be safe, effective and probably more economical (there are no clear data that confirm this).[7] In addition, another advantage demonstrated in this case in particular–and to date not studied–is the potential for home administration of the antibiotic. This would significantly decrease the potential for transmission of the bacterium.

In conclusion, administration of ceftazidime/avibactam in the HAH setting in selected cases would drastically decrease costs deriving from hospital admission, as well as complications related to hospital stay; would not undermine the treatment indicated for the patient; and would help control intrahospital transmission. Therefore, we believe that its home use should be considered under suitable circumstances.

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References

1. Highlights of prescribing information for Avycaz (ceftazidime and avibactam). Available in: http://www.allergan.com/assets/pdf/avycaz_pi [accessed February 2015].
2. European Medicines Agency (Internet). Committee for Medicinal Products for Human Use. Available in: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/04/news_detail_002518.jsp&mid=WC0b01ac058004d5c1 [accessed 28.04.16].
3. Peleg AY, Hooper DC. Hospital-acquire infections due to gram-negative bacteria. N Engl J Med. 2010;362:1804–13.
4. Liscio JL, Mahoney MV, Hirsch EB. Ceftolozane/tazobactam and ceftazidime/avibactam: two novel β-lactam/β-lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2015;46:266–71.
5. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis. 2016;16:661–73.
6. Toussaint KA, Gallagher JC. β-lactam/β-lactamase inhibitor combinations: from then to now. Ann Pharmacother. 2015;40:86–9.
7. Mirón-Rubio M, González-Ramallo V, Estrada-Cuxart O, Sanroma-Mendizábal P, Segado-Soriano A, Mujal-Martínez A, et al. Intravenous antimicrobial therapy in the hospital-at-home setting: data from the Spanish Outpatient Parenteral Antimicrobial Therapy Registry. Future Microbiol. 2016;11:375–90.

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Comparative activity of tedizolid against clinical isolates of linezolid-resistant coagulase-negative staphylococci and methicillin-resistant *Staphylococcus aureus*☆

Actividad comparativa de tedizolid frente a Staphylococcus *coagulasa negativos resistentes a linezolid y* Staphylococcus aureus *resistentes a meticilina*

Tedizolid phosphate is an antibiotic from the oxazolidinone group that was recently approved for the treatment of acute bacterial skin and soft-tissue infections caused by Gram-positive cocci.[1] This second-generation drug has higher activity *in vitro* than its analogue linezolid.[2–4] Although the breakpoints for susceptibility to tedizolid against *Staphylococcus* were recently established,[5] its activity against linezolid-resistant (LR) isolates has not been well studied. Our objective was to evaluate *in vitro* the susceptibility to tedizolid of methicillin- and linezolid-resistant coagulase-negative *Staphylococcus* (LR-CNS) and methicillin-resistant *Staphylococcus aureus* (MRSA). Our secondary objective was to compare the susceptibility of our isolates to other antibiotics used as an alternative in MRSA infections.

Susceptibility *in vitro* to tedizolid was studied in 22 LR-CNS and 33 MRSA isolates in the Department of Microbiology at Hospital Universitario San Cecilio in Granada, Spain, from 2007. Nine of the LR-CNS isolates were recovered from a previous study conducted by Sorlozano et al.[6] Identification was performed using MALDI-TOF (Bruker Daltonics®, Germany) and all isolates underwent a study of the minimum inhibitory concentration (MIC) against tedizolid, linezolid, vancomycin, ceftaroline and daptomycin through the disk diffusion method with a gradient strip (Liofilchem®, Italy). All LR isolates also underwent a study of the MIC against erythromycin, clindamycin, chloramphenicol and streptogramin A, and the different profiles of resistance linked to different mechanisms of resistance to linezolid were evaluated[7]: point mutations in the V domain of 23S ribosomal RNA (*rrn* gene), presence of the *cfr* gene or mutations in the genes that encode the L3 and L4 proteins of the 50S ribosomal subunit. All isolates were seeded in Mueller-Hinton agar with a 0.5 McFarland inoculum and incubated for 24 h at 37 °C. Methicillin resistance was confirmed using 5 μg cefoxitin. The MIC of the different antibiotics was interpreted according to the EUCAST recommendations (v. 6.0). All redundant isolates with a period less than 5 days for a single patient were excluded. In addition, a clonality study was conducted using pulsed-field gel electrophoresis (PFGE)[6] on the isolates that had signs of epidemiological outbreak: isolates that were grouped in time and space.[8]

