Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials?

Luca Lazzarini\textsuperscript{a,}*, Benjamin A. Lipsky\textsuperscript{b}, Jon T. Mader\textsuperscript{c,}*

\textsuperscript{a} Department of Infectious Diseases and Tropical Medicine, S. Bortolo Hospital, 36100 Vicenza, Italy
\textsuperscript{b} Medical Service, and Antibiotic Research Clinic, VA Puget Sound Health Care System and Department of Medicine University of Washington, Seattle, WA, USA
\textsuperscript{c} Department of Orthopaedics and Rehabilitation, Department of Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA

Received 12 January 2004; received in revised form 1 July 2004; accepted 29 September 2004

Corresponding Editor: Marguerite Neill, Pawtucket, USA

KEYWORDS
Osteomyelitis;
Infection;
Bone;
Antibiotic;
Therapy;
Treatment

Summary

Objectives and design: To determine the most appropriate approach to antibiotic therapy for osteomyelitis, the medical literature for articles published from 1968 to 2000 was reviewed.

Results: Ninety-three clinical trials in children and adults were identified using almost every antibiotic class. Most studies were non-comparative and the comparative trials involved relatively few patients. Publications generally did not provide clinically important information regarding infection staging or classification, surgical treatment provided, or the presence of orthopedic hardware. The median duration of follow-up after treatment was only 12 months.

The clinical outcome was better for acute than chronic osteomyelitis in eight of the 12 studies allowing comparison. In the comparative trials, few statistically significant differences were observed between the tested treatments. In one small trial, the combination of nafcillin plus rifampin was more effective than nafcillin alone. In pediatric osteomyelitis, oral therapy with cloxacillin was more effective than tetracycline in one study, and oral clindamycin was as effective as parenteral anti-staphylococcal penicillins in another. In several investigations oral fluoroquinolones were as effective as standard parenteral treatments.

Conclusions: Although the optimal duration of antibiotic therapy remains undefined, most investigators treated patients for about six weeks. Despite three decades of research, the available literature on the treatment of osteomyelitis is inadequate to determine the best agent(s), route, or duration of antibiotic therapy.

\textcopyright{} 2005 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
Introduction

The introduction of antibiotics for treating bacterial infections revolutionized the natural history of many of these common and deadly diseases. In the first decades of the antibiotic era, the remarkable clinical successes with antibiotics led to an atmosphere of optimism. Based upon these early successes, Florey and Florey believed that osteomyelitis, if treated with antibiotics early, would no longer be a surgical condition. With a mounting record of clinical failures, however, this optimism vanished within a few years. By 1968, Bick’s book reviewing 25 years of experience with antibiotic treatment led him to conclude that it was invaluable for eliminating osteomyelitis-related septicemia and abscesses, but that chronic bone infection could only be cured with surgery.

Today, most authorities still believe that chronic osteomyelitis generally requires both antibiotic and surgical treatment. But, despite continued research, most aspects of antibiotic treatment for osteomyelitis are still poorly understood. Data are sparse about which are the most effective antimicrobial agents, for how long, and by what routes they should be administered for various types of osteomyelitis. Animal models have been useful in studying this complex disease, but they cannot replicate many aspects of human bone infection. Thus, the treatment of osteomyelitis is still mostly based on expert opinions, and no consensus guidelines are currently available. Many human trials on treating osteomyelitis in the last 30 years have been published, but only the randomized ones have been systematically reviewed. To supplement the data from randomized trials with those of non-controlled trials, the most relevant studies of antibiotic therapy of human osteomyelitis published between 1968 and 2000 are reviewed here.

Materials and methods

All clinical studies investigating antibiotic treatment of osteomyelitis were searched by means of the MEDLINE search engine (National Library of Medicine, Washington, DC, USA), applying no language limitation. The terms ‘antibiotic’, ‘antimicrobial’, ‘therapy’, ‘treatment’, ‘bone’, and ‘osteomyelitis’ were used as keywords in various combinations. Studies were found that enrolled both pediatric and adult cases of osteomyelitis, recognizing that the former are more often hematogenous and the latter more often contiguous infections. While there are other commonly used methods of treating osteomyelitis, e.g., local administration of antibiotics by beads, this review was aimed exclusively at systemic antibiotic therapy.

