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EXPERIMENTAL THERAPEUTICS

Activity of Different Antistaphylococcal Therapies, Alone or Combined, in a Rat Model of Methicillin-Resistant *Staphylococcus epidermidis* Osteitis without Implant

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ABSTRACT We developed a rat model of methicillin-resistant *Staphylococcus epidermidis* (MRSE) osteitis without implant to compare the efficacy of vancomycin, linezolid, daptomycin, ceftaroline, and rifampin either alone or in association with rifampin. A clinical strain of MRSE was inoculated into the proximal tibia. Following a 1-week infection period, rats received either no treatment or 3, 7, or 14 days of human-equivalent antibiotic regimen. Quantitative bone cultures were performed throughout the 14-day period. The mean ± SD quantity of staphylococci in the bone after a 1-week infection period was 4.5 ± 1.0 $\log_{10}$ CFU/g bone, with this bacterial load remaining stable after 3 weeks of infection (4.9 ± 1.4 $\log_{10}$ CFU/g bone). Vancomycin monotherapy was the most slowly bactericidal treatment, whereas ceftaroline monotherapy was the most rapidly bactericidal treatment. The addition of rifampin significantly increased the bacterial reduction for vancomycin, linezolid, and daptomycin. All tibias were sterilized after 2 weeks of treatment except for animals receiving vancomycin or daptomycin alone (66.6% and 50% of sterilization, respectively). These results show that ceftaroline and linezolid alone remain good options in the treatment of MRSE osteitis without implant. The combination with rifampin increases the antibiotic effect of vancomycin and daptomycin lines.

KEYWORDS MRSE, osteitis, preclinical drug studies, rifampin combination

Osteomyelitis are damaging bone infections that can lead to sequelae and major morbidity, resulting in significant medical and economic burdens. In adults, surgical procedures are becoming increasingly responsible for such infections due to direct contamination of bone tissue, especially in the presence of medical devices (1). The most common causative species is usually the staphylococci, including *Staphylococcus aureus* and also commensal coagulase-negative staphylococci (CoNS) (2, 3). A prospective cohort study, evaluating the microbiological etiology of prosthetic joint infections, revealed 28.9% of infections were due to *Staphylococcus aureus* and 28.6% due to coagulase-negative staphylococci (4). Even if the vast majority of CoNS infections are associated with medical devices, CoNS can be isolated from surgical site infections, with up to 44% of patients developing a deep sternal wound infection after sternotomy (5–7). Finally, osteitis is one of the common challenging complications of diabetic foot infections. The epidemiology is more often polymicrobial (8), with coagulase-negative staphylococci being isolated in ~25% of cases (3). *Staphylococcus epidermidis* is by far the most prevalent CoNS in microbiological samples and the primary cause of CoNS-related infections, particularly in nosocomial settings (9, 10).

Biofilm formation provides a substantial advantage to CoNS, through its complex matrix of exopolysaccharides, rendering the cells less accessible to the immune system

Citation Albac S, Labrousse D, Hayez D, Anzala N, Bonnot D, Chavanet P, Aslangul E, Croisier D. 2020. Activity of different antistaphylococcal therapies, alone or combined, in a rat model of methicillin-resistant *Staphylococcus epidermidis* osteitis without implant. Antimicrob Agents Chemother 64:e01865-19. https://doi.org/10.1128/AAC.01865-19.

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Received 13 September 2019
Returned for modification 21 October 2019
Accepted 11 November 2019
Accepted manuscript posted online 18 November 2019
Published 27 January 2020

of the host and also impairing the penetration and action of antibiotics. The success of antibiotic treatment is also a major challenge in the field of orthopedic CoNS infections because 60% to 70% of clinically recovered CoNS isolates are methicillin resistant (4, 7).

