
REVIEW

Experimental Osteomyelitis: What Have We Learned from Animal Studies about the Systemic Treatment of Osteomyelitis?

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Summary

Clinical trials of systemic antibiotic treatment of osteomyelitis are difficult to perform for many reasons, such as low incidence rate of osteomyelitis, variety of anatomic locations, stage and etiologic agents. In this article, we reviewed the experimental studies on osteomyelitis available in the English medical literature since 1968, to ascertain their actual and potential impact on the treatment of human osteomyelitis. Major results are summarized and topics of major interest, such as reproducibility of animal models, predictive value of animal models, correlation of pharmacokinetics between different animals and humans, and the correlation of outcome between animal and clinical studies are discussed. Most of the reviewed animal models are reproducible and dependable. However, establishing the right dose regimen in animals appeared a critical factor, which might undermine the predictive value of the experimental study. Due to difficulties in comparing results of animal and human studies, the predictive value of animal studies about osteomyelitis is still unclear. However, animal models gave valuable information to the clinician for choosing the minimal duration of antibiotic treatment. Even though the use of antibiotic combinations was associated with better outcome in the majority of animal studies, such a finding seems to have limited impact on clinical practice.

Key words: Osteomyelitis, animal models of osteomyelitis.

INTRODUCTION

The treatment of acute and chronic orthopedic infections is difficult, time consuming and expensive and often involves considerable morbidity¹⁻⁶. Despite combined medical and surgical treatment, many cases continue to have unfavorable outcomes.

Clinical trials are difficult to perform and, to date, have been of poor value in elucidating many aspects of the systemic antibiotic treatment of osteomyelitis. The reasons for the difficulty of performing these studies are due to a number of fac-

tors. First and foremost is the relatively low incidence rate of osteomyelitis⁷ resulting in a patient population that is often insufficient for appropriate clinical studies within a single institution. In addition, this disease occurs in a variety of anatomic locations with various extensions, in a wide range of patient age, immune function, and disease state. Also, osteomyelitis may be due to many different microorganisms, each species with strain-specific differences in virulence and ability to cause infection, persist, and resist clearance by appropriate treatment modalities. As a result, treatment must be specifically tailored for each patient, which presents a problem for

standardized clinical protocols as well as pooling patients between multiple healthcare facilities. In order to overcome such difficulties, many animal models have been used to study the efficacy of systemic antibiotics in the treatment of osteomyelitis.

Early animal models of osteomyelitis were aimed primarily at elucidating the pathology and pathogenesis of the disease. The rabbit model of osteomyelitis was preferred by many due to the low cost, effectiveness, ease of infection initiation, low mortality rate, and the close approximation to human histological and pathological patterns of this disease^{4-6,8}. Later, most studies were aimed at providing insights regarding diagnosis and treatment. Although most of these studies provided valuable information, inherent limitations of animal studies sometimes obscure the studies' predictive value in human trials. As a result, the results of experimental studies are difficult to interpret for the clinician, and the clinical impact of the published experimental literature seems to be, at present, quite limited. In order to ascertain what may be learned from these animal studies, we reviewed the animal studies available in the medical literature regarding the use of systemic antibiotics in the treatment of osteomyelitis.

RABBIT MODELS OF STAPHYLOCOCCAL OSTEOMYELITIS

In the late 1960s, Carl Norden developed the first rabbit model of chronic osteomyelitis⁹. The tibias of New Zealand White rabbits were inoculated with a strain of *Staphylococcus aureus* with a needle. An irritating agent, sodium morrhuate (5% w/v), was also injected in order to facilitate bone necrosis and the establishment of chronic infection. The animals were sacrificed 60 - 70 days after the inoculum, and the tibias were crushed and cultured.

