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Short communication

The efficacy of telavancin in comparison with linezolid on endotracheal tube biofilm in pigs with methicillin-resistant *Staphylococcus aureus* pneumonia

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ABSTRACT

Background: The effect of systemic treatment of ventilator-associated pneumonia (VAP) with telavancin, a semisynthetic lipoglycopeptide with good penetration in *vitro* biofilms, has not been tested in vivo during mechanical ventilation. This study examined the efficacy of telavancin compared with linezolid against endotracheal tube (ETT) biofilms in a porcine model of methicillin-resistant *Staphylococcus aureus* (MRSA) VAP.

Methods: VAP was induced in 18 pigs by instilling 10^7 colony-forming units (CFU/mL) of an MRSA strain susceptible to telavancin and linezolid into each pulmonary lobe. Randomization into three groups was done at pneumonia diagnosis: control (IV glucose 0.5% solution q24); linezolid (10 mg/kg q12) and telavancin groups (22.5 mg/kg q24). After 72 h of MV, data regarding bronchoalveolar lavage (BAL), tracheal aspirate (TA), ETT MRSA biofilm load and thickness measured by scanning electron microscopy were obtained.

Results: All 18 pigs completed the study. MRSA was isolated in 100% of ETTs from the control and linezolid groups and in 67% from the telavancin group. Telavancin treatment presented a lower MRSA load compared to the control and linezolid treatments (telavancin median [interquartile range (IQR)] = 1.94 [0.00–5.45], linezolid 3.99 [3.22–4.68] and control 4.93 [4.41–5.15], $P = 0.236$). Telavancin treatment also resulted in the lowest biofilm thickness according to the SEM (4.04 [2.09–6.00], $P < 0.001$). We found a positive correlation between ETT and BAL load (rho = 0.511, $P = 0.045$).

Conclusions: In our VAP model, systemic telavancin treatment reduced ETT MRSA occurrence, load, and biofilm thickness. Our findings may have a bearing on ICU patients' clinical outcomes.

1. Introduction

Endotracheal (ETT) biofilm is constituted by pathogens that grow in a self-produced polymeric matrix which in vivo, during orotracheal intubation, are also mixed with respiratory secretions from the host [1].

Although some experimental studies and clinical trials on anti-biofilm strategies have been conducted, none of their findings have

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been routinely implemented in clinical practice [2,3]. The NASCENT clinical trial evaluated the efficacy of silver-coated ETTs in reducing ventilator-associated pneumonia (VAP) incidence [2]. Without significant adverse events or any relevant impact on other clinical outcomes, the silver-coated ETTs markedly reduced the incidence of microbiologically proven VAP and were most effective during the peak time of VAP occurrence [2].

The mechanism by which ETT biofilm is reduced by systemic antimicrobials used for the treatment of VAP is a matter of interest, although it is not easy to investigate since ETTs are only available upon extubation and because there is high heterogeneity in the underlying comorbidities and patients' treatments during intensive care unit (ICU) stay [4]. In vitro studies have shown that biofilms exhibit tolerance to antimicrobials [5]. However, the in vivo effects of systemic antimicrobials on ETT biofilms during mechanical ventilation have shown promising results, especially for those antimicrobials that penetrate well into respiratory secretions such as linezolid [1,6,7].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the most concerning Gram-positive pathogens in VAP. MRSA can form biofilms on medical devices, increasing the risk of its dissemination into the airways [6,8]. Current first-line recommended therapy against MRSA pneumonia includes glycopeptides and oxazolidinones, such as vancomycin and linezolid [7,9].

Previous data corroborate that telavancin is a potential alternative to vancomycin in both animal models and patients with MRSA VAP [10,11], although to the best of our knowledge, no studies have evaluated the efficacy of telavancin in comparison to linezolid in ETT-MRSA biofilm in vivo [12]. Therefore, we aimed to compare the effect of telavancin and linezolid on the ETT biofilm MRSA occurrence, load and thickness in a validated model of mechanically ventilated piglets with MRSA pneumonia reproducing ICU conditions.