After reading the abstracts of all retrieved articles, 120 papers published between January 1968 and January 2001 were identified as possibly being clinical trials. Trials were selected for analysis only when they met all of the following criteria: (1) more than six cases of osteomyelitis were treated; (2) data about the clinical outcome of the infections were available; and, (3) a single drug or class of drugs was used, or, in the case of comparative studies, in at least one arm of the study. Studies about ‘bone and joint infections’, or infections other than osteomyelitis (such as endocarditis, meningitis) were included only if separate data about the outcome of bone infection were provided. Patients identified as having prosthetic joint infections or infected orthopedic hardware or implants were not included because these infections generally require surgical interventions and do not respond to antibiotic therapy alone. The criterion for requiring at least six treated cases was arbitrarily selected by the authors to avoid considering small anecdotal studies and because one potentially relevant comparative trial included only six patients per arm. Of the 123 papers initially identified, it was not possible to obtain three of them despite requests to an inter-library loan service, five were discarded because they were review articles rather than clinical trials, five because they pooled the outcome of different musculoskeletal infections, five because they enrolled less than six cases of osteomyelitis, four because of incomplete outcome data, and seven because they utilized many different antibiotics and pooled the outcome of all the patients.

For each study the following were recorded: the study design, criteria for diagnosis of osteomyelitis (clinical, microbiological, radiological, histological), name(s) of the antibiotic(s) used, mean age and sex of the patients, number of pediatric patients, number of cases treated, number of cases of long bone osteomyelitis, use of a classification system, presence of orthopedic hardware and whether or not it was removed, bone culture isolates, duration of antibiotic treatment, occurrence of side effects requiring treatment discontinuation, antibiotic levels in serum and bone, number of patients undergoing surgery, treatment outcome, explanation for failure given by the authors, and duration of follow-up after treatment.

Data were analyzed by means of statistical software (Epi Info 2000, Centers for Disease Control and Prevention, Atlanta, GA, USA). Because different definitions of outcome were used in the studies reviewed, the authors devised their own. For each
study outcomes were defined as follows: ‘cure’ was the absence of clinical evidence of osteomyelitis after the follow-up period; ‘failure’ was any outcome not fulfilling the criteria for ‘cure’. Discontinuation of treatment due to side effects of the study drug was considered separately.

Results

Study features and overall population enrolled

This review uncovered 93 studies that fulfilled the selection criteria, with a total of 2476 cases of osteomyelitis. Among these, 17 studies (18%) were comparative, ten of which were randomized; the other 76 were non-comparative. In the studies providing this information, 1090 patients (44%) were male, and the mean age was 42 years (range 5–66 years, ±12.2 [SD]). The mean number of patients enrolled per study was 26 (range 6–169, ±24.5 [SD]); 483 of the cases were pediatric osteomyelitis and 603 were long bone osteomyelitis.

The authors diagnosed osteomyelitis by various combinations of clinical, radiological and microbiological findings in 29 studies. The generally accepted standard criterion for diagnosis, a bone biopsy for microbiology, was mandatory in only 24 studies, four of which also required a histological diagnosis. Four studies required clinical, microbiological, and radiological criteria, whereas in seven studies either compatible clinical and microbiological criteria, or microbiological and radiological criteria, were sufficient. Five other studies required just clinical and radiological criteria, not microbiological confirmation. No criteria for diagnosis were specified in 24 studies.

A classification of the type of osteomyelitis was provided in 45 (48%) of the studies; ‘acute or chronic’ was used in 44, the Cierny–Mader classification was used in one, and a radiological classification was used in one. Information about hardware implantation was available in 12 studies (89 patients) and information about hardware removal was provided in 11 studies (17 patients). Data about the duration of the antibiotic treatment were available in 88 studies; in these, the mean duration of treatment was 51 days and the median duration of treatment was 40 days (range 6–180 days, ±42.29 [SD]). Serum and bone antibiotic levels were measured in 32 and 11 studies, respectively. Information about surgical treatment for osteomyelitis was available in 27 studies, involving 455 patients. Dura-