Norden's model was used to test several, mostly anti-staphylococcal, antibiotic regimens (Table 1). First, cephalothin was compared with lincomycin after a 14- or 28-day period of treatment¹⁰. The two major findings were that lincomycin was significantly more effective than cephalothin, and more prolonged treatment with either drug was more effective than a shorter treatment. It was puzzling that a delayed treatment (i.e., started 14 days after infection) was as effective as an early one (i.e., started one day after infection) in the case of cephalothin, but not in the case of lincomycin. The author also noticed less severe bone disease (i.e., less sequestra formation and radiological changes) at the end of treatment in the lincomycin group. The same study also evaluated the bone penetration of cephalothin and lincomycin, and displayed that lincomycin reached a 2-3 fold higher concentration than cephalothin in both the cortex and the medullary portions of the bone. None of drugs were able to eradicate the infection from the sequestra.

In a second study, Norden and Dickens administered cephaloridine to rabbits with osteomyelitis¹¹. Treatment started 14 days after infection (after this study, this modality was established as a standard feature of Norden's model and repeated in all the subsequent studies). While cephaloridine was unable to eradicate bacteria from the bone after 14 or 28 days, a 42-day treatment was effective. The authors underlined that, although cephaloridine reached higher bone concentrations than cephalothin, the results of experimental treatment were poor.

In 1975, Norden conducted a therapeutic trial with rifampin alone and in combination with gentamicin, sisomicin, and cephalothin¹². Treatment with either the two aminoglycosides alone or with rifampin alone produced no effects after 14 days. After 28 days, rifampin alone reduced the severity of bone disease (in terms of gross pathology and radiology), whereas aminoglycosides alone did not. Treatment with cephalothin alone for 28 days did not eradicate the pathogen from bone in more than half of samples. The association of two or more antibiotics was significantly more effective than a single antibiotic, and a better result was achieved with the use of three drugs.

In another study¹³, Norden conducted a therapeutic trial with oxacillin and sisomicin, alone and in association. Treatment with either drug alone was almost ineffective. The use of an association of the two drugs produced better results, with 22% and 15% positive cultures after 14 and 28 days, respectively. Similarly, vancomycin gave unfavorable results when used alone, but its combination with rifampin produced eradication of microorganisms from bone in 90% of samples after 28 days¹⁴. These results were confirmed by a subsequent study with rifampin, cephalothin, sisomicin, and trimethoprim¹⁵. In the same study, the authors found no clear correlation between eradication and results of *in vitro* synergy studies, thereby underlining the problems associated with extending *in vitro* findings to the *in vivo* situation. In the next study, clindamycin was shown to be the first antibiotic that was able to eradicate infection in more than 90% of the samples, even when given alone for 28 days¹⁶. The subsequent studies tested ampicillin-sulbactam, teicoplanin, daptomycin, and cefepime¹⁷⁻²⁰. It is noteworthy that the two glycopeptides were unable to eradicate bacteria from any sample.

Using Norden's model, Mader and Wilson evaluated the efficacy of cephalothin and cefamandole, which were found to be equally effective, even though cefamandole reached higher bone concentrations²¹. Subsequent studies compared two experimental quinolones, difloxacin and sarafloxacin, with the "standard" treatment with nafcillin, and also compared daptomycin with vancomycin^{22,23}. The latter two were equally effective. The former three antibiotics showed similar penetration in bone, and difloxacin was equally effective as nafcillin in eradi-

TABLE 1 - Principal findings of the studies with rabbit models of osteomyelitis.

