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Pneumonia clinical reports

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Recurrent ventilator-associated pneumonia caused by "difficult to treat" resistance *Pseudomonas aeruginosa*

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Sir,

We hereby present a clinical report with three key points. Firstly, ventilator-associated pneumonia is the most frequent nosocomial infection in Intensive Care Units (ICU). Second, *Pseudomonas aeruginosa* is currently the most frequently isolated causative microorganism in Spanish ICUs. And third, this non-fermenting gram-negative bacillus has multiple virulence mechanisms that enable colonization and subsequent tissue invasion. It also has the ability to form biofilms that facilitate its persistence and therefore, infection recurrence. Likewise, it is characterized by a remarkable intrinsic resistance, along with an extraordinary capacity to acquire resistance to practically all available antibiotics, including the new β-lactams with β-lactamase inhibitors (BL/BLI), such as ceftazidime–avibactam, as we describe in the following case report.

A 62-year-old male patient with the following medical history: arterial hypertension, dilated heart disease of ischemic origin with severe left ventricular dysfunction, and chronic hepatitis B infection. The patient had a left colostomy carrier after a complicated acute diverticulitis. He was admitted to the hospital with the diagnosis of bilateral SARS-CoV-2 pneumonia, 3 weeks after the onset of symptoms. Pulmonary CT was compatible with severe bilateral SARS-CoV-2 lung infection (CO-RADS 6) (Figure 1). He remained in the respiratory care unit for 20 days, requiring high-flow oxygen therapy. He received treatment with dexamethasone (initial dose 6 mg/day) along with ceftriaxone and piperacillin-tazobactam as empirical antibiotic treatment for suspected coinfection. He was admitted to the ICU and required intubation, mechanical ventilation and two prone position sessions due to severe acute respiratory distress syndrome (ARDS) with PaO_2/FiO_2 <100mmHg. APACHE II: 11 points. SOFA score: 9 points.

On day 11 upon admission to the ICU, he met clinical, radiological and microbiological criteria for nosocomial pneumonia. Empirical therapy was initiated using meropenem and linezolid. *P. aeruginosa* (AmpC profile) was isolated in a tracheobronchial aspirate (meropenem MIC 1 mg/L). Antibiotic treatment was adjusted and the patient continued receiving meropenem for 10 days. On day 36, the patient developed a new episode of nosocomial pneumonia complicated by secondary bacteremia. Carbapenem-resistant *P. aeruginosa* (meropenem MIC > 16 mg/L) was isolated. Initial empirical treatment with meropenem and colistin was adjusted to ceftazidime-avibactam for 14 days based on *in vitro* susceptibility test results. Finally, on day 78 upon admission to the ICU, whilst on weaning, the patient presented tracheobronchitis due to extensively drug-resistant *P. aeruginosa*, which included ceftazidime-avibactam resistance (MIC 32 mg/L). The isolate showed optimal in vitro activity to ceftazolane-tazobactam, colistin, and tobramycin. The patient was treated with ceftalozane-tazobactam and inhaled colistin.

Prolonged mechanical ventilation, the need for a tracheostomy, and multiple weaning attempts determined the evo-

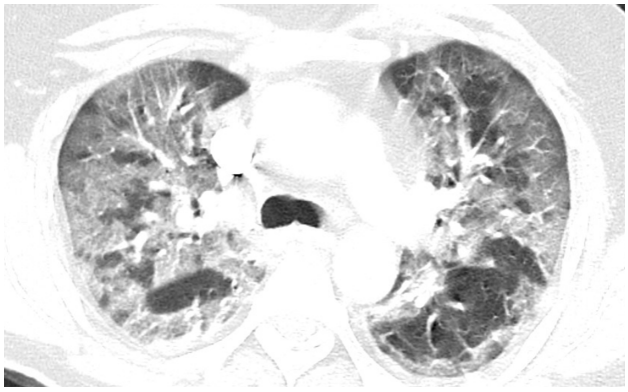

Figure 1 CT: Highly suggestive of severe bilateral SARS-CoV-2 lung infection.

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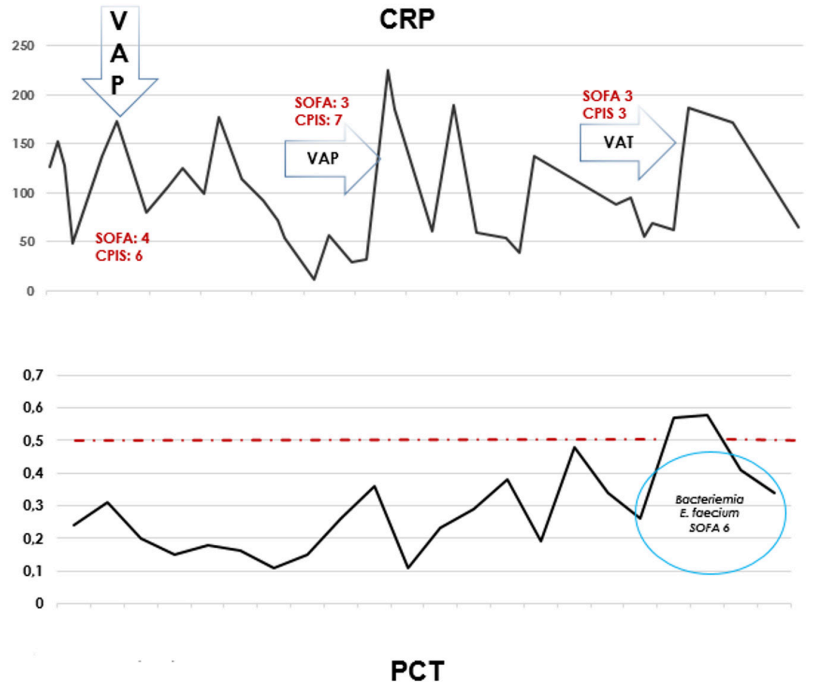

