Efficacy of linezolid versus a pharmacodynamically optimized vancomycin therapy in an experimental pneumonia model caused by methicillin-resistant Staphylococcus aureus

Fernando Docobo-Pérez1*, Rafael López-Rojas1, Juan Domínguez-Herrera1, Manuel E. Jiménez-Mejias1, Cristina Pichardo1, José Ibáñez-Martínez2 and Jerónimo Pachón1

1Unit of Infectious Diseases, Microbiology, and Preventive Medicine, Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocio/Universidad de Sevilla/CSIC, Sevilla, Spain; 2Department of Pathology, University Hospital Virgen Macarena, Sevilla, Spain

*Corresponding author. Tel: +34-955923100; Fax: +34-955923101; E-mail: fdocobop@yahoo.es

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Objectives: The British Thoracic Society, American Thoracic Society and Infectious Diseases Society of America guidelines recommend vancomycin for methicillin-resistant Staphylococcus aureus (MRSA) pneumonia, based on evidence suggesting that a vancomycin AUC 0–2 4/MIC ratio of 400 predicts clinical success against MRSA pneumonia. The aim of this study was the evaluation of an optimized dose of vancomycin in the treatment of MRSA experimental pneumonia versus linezolid.

Methods: In vitro activities of vancomycin and linezolid were tested using time–kill curves. Experimental pneumonia in neutropenic C57BL/6 mice was achieved using two clinical MRSA strains, MR30 and MR33 (vancomycin and linezolid MICs of 1 and 4 mg/L, respectively). In vivo dosages were 30 and 110 mg/kg vancomycin (obtaining an AUC 0–2 4/MIC ratio lower and higher than 400, respectively), and 30 mg/kg linezolid.

Results: Survival rates in controls, and in the groups treated with 120 mg/kg/day vancomycin, 440 mg/kg/day vancomycin and 120 mg/kg/day linezolid were 85.7%, 92.9%, 76.9% and 100%, and 66.7%, 100%, 75% and 100% for MR30 and MR33, respectively. Sterile blood cultures occurred at rates of 21.4%, 64.3%, 100% and 93.8%, and 40%, 66.7%, 100% and 93.3% for MR30 and MR33 strains, respectively. Finally, the respective bacterial lung concentrations (log10 cfu/g) were 8.93 ± 0.78, 6.67 ± 3.01, 3.25 ± 1.59 and 2.87 ± 1.86 for MR30, and 8.62 ± 0.72, 5.76 ± 2.43, 3.97 ± 1.52 and 1.59 ± 1.40 for MR33.

Conclusions: These results support that a vancomycin AUC 0–2 4/MIC ratio >400 is necessary to obtain a high bacterial lung reduction in MRSA pneumonia, comparable to that achieved with linezolid and better than that with the low dose of vancomycin tested. Linezolid was more efficacious than the pharmacodynamically optimized vancomycin dose in the pneumonia caused by the most virulent strain (MR33).

Keywords: MRSA, pharmacokinetics, pharmacodynamics, pneumonia

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is an important cause of pneumonia. A survey of 59 US hospitals, involving 4543 patients with aetiology-proven pneumonia, from 2002 to 2004, identified MRSA in 8.9% of community-acquired pneumonia cases, 26.3% of healthcare-associated pneumonia cases, 22.9% of hospital-acquired pneumonia cases and 14.6% of ventilator-associated pneumonia (VAP) cases. Indeed, in this study, S. aureus was identified as the only pathogen independently associated with mortality.1 In Spanish intensive care units during 2009, the rate of VAP caused by S. aureus was 11.5%, of which 18.03% were caused by MRSA.2

Community-associated MRSA (CA-MRSA) strains have also emerged as a major cause of skin and soft-tissue infections, and with a lower frequency as a cause of pneumonia3,4 in the USA, Canada, Asia, South America, Australia and throughout Europe, although in Spain CA-MRSA represents only 0.8% of MRSA bacteraemia.5