To date, vancomycin is the recommended treatment for infections caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE) (3), but the emergence of strains with reduced vancomycin susceptibility (11, 12), its potential for nephrotoxicity in certain patients, and its slow bactericidal activity make the evaluation of other therapeutic alternatives a necessity. Rifampin has shown activity in bone infections with consequent high rifampin bone concentrations achieved, but it cannot be used as monotherapy because of the potential risk of selection of resistance (13). Similarly, linezolid is also an active treatment (14) but may be associated with biological side effects, such as myelosuppression, when administered for a long time (15) and, even if occasional, to the emergence of resistant mutants (16).

Therefore, new alternatives are being developed to overcome the resistance of CoNS and to improve the antimicrobial therapy of osteitis. However, the existing recommendations suffer from a lack of high-quality clinical studies indicating the superiority of one type of therapy over another, as shown in the last Infectious Diseases Society of America guidelines (3).

Among new alternatives, daptomycin, a cyclic lipopeptide with bactericidal activity against Gram-positive bacteria, represents a clinical therapeutic option (17). Ceftaroline, a new fifth-generation cephalosporin with potent activity against methicillin-resistant staphylococci, has also demonstrated very interesting activity in preclinical models of MRSA osteomyelitis (18, 19). However, little is known about the *in vivo* activity of daptomycin and ceftaroline on CoNS strains, especially in bone infections. Respective recommendations of combined therapies using rifampin are also based on limited, partly uncorroborated studies and some case reports for the treatment of severe infections, mostly by *S. aureus*.

In the present study, we describe the development of a rat model of MRSE-induced osteitis without implant and compared the efficacy of different antistaphylococcal antibiotics, alone or in combination with rifampin.

RESULTS

Experimental rat model. A total of 150 rats were used for the whole study; 6 of them died during anesthesia meaning a total of 144 rats were included in the analysis. Overall, no mortality was recorded after bacterial challenge, and all animals recovered their mobility 12 h after the surgery.

The growth curve of all animals (including controls) was in the correct range of body weight (data not shown). The quantitative results of experimental MRSE osteitis are presented in Table 1 and Fig. 1.

At the start of therapy (day 7 [D7]), the mean bacterial count $\pm$ standard deviation in the control group ($n = 10$) was 4.5 ± 1.0 $\log_{10}$ CFU/g. The bacterial load in these control animals slightly decreased between D3 (5.8 ± 0.7 $\log_{10}$ CFU/g) and D7 but was overall stable between D7 and D21 (4.9 ± 1.4 $\log_{10}$ CFU/g).

As shown in Fig. 1 and in Table 1, a 3-day treatment significantly reduced the bacterial load in the bone of animals receiving ceftaroline alone (2.0 ± 1.2 $\log_{10}$ CFU/g; $P = 0.0022$) and rifampin alone (2.0 ± 1.0 $\log_{10}$ CFU/g; $P = 0.0001$). A bacterial decrease was also observed in animals that received a monotherapy using vancomycin, linezolid, or daptomycin after 3 days of therapy but that was not significant. The bacterial reduction became significant when these antibiotics were associated with rifampin. A 3-day treatment using the combination vancomycin plus rifampin or linezolid plus rifampin resulted in sterilization in all animals. Treatment using the combination daptomycin plus rifampin resulted in sterilized bones in 5 out of 6 tibias.

A 7-day treatment using linezolid, daptomycin, ceftaroline, rifampin, and, to a lesser extent, vancomycin alone significantly decreased the bacterial load in tibias. Again, similar to results obtained after a 3-day treatment, a combined therapy using rifampin (vancomycin plus rifampin, linezolid plus rifampin, and daptomycin plus rifampin) was

TABLE 1 Residual bacterial load in tibias of *Staphylococcus epidermidis* 9120486910-1-infected rats untreated or treated with each of the eight therapies[a]

