data, including the type of bacterial infection and fixation method, the heterogeneity within the cohort may have affected the results. Second, the abnormality of ALT and urinary protein suggested possible liver and renal damage, but the extent of the damage was not determined. Third, recurrence is common in bone infection, and the long-term recurrence rate for patients (after the six months follow-up) is unknown.

Conclusions

After debridement of bone infection, short term antibiotic treatment regimens might offer similar rates of eradication of infection while avoiding the risk of renal and hepatic damage associated with prolonged antibiotic use.

List Of Abbreviations

ALT, Alanine aminotransferase; AST, Aspartic transaminase; Cr, Creatinine; MSSA, Methicillin-susceptible Staphylococcus aureus; MSSE, Methicillin-susceptible epidermidis.

Declarations

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Availability of data

We are unable to share the raw data because ethical approval was not obtained for data sharing. In addition, all data are presented in the Tables.

Authors' contributions

XW and LF contributed to data collection, paper writing, data analysis, and performed the surgeries. SW contributed to data collection. YC contributed to paper writing and article revision. HM and LF contributed to medication guidance and assessment of liver and kidney damage. ZX and HZ contributed to overall planning, data analysis, and performed surgeries. All authors have read and approved the final version of this manuscript.

Competing interests

We declare that there are no conflicts of interest with any institution.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethics approval was obtained from the Ethics Committee of the first affiliated hospital of Army Medical University, PLA. All the participants had provided written informed consent.

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Tables

Table.1 The bacteria and the antibiotics we used

Bacteria	Intravenous antibiotics		Oral antibiotics	
	Adults	Pediatrics	Adults	Pediatri
MSSA/MSSE	Cefazolin:2g q8h. Cefuroxime:1.5g q8h. Ceftriaxone:2g q12h. Levofloxacin:600mg qd, Moxifloxacin:400mg qd	Cefazolin:50-100mg/(kg.d) q8h. Cefuroxime: 30-100mg/(kg.d) q8h. Ceftriaxone:20-80mg/(kg.d) qd	Levofloxacin:500mg qd, Moxifloxacin:400mg qd) . Cefuroxime:500mg bid	Cefuro bid
MRSA/MRSE	Vancomycin:15~20mg/Kg q8~12h. Linezolid:600mg q12h	Vancomycin:40mg/(kg.d) 2 to 4 times/d. Linezolid: 10mg/kg q8h	Linezolid:600mg q12h. Fluoroquinolone.	Linezoli
P.aeruginosa/E.coli/E.cloaca/K. pneumoniae	Ceftazidime:2g q8h/Cefepime:2g q12h/PiperacillinTazobactam:4.5g q8h / Levofloxacin;500mg qd/Amikacin:15mg/Kg qd (usually used in combination)	Ceftazidime:30-100mg/(kg.d) q8h. Cefepime:40mg/Kg q12h. PiperacillinTazobactam:112.5mg/Kg q8h	Levofloxacin: 500mg qd	No ora
Others	According to drug sensitivity	According to drug sensitivity	According to drug sensitivity	Accordi sensitivi
Negative	Ceftazidime / Cefepime / Fluoroquinolone	Ceftriaxone 20-80mg/(kg.d) qd	Fluoroquinolone	Cefuro bid

MSSA/MSSE: Methicillin-susceptible *Staphylococcus aureus/ epidermidis*. The dosage is suitable for patients with no serious liver and renal dysfunction.

