



The Antibiotic Use in Osteomyelitis Infection: A Systematic Review

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Abstract

BACKGROUND: Osteomyelitis is a serious infection of the bone. One of the therapies for osteomyelitis is antibiotic treatment. Antibiotic treatment has evolved substantially, but bone infections are still a challenge. Antimicrobial therapy is also difficult, caused by antibiotic-resistant organisms. Therefore, a systematic review is needed to assess antibiotic use in osteomyelitis infection.

METHODS: Articles were searched using PubMed with keywords “antibiotics,” “osteomyelitis,” and its combination. The authors used 5 years publication date and English language to select the appropriate journal.

RESULTS: The author identified 13 relevant articles with antibiotics use in osteomyelitis. All of the cases were about chronic osteomyelitis and osteomyelitis in diabetic foot ulcers. Osteomyelitis in other sites of long bones needs longer duration treatment than long bone osteomyelitis. In acute osteomyelitis in children, antibiotic treatment can switch from IV to oral antibiotics. Furthermore, chronic osteomyelitis needs longer treatment to resolve than acute osteomyelitis.

CONCLUSION: Antibiotics still mainstay treatment with surgery for osteomyelitis treatment. With acute, children, and long bone only need shorter treatment than chronic, adult, and non-long bone osteomyelitis.

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Introduction

Osteomyelitis is a serious infection of the bone that can be either acute or chronic [1]. The annual incidence of osteomyelitis was 21.8 cases/100.000 person-years. Rates increased, from 11.4 cases/100.000 person-years from 1969 to 1979 to 24.4/100.000 person-years in the period from 2000 to 2009 [2]. There is still limited data about osteomyelitis incidence in Indonesia. However, there is data from the orthopedic department in Hasan Sadikin Hospital in Bandung, the incidence of chronic osteomyelitis in Indonesia is 0.5–2.4/100.000 populations. And from a study, they found 151 cases of chronic osteomyelitis in Hasan Sadikin Hospital from 2011 to 2016 [3].

Antibiotics are one of the therapies for osteomyelitis. Antibiotics treatment of osteomyelitis has evolved substantially over the past 80 years. Numerous antimicrobial agents with distinct spectrums of action, pharmacokinetics, and pharmacodynamics have been used in its treatment. Surgical techniques, including muscle grafts, Ilizarov technique, and antibiotic bone cement, have been applied for osteomyelitis. However, bone infections are still a challenge [4]. New studies challenge the dogma, and for example, the antimicrobial

must be given parenterally [5]. Antimicrobial therapy is now also difficult by the increasing prevalence of antibiotic-resistant organisms, especially methicillin-resistant *Staphylococcus aureus* [6]. Therefore, a systematic review is needed to assess the antibiotics used in osteomyelitis infection.

Methods

The following strategy was used terms on the PubMed search engine were “antibiotics,” “osteomyelitis,” and its combination. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to perform the comprehensive data collection. A bibliometric evaluation was done on all the search results. After searching those keywords, the authors used 5 years of the publication date and English language to select the appropriate journal and documents. Journals and documents were reviewed from title and abstract and followed inclusion and exclusion criteria. The inclusion criteria were an original article, with type are a clinical trial, meta-analysis, or randomized controlled trial which discuss antibiotics

use in osteomyelitis. The exclusion criteria were case reports, review articles, and no full-text paper. Journal search strategy showed in Figure 1.

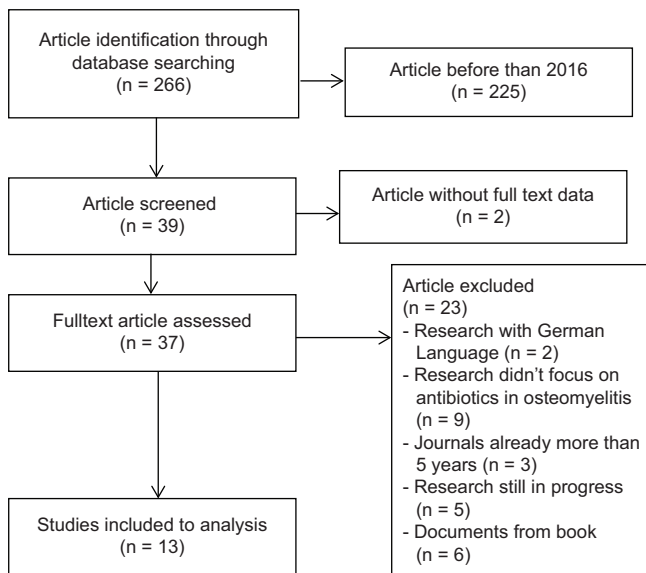


Figure 1: Flow diagram of the search strategy

Results

The initial PubMed search yielded 266 titles with 39 full-text articles and documents assessed according to the inclusion and exclusion criteria. There were 253 articles and documents eliminated according to the exclusion criteria. The final total number of articles analyzed was 13 articles and documents.