| Study (Reference) | Antibiotic(s) and dosage (mg/kg) | Number of culture positive samples following treatment/total number |
|------------------------|---|---|
| Norden ¹⁰ | Cephalothin 50 mg/kg qid | 4/14 |
| | Lincomycin 10 mg/kg bid | 6/15 |
| Norden ¹¹ | Cephaloridine 30mg/kg qid | 15/17 |
| Norden ¹² | Rifampin 40 mg/kg qid | 5/20 |
| | Cephalothin 50 mg/kg tid | 7/18 |
| | Gentamicin 5 mg/kg bid | 10/20 |
| | Sisomicin 10 mg/kg bid | 10/20 |
| | Rifampin + Cephalothin | 1/20 |
| Norden ¹³ | Oxacillin 50 mg/kg qid | 14/20 |
| | Sisomicin 10 mg/kg bid | 19/20 |
| | Oxacillin + Sisomicin | 3/20 |
| Norden ¹⁴ | Vancomycin 60 mg/kg bid | 20/22 |
| | Rifampin 40 mg/kg qd | 9/21 |
| | Rifampin+Vancomycin | 2/20 |
| Norden ¹⁵ | Rifampin 40 mg/kg qd | 11/25 |
| | Cephalothin 50 mg/kg tid | 16/25 |
| | Trimethoprim 40 mg/kg qid | 23/25 |
| | Sisomicin 10 mg/kg bid | 23/25 |
| | Rifampin + Sisomicin | 1/25 |
| | Rifampin + Cephalothin | 2/25 |
| | Rifampin + Trimethoprim | 6/25 |
| | Rifampin + Sisomicin + Trimethoprim | 0/25 |
| Norden ¹⁶ | Clindamycin 30 mg/kg tid | 3/20 |
| Norden ¹⁷ | Ampicillin-Sulbactam 200/100 mg/kg tid | 12/20 |
| Norden ⁷¹ | Rifampin + Trimethoprim | 5/20 |
| Norden ¹⁹ | Teicoplanin 60 mg/kg bid | 19/19 |
| Norden ²⁰ | Daptomycin 10 mg/kg bid | NA (100%) |
| | Daptomycin 20 mg/kg tid | NA (100%) |
| Norden ¹⁸ | Cefepime 40 mg/kg qid | 7/15 |
| Mader ²¹ | Cefamandole 30 mg/kg qid | 9/13 |
| | Cephalothin 50mg/kg qid | 7/15 |
| Mader ²² | Difloxacin 15 mg/kg bid | 6/20 |
| | Sarafloxacin 20 mg/kg/bid | 14/20 |
| | Nafcillin 40 mg/kg qid | 8/20 |
| Mader ²³ | Daptomycin 4mg/kg bid | 10/17 |
| | Vancomycin 40 mg/kg qid | 11/18 |
| Mader ²⁴ | Cefazolin 5mg/kg qid | 12/22 |
| | Cefazolin 15 mg/kg qid | 12/23 |
| | Clindamycin 70 mg/kg qid | 2/20 |
| Shirliff ²⁵ | Levofloxacin 30 mg/kg qd | 10/20 |
| | Nafcillin 30 mg/kg qid | 2/20 |
| Shirliff ²⁶ | Gatifloxacin 40 mg/kg bid | 1/15 |
| | Nafcillin 30 mg/kg qid | 0/10 |
| Shirliff ²⁷ | Azithromycin 50 mg/kg + Rifampin 40 mg/kg bid | 3/15 |
| | Clarithromycin 80 mg/kg bid + Rifampin 40 mg/kg bid | 2/15 |
| | Nafcillin 30 mg/kg qid + Rifampin 40 mg/kg bid | 0/10 |

NA, not available.

cating staphylococci from the bone. In a later study, Mader *et al* showed the superiority of clindamycin to cefazolin, and confirmed that clindamycin alone gave better results than any other drug tested with Norden's model ²⁴.

More than 10 years later, Shirliff *et al* compared oral levofloxacin with nafcillin and gatifloxacin with nafcillin ^{25,26}. Gatifloxacin was as effective as nafcillin, whereas levofloxacin was significantly less effective than nafcillin. A noteworthy result is that eradication rate of nafcillin was higher (although not statistically significantly higher where $p > 0.05$ - Fisher's Exact Test) in these three studies than in Mader's original study, despite the use of a lower dosage of nafcillin. Shirliff also studied combination oral antimicrobial therapy using rifampin combined with azithromycin, clarithromycin, or nafcillin and found the two oral macrolides (azithromycin and clarithromycin) were an equally effective partner for rifampin as nafcillin in the eradication of staphylococcal osteomyelitis from rabbit tibias ²⁷.