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Drug(s)</th>
<th>Duration of treatment in weeks</th>
<th>Duration of follow-up in months</th>
<th>Number of cured patients/total</th>
<th>Severe adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norden*5</td>
<td>Nafcillin iv vs nafcillin iv + rifampin po</td>
<td>6</td>
<td>6</td>
<td>7/8</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/6</td>
<td></td>
</tr>
<tr>
<td>Norden*6</td>
<td>Nafcillin iv vs nafcillin iv + rifampin po</td>
<td>6</td>
<td>24</td>
<td>2/8</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/10</td>
<td></td>
</tr>
<tr>
<td>Leder7</td>
<td>Flucloxacillin, continuous iv infusion</td>
<td>6</td>
<td>15</td>
<td>9/11</td>
<td>No</td>
</tr>
<tr>
<td>Bell8</td>
<td>Cloxacillin po vs dicloxacillin po</td>
<td>24</td>
<td>7–30</td>
<td>18/19</td>
<td>1 allergic reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 hepatotoxicity</td>
</tr>
<tr>
<td>Hodgkin9</td>
<td>Cloxacillin po vs dicloxacillin po</td>
<td>24</td>
<td>17</td>
<td>9/14</td>
<td>No</td>
</tr>
<tr>
<td>Bryson10</td>
<td>Dicloxacillin po</td>
<td>6</td>
<td>60</td>
<td>18/18</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cole11</td>
<td>Cloxacillin po vs tetracycline po</td>
<td>6</td>
<td>24</td>
<td>53/64 (83%)</td>
<td>No</td>
</tr>
<tr>
<td>Hubbard*12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14/27</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hedstrom*13</td>
<td>Cloxacillin po vs dicloxacillin po</td>
<td>24</td>
<td>NA</td>
<td>4/6</td>
<td>1 with dicloxacillin</td>
</tr>
</tbody>
</table>

* Comparative trial; GPC: Gram-positive cocci; GNR: Gram-negative rods; ad: adult; ch: children; c: chronic osteomyelitis; a: acute osteomyelitis; iv: intravenous; im: intramuscular; po: oral; Unless otherwise specified, the studies involved adult osteomyelitis.
tion of follow-up was explicit in 73 studies, the mean being 16.6 months (range 1–67 months, median 12).

In 12 studies, the outcome of acute and chronic cases of osteomyelitis was detailed separately. In eight (67%) of these studies patients with acute osteomyelitis achieved a higher cure rate than patients with chronic osteomyelitis, in three studies outcome was better in patients with chronic osteomyelitis, and in one study the outcome was similar in each type. These differences were not statistically significant in any single study.

Studies by type of antibiotic therapy

Three studies were found that used intravenous antistaphylococcal penicillins and six studies with oral antistaphylococcal penicillins (Table 1). Seven trials investigated a beta-lactam/beta-lactamase inhibitor, aztreonam was used in six trials, moxalactam and imipenem/cilastatin in one study each (Table 2). There were 30 trials investigating cephalosporins, ranging from first generation agents in the late 1970s to fourth generation agents in the 1990s (Table 3). Among glycopeptides, teicoplanin was used in seven studies and vancomycin was administered by continuous infusion in one study (Table 4). Fluoroquinolones were used in 16 non-comparative and six comparative trials (Table 5). Finally, the results of trials of miscellaneous antibiotics are reported in Table 6. The pertinent details of all trials are shown in the tables.

Discussion

Osteomyelitis is a relatively common infection, but a surprisingly small number of comparative trials about its treatment have been published. Moreover, most of the studies involve relatively few patients and are not randomized. The aim of these trials was...
generally to determine if a ‘new’ drug was at least equivalent to an established treatment, in order to justify using it for treating bone infections. Most of the trials failed to detect statistically significant differences between the two groups, thus providing little understanding about the relative effectiveness of various regimens for treating osteomyelitis. Another limitation of the available literature is that trials involving ‘bone and joint infections’ include a heterogeneous spectrum of diseases, with different