Day postinfection	Bacterial load in tibia (log_{10} CFU/g) expressed as mean ± SD (no. of tibias) [% sterilized tibias] by treatment								
	Untreated	Vancomycin	Linezolid	Daptomycin	Ceftaroline	Rifampin	Vancomycin + rifampin	Linezolid + rifampin	Daptomycin + rifampin
3	5.8 ± 0.7 (8) [0]								
7	4.5 ± 1.0 (10) [0]								
10	4.9 ± 0.9 (8) [0]	3.7 ± 1.4 (6) [16.6]	3.7 ± 1.3 (6) [16.6]	2.7 ± 2.1 (6) [50]	2.0 ± 1.2* (6) [50]	2.0 ± 1.0*** (12) [41.6]	1.0 ± 0.0*** (6) [100]	1.0 ± 0.0*** (6) [100]	1.4 ± 1.1*** (6) [83.3]
14	4.8 ± 1.2 (14) [0]	3.1 ± 1.7** (12) [25]	1.3 ± 0.7*** (6) [83.3]	2.7 ± 1.2*** (10) [20]	1.4 ± 0.7*** (12) [83.3]	2.3 ± 1.0*** (14) [28.5]	1.0 ± 0.0*** (12) [100]	1.1 ± 0.4*** (12) [83.3]	1.0 ± 0.0*** (10) [100]
21	4.9 ± 1.4 (16) [0]	2.1 ± 1.6*** (12) [66.6]	1.0 ± 0.0*** (6) [100]	2.0 ± 1.0*** (10) [50]	1.0 ± 0.0*** (12) [100]	1.1 ± 0.2*** (16) [93.7]	1.3 ± 0.8*** (12) [83.3]	1.1 ± 0.4*** (12) [91.6]	1.1 ± 0.3*** (10) [90]

[a]Results are expressed as mean ± SD (number of tibias) [percentage of sterilized tibias]. D7, start of therapy. Quantitative variables were compared to Mann-Whitney test, *$P < 0.05$, **$P < 0.005$, ***$P \leq 0.0001$, versus untreated.

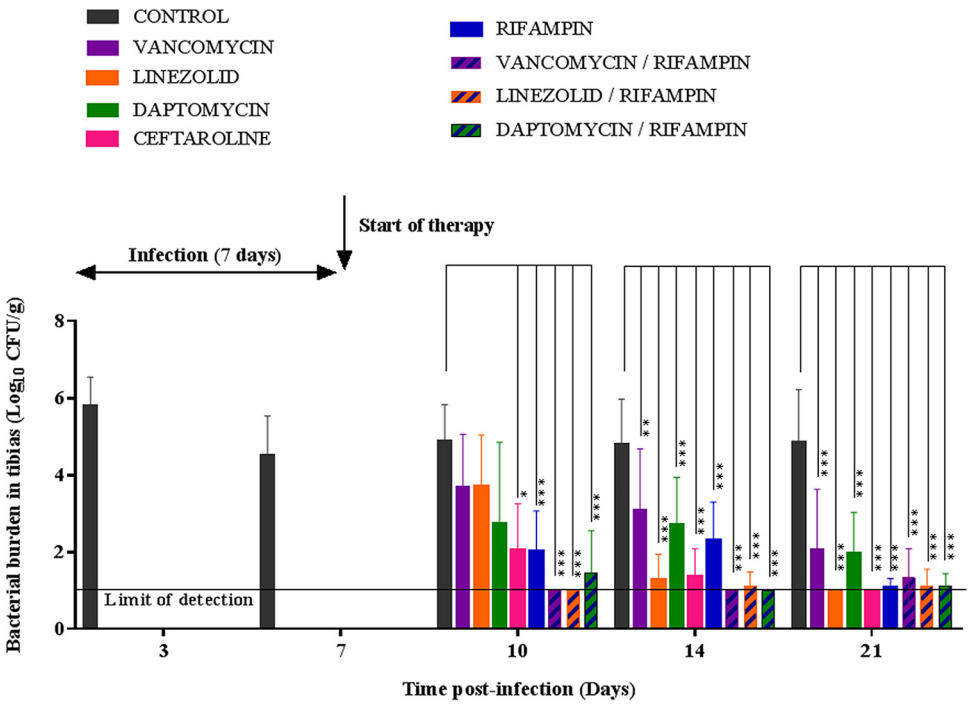

FIG 1 Results of quantitative bone culture of *Staphylococcus epidermidis* 9120486910-1-infected rats untreated or treated with each of the eight therapies (log_{10} CFU per gram of bone). Results are shown as mean ± SD (number of tibias). D7, start of therapy. Quantitative variables were compared to Mann-Whitney test, $^{*}P < 0.05$, $^{**}P < 0.005$, *** $P \leq 0.0001$, versus untreated.

associated with the sterilization of tibias in almost all animals. Indeed, only one out of the 12 tibias from the linezolid plus rifampin group remained positive (2.31 log_{10} CFU/g of bone) after 7 days of treatment.

