Oral versus Intravenous Antibiotic treatment for Osteomyelitis in Adults: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The worldwide incidence of osteomyelitis is approximately 21.8 cases per 100,000 person-years. The cornerstone of treatment is prolonged (4-6 weeks) intravenous antibiotic administration. This entails additional cost, inconvenience, and added manpower from the healthcare system. Thus, studies have explored the possible use of oral antibiotics as alternatives to improve patient compliance and reduce costs. Our meta-analysis aimed to compare the efficacy of oral versus intravenous antibiotics in treating adult patients with osteomyelitis.

Materials and Methods: Electronic databases (PubMed, Medline, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and Research Gate) from 1966 to April 2020 were searched using the terms "oral antibiotics", "osteomyelitis", "randomized controlled trial". Only studies that directly compared oral versus intravenous antibiotics and confirmed osteomyelitis through biopsy and/or imaging were included. Primary outcome is remission (resolution of symptoms with no relapse and bacteriologic eradication); secondary outcomes, (a) relapse (persistence of the pathogen after treatment) and (b) adverse events. The validity of included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions. We performed a random-effects model in Review Manager Version 5.3 with 95% confidence interval. The I^2 test was used to assess heterogeneity.

Results: Seven of 89 trials comprised of 1,282 patients were included in the final analysis. All studies included patients with osteomyelitis of the lower extremities. Oral antibiotics used were Ciprofloxacin, Ofloxacin, and Co-trimoxazole; intravenous antibiotics used were deemed appropriate by the infectious disease specialist. Patients were only given either oral or intravenous antibiotics. Results showed an 8% increase in remission rates [RR 1.08 (0.81 to 1.44, 95% CI, Z = 0.52*, p=0.60*)] with no heterogeneity (I^2 = 0%) in the intravenous antibiotics group. However, this was not statistically significant. Furthermore, there was a 62% decrease in relapse rates in the intravenous antibiotics group [RR 1.62 (0.85 to 3.07, 95% CI, Z = 1.47, *p = 0.14*)] with no heterogeneity (I^2 = 0%) but was not statistically significant.

Conclusions: Oral are comparable to intravenous antibiotics in treating osteomyelitis in terms of remission and relapse rates. However, larger and double-blinded trials should be done to generate more robust data to validate these claims.

Keywords: *Oral, Intravenous, Parenteral, Osteomyelitis, Randomized Control Trials*

INTRODUCTION

Osteomyelitis is defined as infection of the bones. It is either the acute or chronic inflammation of the bone secondary to infection with bacteria, fungi, and mycobacteria.[1] The overall incidence of osteomyelitis is unknown worldwide, but studies have been done and one study show it to be as high as 21.8 cases per 100,000 person-years. There was also a trend noted in the study that shows increased incidence in patients with comorbidities such as diabetes mellitus and peripheral vascular disease.[2]

Intact bone is protected against infection. Bone becomes susceptible to infection due to the following: introduction

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of a large inoculum of bacteria, from trauma, ischemia or the presence of foreign bodies. One mechanism as to how the bones get infected is by the hematogenous route by means of bacteria seeding from a distant source, contiguous spread from nearby tissue and joints, or by direct inoculation of the bone from trauma or surgery.[3] In adults, the vertebrae are the most commonly affected by the hematogenous route. Contiguous osteomyelitis in young adults is usually caused by trauma and surgery. In older adults, infection is brought about by decubitus ulcers and infected joint arthroplasties.[1]

Osteomyelitis that is associated with vascular insufficiency frequently occurs in patients who have diabetes mellitus.[1] This occurs by means of a compromised blood supply to the lower extremities which would result in impaired immunity in the area and healing, worsening the infection. Diabetic polyneuropathy further promotes the formation of ulcers at dependent and trauma areas further complicating it.[1,2]

Treatment of osteomyelitis consists of medical and surgical modalities. These are source control by surgery and antibiotics. Debridement of the infected tissue and bone is usually needed since antibiotics poorly penetrate abscesses and necrotic or gangrenous bone.[1] Prolonged antibiotic therapy is the cornerstone of treatment for osteomyelitis, and this usually is around 4-6 weeks.