RABBIT MODELS OF OSTEOMYELITIS DUE TO OTHER MICROORGANISMS

Norden *et al* used the same rabbit model to test several antibiotic regimens against infections due to *Pseudomonas aeruginosa* (Table 2) ²⁸⁻³³. These studies confirmed the principal findings of the studies involving staphylococcal infection: a) prolonged treatment was more successful in eradicating infection than shorter treatments and b) an association of two antibiotics was more effective than administration of single antibiotic alone. The only drugs able to eradicate microorganisms from more than 90% of samples were the fluoroquinolones, ciprofloxacin, and ofloxacin.

Another rabbit model of osteomyelitis due to *P. aeruginosa* was described by van Wingerden *et al*

³⁴. The major differences with Norden's model were the use of prophylaxis with gentamicin for four days after infection (to avoid systemic sepsis), the use of different times between infection and treatment, and the timing of animal sacrifice (10 to 17 days after the end of treatment). The major findings of the study were that a treatment of at least 3 weeks was needed to sterilize bone samples, and that an association of carbenicillin and sisomicin was more effective than either drug alone. This model has not been used as extensively in the literature as Norden's.

Mayberry-Carson *et al* and Johansson *et al* described two models of mixed aerobic-anaerobic and anaerobic osteomyelitis in rabbits, with the use of a foreign body in the medullary to facilitate infection ^{35,36}. After 2 and 4 weeks of treatment with ciprofloxacin and metronidazole, respectively, despite high bone levels of the drugs, there was a complete failure to eradicate bacteria from the bone. These models confirmed the difficulty in eradicating a foreign body infection without removing the foreign body.

Other models of experimental osteomyelitis in rabbits were described by Bernat *et al* ³⁷, Erenberg *et al* ³⁸, Smeltzer *et al* ³⁹, Worlock *et al* ⁴⁰, and Sande *et al* ⁴¹. However, none of these models was used for antibiotic trials.

RAT MODELS OF STAPHYLOCOCCAL OSTEOMYELITIS

Henry *et al* ⁴² described a rat model of methicillin-resistant *S. aureus* infection. They injected the tibias of Wistar rats with a strain of methicillin-resistant *S. aureus* along with sodium morrhuate, without implanting any foreign bodies. Treatment lasted 21 days. Some animals were sacrificed at the end of treatment and others were sacrificed 28 days after the last dose of antibiotic was given. Tibias were

TABLE 2 - Major results of antibiotic trials in experimental osteomyelitis due to *Pseudomonas aeruginosa*

| Author (Reference) | Antibiotic and dosage (mg/kg) | Number of culture positive samples following treatment/total number |
|-----------------------------|--|---|
| Norden ³² | Sisomicin 10 mg/kg bid | 19/22 |
| | Carbenicillin 400mg/kg qid | 20/21 |
| | Sisomicin+Carbenicillin | 6/20 |
| Norden ³¹ | Azlocillin 400 mg/kg qid | 20/21 |
| | Tobramycin 10 mg/kg bid | 16/21 |
| | Azlocillin+Tobramycin | 12/20 |
| Norden ³⁰ | Tobramycin 10 mg/kg bid | 17/18 |
| | Ciprofloxacin 40 mg/kg tid | 1/18 |
| Norden ²⁸ | Ofloxacin 200 mg/kg bid | 1/17 |
| Norden ²⁹ | Aztreonam 150 mg/kg tid | 17/20 |
| Van Wingerden ³⁴ | Carbenicillin 500mg/kg/die + Sisomicin 1.5 mg/kg/die | 0/5 |

harvested and analyzed with methods similar to those used in the rabbit models. The model was used to evaluate the use of rifampin, ciprofloxacin, and vancomycin for the treatment of methicillin-resistant staphylococcal osteomyelitis. All the animals had positive bone cultures at the end of treatment, and significantly higher bone counts were observed after the additional 28 days. The most effective single drug for reducing the bacterial counts in bone was rifampin and the association of ciprofloxacin and rifampin was more effective than vancomycin plus rifampin.