Based on Table 1, the most of the cases from this journal are chronic osteomyelitis and diabetic foot ulcers. Four studies used the retrospective cohort method, six studies used the prospective method, and four studies were review articles. The total number of patients was 5419 samples, with the largest number of samples in a study by Huang *et al.*, 2019, which had 3598 patients with lower extremity osteomyelitis.

Table 1: Studies included to the analysis

Author	Σ Sample	Design	Case
Menetrey <i>et al.</i> , 2018 [7]	17	Prospective	Osteomyelitis, hip surgery
Alcobendas <i>et al.</i> , 2018 [8]	253	Prospective	Osteomyelitis and septic arthritis
Chen <i>et al.</i> , 2017 [9]	1526	Prospective	Osteomyelitis, diabetic foot ulcer
Mangwani <i>et al.</i> , 2016 [10]	100	Prospective	Toe osteomyelitis
Huang <i>et al.</i> , 2019 [11]	3598	Review	Osteomyelitis
Lavery <i>et al.</i> , 2020 [12]	155	Prospective	Osteomyelitis, diabetic foot ulcer
Lemaigen <i>et al.</i> , 2017 [13]	394	Retrospective	Vertebral osteomyelitis
Luo <i>et al.</i> , 2016 [14]	51	Retrospective	Chronic osteomyelitis
Mortazavi <i>et al.</i> , 2018 [15]	183	Review	Chronic osteomyelitis
Van Vugt <i>et al.</i> , 2018 [16]	413	Review	Chronic osteomyelitis
Wunsch <i>et al.</i> , 2019 [17]	101	Retrospective	Tibial Osteomyelitis
Sun <i>et al.</i> , 2018 [18]	72	Retrospective	Chronic osteomyelitis
Graaf <i>et al.</i> , 2017 [19]	313	Prospective	Acute osteomyelitis in children

Based on the Table 2, all of the studies agree with antibiotics as one of the treatments for osteomyelitis besides the surgery. Four studies use chronic osteomyelitis cases for their study. From the site of osteomyelitis, the most studies use lower extremity osteomyelitis cases.

Table 2: Summary antibiotics use in osteomyelitis

Author	Case	Antibiotics use
Menetrey <i>et al.</i> , 2018 [7]	Osteomyelitis, hip surgery	Duration is 4 to 6, with chronic is 8 to 12 weeks
Alcobendas <i>et al.</i> , 2018 [8]	Osteomyelitis and septic arthritis	Oral antibiotics save and effective in children case
Chen <i>et al.</i> , 2017 [9]	Osteomyelitis, diabetic foot ulcer	Osteomyelitis in diabetic foot related to drug resistant infection
Mangwani <i>et al.</i> , 2016 [10]	Toe osteomyelitis	Prophylactic antibiotic does not reduce incidence osteomyelitis in the toe
Huang <i>et al.</i> , 2019 [11]	Osteomyelitis	Short course antibiotics (< 4 weeks) as effective as long course
Lavery <i>et al.</i> , 2020 [12]	Osteomyelitis, diabetic foot ulcer	Duration of antibiotics for osteomyelitis did not change even use NPWT as treatment
Lemaigen <i>et al.</i> , 2017 [13]	Vertebral osteomyelitis	Majority of the case in acute vertebral osteomyelitis received antibiotics in 90 days
Luo <i>et al.</i> , 2016 [14]	Chronic osteomyelitis	Combination therapy (with loaded calcium sulfate) have better results than monotherapy
Mortazavi <i>et al.</i> , 2018 [15]	Cranial osteomyelitis	Broad-spectrum antibiotics 8-20 weeks
Van Vugt <i>et al.</i> , 2018 [16]	Chronic osteomyelitis	The use of antibiotic-loaded sponges in the treatment of osteomyelitis is limited
Wunsch <i>et al.</i> , 2019 [17]	Tibial Osteomyelitis	Dalvabancin as alternative antibiotics for osteomyelitis
Sun <i>et al.</i> , 2018 [18]	Chronic osteomyelitis	Implanted antibiotics can improve results for chronic osteomyelitis
Graaf <i>et al.</i> , 2017 [19]	Acute osteomyelitis in children	IV switch to oral antibiotic < 7 weeks have a better outcome than > 7 days