The need for prolonged treatment of osteomyelitis with intravenous antibiotics is a source of heavy burden to the patient, healthcare provider, and economy. The patient would need to be admitted for a long time and this would cause them to be incapable of being productive at the same time incurring a sizeable hospitalization bill. In some countries, the government shoulders the hospital bill of its citizens, thus treatment of patients with this disease could be an economic burden as well.

This has led the researchers to ask "*Among adult patients with osteomyelitis, is there a difference in effectiveness between oral versus intravenous antibiotics?*" Some studies have explored the use of oral versus intravenous antibiotics. And some have been successful in proving the non-inferiority of oral to intravenous antibiotics. To our knowledge, there has been no meta-analysis done to show the non-inferiority between oral and intravenous antibiotics. If proven non-inferior or superior, this study could guide clinicians in using oral antibiotics in treating patients with osteomyelitis thus allowing them to be discharged and followed-up on an outpatient basis. This would reduce hospital stay, and subsequently the financial and economic burden caused by the disease.

In this study, the researchers aim to determine the effectiveness of oral compared to intravenous antibiotics in the treatment of adult patients with osteomyelitis. Specifically, we aim: to determine the relapse rate of patients with osteomyelitis given oral compared to intravenous antibiotics; and determine the incidence of adverse events following the administration of oral antibiotics.

MATERIALS AND METHODS

Types of Participants**.** The researchers included adult patients (more than or equal to 18 years of age) with either acute or chronic osteomyelitis.

Types of Interventions**.** The researchers included studies that used different antibiotics, different routes of administration (oral or parenteral) or different treatment durations. The parenteral route is defined as any route other than the mouth or rectum. Studies that only focused on local antibiotic treatment were excluded in the study.

The participants in the interventional group were given a course of oral antibiotics as deemed necessary by the infectious disease specialist at their respective centers, while those in the control group were given intravenous antibiotics. The detailed description as to the dose and type of antibiotics given are shown in Table 1.

Types of Outcome Measures

Primary outcomes. The number of patients who presented with remission of infection at follow-up of at least one year. Remission is defined as the resolution of all signs and symptoms of active infection at the end of therapy and after a minimal post-treatment observation of one year.

Secondary outcomes. 1.) The number of participants with relapse (early and late). Relapse is defined as the recurrence of signs and symptoms plus isolation of the same pathogen(s) within four to six weeks (early) and six weeks to 12 months (late) after the end of therapy. 2.) The number of participants who presented with adverse events from the administration of antibiotics.

Types of Studies. The researchers included randomized controlled trials (RCTs) in this study.

Search Methods for Identification of Studies

Electronic Searches. A highly sensitive search strategy was used for identifying randomized controlled trials. Both electronic and manual means of retrieving relevant studies were performed. Electronic searches (search strategy not limited by language and publication status) were completed of PUBMED, MEDLINE (1966 to April 2020; National Library of Medicine, Bethesda, USA), EMBASE (1974 to April 2020; Elsevier Science, New York, USA), Cochrane Central Register of Controlled Trials, Google Scholar, and Research Gate. The reference lists of all identified papers were searched for further information.

The search strategy combined the search terms ((("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotics"[All Fields])) AND ("osteomyelitis"[MeSH Terms] OR "osteomyelitis"[All Fields]) AND Clinical Trial[ptyp] were used in the PubMed search engine.