Rissing *et al*⁴³ used a similar model in the Sprague-Dawley rat. An antibiotic trial with either oxacillin (120 mg/kg q12) or ceftriaxone (25 and 50 mg/kg q12) resulted in no eradication of infection after 28 days of treatment. The authors commented that this failure indicates that the method is adequate for studying chronic osteomyelitis. Using the same model, Nelson *et al*⁴⁴ confirmed the persistence of *P. aeruginosa* infection after 2 weeks of treatment with ceftazidime and tobramycin.

The Rissing model was also used by Gisby *et al*⁴⁵ to show the equivalence between amoxicillin-clavulanic acid, clindamycin, and flucloxacillin, and Luu *et al*⁴⁶ used the model to show the equivalence between daptomycin and vancomycin.

In a rat model of staphylococcal osteomyelitis similar to Rissing's, O'Reilly *et al*⁴⁷ tested the efficacy of clindamycin, azithromycin, and rifampin, alone or in combination. The most effective treatment group was rifampin plus azithromycin, sterilizing 80% of samples, followed by clindamycin plus rifampin (66%), rifampin (53%), clindamycin (20%). Treatment with azithromycin alone did not sterilize any bone samples, even though the drug reached the highest bone concentration. Gomis *et al*⁴⁸ used a rat model of *Escherichia coli* osteomyelitis to test a treatment with cefotaxime. The treatment eradicated bacteria from 85% of bone samples after 28 days. More recently, Patel *et al*⁴⁹ used a similar model to test the efficacy of linezolid, in comparison with cefazolin, to treat *S. aureus* osteomyelitis. Treatment with linezolid had no effect at all, whereas treatment with cefazolin was significantly more effective.

OTHER OSTEOMYELITIS MODELS

Emslie *et al*^{50,51} described a model of acute hematogenous osteomyelitis in chickens, in which *S. aureus* was inoculated by the intravenous route. This model was used in another study⁵² to test the efficacy of intramuscular cloxacillin in the treatment of acute osteomyelitis. The drug, given once daily, was completely ineffective.

A canine model of chronic hematogenous osteomyelitis was described by Deysine⁵³ *et al*. Bacteria were injected into the bone in another

canine model without the use of any promoting agent. The authors were able to maintain a chronic osteomyelitis due to either *S. aureus* or *Salmonella* for two years after intravenous inoculation⁵⁴.

Matsushita *et al*⁵⁵ injected *S. aureus* intravenously in mice, establishing a hematogenous acute osteomyelitis.

BENEFITS OF UTILIZING ANIMAL MODELS

As mentioned previously, a number of inherent limitations exist when attempting an evaluation of antibiotic therapies for osteomyelitis in human, including limited patient populations, large variations in the disease and host, and lack of standardized treatment regimens. The utilization of animal models averts some of these difficulties. Using models enables the comparison of alternative antimicrobial regimens since a number of aspects of the infectious process can be standardized, thereby allowing appropriate comparisons between treatment groups. The length of time and causal pathogenic species and strains of the infection can be standardized. Also, the variability introduced by systemic or local factors of the patient that affect immune surveillance, metabolism, and local vascularization in clinical studies is drastically reduced by using a single species and breed of animals.

Another source of variability reduction in animal models is that they generally utilize localized osteomyelitis infection induction by direct inoculation of the pathogen into the bone of experimental animals, with or without the use of a promoting agent. This generates a bone infection in a standard, localized site. The extent of the infection can also be standardized since animals may be grouped before treatment by staging bone infection according to a standardized system of classification based on gross pathology and radiographic findings described by Mader, *et al*⁵⁶ and later Shirliff *et al*⁵⁷. In addition, treatment groups can be compared to untreated controls in order to evaluate the efficacy of the treatment, in comparison with the rate of spontaneously resolving infections. Such a comparison can obviously not be performed in clinical practice.