le.2 Comparisons of general information, clinical efficacy of the three groups

nts	IV group	Oral group	Rifampicin group	P Value
nber	727	89	86	-
ratio (male/female)	3.9 (578/149)	4.6 (73/16)	3.3 (66/20)	0.688
rage age(years)	37.11±1.62	40.30±3.22	38.91±2.54	0.130
rage duration of infection(months)	70.3±6.5	68.1±11.8	75.9±8.1	0.255
e of infection (posttraumatic/hematologic)	541/186	67/22	58/28	0.360
urrence rate of infection	17.9%130/727	10.1%9/89	10.5%9/86	0.051
urrence time(days)	62.37±6.93	58.56±13.44	76.33±17.48	0.851
ormal rate of ALT	15.1%110/727	18.0%16/89	27.9%24/86	**0.026**
ormal rate of AST	16.4%119/727	14.6%13/89	13.9%12/86	0.798
ormal rate of Cr	1.1%8/727	1.1%1/89	2.3%2/86	0.620
tive rates of proteinuria	3.2%23/727	4.5%4/89	9.3%8/86	**0.020**

: Alanine aminotransferase; AST: Aspartic transaminase; Cr: Creatinine

Figures

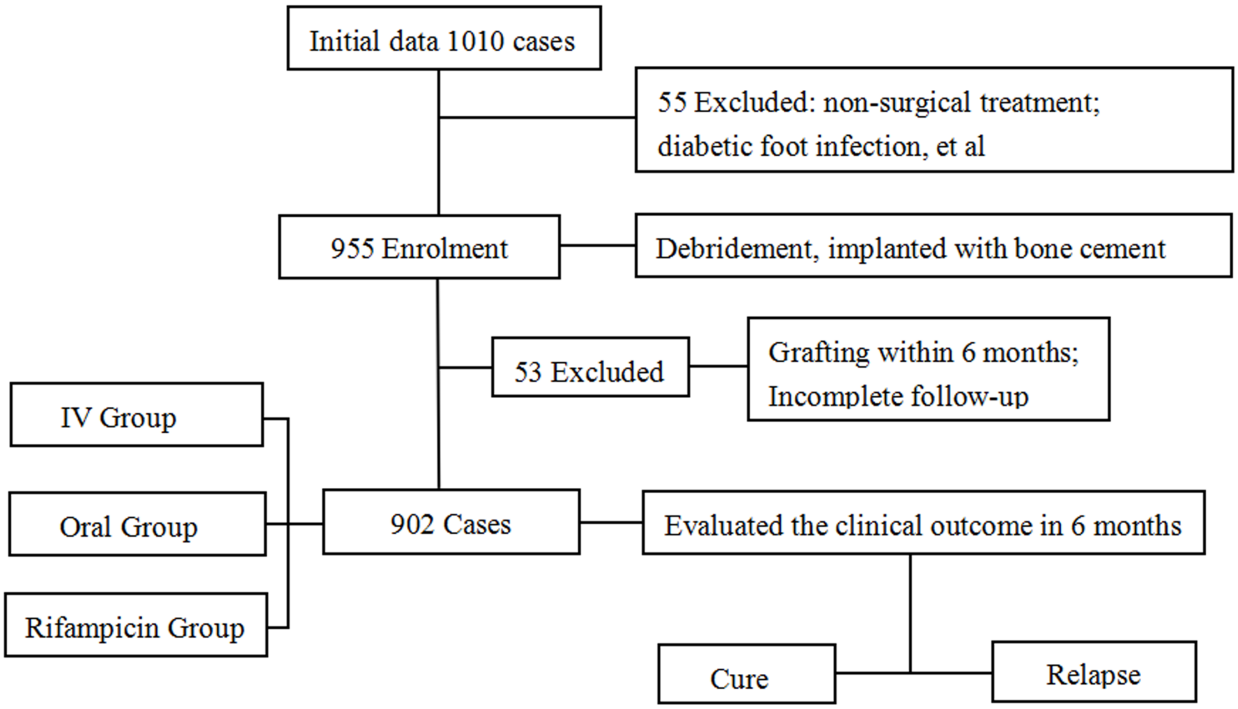

Figure 1

A study flow chart for this study. Data from 1010 patients with bone infections were initially collected. After inclusion and exclusion criteria, 902 cases were finally entered into the study and were divided into three groups. The infection control rate and complications were compared.