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Drug(s)</th>
<th>Commonest microorganism(s)</th>
<th>Duration of treatment in weeks</th>
<th>Duration of follow-up in months</th>
<th>Number of cured patients/total (%)</th>
<th>Severe adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arango46</td>
<td>Cefazolin im(a) or cephaolin im (c)</td>
<td>S. aureus</td>
<td>4–7 a</td>
<td>6</td>
<td>8/20 a (40)</td>
<td>7/10 c</td>
</tr>
<tr>
<td>Fass47</td>
<td>Cefazolin iv</td>
<td>S. aureus</td>
<td>4</td>
<td>13</td>
<td>12/13</td>
<td></td>
</tr>
<tr>
<td>Liu48</td>
<td>Cefoxitin iv</td>
<td>GPC and GNR</td>
<td>2</td>
<td>NA</td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>Schurman49</td>
<td>Cefoxitin iv</td>
<td>GPC and GNR</td>
<td>2</td>
<td>6</td>
<td>6/9</td>
<td></td>
</tr>
<tr>
<td>Levine50</td>
<td>Cefamandole iv</td>
<td>S. aureus</td>
<td>3</td>
<td>NA</td>
<td>14/16</td>
<td></td>
</tr>
<tr>
<td>Bernstein51</td>
<td>Cefamandole iv</td>
<td>S. aureus</td>
<td>4</td>
<td>5–23</td>
<td>5/5 a</td>
<td>5/9 c</td>
</tr>
<tr>
<td>Levine52</td>
<td>Cefamandole iv</td>
<td>S. aureus</td>
<td>4</td>
<td>NA</td>
<td>20/25 a (80)</td>
<td>NA separately for osteomyelitis</td>
</tr>
<tr>
<td>LeFrock53</td>
<td>Cefamandole iv</td>
<td>S. aureus</td>
<td>4</td>
<td>NA</td>
<td>12/12</td>
<td></td>
</tr>
<tr>
<td>Nelson54</td>
<td>Cefamandole iv and cefaclor (sequentially)</td>
<td>S. aureus</td>
<td>3</td>
<td>NA</td>
<td>22/23 (96)</td>
<td>0</td>
</tr>
<tr>
<td>Temple55</td>
<td>Cefoperazone iv</td>
<td>NA</td>
<td>4</td>
<td>NA</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Biehl56</td>
<td>Cefoperazone iv</td>
<td>S. aureus</td>
<td>1</td>
<td>NA</td>
<td>18/24 (75)</td>
<td></td>
</tr>
<tr>
<td>LeFrock57</td>
<td>Cefotaxime iv</td>
<td>GPC</td>
<td>3</td>
<td>NA</td>
<td>6/7 a</td>
<td>25/32 c (78)</td>
</tr>
<tr>
<td>Mader58</td>
<td>Cefotaxime iv</td>
<td>S. aureus</td>
<td>4</td>
<td>12</td>
<td>23/25 a (92)</td>
<td>24/27 c (89)</td>
</tr>
<tr>
<td>Mader59</td>
<td>Cefotaxime iv</td>
<td>S. aureus</td>
<td>6</td>
<td>6 a</td>
<td>21/22 a (96)</td>
<td>38/46 c (83) 2 neutropenia at end of treatment</td>
</tr>
<tr>
<td>LeFrock60</td>
<td>Cefotaxime iv</td>
<td>GPC</td>
<td>4</td>
<td>12–24</td>
<td>12/12 a</td>
<td>17/20 c (85)</td>
</tr>
<tr>
<td>Jacobs61</td>
<td>Cefotaxime iv</td>
<td>GPC</td>
<td>2</td>
<td>NA</td>
<td>23/24 (96)</td>
<td></td>
</tr>
<tr>
<td>Mader62</td>
<td>Ceftizoxime iv</td>
<td>GPC and GNR</td>
<td>6</td>
<td>1–12</td>
<td>13/14</td>
<td>4</td>
</tr>
<tr>
<td>Gomis53</td>
<td>Cefotaxime iv</td>
<td>E. coli</td>
<td>4</td>
<td>6</td>
<td>40/50 (80)</td>
<td></td>
</tr>
<tr>
<td>Dutoy64</td>
<td>Ceftazidime iv</td>
<td>P. aeruginosa</td>
<td>4</td>
<td>6</td>
<td>7/7 a</td>
<td>11/14 c</td>
</tr>
<tr>
<td>Eron65</td>
<td>Ceftazidime iv</td>
<td>P. aeruginosa</td>
<td>6</td>
<td>NA</td>
<td>4/8</td>
<td>1 leukopenia</td>
</tr>
<tr>
<td>Bach66</td>
<td>Ceftazidime iv</td>
<td>P. aeruginosa</td>
<td>4</td>
<td>6 a</td>
<td>9/11 a</td>
<td>7/15 c</td>
</tr>
<tr>
<td>De Bastiani67</td>
<td>Ceftazidime iv</td>
<td>GPC and GNR</td>
<td>4</td>
<td>12–48</td>
<td>9/10</td>
<td></td>
</tr>
<tr>
<td>Giammarell26</td>
<td>Ceftiraxone iv</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>3/7</td>
<td></td>
</tr>
<tr>
<td>Yogev69</td>
<td>Ceftiraxone iv</td>
<td>GPC and GNR</td>
<td>4</td>
<td>2</td>
<td>6/6</td>
<td></td>
</tr>
<tr>
<td>Pottage70</td>
<td>Cefosolon iv</td>
<td>P. aeruginosa</td>
<td>4</td>
<td>12</td>
<td>3/8</td>
<td>3</td>
</tr>
<tr>
<td>Routman71</td>
<td>Cefosolon iv</td>
<td>P. aeruginosa</td>
<td>24</td>
<td>12</td>
<td>12/16</td>
<td></td>
</tr>
<tr>
<td>Lucht72</td>
<td>Cefosolon iv</td>
<td>P. aeruginosa</td>
<td>24</td>
<td>36</td>
<td>11/15</td>
<td></td>
</tr>
<tr>
<td>Sheftel73</td>
<td>Cefmenoxime iv</td>
<td>GPC</td>
<td>6</td>
<td>12</td>
<td>6/15</td>
<td></td>
</tr>
<tr>
<td>Jauregui74</td>
<td>Cefepime iv</td>
<td>S. aureus, GPC, and GNR</td>
<td>4</td>
<td>12</td>
<td>19/23 (83)</td>
<td></td>
</tr>
<tr>
<td>Kunkel75</td>
<td>Cefonicid iv or im</td>
<td>S. aureus</td>
<td>6</td>
<td>3–13</td>
<td>12/12</td>
<td></td>
</tr>
</tbody>
</table>