The researchers used the following search terms in the Cochrane search strategy: "Oral Antibiotics" in Title,

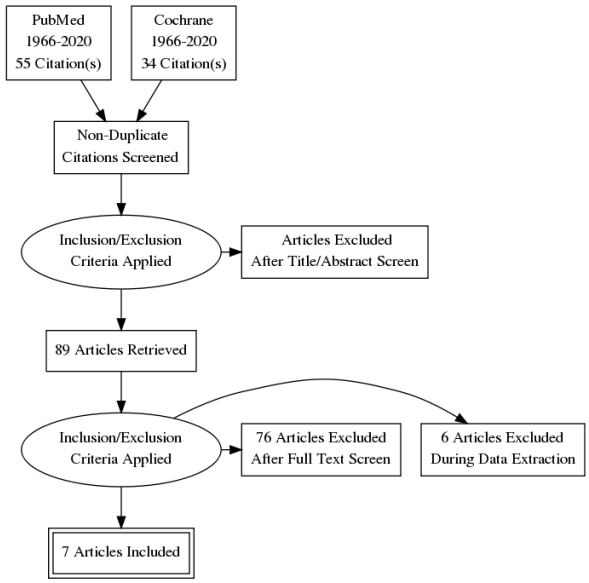

Figure 1. PRISMA flow chart showing the inclusion and exclusion of articles.

Abstract, Keywords AND "Osteomyelitis", "Randomized Controlled Trial" in Search All Text in the Trials. The summary of the search strategy is demonstrated in *Figure 1*.

Other Sources. Manual searches were also conducted in Google Scholar and http://www. researchgate.net. In addition, for articles that were either unpublished or full-text not available in the internet, the authors were contacted via their respective emails.

Selection Criteria. The investigators included randomized controlled trials that at least compared one group that used oral antibiotics with a group that used intravenous antibiotics. Each of the coauthors independently assessed the suitability of each study for inclusion in the meta-analysis.

Data Collection and Analysis

Data Extraction. The two independent reviewers assessed the quality of the studies based on the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions; the results of these individual assessments were then compared by a third and independent reviewer. In cases in which the assessments varied, these differences were resolved by the third and independent reviewer. Studies were assessed as high-quality or low risk of bias if they fulfilled the following criteria: (1) treatment allocation was randomized with adequate concealment; (2) the treatment and control groups were balanced in terms of known determinants of outcome; (3) outcome assessment was done in a double-blind manner; (4) outcome detection methods used were similar for both groups; (5) treatment and control groups were treated equally in terms of other therapeutic and co-interventions received, frequency of follow-up and general quality of care; (6) an intention-to-treat analysis was conducted; and (7) drop-out rates between groups were comparable. On the other hand, studies were considered fair-quality or moderate risk of bias if any subtle biases were present, such as: (1) unclear allocation concealment; (2) absence of blinding; and (3) no intent-to-treat analysis. And lastly, studies were considered low-quality or high risk of bias if any of the frank biases was seen: (1) significant differences between the treatment and control group in terms of known predictors of outcome; (2) obvious differences in the general quality of care received by subjects in both groups; (3) marked difference in drop-out rates; and (4) outcome detection methods were different for both groups. The outcomes of interest were the cure/remission rate in all study groups in each study.

Data Analysis. The clinical success rates were combined and analyzed using a random-effects model in Review Manager (Rev Man) Version 5.3. A 95% confidence interval was used. These were classified as dichotomous; it is one of only two possible categorical responses. For dichotomous data, the risk ratio or the probability that an event will occur were determined for each comparison. A forest plot was constructed to show the overall effect of intervention against control in all the studies grouped together. Other outcomes included incidence of relapse and adverse effects were presented as narratives.

Test for Heterogeneity. Heterogeneity was quantified using the chi square test for heterogeneity with $p < 0.10$ as the cut-off for significant heterogeneity. Heterogeneity can be interpreted as a percentage of total variation between studies that is attributable to heterogeneity rather than to chance. The I^2 test will be used to assess the degree of heterogeneity, i.e., $I^2 > 50\%$ suggests significant degree of heterogeneity or a value of 0% indicates no observed heterogeneity.