After 14 days of treatment, all animals receiving the different therapies had sterilized tibias, except in the group receiving vancomycin alone (2.0 ± 1.6 log_{10} CFU/g of bone; 50% of sterilization) or daptomycin alone (2.0 ± 1.0 log_{10} CFU/g of bone; 66.6% of sterilization), but the bacterial load remained very close to our detection threshold.

The regression curves for each treatment group are presented in Fig. 2. Overall, the obtained root-mean-square error (RMSE) values were low (between 0.72 and 1.40) for each curve. This graphic representation allows us to visualize the *in vivo* kinetics of bactericidal activity according to the different treatment groups. It confirms that all combinations using rifampin are more rapidly efficient than the monotherapies.

DISCUSSION

In the present study, we established a rat model of MRSE osteitis without implant that has not been described before to the best of our knowledge.

The efficacy of different antibiotic strategies was compared in this model. Among monotherapies, the more active treatments were linezolid and ceftaroline, followed by daptomycin and rifampin. Vancomycin was the least active treatment in this model, despite being considered the clinical therapy of choice (20). We demonstrated that combinations using rifampin (linezolid plus rifampin, daptomycin plus rifampin, and vancomycin plus rifampin) were more rapidly bactericidal and sterilized bone in most of the animals, compared with antibiotics administered alone, without demonstrating a synergy between rifampin and other antibiotics. Unfortunately, the combination of ceftaroline plus rifampin was not been tested in this study.

The superiority of regimens using rifampin in combination with other antistaphylococcal antibiotics has also been demonstrated in other successful MRSE osteitis rat models using a foreign body (21) and also in many MRSA osteitis models, including prosthetic joint infection in rabbits (22). In particular, a combination including rifampin