Last, the model allows for standardized treatment protocols which can be the same between groups and between different investigators. In humans, antibiotic therapy is used in conjunction with operative treatment of osteomyelitis with the exception of most pediatric hematogenous osteomyelitis, which are usually treated with antibiotics alone⁵⁸⁻⁶¹. The reliance upon surgical treatment creates further unpredictability since débridement may be more or less radical, even compensating for poor antimicrobial therapy, and dead space management and stabilization may also be performed in different ways.

Therefore, hematogenous osteomyelitis in humans and an infection with similar features in the

experimental animal are probably the best situations to test different antimicrobial regimens. However, questions remain concerning the reproducibility of these models and whether these models can accurately mimic the antibiotic pharmacokinetic profiles and the therapeutic success rates seen in clinical practice.

THE REPRODUCIBILITY OF OSTEOMYELITIS MODELS

One of the first tests of a model's ability to predict clinical outcome is its ability to provide results that are reproducible, even though the studies are performed by different investigators. In order to test the reproducibility of the osteomyelitis models discussed thus far, the number of positive bone cultures in each of the studies with comparable antimicrobial treatment regimens was evaluated (Table 3). A total of 23 studies had at least one counterpart study involving similar antibiotic treatment and a reasonably close dosing level and interval, thereby allowing a comparison of studies to determine model reproducibility. The number of positive bone cultures in three studies showed statistically significant ($p < 0.05$) differences from their antibiotic treatment study counterparts^{10,12,23}. However, a possible reason for differences in two of these studies^{10,23} was the use of alternative antibiotic regimens in their partner studies. In particular, the statistically significant reduction in positive bone cultures in Norden's 1971 cephalothin study¹⁰ compared to other cephalothin studies^{12,15,21} was probably due to higher antibiotic dosing, since the Norden 1971 study

dosed 50 mg/kg four times daily while the other studies only dosed 50 mg/kg three times daily. This difference in antibiotic dosing regimens was also most likely responsible for the statistically significant reduction in positive bone cultures seen in Mader's 1989 vancomycin study²³ compared to Norden's 1983 study since Mader dosed vancomycin at 40 mg/kg four times daily while Norden dosed at 60 mg/kg, twice daily. Therefore, of the 23 studies that were capable of being compared, only one study¹² showed an unexplained statistically significant difference in the determination of antibiotic efficacy using animal models of osteomyelitis. The 95.7% reproducibility rate was obtained in the face of different animal models, different investigators, and over 30 years in different studies. Therefore, one might conclude that the animal models of osteomyelitis are both reproducible and dependable.

CORRELATION OF PHARMACOKINETICS

A weakness of animal models is the uncertainty of a correct reproduction of drug levels between different animals and humans⁶². Peak serum levels, bone penetration of the antibiotic, and pharmacokinetics in the animal may be different than those seen in humans. A glance at the regimens used in the reviewed trials (Table 4) may confirm that antibiotics were used not only at dosages which are very different from those used in humans, but also with different dose intervals. While it is often unstated, the justification for an investigator's choice of administering a particular antibiotic regimen to animals is to match the human pharmacokinetic profile

TABLE 3 - Comparison of results obtained from different rabbit studies evaluating comparable doses of antibiotics.