A total of 55 isolates from 30 men (54.5%) and 25 women (45.5%), from different locations, were analysed: 29 blood culture samples (13 *S. aureus*, 7 *Staphylococcus epidermidis* and 9 *Staphylococcus hominis*), 15 respiratory samples (15 *S. aureus*) and 11 samples from exudates (5 *S. aureus* and 6 *S. epidermidis*).

The epidemiological relationship of the patients infected with LR-CNS was as follows: 9 of the patients infected with *S. hominis* between 2007 and 2008 were admitted to the intensive care unit (n = 8) or the emergency department (n = 1). All other patients infected with LR-CNS (*S. epidermidis*, n = 13) were admitted to different departments between 2009 and 2015: general surgery (n = 2, 2009–2013), internal medicine (n = 3, 2010–2015), gastroenterology (n = 1, 2009), vascular medicine (n = 2, 2009–2014), nephrology (n = 3, 2011–2015), anaesthesia (n = 1, 2010) and emergency medicine (n = 1, 2013). The clonality study for the *S. hominis* isolates that had signs of epidemiological outbreak confirmed

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Table 1
Summary of the *in vitro* activity of different antibiotics in 22 LR-CNS and 33 MRSA isolates.

	MIC (mg/l)			Percentage of resistance[a]
Antibiotics	Range	50%	90%	
LR-CNS (22)				
Linezolid	8 to >256	48	>256	100
Tedizolid	1–8	4	8	100
Vancomycin	0.5–2	1	1.5	0
Ceftaroline	0.125–0.75	0.5	0.75	0
Daptomycin	0.19–0.38	0.19	0.38	0
MRSA (33)				
Linezolid	1–3	2	2	0
Tedizolid	0.25–0.5	0.38	0.5	0
Vancomycin	0.38–1	0.5	1	0
Ceftaroline	0.25–1	1	1	0
Daptomycin	0.125–1.5	0.38	0.5	0

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; LR-CNS, methicillin- and linezolid-resistant coagulase-negative *Staphylococcus*.

[a] According to the breakpoint points established by EUCAST (v 6.0).

the presence of 2 different clones: clone A (n = 8) and clone B (n = 1).[6] All other isolates had no signs of epidemiological outbreak.

All isolates were resistant to methicillin. The susceptibility profile for the isolates is presented in Table 1. Tedizolid proved to have higher activity *in vitro* compared to linezolid. The MIC_{90} for tedizolid *versus* LR-CNS and MRSA was lower (8 and 0.5 mg/l) compared to that observed for linezolid (>256 mg/l and 2 mg/l). In addition, intervals were estimated for the MIC of tedizolid *versus* LR-CNS and MRSA from 1 to 8 mg/l and from 0.25 to 0.5 mg/l, respectively, compared to linezolid (MIC of 8 to >256 mg/l for LR-CNS and 1 to 3 mg/l for MRSA). We found resistance to tedizolid in all LR-CNS (MIC > 0.5 mg/l, the EUCAST breakpoint to consider them resistant). In addition, 4 MRSAs had a MIC of 0.5 mg/l against tedizolid. No resistance to vancomycin, ceftaroline or daptomycin was found in any of the isolates that we studied.

The resistance phenotypes of the LR-CNS isolates were consistent with the presence of a single strain carrying the *cfr* gene (cross-resistance to linezolid, amphenicols, lincosamides and streptogramin A, as well as susceptibility to macrolides), with a MIC to linezolid higher than 256 mg/l and a MIC to tedizolid higher than 3 mg/l. In addition, we found another strain consistent with the presence of mutations in the V domain of 23S ribosomal RNA (resistance to linezolid and susceptibility to amphenicols, lincosamides, streptogramin A and to macrolides), with a MIC for linezolid and tedizolid of 32 and 6 mg/l, respectively. All other isolates had phenotypes consistent with the coexistence of multiple mechanisms of resistance.