2. Materials and methods

This experimental, prospective, randomized study on ETTs obtained from pigs with MRSA VAP was conducted at the Department of Pulmonary and Critical Care Medicine, Division of Animal Experimentation, at the Hospital Clínic de Barcelona, C/ Villarroel, 170, 08,036 Barcelona, Spain.

Supplementary Material (SM)—Item S1 and Item S2 contain additional experimental information.

2.1. Randomization

Upon diagnosis of VAP, approximately 24 h after MRSA inoculation, animals were randomized into three groups as previously reported: (1) six animals receiving intravenous (IV) glucose 0.5% solution q24 h (control group); (2) six animals receiving IV linezolid 10 mg/kg q12 h (linezolid group); and (3) six animals receiving IV telavancin 22.5 mg/kg over a 60-min period q24 h (telavancin group). Antibiotic dosage was based on the preliminary pharmacokinetic/ pharmacodynamic (PK/PD) studies [11]. In addition, all procedures in this study were performed in single blind.

2.2. ETT biofilm study

Eighteen ETTs were obtained from Large White-Landrace pigs (32.11 ± 1.18 kg approximately 6 months aged) included in our randomized animal study [11]. Following animal extubation, ETTs were retrieved and stored in a sealed specimen bag at −80 °C prior to analysis [13]. Qualitative and quantitative (colony forming unit counts (LogCFU/ml)) analyses of MRSA and all aerobic bacteria were performed within the ETT lumen and in the ETT-cuff (Figure S2) [11] A 1-cm section of each ETT was processed for obtaining Scanning electron microscopy images, that were processed in Image J to measure biofilm thickness [14].

3. Results

Eighteen pigs completed the 76-hour study. Eighteen ETTs (7.5 internal diameters) from the control, linezolid, and telavancin groups obtained after 72 h of mechanical ventilation were included in the analyses. Before analysis, ETTs were frozen for a mean time of 229.67 (143.95), 219.67 (115.81), and 52.50 (54.42) days in the control, linezolid and telavancin groups, respectively, $P = 0.0244$ (post-hoc control vs. linezolid $P = 0.9824$, control vs. telavancin $P = 0.0268$).

3.1. ETT biofilm MRSA load

3.1.1. ETT load

MRSA was isolated from 6/6 (100%), 6/6 (100%), and 4/6 (66.66%) ETTs in the control, linezolid and telavancin groups, respectively ($P = 0.105$).

There were no statistically significant differences in the ETT MRSA load between the control, linezolid, and telavancin groups, but the telavancin group presented the lowest load (median [interquartile range = IQR] 1.94 [0.00–5.45] log CFU/mL) when compared to the control (4.93 [4.41–5.15] log CFU/mL) and linezolid (3.99 [3.22–4.68] log CFU/mL) groups, respectively, $P = 0.236$) (Fig. 1A). The load of other concomitant aerobic bacteria and fungi also did not differ significantly between the control, linezolid, and telavancin groups 3.37 [1.76–4.17], 4.37 [2.25–5.01], and 1.77 [0.00–4.64], log CFU/mL, respectively, $P = 0.392$. SM Item S3 summarizes the most frequently isolated microorganisms within ETTs. There was no significant correlation between ETT MRSA load and MRSA tracheal aspirate (TA) (rho = 0.338, $P = 0.183$), but we did find a correlation among ETT MRSA load and MRSA bronchoalveolar lavage (rho = 0.511, $P = 0.045$) at 72 h (Fig. 1D). MRSA load was significantly higher in ETT in comparison with BAL at 72 h in the control ($P = 0.0028$) and linezolid ($P = 0.0046$) groups, but not in the telavancin group ($P = 0.0688$) (Fig. 1C).

3.1.2. ETT-cuff load

The load of MRSA in ETT-cuffs did not show a significant difference between control (1/6, 16.67%), linezolid (1/6, 16.67%), and telavancin groups (2/6, 33.33%), respectively, $P = 0.725$. The control, linezolid, and telavancin groups did not differ significantly in terms of ETT-cuff MRSA load, with values of 0.00 [0.00–3.54], 0.00 [0.00–0.18], and 0.00 [0.00–3.32] CFU/mL, respectively, $P = 0.638$ (Fig. 1B). Nor did the load of other concomitant aerobic bacteria differ significantly between the control, linezolid, and telavancin groups, at 6.15 [5.94–6.73], 6.49 [5.73–6.70], and 6.63 [5.80–6.72] CFU/mL, respectively, $P = 0.810$.