*: Comparative trial; GPC: Gram-positive cocci; GNR: Gram-negative rods; ad: adult; ch: children; c: chronic osteomyelitis; a: acute osteomyelitis; iv: intravenous; im: intramuscular; po: oral; Unless otherwise specified, the studies involved adult osteomyelitis.
prognoses. For example, the cure rate with antibiotics alone of pediatric hematogenous osteomyelitis is much higher than that of a prosthetic joint infection. Thus, in this review only studies that provided separate outcomes for patients with osteomyelitis are included. Moreover, to avoid anecdotal information, trials involving fewer than six patients were excluded. Finally, it has been noted that studies reporting poor outcomes may be less likely to be published, introducing the possibility of publication bias. While an exhaustive literature search was not performed, it is believed that these methods are likely to have revealed the best quality published papers. The similarity of the reported cure rates for the various studies suggests that the results are likely to be accurate and generalizable.

Another problem for studies on osteomyelitis is that of defining the outcome. Virtually every study offered a different definition, using terms such as ‘cure’, ‘improvement’, ‘eradication’, ‘failure’, and ‘recurrence’, each having a different meaning. Using the Infectious Disease Society of America (IDSA) guidelines on the requirements of human trials on osteomyelitis,99 a common definition was adopted that reflects what can be expected from a course of treatment with antibiotics: a favorable outcome means that the patient is clinically free of disease at the end of the follow-up period. Furthermore, clinical trials should have at least a one-year follow-up period. Unfortunately, many studies did not have this minimum follow-up. Moreover, the duration of follow-up varied markedly, making it difficult to compare data from different studies on the same antibiotic.

Another problem is the disease classification schemes used in the studies. About half of the reviewed studies did not use any osteomyelitis classification system. In the others, the most commonly used classification was simply ‘acute’ versus ‘chronic’. Unfortunately, most authors did not provide definitions of acute and chronic osteomyelitis and when given, the threshold between acute and chronic ranged from 20 days to six months. The hallmark of chronic osteomyelitis is the presence of necrosis on bone histology. Since this finding may be present early on during the natural history of the disease, classification into acute versus chronic by duration of disease is inaccurate.100 Although several classifications of osteomyelitis have been advocated,100 none is universally accepted.