One article discusses cranial osteomyelitis and one article discusses vertebral osteomyelitis. Furthermore, from age perception, two journals focus on osteomyelitis in children, while the other journal discusses general osteomyelitis in children and adults.

Based on the Table 3, all of the studies said *S. aureus* is the most common etiology of osteomyelitis. Another microorganism who also found in many studies is *Streptococcus*, even not as many as *Staphylococcus*. Three studies do not mention the specific organism for the etiology of osteomyelitis.

Cephalosporine and quinolone became the first choice in ten studies, while the other studies used other antibiotics or did not mention the choice.

Discussion

This systematic review shows that antibiotics are one of the treatments for osteomyelitis besides surgery. In many cases, even in children or adults, in acute or chronic conditions, and many locations, such as extremity, spinal, and cranial, antibiotics, still have a crucial part of therapy for the patient, although every case has a different approach.

An observational study by Lemaigen *et al.* showed that antibiotics therapy in vertebral osteomyelitis needs a long treatment time. The median duration of antibiotics treatment was 90 days, with only 27.1% of cases received less than 45 days of antibiotics treatment [13]. In the other study, a comprehensive review from Mortazavi, the result was that an appropriate broad-spectrum antibiotics therapy for 8–20 weeks is one of the

Table 3: Summary of microorganism and choice of antibiotics

Author	Microorganism	Choice of antibiotics
Menetrey <i>et al.</i> , 2018 [7]	<i>S. aureus</i>	Afabicin
Alcobendas <i>et al.</i> , 2018 [8]	<i>S. aureus</i> , <i>Kingella kingae</i>	Cephalosporin, amoxicillin-clavulanate, clindamycin
Chen <i>et al.</i> , 2017 [9]	Methicillin-Resistant <i>S. aureus</i> (MRSA)	No specific antibiotics
Mangwani <i>et al.</i> , 2016 [10]	No specific microorganism	Flucloxacillin
Huang <i>et al.</i> , 2019 [11]	No specific microorganism	No specific antibiotics
Lavery <i>et al.</i> , 2020 [12]	No specific microorganism	No specific antibiotics
Lemaigen <i>et al.</i> , 2017 [13]	<i>S. aureus</i> , <i>Enterobacteria</i> , <i>Streptococci</i>	Anti-staphylococcal beta-lactam/Fluoroquinolone + rifampicin, 3 rd gen cephalosporin and/or fluoroquinolone, amoxicillin
Luo <i>et al.</i> , 2016 [14]	<i>S. aureus</i> , MRSA, <i>P. aeruginosa</i>	Levofloxacin, Cefazolin, Ceftazidime, Vancomycin + calcium sulfate (local)
Mortazavi <i>et al.</i> , 2018 [15]	<i>S. aureus</i> , <i>Streptococci</i> , <i>anaerob microorganism</i>	Carbapenem + ciprofloxacin
Van Vugt <i>et al.</i> , 2018 [16]	<i>S. aureus</i> , <i>Escherichia coli</i>	Gentamycin-sulfate/gentamycin-crofebate implant
Wunsch <i>et al.</i> , 2019 [17]	<i>S. aureus</i> , MRSA, <i>Enterococci</i> , <i>Streptococci</i> , <i>Propionibacterium acne</i>	Dalvabancin
Sun <i>et al.</i> , 2018 [18]	<i>S. aureus</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>Streptococcus pneumonia</i>	Broad-spectrum antibiotics + Gentamycin (for impregnated bead)
Graaf <i>et al.</i> , 2017 [19]	<i>S. aureus</i> , <i>K. kingae</i> , <i>Streptococcus</i>	Flucloxacillin and ceftriaxone