3.2. ETT biofilm MRSA thickness

Overall, we analyzed 76 scanning electron microscopy analysis images with an average of 4.00 [2.00–5.00], 4.00 [2.75–4.25], and 5.50 [2.75–7.50], $P = 0.332$ images per animal from the control, linezolid, and telavancin groups. We performed a median [IQR] of 38.00 [23.75–48.25] thickness measurements. There were no differences in the number of measurements for minimal thickness (17.25 [9.00–21.50], 13.50 [9.50–22.00], and 23.50 [8.50–48.50], $P = 0.501$) (Micron), and maximal thickness (16.00 [10.00–18.00], 15.50 [11.25–20.00], and 23.00 [15.00–36.25], $P = 0.166$) between groups.

Significant differences in biofilm thickness between the control, linezolid and telavancin groups were found (minimum thickness $P < 0.001$, maximum thickness $P < 0.001$). The minimum thickness

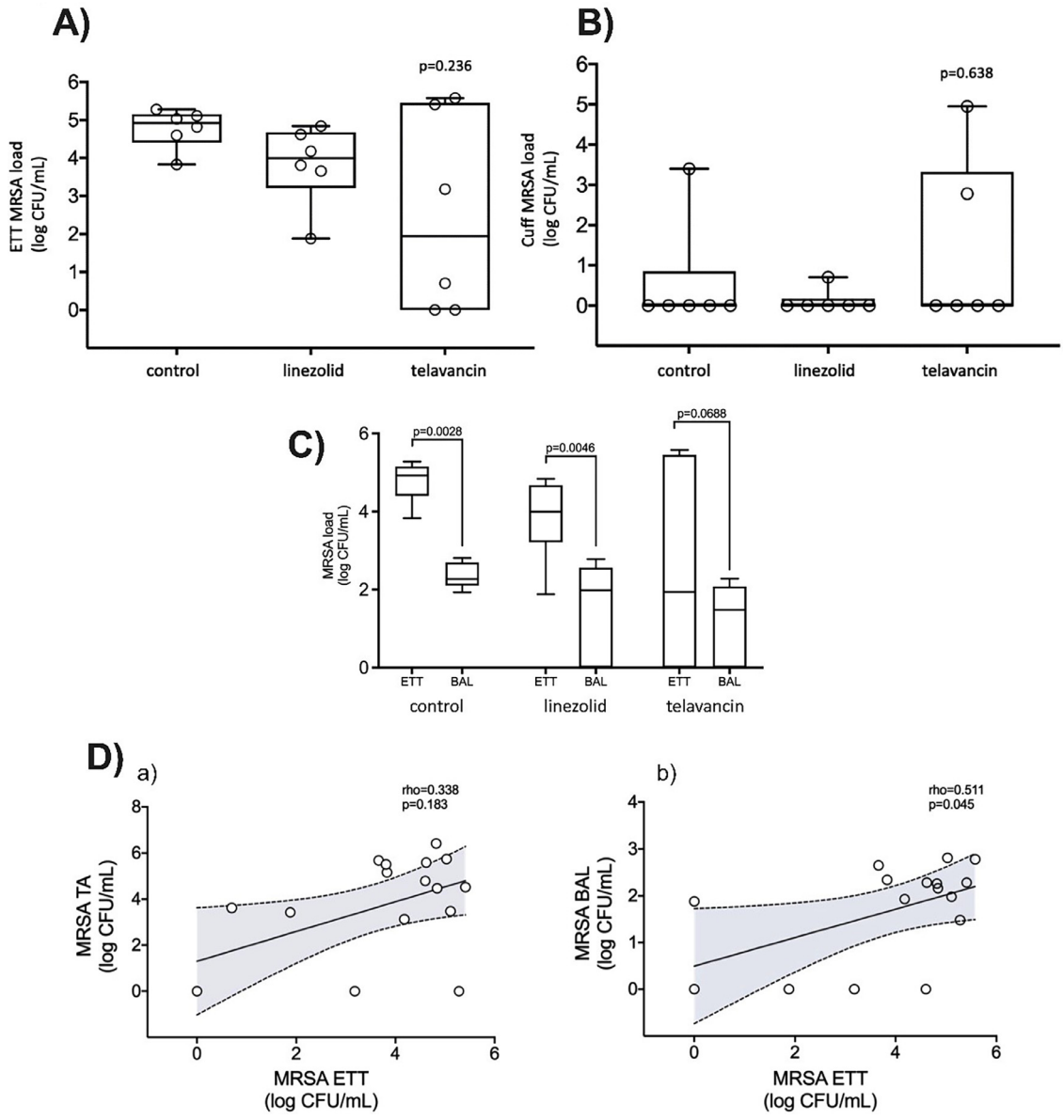

Fig. 1. ETT MRSA load (A) and Cuff MRSA load per study group (B). MRSA load between ETT and BAL per study group (C), and linear regression of TA and BAL and ETT MRSA load at 72 h (D). (A) In each box plot, the median value is indicated by the horizontal line ($P = 0.236$), the 25th and 75th percentiles are indicated by the lower and the upper horizontal lines, whereas whiskers represent the 10th and 90th percentiles. Each dot represents MRSA colonization within ETT. (B) In each box plot, the median value is indicated by the horizontal line, the 25th and 75th percentiles are indicated by the lower and the upper horizontal lines, whereas whiskers represent the 10th and 90th percentiles. Each dot represents MRSA colonization in the external cuff. No differences between control, linezolid and telavancin were found ($P = 0.638$). (C) This figure depicts box plots of MRSA load in ETT and BAL at 72 h in each group. MRSA load significantly differed between ETT and BAL in the control ($P = 0.0028$) and