Empirical Antibiotic Treatment of Disabled Veterans with Chronic Osteomyelitis

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Abstract

Aims: Osteomyelitis is a bone infection caused by pyogenic bacteria, Mycobacterium tuberculosis, or fungi. This study aims at determining the best empirical antibiotic treatment of chronic osteomyelitis caused by Staphylococcus aureus infections.

Methods: This cross-sectional study was conducted in the years 2007-2012 on 164 disabled imposed war veterans with confirmed diagnosis of osteomyelitis. The E-Test method was used to detect antibiotic sensitivity and resistance in patients with Staphylococcus aureus in their culture.

Results: The results of this research were classified into 3 categories: susceptible, resistant and moderately susceptible. The most effective antibiotic on S. aureus was Vancomycin that was resisted in none of the cultures. In 3.6% of the cultures, S. aureus showed moderate sensitivity to vancomycin. Teicoplanin came second with 5.9% resistance. The most ineffective antibiotic was Cotrimoxazole to which 73.2% of cultures were resistant. In 54.8% of cultures, Staphylococcus was reported as resistant to Methicillin. 0.7% of the Staphylococcus aureus bacteria resistant to methicillin were sensitive to cotrimoxazole.

Conclusion: Since the results of the culture and antibiogram may take 24 hours to 15 days to be obtained, it is recommended that the specimens prepared in smear should be taken from wounds with gram-positive cocci. Vancomycin or Ticoplanin can be used before culture results are obtained. Factors such as the medication cost, availability of the medicine, patients discharge time and the drugs side effects should be taken into consideration when choosing between these two antibiotics.

Keywords: Chronic Osteomyelitis, Staphylococcus Aureus, Resistance, War Handicaps, Empirical Antibiotic

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Introduction
Osteomyelitis is a bone infection that is caused by pyogenic bacteria, Mycobacterium tuberculosis, or fungi, and which affects both trabecular and cortical bones, and sometimes the bone marrow and its surrounding soft tissue [2]. This disease occurs in two forms: acute and chronic [1, 3]. The acute type is mainly observed in children and is cause by a second contiguous source of infection, by the direct spread of an infection from a surgery, by trauma or by a foreign body [4]. More than 95% of the instances of acute hematogenous osteomyelitis are caused by a type of bacteria which, in about 50% of the cases, turn out to be Staphylococcus aureus. A polymicrobial type is more common in chronic osteomyelitis than in acute one. In addition to Staphylococcus aureus, gram-negative and anaerobic bacteria and, in some cases, mycobacteria and fungi could be found in the chronic type. Nevertheless, Staphylococcus aureus is the most common microorganism in the chronic instances. Identifying the microorganism most responsible for osteomyelitis and finding the best antibiotic to treat it, are still a great challenges for the physicians [5]. The significance of antimicrobial treatment is evident although an efficient antibiotic regimen has not been clearly identified yet. Delayed, inefficient or insufficient antimicrobial treatment may lead to severe problems, including chronic pain, a need for amputation, repeated surgeries, and finally an increased severity of the illness [6]. There are various factors involved in choosing the appropriate antibiotic, such as the type of infection, the microorganism responsible for the infection, sensitivity and resistance to antibiotics and reasons related to the host [7]. Exactly how the organisms get resistant to antibiotics has not been clearly explained yet. Tolerance is proved when bactericidal concentration is 32 (or more) times the average of the inhibitory concentration [8]. There are different and at times opposite ideas concerning the signs of tolerance; nonetheless, gradual recovery can be considered as a good sign. In preliminary empirical treatments, the proper antibiotic is chosen firstly according to the common pathogens. Thereafter, based on the agent identified in the culture as well as its antibiotic sensitivity profile, the preliminary medication can be changed. This study concentrates on the antibiotic sensitivity and resistance to staphylococcus aureus, which is a microorganism most commonly responsible for causing chronic osteomyelitis, in order to find a proper treatment for diseases induced by this pathogen.

Methods
This cross-sectional study was conducted on 164 war handicaps with confirmed diagnosis of chronic osteomyelitis. The patients selected for this study frequently visited Sasan Osteomyelitis Clinic or Baqiyatallah Hospital from 2007 to mid 2012. Diagnosis was carried out on the basis of a clinical pattern and radiographic evidence, and was confirmed by bone culture results or by histopathology. The clinical pattern included fever, bone pain, purulent discharge and decreased use of the affected limb [9]. The radiographic evidence included periosteal reaction, cortex destruction, medullary and soft tissue involvement, sequestration and an abnormally increased bone density. Most patients had suffered from the recurrent disease symptoms, had been treated for a long period of time with a great variety of antibiotics and had undergone several surgeries. Specimens from the patients wound and sinus cavities discharges were cultured. Then all of the patients underwent surgical debridement and curettage. In the process of the surgery, specimens were taken for culture from the bone tissues involved in
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the infection. In the present study, all cultures were kept for 8 weeks for bacterial infections and up to 12 weeks for fungal and acid-fast bacilli infections. We deployed the E-test method to detect resistance and sensitivity to antibiotics in the patients whose culture results confirmed the presence of Staphylococcus aureus. In order to determine the MIC (Minimum Inhibitory Concentration) using the E-test method, the antibiotics effective in fighting Staphylococcus aureus were applied, namely, Vancomycin, Clindamycin, Ciprofloxacin, Methicillin, Cotrimoxazole, and Teicoplanin. The results of using these antibiotics were categorized in three classes: susceptible, resistant, and moderately susceptible (with intermediate sensitivity). The data gained in this cross-sectional study were analyzed with the SPSS16 software. Appropriate tables and histograms were used to present the data. Comparative analysis was performed with Chi Square Tests.

