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Is oral antibiotic therapy as effective as intravenous treatment in bacterial osteomyelitis? A real-life experience

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Abstract. – OBJECTIVE: Osteomyelitis is a relatively understudied disease with no standardized and evidence-based approach to treatment. We aimed to evaluate a cohort of patients with osteomyelitis, comparing the outcomes between intravenous (IV) and oral treatment.

PATIENTS AND METHODS: We performed an observational retrospective study on osteomyelitis cases in adult patients seen for care between 2017 and 2019. We collected information on patient characteristics, microbiological etiology, infection treatment, and outcome. In addition, we divided osteomyelitis cases by antibiotic regimens [oral (OTG) *vs.* intravenous±oral (ITG)] and therapy durations to evaluate outcomes differences.

RESULTS: A total of 235 episodes of osteomyelitis were evaluated, with a higher prevalence in male gender. Staphylococci, especially *S. aureus*, were the most common strains. Out of the 235 evaluated episodes, we selected 142 cases. Of these, 75 were treated with OTG and 67 with ITG. Gram-positive bacteria were the most frequent aetiological agents, with 81 isolates (61.8%). Full recovery was observed in 79 (55.6%) cases; of these, 36 (53.7%) were in the ITG and 43 (57.3%) in the OTG ($p = 0.666$). At the logistic regression, a polymicrobial infection [OR 4.16 (95%CI 1.28-13.4), $p = 0.017$] and a less than six weeks treatment duration [OR 4.24 (95%CI 1.38-5.43) $p = 0.004$] were significantly associated with a higher risk of treatment failure.

CONCLUSIONS: Our study suggests that oral treatment efficacy is comparable to ITG therapy for osteomyelitis, confirming the most recent evidence suggesting that oral therapy is non-inferior to intravenous therapy to treat osteomyelitis.

Key Words:
Osteomyelitis, Polymicrobial infection, Antibiotic treatment, Oral treatment, Intravenous treatment.

Introduction

Osteomyelitis is a common disease with a wide spectrum of clinical features and variable management[1]. Consequently, many different approaches, both surgical and pharmacological, have been proposed during the years. In addition, different strategies have been proposed regarding antibiotics, including home intravenous antibiotic therapy, elastomers use, daily intravenous (IV) treatment in outpatients' clinics, and long-acting antibiotics[2-5].

However, there is no standardized and evidence-based approach to treatment. In particular, although treatment with IV antibiotics is traditionally recommended for at least the first two weeks of treatment, there are limited data to support this recommendation, and most of them descend from old studies[2,6].

Furthermore, few data[2] about the use of oral treatment *vs.* IV in real life are available. Therefore, this study aims to retrospectively evaluate a cohort of patients with osteomyelitis, comparing IV and oral treatment outcomes.

Patients and Methods

Study Design, Data Collecting, and Definitions

We performed an observational, retrospective study on acute and chronic osteomyelitis cases among adult patients, followed between 2017 and 2019 in the Sant'Andrea Hospital of Vercelli, Italy.

We collected information on patients' characteristics, microbiological etiology, infection treatment, and outcome.

Osteomyelitis diagnosis was based on clinical features and radiologic findings associated with a

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positive bacterial culture on intraoperative samples or a purulent aspect during surgical intervention.

We divided osteomyelitis cases by antibiotic regimens (oral *vs.* IV ± oral) and treatment duration to evaluate outcome differences. In the oral therapy group (OTG), we also included patients who were administered intravenous antibiotics for four days or less to treat sepsis or other concurrent infections. In the other group, we included patients with more than four days of IV antibiotic therapy, associated or not with oral antibiotics (ITG).

Exclusion criteria were: the lack of complete information about the therapy length, a treatment with long-acting intravenous antibiotics, and a follow-up < 1 year.

Treatment failure was defined as meeting one of the following conditions: (1) reactivation of the infection in the same site of the previous osteomyelitis; (2) persistence of infection at the end of treatment; (3) amputation of the limb involved.

This research was conducted according to the Helsinki Declaration. All patients' data were fully anonymized and were analyzed retrospectively. For this type of study, formal consent is not required according to current national law from Italian Medicines Agency and to the Italian Data Protection Authority. Therefore, neither Ethical Committee approval nor informed consent was required for our study[7].