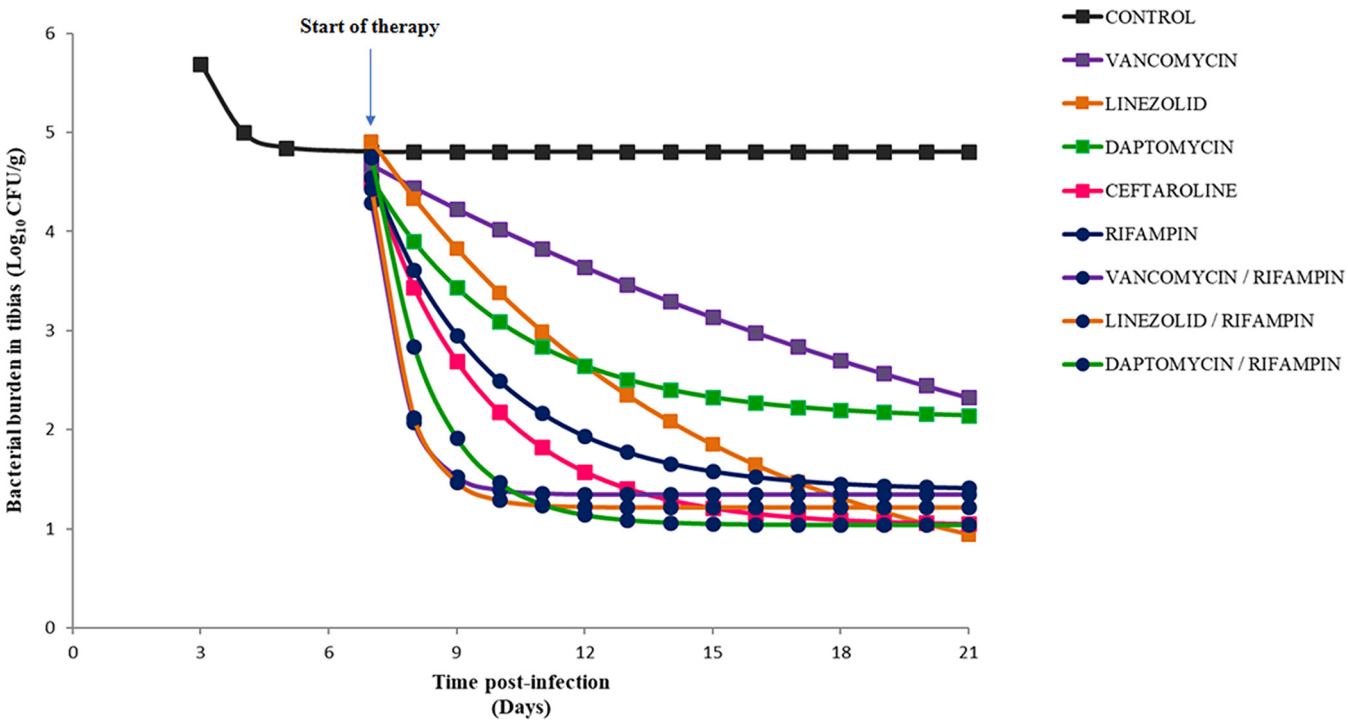

FIG 2 Graphic representation of the bacterial decrease in infected rats according to treatment groups (first-order decay kinetics 3 P).

is associated with the prevention of the emergence of resistance. In our study, the detection of resistant mutants was not performed in animals receiving rifampin alone or combined therapies, but considering both the size of the inoculum at the initiation of the treatment (around 6 log CFU/g) and the rate of sterilization obtained after 2 weeks of therapy, the incidence of expected mutations was estimated to be very low.

Despite the usual subacute and low inflammatory course of MRSE bone infections, these situations present a substantial clinical burden because of broad and severe treatment difficulties. Their management requires a multidisciplinary approach and experience in handling the most complicated cases to limit treatment failure, motor disability, and risk of amputation (4). We aimed to develop an osteitis model without using any foreign body or any adjuvant in order to mimic the osteitis which can be seen in the field of diabetic foot infection (even in this case infections are mostly polymicrobial not monomicrobial) or postchirurgical situations (direct inoculation).

Several studies have evaluated the efficacy of ceftaroline against MRSA in experimental infection models, but few preclinical studies have evaluated its potential in MRSE models (23). In our MRSE osteitis model, ceftaroline alone showed a bacterial reduction of between 3 $\log_{10}$ and 4 $\log_{10}$ in the bone, with a complete sterilization obtained after 2 weeks of treatment. Similarly, although the efficacy of daptomycin against MRSE has been analyzed in several experimental studies, including endocarditis, tissue cage, and biofilm-associated catheter infection, little is known about its potential in bone-related infections. In our model, daptomycin alone showed a bacterial reduction of 3 $\log_{10}$ CFU, and these data are consistent with the good penetration of daptomycin into bone tissue, even in diabetic patients (24). However, the bactericidal activity of daptomycin in our model was slower than the one observed in animals receiving linezolid or ceftaroline alone.

There are some limitations to our study that should be recognized. (1) Like most experimental studies, we used a single MRSE strain, taking into account the heavy workload of these experiments and the management of their ethical aspects. (2) The most important requirement of a reliable animal model is an infection rate of 100% without spontaneous curing. Thus, considering *S. epidermidis* can be a low-virulence