RESULTS

Description of Studies. After thoroughly searching PUBMED, the Cochrane Central Register of Controlled Trials (CENTRAL), in addition to manual searches in www.researchgate.net and Google Scholar, a total of 89 studies were identified to be potentially eligible for inclusion in the meta-analysis. After thorough scrutiny, 82 articles were excluded (*Figure 1*). Seven studies were included and underwent data extraction. Those studies were left for more detailed review; reference lists of articles were reviewed, and no additional trials were identified.

Quality assessment of included studies**.** Based on the criteria set by Cochrane Group, the quality of the retrieved studies was assessed independently by the two authors (*Figure 2*). The assessment done was then checked by a third party (senior co-author) to amend the differences.

All studies had high risks for performance and detection bias. This is due to the fact that blinding was not used due to the investigators of the respective studies to consider it unethical to expose participants in the oral group to the risks associated with prolonged courses of intravenously administered placebo.

ıble 1. Description of the Individual Studies

ef.	Author, Year	Study Design	Sample size (n)	Inclusion Criteria	Population			Intervention/s	Control	Outcome
					Organism	Type of Osteomyelitis	Diagnosis of Osteomyelitis			
4	Euba 2009	Prospective, Randomized, Controlled Trial	48	Patients who had undergone surgery for chronic nonaxial osteomyelitis due to S. aureus, with or without foreign bodies.	*Staphylococcus aureus*	Chronic Non-axial Osteomyelitis	Inflammatory signs and/or sinus drainage for 10 days Compatible X-ray results Presence of necrotic bone.	Oral Trimethoprim-Sulfamethoxazole (TMP 7-8mg/kg/day) plus rifampin 600mg/day for 8 weeks; Debridement as deemed necessary.	IV cloxacillin 2gm q4h for 6 weeks plus oral cloxacillin for 2 weeks; Debridement as deemed necessary.	Cure rate immediately after treatment and at 10 years follow-up.
5	Gentry 1990	Prospective, Randomized, Comparison Trial	59	Hospitalized adult patients with bone biopsy confirmed osteomyelitis which required antimicrobial therapy.	*S. aureus* *S. faecalis* *Enterococcus faecalis* *Pseudomonas aeruginosa* *Escherichia coli* *Proteus mirabilis* *Enterococcus cloacae* *M. morganii* *Klebsiella pneumoniae* *Enterobacter aerogenes* *S. marcesens* *P. stuartii* *P. fluorescens*	Osteomyelitis both prosthesis and non-prosthesis	Bone biopsy proven	Ciprofloxacin 750mg BID ceftazidime or nafcillin plus oral aminoglycoside of at least 6 weeks.	IV Ceftazidime or nafcillin plus aminoglycoside of at least 4 weeks, not to exceed 6 weeks.	Clinical success rate immediately on completion of treatment and at 1-year follow-up.
6	Gentry 1991	Parallel group, Randomized, Controlled Trial	33	Adult patients with osteomyelitis biopsy-confirmed; and those with no prosthesis-related osteomyelitis.	*S. aureus* *Enterococcus faecalis* *Pseudomonas aeruginosa* *Escherichia coli* *Proteus mirabilis* *Enterococcus cloacae* *M. morganii* *Klebsiella pneumoniae* *Enterobacter aerogenes* *S. marcesens*	Non-prosthesis osteomyelitis	Bone biopsy-confirmed	Oral ofloxacin 400 mg orally twice a day.	Cefazolin 1.0 g intravenously every 8 hours or ceftazidime 2.0 g intravenously every 12 h (every 8 h for P. aeruginosa infections).	Cure rate immediately after treatment and on 18 months follow-up.