linezolid ($P = 0.0046$) but not telavancin ($P = 0.0688$) group. (D) This figure depicts linear regression of between MRSA TA (a) and MRSA BAL (b) and ETT MRSA load at 72 h. Spearman correlation for non-parametric data was performed. MRSA TA did not correlate with MRSA ETT (rho = 0.338, $P = 0.183$), while MRSA BAL correlated with MRSA ETT (rho = 0.511, $P = 0.045$).

of biofilm was lower in the telavancin group in comparison to the control group (post-hoc $P < 0.001$) but not in comparison with the linezolid group (post-hoc $P = 0.101$). Whereas the maximum thickness of biofilm was lower in the telavancin group than in both the control (post-hoc $P < 0.001$) and linezolid (post-hoc $P < 0.001$) groups (Fig. 2A and B).

4. Discussion

The main finding of this experimental study is that telavancin treatment achieved lower MRSA load occurrence and biofilm thickness in ETTs than the control and linezolid treatments. To our knowledge, this is the first study to assess the effect of systemic treatment with telavancin on ETT-biofilm in a previously validated in vivo animal model of VAP due to MRSA [15].

Multiple antibiofilm and VAP prevention strategies have been investigated to date, including the use of silver-coated ETTs [2], and the orientation of the trachea or the positioning of the patient [13]. Accordingly, it is important to determine the anti-biofilm activity of the systemic antimicrobials currently approved for VAP treatment. Although antimicrobials do not eradicate mature biofilm, during mechanical ventilation their administration coincides with the early stages of biofilm formation and has demonstrated anti-biofilm efficacy [1,7,14].

MRSA ETT biofilm depends on the patient's mucus production which is influenced by clinical cure, the length of time under mechanical ventilation and the patient's underlying comorbidities. In