Vancomycin has been considered the gold-standard treatment in pneumonia caused by MRSA,6 but in spite of these recommendations, a mortality rate of 33%–55% occurred in patients with MRSA pneumonia treated with vancomycin.7–9 Thus, more recent recommendations include linezolid as an alternative to vancomycin,10 but without any antimicrobial prioritization.
In recent years, the poor prognosis of severe infections caused by MRSA treated with vancomycin has driven many studies evaluating the relationship between the MIC of vancomycin and the outcome of these infections. Soriano et al., in a study in patients with MRSA bacteraemia, concluded that mortality was higher when the empirical antibiotic was inappropriate and when vancomycin was empirically used for the treatment of cases caused by strains with a vancomycin MIC \geq 1 mg/L. Wang et al., found that a vancomycin MIC of 2 mg/L was an independent risk factor for mortality in MRSA bacteraemia. A drawback of these studies was the lack of information on vancomycin pharmacodynamic parameters; however, they suggest that for increased vancomycin MICs, the dosage should be adjusted to allow optimized pharmacodynamics, as the parameter associated with a good therapeutic outcome is the AUC0–24/MIC ratio. Human data appear to demonstrate that therapeutic efficacy with vancomycin is related to an AUC0–24/MIC ratio \geq 400.

On the other hand, the efficacy of linezolid, an oxazolidinone with activity against Gram-positive cocci, was compared with that of vancomycin in MRSA nosocomial pneumonia in two double-blind studies. This post-hoc analysis concluded that linezolid therapy was associated with significantly higher survival and clinical cure rates than vancomycin therapy. However, the conclusions of these studies have been questioned by other authors, because the clinical trials were not initially designed to analyse the MRSA subgroup. Further, due to the absence of vancomycin pharmacodynamic data in the two double-blind studies, a suboptimal dosage may have occurred in the group treated with vancomycin.

Due to these remaining questions about the in vivo efficacy of vancomycin and linezolid, the aim of the present study was to evaluate two different pharmacodynamically adjusted regimens of vancomycin and compare them with linezolid in an experimental pneumonia model caused by two clinical MRSA strains.

Materials and methods

Bacterial strains

Two bacteremic MRSA strains (MR30 and MR33) were selected from 15 consecutive bacteremic strains isolated from 2002 to 2003 in our hospital. The selection criterion was to have an MIC of vancomycin and linezolid equal to the MIC90 of the collection.

Antibiotics

For in vitro assays, vancomycin (Sigma–Aldrich, Madrid, Spain) and linezolid (Pfizer, Kalomazoo, MI, USA) were used as standard laboratory powders. For in vivo experiments, clinical vials were used: vancomycin (Laboratorios Normon S.A., Tres Cantos, Spain) and linezolid (Pfizer S.A., Alcobendas, Spain).

In vitro studies

The MICs of vancomycin and linezolid were determined according to standard microdilution methods. S. aureus ATCC 29213 was used as a control strain. Also, the MIC of vancomycin was determined using Etest strips (bioMérieux, Marcy l’Etoile, France). The breakpoints for resistance were those defined by the CLSI (formerly NCCLS).

The bactericidal activity of the antimicrobials was evaluated by the time–kill method using concentrations of 1×, 2× and 4× MIC. Bacterial growths were quantified 0, 2, 4, 8 and 24 h after incubation at 37 °C, by plating 10-fold dilutions on sheep blood agar (SBA). The limit of detection was 10 cfu/mL, corresponding to 1 log10 cfu/mL. An antimicrobial was considered bactericidal when a 3 log10 decrease in the cfu/mL was reached compared with the initial inoculum.

Animals

C57BL/6 female mice, weighing 16–20 g (Animal Facility, Universidad de Sevilla, Seville, Spain) were used. The studies were approved by the Ethics Committee of the University Hospital Virgen del Rocío (Seville, Spain). Mice were rendered neutropenic by cyclophosphamide (Baxter Oncology GmbH, Halle/Westfalen, Germany) injected intraperitoneally (ip) 4 days (150 mg/kg body weight) and 1 day (100 mg/kg) before the experiments. These doses obtained a sustained neutropenia during the 72 h of experimentation, as assessed by neutrophil counts (Sysmex XE-5000 Analyzer, Sysmex Europe GmbH, Hamburg, Germany).