Tedizolid is presented as a highly potent drug, and in line with other series, we present data showing a MIC_{90} 4 to 16 times lower compared to linezolid.[9] Although our results suggest that this antibiotic has higher activity *in vitro*, as in other studies conducted in LR Staphylococcus,[10,11] the MIC of tedizolid often exceeds the breakpoint established by EUCAST. In our study, the MIC_{50} and MIC_{90} *versus* LR-CNS were 4 and 8 mg/l, respectively, and all were resistant.

Although some studies have demonstrated greater susceptibility to tedizolid in LR isolates carrying the *cfr* gene,[12] we were unable to demonstrate this. However, we present results that demonstrate high resistance to tedizolid in isolates that often have phenotypic profiles of resistance consistent with the presence of multiple mechanisms of resistance to linezolid. In light of these facts, the existence of a new plasmid (*optr*A) conferring resistance to linezolid and to amphenicols was recently reported.[13] Therefore, new studies are needed that provide definitive data on the efficacy of tedizolid in LR isolates, which often possess multiple mechanisms of resistance to this drug.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eimce.2017.03.012.

References

1. European Medicines Agency. Authorisation details. Available in: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002846/human_med_001856.jsp&mid=WC0b01ac058001d124 [accessed 05.06.16].
2. Kanafani ZA, Corey GR. Tedizolid (TR-701): a new oxazolidinone with enhanced potency. Expert Opin Investig Drugs. 2012;21:515–22.
3. Thomson KS, Goering RV. Activity of tedizolid (TR-700) against well-characterized methicillin-resistant *Staphylococcus aureus* strains of diverse epidemiological origins. Antimicrob Agents Chemother. 2013;57:2892–5.
4. Zhanel GG, Love R, Adam H, Golden A, Zelenitsky S, Schweizer F, et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. Drugs. 2015;75:253–70.
5. European committee on antimicrobial susceptibility testing. Available in: http://www.eucast.org/clinical_breakpoints [accessed 10.06.16].
6. Sorlozano A, Gutierrez J, Martinez T, Yuste ME, Perez-Lopez JA, Vindel A, et al. Detection of new mutations conferring resistance to linezolid in glycopeptide-intermediate susceptibility *Staphylococcus hominis* subspecies *hominis* circulating in an intensive care unit. Eur J Clin Microbiol Infect Dis. 2010;29:73–80.
7. Morosini MI, Cercenado E, Ardanuy C, Torres C. Phenotypic detection of resistance mechanisms in gram-positive bacteria. Enferm Infecc Microbiol Clin. 2012;30:325–32.
8. Pujol M, Limón E. General epidemiology of nosocomial infections. Surveillance systems and programs. Enferm Infecc Microbiol Clin. 2013;31:108–13 [Article in Spanish].
9. Locke JB, Zurenko GE, Shaw KJ, Bartizal K. Tedizolid for the management of human infections: In vitro characteristics. Clin Infect Dis. 2014;58:S35–42.
10. Rodríguez-Avial I, Culebras E, Betriu C, Morales G, Pena I, Picazo JJ. In vitro activity of tedizolid (TR-700) against linezolid-resistant staphylococci. J Antimicrob Chemother. 2012;67:167–9.
11. Shaw KJ, Poppe S, Schaadt R, Brown-Driver V, Finn J, Pillar CM, et al. In vitro activity of TR-700, the antibacterial moiety of the prodrug TR-701, against linezolid-resistant strains. Antimicrob Agents Chemother. 2008;52:4442–7.
12. Rybak JM, Roberts K. Tedizolid phosphate: a next-generation oxazolidinone. Infect Dis Ther. 2015;4:1–14.
13. Shore AC, Lazaris A, Kinnevey PM, Brennan OM, Brennan GI, Connell BO, et al. First report of CFR-encoding plasmids in the pandemic sequence type (ST) 22 methicillin-resistant *Staphylococcus aureus* staphylococcal cassette chromosome mec type-iv clone. Antimicrob Agents Chemother. 2016;60:3007–15.

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