organism even for a clinical strain, the necessary dose for induction of a stable infection was much higher than those used in comparable MRSA models. In our MRSE rat model, we used an infective dose of 5.2×10^9 CFU/tibia to obtain a stable bacterial load all along the study period (3 weeks). Nevertheless, we previously developed a similar model using a clinical methicillin-susceptible *Staphylococcus epidermidis* (MSSE) strain and used the same inoculum size to avoid a spontaneous bacterial clearance (25, 26). Also, the same issue can be encountered in some implant models, which also require the increase of the inoculum, the precolonization of the implant, or the use of any adjuvant/sclerosing agents (21). The bacterial bone load obtained in the control rats in this implant MRSE model was also close to the one obtained in our model without implant (4.89 $\log_{10}$ CFU/g versus 4.5 $\log_{10}$ CFU/g after one week of infection). (3) Also, the infection was induced into the tibial medullary cavity, which can simulate a postoperative infection, but which can be very different from the clinical situation of foot osteitis in diabetic population. Moreover, one of our study limitations is that we did not use any diabetic animal; the main issue is to get animals that develop neuropathic and vascular disorders, in addition to hyperglycemia. This question will be addressed in further studies. (4) Finally, the duration of the experiment is rather short (3 weeks). Treatment was started 7 days postinoculation, and the infection is probably an acute rather than a chronic one.

In summary, we set up the first model of methicillin-resistant *Staphylococcus epidermidis*-associated osteitis without implant in rat. In this model, the more active monotherapies were linezolid and ceftaroline, followed by daptomycin and rifampin, and, finally, vancomycin. In addition to linezolid, ceftaroline and daptomycin appear to be promising antimicrobial agents for the treatment of MRSE osteitis without implant. The adjunction of rifampin to these monotherapies significantly increased the *in vivo* bactericidal effect in the first days of treatment. These results could be considered in future guidelines for the treatment duration in MRSE osteitis without implant in order to limit the toxicity and dysbiosis.

MATERIALS AND METHODS

Bacterial strain, growth conditions, and antibiotics. The clinical methicillin-resistant *S. epidermidis* isolate 9120486910-1, originally recovered from a patient suffering from diabetic foot infection, was studied (Assistance Publique des Hôpitaux de Paris). Bacterial stocks were kept at −80°C in cryobeads (bioMérieux, Marcy l'Etoile, France). This strain was resistant to methicillin but fully susceptible to each tested antibiotic (vancomycin, linezolid, daptomycin, ceftaroline, and rifampin). It was grown either on Chapman agar plates or Mueller-Hinton agar plates or in brain heart infusion liquid medium (bioMérieux).

For *in vivo* studies, commercial formulations were reconstituted according to the manufacturer's instructions: vancomycin (500 mg; Mylan), zyvoxid (600 mg; Pfizer), Cubicin (500 mg; Novartis), Zinforo (600 mg; Astra Zeneca), and rifadine (600 mg; Sanofi-Aventis).

Preparation of bacterial inocula. Before each animal experiment, the staphylococcal strain from one frozen aliquot was freshly cultured onto a Chapman agar plate (bioMérieux, Marcy l'Etoile, France) and incubated aerobically for 48 hours at 37°C. One colony was inoculated into 10 ml of brain heart infusion (bioMérieux) and incubated for 6 hours at 37°C with agitation. The resulting bacterial suspension was then spread onto Mueller-Hinton agar plates (bioMérieux) and incubated for 18 h at 37°C. The bacterial layer was scraped and homogenized in 10 ml of sterile serum saline. Based on preliminary experiments (data not shown), an infective dose of 5.2×10^9 CFU/tibia was selected to induce a stable osteitis for 3 weeks of infection. Viable bacterial counts were determined using optical density measurements in reference to a standard curve and then confirmed by plating successive dilution cultures onto agar.

Animals and ethical aspects. The experimental osteitis model was established in immunocompetent male Wistar rats weighing 250 to 300 g, as described by O'Reilly and Mader (27). Animals were placed in individual cages, with access to water and food *ad libitum*, according to the current recommendations of the European Institute of Health EU Directive 86/609. The experimental protocol was approved by the local ethics committee for animal experimentation (APAFIS number 15280).