### Table 4 Major findings of the studies using glycopeptides for treating staphylococcal osteomyelitis.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Drug(s)</th>
<th>Duration of treatment (weeks)</th>
<th>Duration of follow-up (months)</th>
<th>Number of cured patients/total (%)</th>
<th>Severe adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard33</td>
<td>Vancomycin, iv continuous infusion</td>
<td>24</td>
<td>14</td>
<td>10/15</td>
<td>no</td>
</tr>
<tr>
<td>de Lalla34</td>
<td>Teicoplanin iv</td>
<td>NA</td>
<td>3</td>
<td>6/8</td>
<td>no</td>
</tr>
<tr>
<td>Marone35</td>
<td>Teicoplanin iv</td>
<td>NA</td>
<td>12</td>
<td>2/7</td>
<td>no</td>
</tr>
<tr>
<td>Greenberg36</td>
<td>Teicoplanin iv</td>
<td>6</td>
<td>12</td>
<td>10/14</td>
<td>no</td>
</tr>
<tr>
<td>Weinberg37</td>
<td>Teicoplanin iv</td>
<td>6</td>
<td>6</td>
<td>3/14 a</td>
<td>no</td>
</tr>
<tr>
<td>Graninger38</td>
<td>Teicoplanin iv, three times weekly</td>
<td>8</td>
<td>12</td>
<td>8/20 c (40)</td>
<td>no</td>
</tr>
<tr>
<td>LeFrock39</td>
<td>Teicoplanin iv</td>
<td>6</td>
<td>6</td>
<td>76/80 a (95)</td>
<td>24 patients</td>
</tr>
<tr>
<td>Testore40</td>
<td>Teicoplanin im</td>
<td>24</td>
<td>12</td>
<td>72/76 (95)</td>
<td>no</td>
</tr>
</tbody>
</table>

*: Comparative trial; GPC: Gram-positive cocci; GNR: Gram-negative rods; ad: adult; ch: children; c: chronic osteomyelitis; a: acute osteomyelitis; iv: intravenous; im: intramuscular; po: oral; Unless otherwise specified, the studies involved adult osteomyelitis.
Some studies were restricted to specific causative organisms, based on the spectrum of the study drug. Most of infections were monomicrobial, but cases of polymicrobial osteomyelitis occurred, especially associated with a diabetic foot infection. Since it is not known if cases of osteomyelitis due to different microbial species have different outcomes, it would probably be more accurate to restrict antibiotic trials to a single microbial species or category. Very few studies specified the antimicrobial susceptibility patterns of the isolated organisms, e.g., the prevalence of methicillin-resistant \textit{Staphylococcus aureus} or Gram-negative organisms with extended spectrum beta-lactamases.

Information about surgical treatment for osteomyelitis, and the presence of surgically implanted bone hardware (and whether or not it was removed) was not provided in most studies. These factors greatly influence the outcome of treatment. Most authorities believe that an incompletely debrided bone infection is prone to treatment failure, no

