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The authors have no conflict of interest to disclose.

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## Successful treatment of Pantón–Valentine leukocidin-positive methicillin-resistant *Staphylococcus aureus* pneumonia with high doses of linezolid administered in continuous infusion



## Tratamiento eficaz de una neumonía comunitaria producida por un *Staphylococcus aureus* resistente a metilicina leucocidina Pantón-Valantin con altas dosis de linezolid en perfusión continua

Pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) strains producing a cytotoxin known as Pantón–Valentin leukocidin (PVL) is a severe and difficult to treat disease.<sup>1–4</sup> Linezolid has excellent epithelial lining fluid (ELF) penetration rates but drug concentrations in critically ill patients are highly variable.<sup>5–8</sup> We describe the clinical case of a patient with septic shock secondary to a community-acquired PVL-secreting MRSA pneumonia, in

which linezolid plasma concentration within the therapeutic range were only reached with the use of higher than recommended doses (600 mg every 8 h) administered in continuous infusion.

A 56-year-old Caucasian man was admitted on February 2, 2015 with a 4-day history of dyspnea, mucopurulent expectoration, and fever (>38 °C). His weight was 80 kg (body mass index [BMI] 27.7 kg/m<sup>2</sup>), smoked 2–3 cigarettes a day, and consumed approximately 7 standard drinks daily. Physical examination revealed sinus tachycardia (160 beats/min), diaphoresis, hypertension (blood pressure [BP] 154/92 mmHg), and marked respiratory distress as well as bilateral crackles and disperse rhonchi up to the apex on lung auscultation. This caused a hypoxemic respiratory insufficiency with an initial PaO<sub>2</sub> of 55 mmHg that did not improve despite an elevated inspired oxygen fraction (FiO<sub>2</sub> 0.5) and noninvasive mechanical ventilation, for which he needed orotracheal intubation and ICU admission. Blood urea nitrogen was 32 mg/dL, serum creatinine 0.88 mg/dL, and glomerular filtration rate (Cockcroft–Gault equation) 106 mL/min, C-reactive protein 25.6 mg/L, procalcitonin 24.17 ng/mL, and lactic acid 5 mmol/L. Other laboratory data were unrevealing. Chest radiography revealed bilateral alveolar and interstitial infiltrates and alveolar condensation in the right upper lobe. The patient was tentatively diagnosed with CAP and was treated empirically with

intravenous ceftriaxone (2 g every 24 h), intravenous levofloxacin (0.5 g every 12 h) (positive urinary detection of pneumococcal antigen), and oseltamivir (positive PCR assay detection of influenza A and B viruses in oropharyngeal swabs). During the first 24 h of ICU admission, the patient's condition deteriorated, with secondary septic shock and need of vasoactive drugs (norepinephrine 0.2  $\mu$ g/kg/min). Microbiologically, a MRSA was isolated in cultures from bronchial aspirates and in four blood culture bottles (linezolid minimum inhibitory concentration [MIC] = 2 mg/L) on the day of admission. Each MRSA isolate carried the PVL genes. The MRSA strain was sent to the National Microbiology Center (Institute of Health Carlos III, Madrid). The initial empirical antibiotic treatment was discontinued and linezolid at a standard dose (600 mg every 12 h infused over 60 min) was administered.

Treatment with linezolid was maintained and the remaining antimicrobials were discontinued. Steady state plasma concentrations of linezolid were determined from the third day of treatment using a high-performance liquid chromatography technique, with a minimum plasma concentration state ( $C_{\min}^{ss}$ ) (or pre-dose) of 0.8 mg/L and maximum ( $C_{\max}^{ss}$ ) (at the end of infusion) of 4.8 mg/L, which were considered subtherapeutic (therapeutic range  $C_{\min}^{ss} > 2$  mg/L). Although blood cultures became negative on the fifth day of treatment, the patient showed a protracted respiratory clinical course with worsening of radiographic images, and according to drug susceptibility testing, antimicrobial coverage was expanded with intravenous clindamycin (600 mg every 8 h) and ciprofloxacin (400 mg every 8 h). In addition, the dosing interval of linezolid as well as the duration of the time of infusion were modified on several occasions based on results of plasma drug concentrations in order to achieve an optimal pharmacokinetic (PK) and pharmacodynamic (PD) ratio (Table 1). Seventeen days after starting treatment with linezolid, therapeutic levels were reached with a regimen of 600 mg every 8 h administered in continuous infusion, which coincided with eradication of PVL producing MRSA in

pulmonary samples. Thoracic computed tomographic (CT) scans performed over the course of treatment revealing extensive involvement of the pulmonary parenchyma with multiple cavities and important necrotic areas in the upper lobes compatible with pneumatoceles and bronchiectasis (Fig. 1). The patient required mechanical ventilation during 73 days (with tracheostomy) with procedural sedation, analgesia, and prolonged muscle relaxation. After 5 weeks of treatment with linezolid, the patient was successfully weaned. Linezolid was administered for a total of 35 days, clindamycin for 29 days and ciprofloxacin for 19 days. He was discharged after a 3-month hospitalization. At the present time, his oxygen saturation on room air is >95%.