Results
This study was conducted upon 164 patients suffering from chronic osteomyelitis who had undergone surgeries. The patients were all male and their average age was (X±SD) 6.03±44.71. The culture of the specimens from the bones revealed the following results: 35.8%: Staphylococcus aureus (52 cases), 27%: Ecoli, 15.5%: Enterococcus, 13.7%: Pseudomonas aeruginosa, 8.3%: Klebsiella, 6.2%: Acinetobacter, and 4.1%: Streptococcus. 65.9% of the patients had monobacterial infection and various pathogens were found in in the bones of 34.1% of the subjects (Table 1).

Table 1) Frequency of Microorganisms Isolated from Cultured Bone

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Prevalence(percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>35.8</td>
</tr>
<tr>
<td>E coli</td>
<td>27</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>15.5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>13.7</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>8.3</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>6.2</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>4.1</td>
</tr>
<tr>
<td>Other organisms</td>
<td>5.5</td>
</tr>
</tbody>
</table>

As mentioned earlier, the effect of Vancomycin, Clindamycin, Ciprofloxacin, Methicillin, Cotrimoxazole, and Teicoplanin on Staphylococcus aureus isolated from cultures was examined in this study. Vancomycin was the most effective antibiotic on Staphylococcus aureus to which none of the cultures were resistant and only 3.6% of the cultures moderately resistance. Teicoplanin came second by facing only 5.9% resistance. The least effective antibiotic on Staphylococcus aureus was Cotrimoxazole with 73.2% resistance. The complete results of the experiments have been provided below (see Table 2).

Table 2) The Susceptibility of Microorganisms of Staphylococcus Aureus Isolated from Cultured Bone

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Vancomycin</th>
<th>clindamycin</th>
<th>Teicoplanin</th>
<th>Methicillin</th>
<th>Cotrimoxazole</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensetive</strong></td>
<td>96.4%</td>
<td>58.3%</td>
<td>94.1%</td>
<td>45.2%</td>
<td>26.8%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>middle</strong></td>
<td>3.6%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>resistant</strong></td>
<td>0%</td>
<td>41.7%</td>
<td>5.9%</td>
<td>54.8%</td>
<td>73.2%</td>
<td>38.2%</td>
</tr>
</tbody>
</table>

Discussion

One of the problems that orthopedists and infectious diseases specialists face is the question of the proper preliminary antibiotic treatment for Osteomyelitis. This is especially important when physicians are waiting for the results of the cultures which could show the susceptibility or resistance of the pathogen(s) to antibiotics. That is why we should know the organisms most commonly responsible for the disease and the antibiotics which could effectively fight it, as well as the advantages and disadvantages of each antibiotic, in order to identify the best treatment. According to the comparison made between the past and the present studies of the author, and despite the fact that in the long term the abundance of the microorganisms and their resistance vary, it is still creditable to say that Staphylococcus is the most common cause and Vancomycin the most effective antibiotic to be utilized against it [10]. It is recommended that the current information concerning the degree of the susceptibility of the antibiotics should be updated in the course of time because microorganisms dynamically react to antibiotics and may gradually become resistant to them. Conversely, a microorganism that has been resistant may become sensitive for different reasons. Thus, there is a need for new studies at different times to find the best antibiotic against the microorganisms. One of the techniques used in treating the patients with osteomyelitis is the use of the antibiotic-loaded cement. The choice of the antibiotic base in the cement must be based on the precise measurement of the compatibility of the antibiotic and the degree of microorganisms’ susceptibility and resistance to it. If we choose an antibiotic which proves to be resisted by the strains found in the culture, not only will the antibiotic be ineffective in the treatment of the patient but in fact the content of the cement, as a foreign body, will worsen the patient condition. It might even impose an additional or early surgery for removing the cement from the patient body.