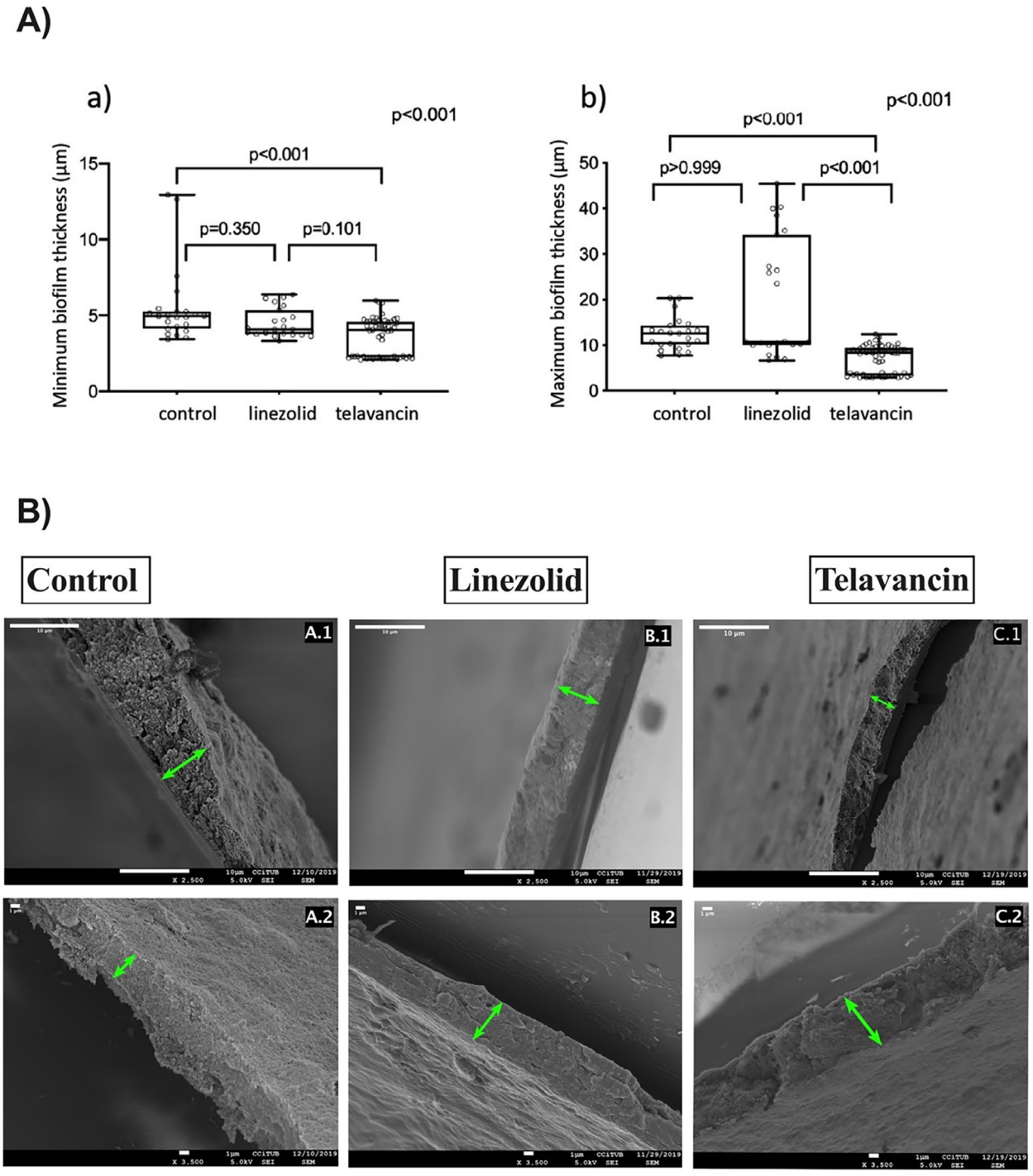

Fig. 2. Biofilm minimum and maximum thicknesses (A), scanning electron microscope (B). (A) Comparison of the minimum (a) and maximum (b) thickness of biofilm between the control, linezolid and telavancin under scanning electron microscope in microns scale. Median (IQR) of minimum biofilm thickness in the control, linezolid and telavancin groups were 4.97 (3.45–12.90), 4.08 (3.33–6.38), and 4.04 (2.09–6.00) µm, respectively. Minimum thickness differed among groups ($P < 0.001$), specifically between control and telavancin (post-hoc $P < 0.001$), median (IQR) of maximum biofilm thickness in the control, linezolid and telavancin groups was 12.6 (7.69–20.30), 10.7 (6.64–45.40), and 8.32 (2.88–12.40) µm, respectively. Maximum thickness differed among groups ($P < 0.001$), specifically between control and telavancin (post-hoc $P < 0.001$) and linezolid and telavancin post-hoc ($P < 0.001$). B) A.1 to C.2 images show the thickness of biofilm which was obtained by scanning electron microscope. A.1 and A.2 are images of an ETT-biofilm from pigs not treated (controls), with a thickness of 3.85 and 6.74 µm, respectively. B.1 and B.2 belong to an ETT-biofilm from pigs treated with linezolid, with a thickness of 5.94. and 5.37 µm, respectively. Finally, C.1 and C.2 correspond to ETT-biofilms from telavancin-treated pigs, with a thickness of 3 and 4.32 µm, respectively. *Images A.1 to C.1 were magnified by x2500 and captured in the lateral position. **Images A.2 to C.2 were magnified by x3500 and captured in the frontal position.