Pharmacokinetic/pharmacodynamic analysis

Serum antibiotic concentrations were determined in groups of 24 neutropenic non-infected mice after a single administration of vancomycin (30 mg/kg, ip), vancomycin (110 mg/kg, ip) or linezolid (30 mg/kg, ip). In sets of three animals at 5, 10, 15, 30, 60, 90, 120 and 240 min after administration, blood samples were obtained from anaesthetized mice [5% (w/v) sodium thiopental ip; B. Braun Medical S.A.] from the periorbital plexus.

Concentrations of vancomycin and linezolid were determined using an agar diffusion bioassay with Bacillus subtilis ATCC 6633 and S. aureus ATCC 29213 as control strains, respectively. Antibiotic assays were performed in triplicate. The maximum serum concentration (Cmax, mg/L), area under the concentration–time curve (AUC0–∞, mg.h/L) and elimination half-life (t1/2, h) were obtained by a computer-assisted method (PK Functions for Microsoft Excel; J. L. Usansky, A. Desai and D. Tang-Liu, Department of Pharmacokinetics and Drug Metabolism, Allergan, Irvine, CA, USA (http://www.boomer.org/klm/soft.html)); AUC0–24/MIC and Cmax/MIC ratios were then calculated. Time (T > MIC, h) and percentage of time (T > MIC, %) during which the serum concentration remained above the MIC between two doses were extrapolated from the regression line of the serum concentrations. The intraday and interday variations of the assays were 2.22% ± 2.76% and 3.27% ± 2.24% for vancomycin, and 2.68% ± 3.23% and 2.29% ± 2.22% for linezolid, respectively; the linearity (r2) of the assay was 0.99±0.01 and 0.98±0.01, respectively; and the lower limits of detection were 3.1 and 4 mg/L, respectively.

The low dose of vancomycin (30 mg/kg) was selected because it showed an AUC/MIC > 125 mg.h/L, which correlates with a low probability of therapeutic failure against Gram-positive infections. The high vancomycin dose (110 mg/kg) was chosen to target an AUC similar to that in humans after doses of 1 g twice daily (440 mg.h/L). In the case of linezolid, a dose of 30 mg/kg was tested, which showed an AUC similar to that obtained in humans after 600 mg given twice daily, intravenously (iv) (160 mg.h/L).

Pneumonia model

A previously characterized pneumonia model was used. Neutropenic anaesthetized C57BL/6 mice [thiopental 5% (w/v) ip] were infected by intratracheal instillation, using 50 μL of 108 cfu/mL mixed 1:1 with 10% porcine mucin (Sigma–Aldrich), with a final bacterial burden inoculated into lungs of 5×106 cfu. Therapy was initiated 4 h after the inoculation. Groups of 15 mice were randomly included as controls (no treatment) and in the following treatment groups: vancomycin at 120 mg/kg/day (30 mg/kg four times daily), ip (low dose); vancomycin at 440 mg/kg/day...
(110 mg/kg four times daily), ip (high dose); and linezolid at 120 mg/kg/day (30 mg/kg four times daily), ip. Mice were observed for 72 h for mortality and the surviving animals were sacrificed 6 h after the last dose by ip administration of a lethal dose of sodium thiopental. Immediately after death, thoracotomy was carried out. Through a cardiac puncture, blood samples were taken and 100 μL plated on SBA for qualitative cultures. Lungs were homogenized in 2 mL of sterile saline solution (Stomacher 80 Tekmar Co., Cincinnati, OH, USA) and 10-fold dilutions were plated on SBA for quantitative cultures. To confirm that the antimicrobial treatments were not toxic to the animals, groups of five neutropenic and non-infected mice were randomly assigned to each receive one of the three antimicrobial treatments (vancomycin low or high doses, or linezolid) for 72 h and assessed for mortality.

**Statistical analysis**

The variables analysed were survival (%), bacterial lung concentration (log_{10} cfu/g lung tissue, mean ± SD) and blood sterility (%). The two-tailed Fisher's exact test, analysis of variance (ANOVA), and Dunnett's and Tukey's post-hoc tests were used. Differences were considered significant at a \( P \) value <0.05.