S. aureus: *Staphylococcus aureus*, *K. kingae*: *Kingella kingae*, MRSA: Methicillin-Resistant *S. aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *E. coli*: *Escherichia coli*, *S. pneumonia*: *Streptococcus pneumonia*.

essential therapies to managing cranial osteomyelitis. Nevertheless, culture-directed antimicrobial therapy for a minimum of three months remains the general protocol because the treatment of cranial osteomyelitis may take several months for complete resolution [15]. In other studies, the diabetic foot becomes one of the main factors for how long the antibiotics must be given. From a journal by Huang *et al.*, the patients with diabetic foot and osteomyelitis need more than 3 months of antibiotics for non-surgically treated patients. This journal also said that patients with vertebral osteomyelitis are treated with 6 weeks of antibiotics, but the chronic osteomyelitis of the long bones need a 4–6 weeks course of parenteral antibiotics, followed by oral therapy [11].

The results of antibiotics treatment in chronic osteomyelitis also have different results between children and adults. Hanley *et al.*, in their journal, said that surgical debridement and culture-directed antibiotics are the mainstays of treatment. Furthermore, if after the appropriate therapy for 4–6 weeks has finished but the osteomyelitis still cannot be resolved, the diagnosis of chronic refractory osteomyelitis (CRO) becomes appropriate [20]. Hence, the conclusion is the standard duration of antibiotics treatment for osteomyelitis is 4–6 weeks. However, another journal researched the duration in children cases by Alcobendas *et al.* In their study, they compare the treatment adjusted by age. The result was that *S. aureus* was more prevalent in older children, while *Kingella kingae* was more frequent in younger children. In 75% of cases still need surgical treatment because of the protocol or diagnostic purpose. *K. kingae* infection involves a less severe process, allowing quick oral therapy. This research suggested IV antibiotics for 2–4 days, followed by oral antibiotics for 2–3 weeks [8]. Journal from Graaf also said that the suggested duration for the parenteral antibiotic treatment ranges from 3 days to 6 weeks, but this recommendation has a relatively poor level of evidence. However, a recent retrospective cohort study of 1969 children in the USA found that early switch to oral therapy (median 4 days) was as effective as prolonged intravenous treatment [19].

Antibiotics treatment duration in chronic osteomyelitis is longer than antibiotics treatment in acute osteomyelitis. One of the journals said that acute osteomyelitis would respond to the therapy for

4–6 weeks, and if not, the diagnosis of CRO becomes appropriate [18], [20]. In chronic osteomyelitis, multitherapy antibiotics can give better results than monotherapy, and oral antibiotics were not administered in most journals.

From the etiology, almost every journal said *S. aureus* is the most common etiology of osteomyelitis. Only three studies do not mention the microorganism. *S. aureus* is part of normal flora, but in some situations, *S. aureus* becomes virulent with a well-armed pathogen [21]. Extensive virulence factors and increased resistance of virulence pathogen make a “new face” of *S. aureus* like MRSA. This condition has a bad impact on decreasing *S. aureus* infection. Another etiology is *Streptococci*, a flora normal and common pathogen beyond the neonatal period through the age of four. However, now become rare because of the vaccination and replaced by *K. kingae* [22].

Antibiotics choice has also become a topic until right now. In osteomyelitis cases, the antibiotics need an excellent penetration into bone and joint tissue to eradicate the microorganism. A literature studied more than 30 antibiotics, and the results almost all antibiotics have good penetration in bone and joint. Of note, studies on joint space penetration were fewer than studies on bone tissue penetration. However, flucloxacillin had poor profiles in terms of joint space penetration [23]. All studies still believe antibiotics are a mainstay treatment for osteomyelitis and culture directed antibiotics for specific etiology. Most of the studies choose beta-lactam and fluoroquinolone for antibiotics treatment. Beta-lactam agents are the drugs of choice for treating Osteomyelitis in Neonatal and children due to *K. kingae*, *Group A Streptococcus*, or *Streptococcus pneumonia* [24].

Conclusion

Antibiotics still mainstay treatment with surgery for osteomyelitis treatment. In acute, children, and long bone only cases, they need shorter treatment than chronic, adult, and non-long bone osteomyelitis. Most of the etiology of osteomyelitis is *S. aureus*

and cephalosporin as beta-lactam antibiotics, and fluoroquinolone is still the drug of choice in culture directed antibiotics treatment for osteomyelitis.

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