\begin{table}
\caption{Major findings of the studies using fluoroquinolones for treating osteomyelitis.} 
\centering 
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Author (ref) & Drug & Commonest microorganism(s) & Duration of treatment & Duration of follow-up & Number of cured patients/total (%) & Severe side effects \\
\hline
\textbf{Non-comparative Trials:} & & & & & & \\
Ramirez\textsuperscript{76} & Ciprofloxacin po & GPC and GNR & 6 & NA & 5/8 & 0 \\
Scully\textsuperscript{77} & Ciprofloxacin po & \textit{P. aeruginosa} & 6 & NA & 4/6 & 0 \\
Slama\textsuperscript{78} & Ciprofloxacin po & GNR & 11 & NA & 22/30 (73) & 0 \\
Gilbert\textsuperscript{79} & Ciprofloxacin po & GNR & 6–14 & 7–21 & 13/20 (65) & 0 \\
Trexler Hessen\textsuperscript{80} & Ciprofloxacin po & \textit{P. aeruginosa} & 9 & 10 & 22/24 (92) & 2 \\
Gudiel\textsuperscript{81} & Ciprofloxacin po & NA & 8 & 11 & 15/20 (75) & 0 \\
Lopez\textsuperscript{82} & Ciprofloxacin po & NA & NA & NA & 1/8 & \\
Yamaguti\textsuperscript{83} & Ciprofloxacin po & GPC and GNR & 23 & 12 & 13/17 (76) & \\
Dan\textsuperscript{84} & Ciprofloxacin po & \textit{P. aeruginosa} & 12 & 27 & 19/22 (86) & \\
Mac Gregor\textsuperscript{85} & Ciprofloxacin po & NA & 20 & 18 & 11/18 (61) & 1 \\
Ketterl\textsuperscript{86} & Ofloxacin po & \textit{S. aureus} & 3 & 6 & 113/115 (98) & \\
Kannelakopoulou\textsuperscript{87} & Ofloxacin po & GNR & 24 & 6 & 15/20 (75) & \\
Eron\textsuperscript{88} & Ofloxacin po & GPC and GNR & 24 & 12 & 6/6 & \\
Liu\textsuperscript{89} & Ofloxacin po & NA & 4 & 3 & 4/7 & \\
Dellamonica\textsuperscript{90} & Oral fluoroquinolones & \textit{S. aureus} & 24 & 36 & 29/39 (74) & \\
Greenberg\textsuperscript{91} & Oral fluoroquinolones & \textit{S. aureus} & 8 & 12 & 16/27 (59) & 3 \\
\textbf{Comparative Trials} & & & & & & \\
Giamarello\textsuperscript{92} & Pefloxacin iv or po vs ceftazidime iv & NA & 25 & 6 & 12 & 7/8 \\
Gentry\textsuperscript{93} & Ofloxacin po vs cefazolin & Polymicrobial & 8 & 18 & 14/19 & no \\
Gomis\textsuperscript{94} & Ofloxacin po vs Imipenem-cilastatin iv & NA & 4 & 6 & 7/11 & 1 Imipenem \\
Gentry\textsuperscript{95} & Ciprofloxacin po vs nafcillin po & \textit{S. aureus} & 7 & 12 & 24/31 (77) & \\
Mader\textsuperscript{96} & Ciprofloxacin po vs nafcillin iv + clindamycin po & GPC & 6 & 32 & 22/28 (79) & 11/14 \\
Greenberg\textsuperscript{97} & Ciprofloxacin po vs parenteral treatments & Enterobacteriaceae & 4 & 13 & 10/12 & 6/14 \\
& & & & & & 11/16 \\
\hline
\textsuperscript{*}: Comparative trial; GPC: Gram-positive cocci; GNR: Gram-negative rods; ad: adult; ch: children; c: chronic osteomyelitis; a: acute osteomyelitis; iv: intravenous; im: intramuscular; po: oral; Unless otherwise specified, the studies involved adult osteomyelitis.
\end{tabular}
\end{table}
matter what antibiotic therapy has been used.3,100,103 Radical debridement of infected or necrotic bone is even more important in the compromised host.101 Therefore, information is required about any surgical treatment provided in a study about antibiotic treatment of osteomyelitis.

Duration of antibiotic therapy is also an important issue when treating osteomyelitis. There is little published evidence upon which to determine the most effective duration. In the reviewed papers two major trends were found: most treated the patients for about six weeks, while a minority treated patients for about six months. Data from animal models show that bacteria can be cultured from infected bone even after two weeks of appropriate antibiotic therapy;102 therefore, treatment for four to six weeks has usually been advised.3,103 One retrospective survey of clinical cases supported a shorter duration of treatment;104 there is no published evidence of better results with longer treatment. Outcomes by treatment duration could not be analyzed as prolonged therapy was administered in only seven of 95 studies.

Considering the difficulties of conducting a human trial, animal models create more controlled conditions for comparing the efficacy of different antibiotics. Animal trials allow control over the type, duration and severity of disease, any surgical debridement provided, the etiologic agents, and the duration of follow-up. When lacking adequate evidence on drug efficacy, antibiotics for osteomyelitis must often be chosen on the basis of their safety profile. Patient adherence to the treatment, which is better with simplified regimens, must also be considered.