| Antibiotic (mg/kg) | Number of culture positive samples following treatment/total number (study reference) | | | |
|--|---|-------------|------------|------------|
| Cephalothin (50 mg/kg tid and 50 mg/kg qid*) | 7/18 (12) | 16/25 (15) | 7/15 (21) | *4/14 (10) |
| Sisomicin (10 mg/kg bid) | 10/20 (12) | 19/20 (13) | 23/25 (15) | |
| Rifampin (40 mg/kg qid) | 5/20 (12) | 9/21 (14) | 11/25 (15) | |
| Nacillin (30-40 mg/kg qid) | 8/20 (22) | 2/20 (25) | 0/10 (26) | |
| Rifampin (40 mg/kg qid) + Cephalothin (50 mg/kg tid) | 1/20 (12) | 2/25 (15) | | |
| Rifampin (40 mg/kg qid) + Trimethoprim (40 mg/kg qid) | 6/25 (15) | 5/20 (71) | | |
| Vancomycin (60 mg/kg bid and 40 mg/kg qid*) | 20/22 (14) | *11/18 (23) | | |
| Clindamycin (30 mg/kg tid and 70 mg/kg qid) | 3/20 (16) | 2/20 (24) | | |
| Tobramycin (10 mg/kg bid) | 16/21 (31) | 17/18 (30) | | |

TABLE 4 - Dosing comparison between animal models of osteomyelitis and clinical dosage recommendations.

| Antibiotic | Dose (mg/kg) in animal studies (Study reference) | Dose (mg/kg) in clinical practice |
|----------------------|---|--|
| Cephalothin | 50 mg/kg qid ^{10,12,15,21} | 20-30 mg/kg qid |
| Lincomycin | 10 mg/kg bid ¹⁰ | NA |
| Cephaloridine | 30mg/kg qid ¹¹ | NA |
| Rifampin | 40 mg/kg qid ^{12,14,15,27} | 8 mg/kg qd |
| Gentamicin | 5 mg/kg bid ¹² | 2 mg/kg bid |
| Sisomicin | 10 mg/kg bid ^{12,13,15} | NA |
| Oxacillin | 50 mg/kg qid ¹³ | 30-40 mg/kg qid |
| Vancomycin | 60 mg/kg bid ¹⁴ | 14 mg/kg bid |
| Trimethoprim | 40 mg/kg qid ¹⁵ | NA alone (usually associated with sulfamethoxazole) |
| Clindamycin | 30 mg/kg tid ¹⁶ | 8 mg/kg qid |
| Clindamycin | 70 mg/kg qid ²⁴ | |
| Ampicillin-Sulbactam | 200/100 mg/kg tid ¹⁷ | 30 mg/kg tid |
| Teicoplanin | 60 mg/kg bid ¹⁹ | 6-8.5 mg/kg qd |
| Daptomycin | 10 mg/kg bid ²⁰ | |
| Daptomycin | 20 mg/kg tid ²⁰ | |
| Daptomycin | 4mg/kg bid ²⁴ | NA |
| Cefepime | 40 mg/kg qid ¹⁸ | 15 mg/kg bid |
| Vancomycin | 40 mg/kg qid ²³ | 14 mg/kg bid |
| Cefazolin | 5mg/kg qid ²⁴ | |
| Cefazolin | 15 mg/kg qid ²⁴ | 20-30 mg/kg qid |
| Levofloxacin | 30 mg/kg qd ²⁵ | 10 mg/kg qd |
| Gatifloxacin | 40 mg/kg bid ²⁶ | 5.7 mg/kg qd |
| Azithromycin | 50 mg/kg ²⁷ | 7 mg/kg qd |
| Clarithromycin | 80 mg/kg bid ²⁷ | 7 mg/kg bid |
| Linezolid | 25 mg/kg tid ⁴⁹ | 8.5 mg/kg bid |

NA, not available.

Note: clinical practice dosages are cited only for purposes of comparison with doses used in animal trials. They may be inaccurate and are not intended as a guideline for clinical practice.

in clinical practice. By the time that a particular antimicrobial agent is slated for animal model studies for efficacy in curing osteomyelitis, toxicity studies and pharmacokinetic studies have been performed in animals and humans.

However, if the pharmacokinetic data have not been determined prior to the animal model studies, the aim is to obtain serum and tissue concentrations well above the minimum inhibitory concentration (MIC) of the pathogen covered by the drug. Such dosages should not cause relevant toxicity to the animals. However, it is evident that these dosages are not necessarily achievable in humans, who might not tolerate them.