Figure 2 | **Biomarker evolution: C-reactive protein (CRP mg/L) and procalcitonin (PCT ng/dl). Sepsis-related Organ Failure Assessment (SOFA) and Clinical Pulmonary Infection Score (CPIS). VAP: Ventilator-associated Pneumonia. VAT: Ventilator-associated Tracheobronquitis.**

lution and ICU length of stay of the patient. During his admission, *Aspergillus fumigatus* was isolated from a respiratory tract sample, which would be treated according to clinical severity criteria. The patient also develops two bacteremias due to *Enterococcus faecium*, and many other febrile episodes for which he received multiple antibiotics.

The evolution of biomarkers throughout the admission is shown below. In our case, CRP kinetics adjusted better to the different infectious episodes compared to procalcitonin, which would only got over 0.5 ng/ml in the course of enterococcal bacteremia. CPIS and SOFA score values are displayed. (Figure 2) A few days after the episode of tracheobronchitis, the patient was discharged from ICU and later transferred to a rehabilitation healthcare center.

In the 2020 ENVIN-HELICS study, 17.3% of patients included developed a nosocomial infection, the most frequent being ventilator-associated pneumonia (VAP) (36.8%). Overall mortality was 44%. *P. aeruginosa* was the most frequently isolated microorganism (22.9%). Resistance to ceftazidime, cefepime, and piperacillin-tazobactam was 35% and imipenem 42% [1].

Risk factors associated with VAP caused by *P. aeruginosa* include older age, diabetes, immunocompromised status, cystic fibrosis, chronic obstructive pulmonary disease, prolonged hospital and ICU stay, presence of tracheostomy, extended ventilation periods, recent surgery, and high baseline severity. Previous antibiotic exposure to anti-pseudomonal beta-lactams, quinolones, and aminoglycosides favours the acquisition of multidrug-resistant strains [2].

P. aeruginosa's pathogenicity is very complex. This pathogen uses a series of functional elements, to move and adhere on living and nonliving surfaces, such as different tissues and medical devices. In addition, *P. aeruginosa* forms bacterial communities with a complex intercelular communication mechanism, surrounded by a polisaccharides-based structure known as biofilm. This structure acts as a barrier, providing a favorable environment for colony survival, and playing and important role in the chronic colonization or infection process [3].

Literature suggests that up to 17% of patients with *P. aeruginosa* bacteremia will have a recurrent infection, frequently associated with the severity of comorbid conditions and a concomitant increase of mortality rates [4]. Recurrent episodes of VAP cause by *P. aeruginosa* occur due to persistence of strains present in a prior infection. Previous studies have shown a considerable disparity in the incidence of this complication (3-50%), most frequently in patients with ARDS [5]. VAP incidence rates among COVID-19 ARDS patients are much higher than pre-pandemic rates in non-Covid patients, and a higher rate of recurrence VAP episodes has been ob-

served (up to four events in a single patient) even in patients with appropriate antimicrobial treatment [6].

"Difficult-to-treat" resistance is defined as *P. aeruginosa* that exhibits non-susceptibility to all of the following antibiotics: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastin, ciprofloxacin, and levofloxacin. Ceftalozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam are first-line options, assuming in vitro susceptibility for infections outside of the urinary tract, and cefiderocol could be an alternative treatment if first-line antibiotics are not available or tolerated [7].

Resistance induction by ceftazidime–avibactam remains an issue of concern, with diminished outer membrane permeability and overexpression of efflux pumps or AmpC as underlying mechanisms. Whilst some studies have reported resistance ceftazidime–avibactam rates of 20%, resistance was not detected in other series [8]. Although AmpC derepression also increases MIC of ceftalozane-tazobactam, clinical resistance to this new combination requires an additional structural modification of AmpC, which could explain the lower development of resistance. Furthermore, in those infections linked to high bacterial load, the probability of resistance development is elevated for most classical antipseudomonials. This is because mutant prevention concentrations are frequently above those achieved by systemic administration, except for colistin and ceftalozane-tazobactam [9]. This is perhaps, an advantage to be taken into account in *P. aeruginosa* VAP treatment.

The increasing prevalence of multidrug-resistant strains is a cause of concern as it compromises the selection of appropriate empirical and definitive antimicrobial treatments. This situation is associated with worse outcomes and higher mortality, mostly in patients with severe infections, as bacteremia and ventilator-associated pneumonia [10]. Empirical antibiotic treatment against *P. aeruginosa* should be initiated taken into account prior antibiotic therapy, local epidemiology and susceptibility of previous isolates.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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