**Results**

**In vitro studies**

Both the MR30 and MR33 strains were susceptible to vancomycin and linezolid. The MICs/MBCs of vancomycin and linezolid were 1/1 and 4/8 mg/L, respectively, for MR30, and 1/2 and 4/>8 mg/L, respectively, for MR33, using the microdilution method. The MICs of vancomycin measured using the Etest method were 1 mg/L for both strains. In the time–kill experiments, vancomycin exhibited bactericidal activity at 24 h for MR30 (at 2× and 4× MIC) and for MR33 (at 4×), but linezolid was not bactericidal against any of the strains (Figure 1).

**In vivo results**

**Leucocytes**

The administration of two doses of cyclophosphamide resulted in sustained neutropenia during the 72 h of experimentation (Table 1).

**Pharmacokinetics and pharmacodynamics**

The serum antimicrobial concentration profiles in non-infected mice after a single administration of vancomycin (30 or 110 mg/kg, ip) or linezolid (30 mg/kg, ip) are shown in Figure 2. The serum pharmacokinetic and pharmacodynamic parameters of each antimicrobial in mice are shown in Table 2. The 30 mg/kg dose of vancomycin reached an AUC_{0–24} of 140.32 mg·h/L and that for the 110 mg/kg dose was 445.44 mg·h/L. For linezolid, the 30 mg/kg dosage showed a \( T_{\geq \text{MIC}} \) of 45.3% and an AUC_{0–24} of 144.88 mg·h/L.

![Figure 1. Time–kill curves of vancomycin and linezolid at 1×, 2× and 4× MIC, with strains MR30 and MR33.](https://academic.oup.com/jac/article-abstract/67/8/1961/746826)
With the MR30 and MR33 strains, survival rates in the control groups were 85.7% and 66.7%, respectively. This survival was not improved by any treatment in the experiments with MR30. With MR33, linezolid and low-dose vancomycin increased the survival compared with the controls (100% and 100% versus 40%; $P < 0.05$). With the MR33 strain, the mortality in the controls (33.3%) was reduced by linezolid and low-dose vancomycin, but not by high-dose vancomycin. Linezolid was better than the high dose of vancomycin in reducing the bacterial lung concentration with only one of the strains (MR33 strain), but not in the sterilization of blood cultures.

In spite of the efficacy shown by the high vancomycin dose, in terms of reducing the bacterial lung and blood concentrations, it must be noted that it did not reduce the mortality in the control groups. In the experiments with the MR30 strain, the low mortality observed in the controls precludes the possibility of finding differences compared with any of the treatment groups. In the case of the MR33 strain, the mortality in the controls (33.3%) was reduced by linezolid and low-dose vancomycin, but not by high-dose vancomycin; although we did not observe toxicity with this dose in the non-infected control animals, we cannot rule out the possibility of increased vancomycin-induced nephrotoxicity in this severe experimental pneumonia model, impeding the reduction in the mortality in spite of improvement of the bacterial parameters. Thus, Andonegui et al.\textsuperscript{25} showed that in an experimental $S$. pneumoniae pneumonia model, renal dysfunction, specifically glomerular filtration impairment, was induced, as shown by an increase in the plasma creatinine levels at 24 h post-infection.

The experimental pneumonia model was chosen because pneumonia is one of the most severe nosocomial infections among those caused by $S$. aureus. We used the well-characterized and reproducible model described by Esposito and Pennington\textsuperscript{26} with two clinical MRSA strains. Although most cases of nosocomial pneumonia occur in non-neutropenic patients, experimental $S$. aureus models usually need neutropenic animals.\textsuperscript{18,27,28} Thus, the non-neutropenic mice model described by Bubeck Wardenburg et al.\textsuperscript{27} would not be useful for the aim of this study, because the bacterial lung concentration diminishes spontaneously in non-treated mice at 48 and
Vancomycin versus linezolid efficacy in MRSA experimental pneumonia