Available evidence suggests that oral antibiotic therapy can be as effective as parenteral treatments. The evidence is strongest for fluoroquinolones, because they were used in more recent, well-planned comparative studies. Oral clindamycin has also compared favorably with parenteral regimens in one trial.24 These favorable results largely derive from the excellent bioavailability and bone penetration of these classes of antibiotics. Oral treatments have the advantage of reduced duration of hospitalization and health care costs. For organisms resistant to oral drugs, outpatient parenteral antibiotic treatment (OPAT) has been successfully employed.105 Newer methods of using parenteral therapy are also available. Vancomycin has been administered by continuous infusion and teicoplanin has been administered three times weekly to treat staphylococcal osteomyelitis.33,38 Indeed, the latter approach appears more feasible and deserves consideration in those countries where teicoplanin is available.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Drug(s)</th>
<th>Commonest microorganism(s)</th>
<th>Duration of treatment (weeks)</th>
<th>Duration of follow-up (months)</th>
<th>Number of cured patients/total (%)</th>
<th>Severe side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beauvais21</td>
<td>Pristinamycin po, Clindamycin po</td>
<td>S. aureus</td>
<td>6–12</td>
<td>18</td>
<td>25/31 (81) ch</td>
<td>6 patients no</td>
</tr>
<tr>
<td>Feigin22</td>
<td></td>
<td>S. aureus</td>
<td>6 a</td>
<td>24</td>
<td>13/19 a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 c</td>
<td></td>
<td>6/6 ch a</td>
<td></td>
</tr>
<tr>
<td>Rodriguez23</td>
<td>Clindamycin po, Clindamycin po, vs nafcillin iv</td>
<td>S. aureus</td>
<td>10</td>
<td>15</td>
<td>28/29 (97) ch a</td>
<td>1 allergy no</td>
</tr>
<tr>
<td>Kaplan24</td>
<td></td>
<td>S. aureus</td>
<td>6</td>
<td>12</td>
<td>11/12 predicts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saengniphandkul41</td>
<td>Cotrimoxazole po vs oral penicillins</td>
<td>S. aureus</td>
<td>4–8</td>
<td>12</td>
<td>30/66 (45)</td>
<td>no</td>
</tr>
<tr>
<td>Sanchez42</td>
<td>Cotrimoxazole po + rifampin po</td>
<td>S. aureus</td>
<td>4</td>
<td>43</td>
<td>21/27 (78)</td>
<td>3</td>
</tr>
<tr>
<td>Fernandez43</td>
<td>Fosfomycin po</td>
<td>S. aureus</td>
<td>3</td>
<td>48</td>
<td>29/37 (78)</td>
<td>no</td>
</tr>
<tr>
<td>Hierolzer44</td>
<td>Fusidic acid po</td>
<td>S. aureus</td>
<td>NA</td>
<td>NA</td>
<td>54/72 (75)</td>
<td>no</td>
</tr>
<tr>
<td>Coombs45</td>
<td>Fusidic acid po</td>
<td>Coagulase negative staphylococci</td>
<td>NA</td>
<td>NA</td>
<td>19/20 (95)</td>
<td>no</td>
</tr>
</tbody>
</table>

*: Comparative trial; GPC: Gram-positive cocci; GNR: Gram-negative rods; ad: adult; ch: children; c: chronic osteomyelitis; a: acute osteomyelitis; iv: intravenous; im: intramuscular; po: oral; Unless otherwise specified, the studies involved adult osteomyelitis.
regimens become available, and the prevalence of methicillin-resistant staphylococci increases, intravenous cephalosporins are likely to become a less widely used treatment of osteomyelitis. New agents with good oral bioavailability, high bone penetration, and activity against MRSA (e.g., linezolid) have great promise, but must be tested in clinical trials.

The published reports on the antibiotic treatment of osteomyelitis have not provided information on most key treatment issues. All the antibiotic classes listed in this review have demonstrated efficacy in treating osteomyelitis, but well-designed comparative studies to elucidate the most appropriate regimens are lacking. Therefore, the choice of anti-biotic, unless limited by the sensitivity of the etiologic organism(s), should be based mostly on the safety of various agents for prolonged use, and the cost and practicality of the chosen regimen. Additional, properly designed, studies are needed to ascertain the best agent(s), route, and duration of antibiotic treatment for patients with osteomyelitis.

Acknowledgments

Thanks to Mark Shirtliff PhD and Jason H. Calhoun MD for their helpful suggestions, to Kristi Overgaard, BSc for manuscript editing and preparation, and the personnel of the UTMB medical library for their help in retrieving the published literature.

Conflict of interest: Benjamin Lipsky has received research sponsorship and has served as a speaker for or a consultant to the following companies: Merck, Pfizer, Wyeth-Ayerst and Ortho-McNeil. Luca Lazzarini has no competing interest to declare.

References

11. Cole WG, Dalziel RE, Leitz S. Treatment of acute osteomyelitis with good oral bioavailability, high bone penetration, and activity against MRSA (e.g., linezolid) have great promise, but must be tested in clinical trials. 107

...


58. De Bastiani G, Nogarin L, Malinaroli F, Bragantini A, Fostini R. Use of cefazidime in the treatment of osteomyelitis...