our study, the ETTs were retrieved after 76 h of mechanical ventilation and anti-MRSA systemic antibiotic administration. Our results for ETT anti-biofilm activity, which favour systemic telavancin over linezolid, are in accordance with a better clinical cure for the animals in the telavancin arm [11]. Besides, MRSA ETT and BAL loads were correlated, with the detection of significantly more biofilm only in ETT from the control and linezolid groups. This finding is noteworthy, but is difficult to measure in mechanically ventilated patients because of their heterogeneity and the presence of confounding factors [1].

In anti-biofilm in vitro *studies*, telavancin has proved useful for inhibiting both cell-wall synthesis and cell-membrane functions against MRSA and vancomycin-resistant, Gram-positive bacteria [16], as well as good activity and penetration in biofilms by multiple *Staphylococcal* strains [17]. However, the ETT in vivo environment may be difficult to reproduce in vitro. To date, no literature on the efficacy of telavancin against in vivo biofilm is available. Our findings of decreased biofilm thickness in the telavancin arm are not only in accordance with previous in vitro biofilm efficacy studies but also with its higher penetration into epithelial lining fluid and lung tissue reported in pharmacokinetic studies [18].

In the ATTAIN clinical trial, similar treatment rates were observed for telavancin (58.9%) and vancomycin (59.5%), although telavancin had a higher cure rate (82.4%) than vancomycin (80.7%) in monomicrobial *infections* but higher serum creatinine levels [3]. Thus, telavancin is not inferior to vancomycin or linezolid [11] in treating VAP caused by Gram-positive pathogens but should be restricted to patients without renal failure [10].

Although telavancin is still not recognized by guidelines as a first-line alternative to vancomycin and linezolid for the treatment of MRSA pneumonia [9], the Food and Drug Administration (FDA) approved this agent in the US in 2013 for VAP and hospital-acquired pneumonia (HAP) when alternative treatments are unsuitable. Furthermore, though authorized by regulatory agencies in Europe and Canada, telavancin has never been marketed in these countries [19]. In Australia, none of the lipoglycopeptide antibiotics are registered for use or have been studied in regional clinical trials [20].

The main limitation of our study is the low statistical power which is influenced by the small sample size. However, previous research by our group has shown that our model's results are representative of VAP scenarios in critically ill patients [1,7,14]. Second, animal models cannot reproduce drug interactions in mechanically ventilated patients [14]. However, an advantage of animal models is the inter-subject homogeneity and the fact that they are not influenced by patient's comorbidities [14].

5. Conclusion

Systemic treatment with telavancin compared to linezolid reduced ETT MRSA biofilm in an animal model of orotracheally intubated pigs with MRSA VAP. The use of telavancin is currently limited because of the risk of renal failure or impairment and the increased mortality in patients with altered baseline creatinine [10]. Nevertheless, its beneficial effects on biofilms may increase its administration in clinical practice in elective patients.

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Ethical approval: This research is approved by the Institutional Review Board and Ethic Committee of our institution (number 344/17). Animal care complied with the Spanish government guidelines and ARRIVE guidelines for animal studies (Publication No. 85–23, revised 1996).

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Author contributions: L.F.B., G.L.B. and A.T designed the study; LFB, K.K, D.B., A.M., L.B.F, A.S.C. performed the experiments. LFB, K.K and L.B.F performed image acquisition; K.K., D.B. and L.F.B. analysed, interpreted data, and wrote the manuscript; All authors critically revised the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107052.

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