Table 1 (cont'd). Description of the Individual Studies

Ref.	Author, Year	Study Design	Sample size (n)	Inclusion Criteria	Population			Intervention/s	Control	Outcome
					Organism	Type of Osteomyelitis	Diagnosis of Osteomyelitis			
7	Gomis 1999	Prospective, Randomized, Open-label Trial	32	Hospitalized patients with diagnosis of chronic osteomyelitis and isolation of susceptible organisms to ofloxacin and imipenem/cilastatin were eligible for enrollment.	Organisms isolated which were susceptible to ofloxacin and imipenem/cilastatin	Chronic osteomyelitis	Physician diagnosed the patients with chronic osteomyelitis	Oral Ofloxacin 400 mg every 12 hours	IV Imipenem-cilastatin 500 mg every 6 hours	Cure rate immediately on completion of treatment.
8	Greenberg 1987	Randomized, Comparative Trial	30	Adult patients diagnosed with chronic osteomyelitis	*Enterobacteriaceae* *Pseudomonas aeruginosa* *Staphylococcus aureus*	Chronic osteomyelitis	Physician diagnosed the patients with chronic osteomyelitis	Oral Ciprofloxacin 750mg BID for =6 weeks	"Appropriate therapy" for = 6 weeks	Cure rate immediately on completion of treatment and after 13 months.
9	Li 2015	Multi-center, open-label, parallel group, Randomized, Controlled, Non-inferiority Trial	1054	Older than 18 years of age	*S. aureus* Coagulase-Negative *Staphylococcus* *Streptococcus spp.* *Pseudomonas spp.* Other gram-negative organisms	Acute or chronic osteomyelitis or joint infection Native osteomyelitis of of the extra axial skeleton, native joint infection requiring excision arthroplasty, prosthetic joint infection, orthopedic fixation device infection, or vertebral osteomyelitis with or without associated diskitis or soft-tissue infection.	Clinical findings (558/1054) Microbiologic findings (Blood; 802/1003) Histologic findings (543/636)	Oral antibiotics for 6 weeks	Intravenous antibiotics for 6 weeks	Definitive Treatment Failure after 1 year of randomization
10	Mader 1990	Prospective Randomized Controlled Trial	26	Adult patients diagnosed with chronic osteomyelitis.	Not-stated	Chronic osteomyelitis	Physician diagnosed patients with osteomyelitis	Oral ciprofloxacin	Standard parenteral antibiotic therapy (consisting of nafcillin, clindamycin, and gentamicin, singly or in combination).	Cure rate at completion of treatment and at follow-up after 30 months.