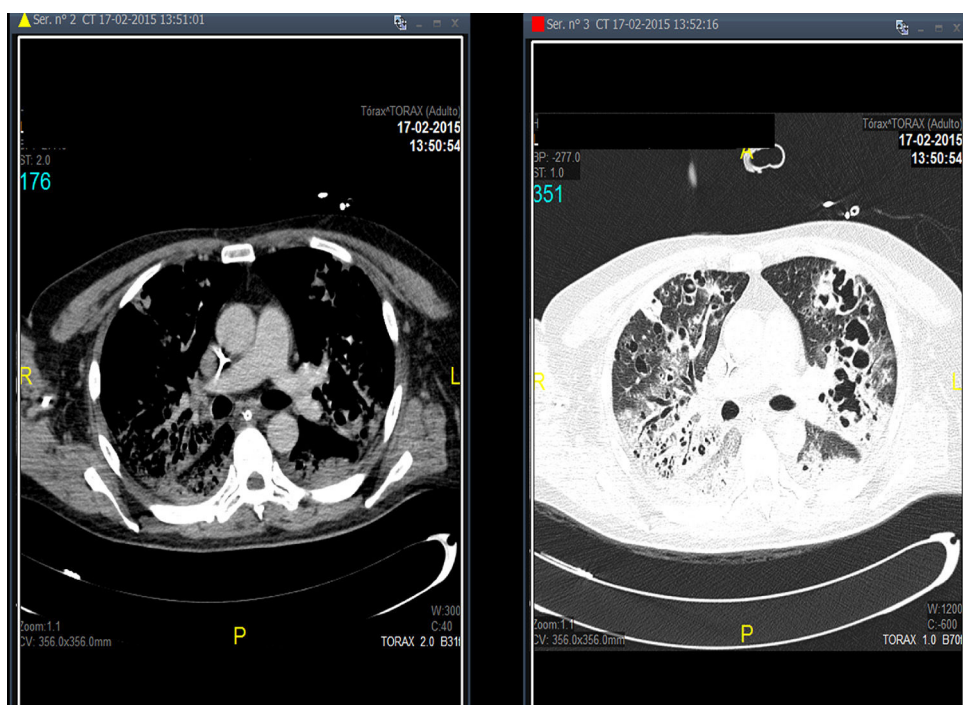
Mortality related to PVL-secreting MRSA pneumonia is around 70% despite the use of appropriate antimicrobials according to results of susceptibility testing.<sup>4</sup> A combination of antimicrobials active against MRSA and with adequate penetration in the pulmonary parenchyma should be selected. Linezolid is a synthetic antibiotic belonging to the oxazolidinone family especially active against Gram-positive bacteria, including multiresistant pathogens, with 100% diffusion in the ELF.<sup>5</sup>

Although in the technical specifications of linezolid, a standard dose of 600 mg every 12 h administered in 60-min intermittent infusion is recommended, recent pharmacokinetic studies have shown that the administration of this fixed dose in some population groups did not allow to reach an optimal predictive pharmacokinetic/pharmacodynamic (pk/pd) ratio of clinical efficacy of the drug ( $C_{\min}^{ss} \geq 2$ –4 mg/L), whereas it has also been related to overexposure ( $C_{\min}^{ss} \geq 10$  mg/L) and higher risk of hematologic toxicity.<sup>9</sup> These circumstances are frequent in ICU patients with severe sepsis or septic shock, in whom most factors associated with underexposure or overexposure to linezolid may be present.<sup>9,10</sup> Subtherapeutic linezolid concentrations have been related to glomerular filtration rates greater than 80 mL/min,<sup>7</sup> which is frequent in septic patients treated with vasoactive drugs as was in our patient.

**Table 1** Changes in doses, intervals between doses, forms of administration, and plasma concentrations of linezolid during the patient's stay in the ICU.

Day of sampling	Dose (mg)	Dosing interval doses	Type and duration of infusion	GFR (mL/min)	$C_{\min}^{ss}$ (mg/L)	Platelet count ( $\times 10^9$ /L)
February 13, 2015	600	12 h	Intermittent (60 min)	176	0.5	112
February 17, 2015	600	12 h	Intermittent (60 min)	239	<0.5	85
February 23, 2015	600	8 h	Extended (2 h)	345	<0.5	456
February 24, 2015	600	6 h	Extended (2 h)	267	1.4	531
February 26, 2015	600	6 h	Extended (2 h)	301	0.6	540
Day of sampling	Dose (mg)	Dosing interval doses	Type and duration of infusion	GFR (mL/min)	$C_{\min}^{ss}$ (mg/L)	Platelet count ( $\times 10^9$ /L)
March 2, 2015	600	6 h	Continuous (6 h)	301	8.5	544
March 6, 2015	600	8 h	Continuous (8 h)	275	2.7	527
March 9, 2015	600	8 h	Continuous (8 h)	333	4.6	467

GFR: glomerular filtration rate.



**Figure 1** Thoracic CT scan at day 7 after hospital admission showing multiple cavities and important necrotic areas in the upper lobes compatible with pneumatoceles and bronchiectasis.

Strategies for optimizing linezolid plasma levels include an increase in the total dose, by-reducing the dosing interval from 12 h to every 8 or 6 h, or extending the duration of infusion to 2–4 h (extended infusion) or using a continuous infusion.<sup>9,10</sup> Our patient in whom glomerular filtration rates >200 mL/min were recorded, a  $C_{\min}^{ss} \geq 4$  mg/L were only obtained with the administration of a linezolid dose of 600 mg every 6–8 h in continuous infusion, which coincided with negativization of pulmonary exudate cultures. This high dose, between 1.5 and 2-fold higher than the standard recommended dose was well tolerated, without signs of toxicity, particularly without a decrease in platelet count or hemoglobin levels.

In ICU patients with severe infections and increased renal clearance, linezolid should be administered at high doses and in continuous infusion with close monitorization of plasma drug levels.

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### Conflicts of interest

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