Table 2. Pharmacokinetics and pharmacodynamics of vancomycin and linezolid in mice serum

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose (mg/kg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0→∞&lt;/sub&gt; (mg·h/L)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt;/MIC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>T&lt;sub&gt;MIC&lt;/sub&gt; (h)</th>
<th>T&lt;sub&gt;MIC&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>30</td>
<td>35.54</td>
<td>0.42</td>
<td>35.08</td>
<td>35.54</td>
<td>140.32</td>
<td>1.85</td>
<td>30.83</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>97.79</td>
<td>0.57</td>
<td>111.36</td>
<td>97.79</td>
<td>445.44</td>
<td>3.9</td>
<td>65</td>
</tr>
<tr>
<td>Linezolid</td>
<td>30</td>
<td>25.31</td>
<td>0.93</td>
<td>36.22</td>
<td>6.33</td>
<td>36.22</td>
<td>2.72</td>
<td>45.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Parameter calculated using the MICs of vancomycin (1 mg/L) and linezolid (4 mg/L) for both strains.

Table 3. In vivo results for the experimental MRSA pneumonia model treated with linezolid and two different doses of vancomycin

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment group</th>
<th>Dose (mg/kg/day)</th>
<th>Survival (%)</th>
<th>Log&lt;sub&gt;10&lt;/sub&gt; cfu/g lung tissue (mean ± SD)</th>
<th>Sterile blood cultures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MR30 control</td>
<td>—</td>
<td>85.7</td>
<td>8.93 ± 0.78</td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>120</td>
<td>92.9</td>
<td>6.67 ± 3.01</td>
<td>64.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>120</td>
<td>76.9</td>
<td>3.25 ± 1.59&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MR33 control</td>
<td>—</td>
<td>66.7</td>
<td>8.62 ± 0.72</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>120</td>
<td>100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.76 ± 2.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td>linezolid</td>
<td>120</td>
<td>75</td>
<td>3.97 ± 1.52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>P<0.05 compared with the control group.
<sup>b</sup>P<0.05 compared with the vancomycin (120 mg/kg/day) group.
<sup>c</sup>P<0.05 compared with the vancomycin (440 mg/kg/day) group.

72 h. Although the treatment duration chosen for the model is shorter than the time required to treat pneumonia in the clinical setting, 72 h is sufficient to observe significant differences in the bacterial burden in lungs related to the antimicrobial treatments. Moreover, the protocol induced neutropenia in mice and ensured it for 72 h.<sup>19</sup>

The low efficacy obtained in this study with the low dose (120 mg/kg/day) of vancomycin is in accordance with the results in previous experimental MRSA murine models,<sup>28–31</sup> which used vancomycin with a suboptimal pharmacodynamic parameter (AUC<sub>0–24</sub>/MIC ratio <400). Several studies have evaluated the efficacy of linezolid and two new antimicrobial compounds (DX-619 or SMP-601) versus vancomycin, using a murine model of haematogenous pulmonary infection caused by a clinical MRSA strain.<sup>28,30,31</sup> These authors used vancomycin dosages of 20 and 100 mg/kg/day, obtaining an AUC<sub>0–24</sub>/MIC of 39.2–96.2. Consequently, the bacterial lung reductions were only ~1 log<sub>10</sub> cfu/g after 7 days of treatment. Reyes et al.<sup>29</sup> compared the efficacy of telavancin versus vancomycin in a murine model of peritoneal sepsis caused by MRSA. In this study, vancomycin was administered at 220 mg/kg/day subcutaneously, reaching an AUC<sub>0–24</sub>/MIC of 152.7 mg·h/L and a bacterial reduction in spleen of ~3 log<sub>10</sub> cfu/g. These results closely mimic those of the present work with both strains and the low dose (120 mg/kg/day) of vancomycin, in terms of pharmacodynamics and efficacy.