![Figure 1](https://example.com/figure1.png)

The goal of this study therefore is to take such conditions into consideration and to propose better approaches to this issue. Since our specimens were from patients who suffered from severe chronic osteomyelitis and who had been treated by antibiotics or had undergone repeated surgeries, resistance to antibiotics might be greater than in simpler and uncomplicated cases. The type of infection, hospital-acquired resistance, general resistance patterns, the PH of the target tissue, the presence of purulent discharge, and decreased blood flow are all important factors in the choice of the antibiotics selected. These factors can affect the choice of the antibiotics and their activity within the target tissue. One of the other important microbial factors is the production of
enzymes that make the organisms resistant to the antibiotics, such as penicillinase [10]. We propose to use the most effective and appropriate antibiotic for empirical treatments while waiting for the culture results in terms of resistance and susceptibility. In choosing this empirical treatment, the previous data concerning the resistance or susceptibility can be helpful. In choosing the right antibiotic, a low degree of resistance to the antibiotic is more significant than a higher degree of susceptibility. In our study, Vancomycin was very effective on Staphylococcus aureus. Lack of resistance to Vancomycin in Staphylococcus aureus showed a slight prevalence of VRSA in our specimens.

Clindamycin is known as a suitable antibiotic for its effect on anaerobic bacteria, especially Bacteroides fragilis. Clindamycin penetrates well into most tissues including bones and abscesses. Some specialists believe that Clindamycin is the effective antibiotic on Staphylococcus aureus, on Staphylococcus Epidermidis, and on Streptococcus species. However, our study showed that 41.7% of Staphylococcus aureus strains were resistant to Clindamycin, which eventually indicates that it cannot be a good choice for fighting Staphylococcus aureus strains which cause chronic osteomyelitis. Oxacillin, Methicillin, and other penicillinase-resistant penicillins are resistant to beta lactamase and can be good in the instances of Staphylococcus aureus susceptible to Methicillin[7]. In our study, about 55% of Staphylococcus aureus strains were resistant to Methicillin, which signifies the widespread prevalence of the MRSA in the cases of chronic osteomyelitis. Teicoplanin is a glycopeptide antibiotic similar to Vancomycin, but with different characteristics which make it distinct from and clinically more suitable than the latter. Teicoplanin is effective upon some of the species of Staphylococcus and especially on the species which have become resistant to Methicillin. One of the advantages of Teicoplanin is its long half-life (60 hours) which makes it effective in qd administrations (once daily doses). Moreover, the intramuscular injections of Teicoplanin after some earlier intravenous doses makes it suitable to outpatients[7].

Cotrimoxazole, an antimetabolite antibiotic, is a compound of Trimetoprim and Sulfamethoxazole (with the ratio of 1 to 5) which is used in the treatment of many types of bacterial infections, especially the Gram-negative and some of the Gram-positive bacteria[7]. In our results, many of the cultures were resistant to Cotrimoxazole but 10.7% of the MRSA were sufficiently susceptible to it. Therefore, despite the fact that it is considered as practically ineffective in the treatment of many instances of chronic osteomyelitis, in the ones whose susceptibility can be proved by MIC, especially when mixed by Rifampin, after the patient is discharged from the hospital, it can be used as a reliable outpatient antibiotic compound for Staphylococcus aureus and Staph epidermidis [11, 12].

Siprofloxacin is the second generation of Fluoroquinolone used against Gram-negative organisms. Although this antibiotic is effective on some of the Gram-positive organisms such as Staphylococcus aureus, it is suggested that its use as a sole treatment should be limited due to the high possibility of its resistance before or during the treatment. As our study also shows, a high percentage of the Staphylococcus aureus bacteria are resistant to Siprofloxacin.

Conclusion
According to the results of our study, Vancomycin and, at a lower degree, Teicoplanin can still be good choices for the empirical treatment of Osteomyelitis caused by Staphylococcus aureus. Therefore, when we see Gram-positive organisms in the smears taken from the wounds cocci, we can...
use one of these two antibiotics until the culture results show the organisms susceptibility or resistance to antibiotics. Meanwhile, if an antibiotic cement is going to be used, we suggest Vancomycin as the cement base to fight possible strains of Staphylococcus aureus in the culture. In our research, we realized that Vancomycin was a little more effective than Teicoplanin. However, in order to choose between the two, some factors such as cost, medicine availability, the patient discharge time, and the drug side-effect should also be taken into consideration. After the patient is released from hospital, in cases of MRSA, and in order to complete the patient treatment, we can prescribe Teicoplanin for intramuscular injection once in a day. And if the culture results reveal susceptibility to Cotrimoxazole, this medicine may be taken orally.

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References
5- Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Mr J Ciampolini, Princess Elizabeth Orthopaedic Centre, Exeter, Devon EX2 5DW, UK; Postgrad Med J. 2000;76:479-483. doi:10.1136/pmj.76.898.479.
12- Vancomycin in Combination with Other Antibiotics for the Treatment of Serious Methicillin-Resistant Staphylococcus aureus Infections.