Statistical Analysis

The Kolmogorov-Smirnov test evaluated data distribution and summarized as means ± standard deviation (SD) or medians and interquartile ranges (IQR); categorical variables were summarized as number + percentage. As appropriate, differences between the two groups were evaluated by *t*-test, Wilcoxon signed-rank test or Pearson's Chi-squared test. We performed uni- and multivariate analyses to evaluate predictors of treatment failure with logistic regression. A significant level of $p < 0.05$ was used for all statistical tests.

Results

A total of 235 episodes of osteomyelitis were evaluated, 169 of them (71.9%) occurred in male patients, and 54 (34.8%) had more than one episode of osteomyelitis. Forty-one of the 235 episodes (17.4%) were associated with metalware-related infection, and only one (0.4%) was treated without surgical intervention. The median hospitalization time was seven days (IQR 3-14).

Regarding the sites of infection, the tibia was involved in 52 episodes (22.1%), followed by the foot (except fingers) in 47 (20%) and by the foot fingers in 43 (18.3%). The surgical intervention was osteotomy in 72 cases (30.6%), followed by limb amputation in 52 (22.1%) and bone flap in 31 (13.1%).

We collected 160 intraoperative cultures (26 negative, 16.5%). *S. aureus* was identified in 46 cases (28.8%), followed by *S. epidermidis* (29 isolates; 18.1%) and *P. aeruginosa* (8.5%). The intraoperative isolates have been shown in Table I.

We selected 142 episodes of the 235 total, based on exclusion criteria. Of these, 75 were in the OTG and 67 in the ITG group. In the OTG group, the most used antibiotic was doxycycline, followed by fluoroquinolones and cotrimoxazole. In the ITG group, the antibiotics mainly used were amoxicillin/clavulanic acid, fluoroquinolones, and linezolid, often associated with oral doxycycline or cotrimoxazole.

Out of the 142 selected episodes, 36 (24.6%) were metalware-related infections; 19 were in the ITG group and 17 in the OTG (28.4% and 22.7%, respectively, $p = 0.464$). The implant material was not removed in three cases (two in the ITG and one in the OTG). The microbiological etiology was established in 111 episodes. Gram-positive bacteria were the most frequent, with 81 isolates (61.8%). In 16 episodes, there was a polymicrobial infection, 12 in the ITG group and 4 in the OTG ($p = 0.018$). The median hospital stay was significantly longer in the ITG than in the OTG [12 (IQR 8-23) *vs.* 4 (IQR 2-5) days, $p < 0.001$)]. Moreover, the total duration of therapy was significantly different between the ITG (median 46 days, IQR 31-58) and the OTG group (median 41 days, IQR 21-48; $p = 0.04$).

Regarding the outcome, full recovery was observed in 79 of the 142 episodes (55.6%); of these, 36 (53.7%) were in the ITG and 43 (57.3%) in the OTG ($p = 0.666$). We did not find any differences among the two groups regarding sites involved, surgical interventions, and meticillin-resistance frequency. The two groups' characteristics have been summarized in Table II.

At the logistic regression, we found that a polymicrobial infection [Odds ratio (OR) 4.16 (95% confidence interval, CI, 1.28 - 13.4), $p = 0.017$], and a duration of therapy shorter than six weeks [OR 4.24 (95% CI 1.38-5.43), $p = 0.004$] were associated with an increased risk of treatment failure. Instead, the administration of IV antibiotics did not reduce the risk of treatment failure.

Discussion

Our retrospective study described a total of 235 episodes of osteomyelitis, with a higher prevalence in male gender, in accordance with the previous literature[1].

According to the major guidelines, 160 intraoperative cultures were performed, considered more reliable than wound swabs or pus drainage[8]. *S. aureus* was the most frequent causative agent (28.8%) of the 160 cultures made in our study, in agreement with the available literature[9].

There is growing evidence on the same efficacy of oral antibiotics to treat osteomyelitis regarding intravenous antibiotics. For example, the randomized clinical trial of the OVIVA group[10] (Oral Versus Intravenous Antibiotics for Bone and Joint Infections), which enrolled 1,054 participants, demonstrated the non-inferiority of oral antibiotic therapy.

We have shown a full recovery in 79 of the 142 episodes (55.6%); of these, 36 (53.7%) were in the ITG and 43 (57.3%) in the OTG, with no statistical difference among the two groups. However, our recovery rates were significantly lower when comparing our results with those of the OVIVA trial. This finding could be explained because our division is a national, highly specialized referral center where the most difficult cases are treated. Moreover, our study did not include prosthetic joint infections, as in the OVIVA trial but just osteomyelitis, with a large number of diabetic foot infections. Thus, our recovery rates were similar to other studies[4,11,12].