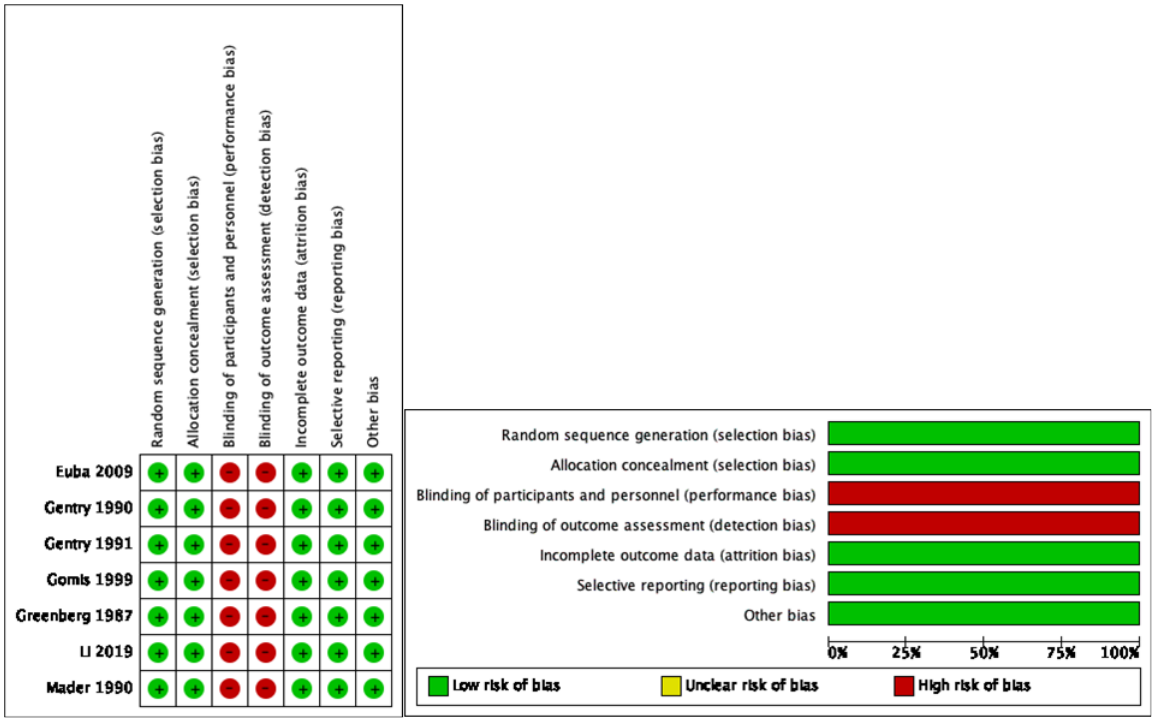

Figure 2. Quality Assessment of the studies included in the Meta-Analysis

However, whether or not blinding was done would not have affected the outcome of the studies which were clinical success rates and cure rates which are both objective and not affected by the subjects' knowledge whether or not they received oral or intravenous antibiotics.

Effect of Intervention on Outcomes of Interest

1.) Comparison between oral versus intravenous antibiotics, Outcome 1 Remission on follow-up. The seven studies showed that the relative risk of remission in patients given oral versus intravenous antibiotics is 1.08 (0.81 to 1.44, 95% CI, Z = 0.52, *p=0.60*). There was also no heterogeneity noted (*p=0.75*, I^2 = 0%); furthermore, they were statistically not significant with *p=0.60*. (*Figure 3*).

2.) Comparison between oral versus intravenous antibiotics, Outcome 2 Relapse. The study of Mader et al. was not included in this analysis because they did not mention the number of patients who experienced relapse or if there were ever any. Our analysis showed a relative risk of 1.62 (0.85 to 3.07, 95% CI, Z = 1.47, *p=0.14*). Heterogeneity was (*p=0.87*, I^2 = 0%) (*Figure 4*).

3.) Comparison between oral versus intravenous antibiotics, Outcome 3 Adverse events (All types). The study of Gomis et al. did not report any adverse event following administration of either oral or intravenous antibiotics; thus, it was not included in this analysis. The adverse events reported are heterogenous (*p=0.12*, I^2=43%), and statistically not significant with the RR=0.93 (0.41 to 2.12, 95% CI, Z=0.17, *p=0.87*).

DISCUSSION

There have been many trials comparing certain oral with intravenous antibiotics in the treatment of joint and bone infections; but to our knowledge, this is the first meta-analysis which compared oral versus intravenous antibiotics regardless of the kind of antibiotic used. This may be due to the fact the individual trials have little population and others have differing kinds of antibiotics used.

The primary outcome of interest is remission on follow-up. Our study showed an 8% increase in remission [RR 1.08 (0.81 to 1.44, 95% CI, Z=0.52, *p=0.60*)] with no heterogeneity (*p=0.75*, I^2 = 0%) favoring the intravenous antibiotics group. This benefit is not only negligible, this is also not statistically significant. This shows that whether oral or intravenous antibiotics were given to treat osteomyelitis, there was little to no difference.

There was also a high risk for bias in the studies because they were open label. But the researchers have reiterated in the previous discussion that knowledge of having been given an oral or intravenous antibiotic would not affect remission rate nor the relapse rate of those patients. Blinding them would also be unethical as this would expose the patients in the oral antibiotic group to complications from prolonged intravenous placebo administration.