Experimental osteitis model. The tibia osteitis rat model was described by O'Reilly and Mader (27). Animals were anaesthetized by intraperitoneal administration of ketamine (90 mg/kg of body weight; Virbac) and xylazine (10 mg/kg of body weight; Bayer). Legs were shaved and disinfected three times with polyvinylpyrrolidone-iodine (Betadine). The anterior tibial metaphysic of each leg was surgically exposed, and a 1.5-mm hole was drilled through the cortex into the medullary cavity using a high-speed drill with a 0.5-mm-diameter bit. A total of 50 μl of the inoculum (1×10^{11} CFU per ml) was slowly inoculated into the bone. No adjuvant was used. The hole was covered with sterile dental gypsum. The fascia and skin were closed with sutures (Ethicon, 5-0), and the wound was sprayed with a transparent film dressing (Ercefilm; Péters Surgical, France) to avoid contamination in the first hours postsurgery. Buprenorphine

(MedVet) was administered subcutaneously for analgesia (0.05 mg/kg). Animals were monitored on a daily basis. In the first days, food access was facilitated by placing croquettes directly into the cage.

Animal treatment. After 7 days of infection, antibiotic treatment was initiated with animals being treated intraperitoneally for up to 14 days (3, 7, or 14 days of treatment period). To confirm the bacterial load in the bone at treatment initiation, control animals were culled after 7 days of infection and quantitative bone cultures were performed. Animals were randomly assigned to one of the following nine study arms: no treatment (saline serum), vancomycin alone (50 mg/kg/12 h), linezolid alone (35 mg/kg/12 h), daptomycin alone (100 mg/kg/24 h), ceftaroline alone (20 mg/kg/12 h), rifampin alone (25 mg/kg/12 h), vancomycin (50 mg/kg/12 h) plus rifampin (25 mg/kg/12 h), linezolid (35 mg/kg/12 h) plus rifampin (25 mg/kg/12 h), or daptomycin (100 mg/kg/24 h) plus rifampin (25 mg/kg/12 h). These doses were selected as per the literature, as they allowed pharmacodynamic values close to those achieved in human serum after administration of a standard regimen (28, 29).

Twelve hours after the end of the therapy, to avoid any carry over effect, animals were intraperitoneally anaesthetized (using the mixture ketamine plus xylazine) and culled by an intracardiac overdose of pentobarbital (Euthasol; Virbac).

Evaluation of infection. Right and left tibias of each animal were dislocated and stored at −80°C until they were crushed in liquid nitrogen using a cryocrusher (Delta Labo, France). The pulverized bone was weighted, an amount was resuspended in 1 ml of sterile phosphate-buffered saline (PBS) and vortexed, and quantitative culture was performed by plating serial dilutions of this sample onto Chapman agar plates. Results were expressed in $\log_{10}$ CFU/g of bone. If the identification of colonies was uncertain on Chapman agar plates, an identification using matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) was performed (Ultra Flex Speed; Bruker Daltonics). Untreated but infected animals were used as controls. Surviving bacteria in bone were assessed on D10, D14, and D21 after infection (meaning D3, D7, and D14 after the initiation of the treatment) depending on the different therapies. For statistical comparisons of the differences between bone bacterial densities, culture-negative samples were considered to contain 1 $\log_{10}$ CFU/g.

Statistical analysis. Statistical analysis was performed with GraphPad Prism 7.00 software. Quantitative variables were compared using Mann-Whitney or analysis of variance and *post hoc* analysis using Bonferroni's test. *P* values of 0.05 or less were considered significant for all tests performed.

Additionally, regression modeling (first order decay kinetics 3 P) was performed using JMP software (version 9.0.2; SAS Institute). Fit was estimated by using the root-mean-square error (RMSE) as the standard deviation of the residuals (prediction errors), measuring how far the data points were from the regression line.

ACKNOWLEDGMENTS

This work was supported, in part, by a research grant from AstraZeneca, Pfizer, and Novartis (France). These funding bodies did not have any role in the design of the experiments; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

We thank Stephen Hawser from IHMA (Switzerland) for final review of the manuscript.

The authors report no conflicts of interest regarding this study.

S.A., D.L., D.H., D.B., N.A., and D.C. are employees of Vivexia.

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