As in the OVIVA trial, the median hospital stay in our study was significantly shorter in the oral therapy group, with clear advantages in terms of costs and reduction of nosocomial infections related to prolonged hospitalization. Shorter hospitalization is becoming more important nowadays since many ordinary wards have been converted into COVID-19 wards, and several SARS-CoV-2 outbreaks started in hospitals and healthcare-related settings[13,14].

Many studies[15-17] have been conducted on polymicrobial etiology in different types of infection, but there are few literature data on the impact of polymicrobial infections on osteomyelitis outcomes. Jorge et al[18] conducted a retrospective study enrolling 193 patients with post-traumatic osteomyelitis, showing how people with a polymicrobial infection had an increased risk of failure and amputations. In our cohort, people with polymicrobial infection had a four-fold risk of treatment failure, compared to monomicrobial infection. Further prospective studies are needed to find the correct approach to this type of infection and understand if there are differences in outcomes between oral and IV treatment.

Table I. Intraoperative cultures of 160 patients.

Bacterium	No. of isolates (n=160)
Staphylococcus aureus	46 (28.8%)
Staphylococcus epidermidis	29 (18.1%)
Other coagulase-negative staphylococci	24 (15%)
Pseudomonas aeruginosa	8 (5%)
Streptococci	5 (3.1%)
Acinetobacter baumannii	5 (3.1%)
Proteus mirabilis	5 (3.1%)
Escherichia coli	4 (2.5%)
Negatives	26 (16.5%)
Polimicrobial aetiology	20 (12.5%)
Others	30 (18.7%)

Table II. Characteristics of 142 patients with osteomyelitis.

Variable	All cases (n=142)	IV±OS (n=67)	Only OS (n=75)	*p*-value
Age (years) mean ± SD	54.1 ± 14.7	53.9 ± 15	54.3 ± 14.5	0.87
Female gender (%)	41 (28.9)	20 (29.9)	21 (28)	0.808
Implant material (%)	36 (25.4)	19 (28.4)	17 (22.7)	0.464
Cultures				
Gram positive (%)	81 (57.1)	34 (50.7)	47 (62.7)	0.523
Gram negative (%)	28 (19.7)	16 (23.9)	12 (16)	
Both (%)	2 (1.4)	1 (1.5)	1 (1.3)	
Negative/not performed (%)	31 (21.8)	16 (23.9)	15 (20)	
Polymicrobial infections (%)	16 (11.3)	12 (17.9)	4 (5.3)	0.018
Hospital stays (days), median (IQR)	6.5 (4-13)	12 (8-23)	4 (2-5)	< 0.001
Duration of therapy (days), median (IQR)	42 (28-51)	46 (31-58)	41 (28-48)	0.045
Recovery (%)	79 (55.6)	36 (53.7)	43 (57.3)	0.666
Follow-up (months), mean ± SD	24.9 ± 6.7	25.9 ± 6.9	24.1 ± 6.5	0.094

IV: intravenous treatment; OS: oral treatment; SD: standard deviation; IQR: interquartile range.

The limitations of our study include those implicit in a retrospective observational design. All cases came from the same hospital, with a long experience in managing osteomyelitis. Therefore, our patients may have received surgical treatments which are not available elsewhere. Therefore, our results may not be generalizable to other hospitals. Furthermore, we have not collected the laboratory tests such as C reactive protein, procalcitonin, white blood cells because they were available for a part of patients only. However, we would specify that they are not a specific marker of infection, and other inflammatory conditions could modify it, or they could be negative[19]. Finally, we lack data about higher treatment failure risk predictors, such as vascular insufficiency or diabetes control.

There are different strengths in our study in addition to a large number of cases, such as the long follow-up time, a detailed description of the involved site, the surgical intervention performed, and the availability of the microbiological aetiology in a large number of cases.

Conclusions

In summary, our study suggests that oral treatment is non-inferior to IV therapy for osteomyelitis. In addition, we found that a polymicrobial infection is a negative prognostic factor. This aspect should be further investigated in future studies and considered at the time of treatment's choice. Clinicians' choice of the proper treatment of osteomyelitis should be based on guidelines which should consider the most recent results of clinical trials and observational studies.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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