One of the secondary outcomes of the study was relapse; the study showed that there was a 62% decrease in relapse rates among patients being given intravenous antibiotics [RR 1.62 (0.85 to 3.07, 95% CI, Z=1.47, *p=0.14*)]. There was no heterogeneity noted (*p=0.87*, I^2 = 0%). This benefit with regards to relapse rate is not

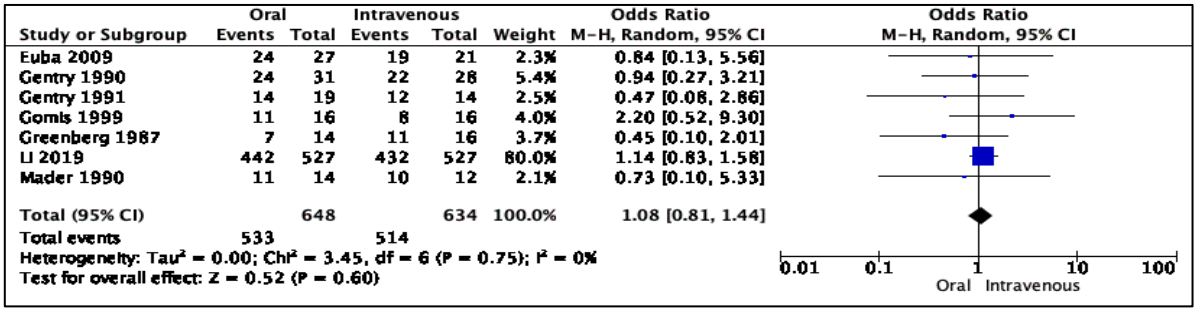

Figure 3. Forrest plot showing the number of patients in remission

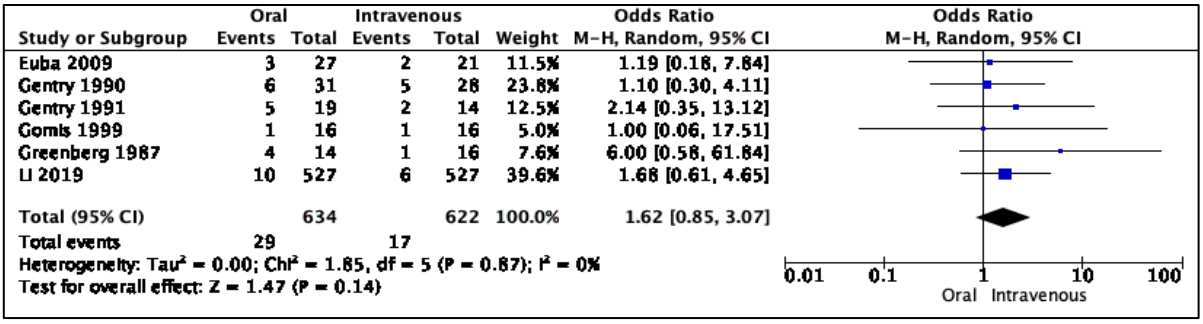

Figure 4. Forrest plot showing the number of patients in relapse after treatment

statistically significant (*p=0.14*), which still does not point to intravenous antibiotics being superior with regards to reducing relapse rates.

The other secondary outcome of the study was adverse events from antibiotic administration. The study showed that there was a decrease in adverse events by 7% in patients given oral antibiotics (RR 0.93, 0.41 to 2.12, 95% CI, Z=0.17, *p=0.87*) with moderate heterogeneity (*p=0.12*, I^2 = 43%). This benefit from oral antibiotic administration is not statistically significant (*p=0.87*). The heterogeneity in this analysis is from the different kinds of adverse events reported (i.e. gastrointestinal, allergy, etc.). This does not point to oral antibiotics being superior in treating osteomyelitis.