On the other hand, the results obtained with the high dose of vancomycin (440 mg/kg/day), obtaining an AUC<sub>0–24</sub>/MIC ratio >400, are in accordance with others from different experimental models. Kihara et al.<sup>28</sup> used a vancomycin dosage of 200 mg/kg/day in a murine model of haematogenous pulmonary infection caused by MRSA, reaching an AUC<sub>0–24</sub>/MIC of 392 and a bacterial lung reduction >3 log<sub>10</sub> cfu/mL after 7 days of treatment. Reyes et al.<sup>32</sup> compared the efficacy of telavancin versus vancomycin and linezolid in an MRSA murine pneumonia model, using a vancomycin dosage of 220 mg/kg/day iv, to reach an AUC similar to that found in humans (440 mg·h/L). Beginning the treatment 12 h after the bacterial challenge, they found a bacterial lung reduction of 4 log<sub>10</sub> cfu/g with respect to controls after 48 h of treatment.

In the present work, linezolid showed the best therapeutic results. Against both strains, the bacterial lung reductions were 6–7 log<sub>10</sub> cfu/g with respect to the controls. All the animals treated with linezolid survived and >90% of the blood cultures were negative. This therapeutic success was obtained with pharmacodynamic parameters of T<sub>MIC</sub> of 45.3% and AUC<sub>0–24</sub>/MIC of 36.22. These data are not concordant with the suggested pharmacodynamic parameters for obtaining therapeutic efficacy in an experimental animal model or in humans.<sup>13,34</sup> Andes et al.<sup>33</sup> in a murine thigh infection model, established an AUC<sub>0–24</sub>/MIC of 82.9 to produce a net static effect against S. aureus. Meanwhile, Rayner et al.<sup>34</sup> suggest an optimal antibacterial effect with linezolid when plasma T<sub>MIC</sub> covers the entire interval between doses and the AUC<sub>0–24</sub>/MIC ratio is >100, as is commonly obtained with administration of the standard dosage of linezolid (600 mg twice daily).
In contrast, our results with linezolid are partially in agreement with those obtained by Yanagihara et al. in a study that compared the efficacy of linezolid versus vancomycin in a murine model of haematogenous pulmonary infection using a clinical MRSA strain (linezolid MIC of 2 mg/L). Using a dose of 100 mg/kg/day ip during 7 days, the pharmacokinetic and pharmacodynamic parameters were similar to those obtained in our study: AUC0–24/MIC ratio of 59 mg·h/L and T >MIC of 43%. With this schedule, the survival increased (85% versus 40%) and the bacterial lung concentration significantly decreased (1.36 log10 cfu/g) with respect to controls. It must be noted that we obtained a higher linezolid bactericidal activity (lung reduction of 6.06 and 7.03 log10 cfu/g, with respect to controls) with a lower AUC0–24/MIC ratio (36.22 versus 59).

With respect to comparative studies of vancomycin and linezolid in patients with nosocomial pneumonia, the results are controversial. Thus, the post-hoc analysis of Wunderink et al. concluded that linezolid therapy was associated with significantly higher survival and clinical cure rates than vancomycin therapy. In a retrospective study in patients with VAP, Chan et al. observed no survival benefit but a trend towards a higher cure rate with linezolid therapy. Two recent meta-analyses of randomized trials comparing the efficacy of linezolid versus glycopeptides in the treatment of nosocomial pneumonia do not demonstrate clinical superiority of linezolid versus glycopeptides or vancomycin, with a more frequent risk of thrombocytopenia and gastrointestinal events being associated with linezolid use.

In summary, the results of the present study in the experimental MRSA pneumonia model provide evidence that a pharmacodynamically adjusted dose of vancomycin, to obtain an AUC0–24/MIC ratio >400, is needed to reach a significant reduction in the bacterial burden in tissues. Our work is in concordance with the American Thoracic Society/Infectious Diseases Society of America and the American Society of Health-System Pharmacists/Infectious Diseases Society of America/Society of Infectious Diseases Pharmacists guidelines, recommending vancomycin therapeutic monitoring to obtain an AUC0–24/MIC ratio >400. Moreover, linezolid was effective in the treatment of the experimental MRSA pneumonia model, being better than low-dose vancomycin and improving the results obtained with the pharmacodynamically adjusted dose of vancomycin in the pneumonia caused by the most virulent strain (MR33).

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