CORRELATION OF OUTCOME BETWEEN ANIMAL AND CLINICAL STUDIES

Another question is whether or not animal models are predictors of outcome in humans. Animal models may be predictors of success in the case where a regimen is successful in the animal and is also successful in humans, or a predictor of failure in the case where failure in the animal correlates with failure in clinical trials.

Prediction of success may be somewhat confounded for animal models of osteomyelitis since we cannot use the term "cure" (when referring to a negative bone culture of an animal sacrificed after a

few months of infection) as synonymous with the term "cure" used in clinical practice. The term cure in animal models refers to a negative bone culture^{8,26,56,57}. However, clinical cure indicates the absence of clinical disease at the end of a 1- or 2-year uneventful follow-up, after completing an antibiotic regimen (and, eventually, undergoing surgical treatment)^{63,64}. Aside from this limitation, we can state that several drugs, such as clindamycin, rifampin, first generation cephalosporins, oral quinolones, anti-staphylococcal penicillins were effective in both experimental and clinical osteomyelitis^{65,66}. However, both clinical and animal studies were often unable to demonstrate the superiority of any regimen, possibly due to limited statistical power.

According to some authors, animal models are predictors of failure, rather than of success, especially in the case of treatment with cephalosporins⁶⁷. In the case of osteomyelitis, prediction of failure cannot be easily demonstrated. Drugs which were unsuccessful in animal models were not used in clinical osteomyelitis, with few exceptions.

Teicoplanin and linezolid were successful in the treatment of osteomyelitis in clinical trials, despite being completely inactive in two animal model studies of staphylococcal osteomyelitis^{19,49,68,69,70}. Therefore, the value of animal models as predictors of failure should also be carefully assessed.

VALUABLE INFORMATION FOR CLINICAL TREATMENT

Despite all the limitations of animal models, we cannot overlook the fact that some data are confirmed in both the rabbit and rat models. Data regarding duration of treatment and the use of antibiotic combinations are often confirmed and are consistent with clinical practice. Therefore, these data are potentially relevant for clinicians.

Almost all animal trials that have tested different durations of antibiotic treatment found that a 4-week treatment eradicated more bacteria from bone than shorter treatment durations. Animal trials, however, were unable to provide information about the efficacy of treatment longer than 4 weeks, which are sometimes used in clinical practice.

The second undisputed finding is that antibiotic combinations were always more effective than the use of single antibiotics. It may be interesting to assess whether or not these findings had an impact on further clinical trials and on clinical practice. As for clinical trials, a number of those published after 1970 tested single antibiotics for a duration of 4 to 6 weeks⁶⁶. In clinical practice, most experts advise the use of antibiotic courses for a similar duration, but do not put any emphasis on the need for antibiotic combination therapy^{1,4,5,6}. In conclusion, the minimal duration of antibiotic treatment suggested by many animal trials seems to have been consid-

ered in clinical practice, whereas the need for antibiotic combinations is probably still overlooked in clinical practice.

CONCLUSION

The role of animal models as an aid to improve human therapeutics is still not completely defined. The information we may expect from an animal model includes information regarding the drug's safety as well as treatment outcome. In clinical trials and clinical practice, the results obtained through animal model studies may have an impact on the way that osteomyelitis is studied and treated. Most clinical trials published after Norden's findings in the early 1970s have used a duration of antimicrobial therapy of 4 to 6 weeks. Also, most experts advise the use of antibiotic courses for a similar duration in clinical practice. However, the successes seen in animal model studies that tested combination antibiotic regimens may have been overlooked since clinicians do not put heavy emphasis on the need for utilizing combination therapy. Therefore, while the minimal duration of antibiotic treatment suggested by many animal trials seems to have been considered in clinical practice, the need for antibiotic combination therapy is often still ignored.

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