To the researchers' knowledge, this is the first meta-analysis done comparing oral versus intravenous antibiotics in the treatment of adults with osteomyelitis. Until now, most of the available studies are limited in terms of their small study population, high risks of bias (most are open label studies), and heterogeneity. Therefore, larger, multi-centered, and double-blinded randomized controlled trials with longer follow-up periods are needed to confirm the results and come up with more robust data to support the claim that oral antibiotics are not inferior to intravenous antibiotics.

Thus, the researchers have concluded that oral antibiotics are not inferior compared to intravenous antibiotics in treating adult patients with osteomyelitis. There was an 8% increase in remission rates among those given intravenous antibiotics, but this is statistically not significant. Furthermore, relapse rates are much less in the intravenous antibiotics group although this analysis is also not statistically significant. For the final outcome, there was a 7% decrease in reported adverse events favoring the oral antibiotic group. But it must be reiterated that larger trials are needed to provide more robust data for these claims.

Clinical Implications

The standard of care in managing patients with osteomyelitis is surgical and medical. Debridement or and amputation is done for source control and long course antibiotics is also given. The duration of antibiotic treatment is around six weeks. This would mean that if intravenous antibiotics were given, the patient would have to be admitted for that duration or would have to frequently visit the health-center for intravenous administration. It is costly for the patient as well as for the hospital whereas if there was another alternative to giving the antibiotics by another route like *per orem*, that would be more convenient, cost-effective, and prone to lesser complications (i.e. phlebitis at IV site).

To our knowledge, this is the first meta-analysis done comparing oral to intravenous antibiotics in treating patients with osteomyelitis.

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Declaration of Conflict of Interest

The authors declare no conflicts of interests.

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REFERENCES

1. Schmitt SK. Osteomyelitis. Infect. Dis. Clin. North Am. 2017 Jun;31(2):325-338.
2. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ, Huddleston PM. Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. J Bone Joint Surg Am. 2015 May 20;97(10):837-45.
3. Lew DP, Waldvogel FA. Osteomyelitis. N. Engl. J. Med. 1997 Apr 03;336(14):999-1007.
4. Euba G, Murillo O, Fernandez-Sabe N, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. *Antimicrobial agents and chemotherapy* vol. 53,6 (2009): 2672-6. doi:10.1128/AAC.01504-08.
5. Gentry LO, and Rodriguez G. Oral ciprofloxacin compared with parenteral antibiotics in the treatment of osteomyelitis. *Antimicrobial agents and chemotherapy* vol. 34,1 (1990): 40-3. doi:10.1128/aac.34.1.40.
6. Gentry LO, and Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. *Antimicrobial agents and chemotherapy* vol. 35,3 (1991): 538-41. doi:10.1128/aac.35.3.538.
7. Gomis M, Barberan J, Sanchez B, et al. Oral Ofloxacin versus Parenteral Imipenem-Cilastatin in the Treatment of Osteomyelitis. *Revista Espanola De Quimioterapia : Publicacion Oficial De La Sociedad Espanola De Quimioterapia*, U.S. National Library of Medicine, Sept. 1999, https://www.ncbi.nlm.nih.gov/pubmed/10878516.
8. Greenberg RN, Kennedy DJ, Reilly PM, et al. Treatment of bone, joint, and soft-tissue infections with oral ciprofloxacin. *Antimicrobial agents and chemotherapy* vol. 31,2 (1987): 151-5. doi:10.1128/aac.31.2.151.
9. Li HK, Scarborough M, Zambellas R, et al. Oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA): study protocol for a randomised controlled trial. *Trials*. 16(583). 21 Dec. 2015, doi:10.1186/s13063-015-1098-y.
10. Mader JT, Cantrell JS, Calhoun J. Oral ciprofloxacin compared with standard parenteral antibiotic therapy for chronic osteomyelitis in adults. Journal of Bone Joint Surgery - American Volume 1990;72(1):104–10.