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Letter to the Editor

Pharmacokinetic/pharmacodynamic target attainment of continuous infusion ceftazidime-avibactam in peritoneal fluid in an orthotopic liver transplant recipient affected by bacteraemic complicated intra-abdominal infection due to OXA-181-producing *Klebsiella pneumoniae*

Editor: Stefania Stefani

Sir,

The widespread prevalence of carbapenemase-producing *Enterobacterales* (CPE) is a worrisome health concern. OXA-181 is a type of OXA-48-like carbapenemase that is increasingly produced by CPE and ceftazidime-avibactam is currently considered to be the first option in this scenario [1].

We describe the case of an orthotopic liver transplant (OLT) recipient affected by OXA-181-producing *Klebsiella pneumoniae* (Kp) bacteraemic complicated intrabdominal infection (cIAI) that was treated with continuous infusion (CI) ceftazidime-avibactam optimized by real-time pharmacodynamic target attainment at the infection site.

A male, 41 years of age with Alagille syndrome, underwent OLT because of severe hyperbilirubinemia and cholestatic jaundice (Model for End-Stage Liver Disease [MELD] score 26). On day 1, according to the finding of a colonizing OXA-48-producing Kp clinical strain from the pretransplant rectal swab (MIC = 0.5 mg/L for meropenem and MIC = 1 mg/L for ceftazidime-avibactam), targeted perioperative prophylaxis with CI meropenem (1g q6h over 6h after 2g loading dose [LD]) plus intravenous tigecycline (50 mg q12h) was administered for 48 hours. Six days after OLT, the clinical conditions worsened with septic shock occurrence, and an OXA-181-producing Kp having the same genotypic and phenotypic pattern was isolated from both blood cultures and peritoneal fluid, whereas bronchoalveolar lavage cultures were negative (Supplementary Table S1). Resistome analysis showed that Kp belonged to ST449, encoded for the *blaOXA-181* carbapenemase gene, and harboured different antimicrobial resistance genes. Genetic analysis found that OXA-181-producing Kp had altered outer membrane porins (truncated OmpK35 and OmpK36). The clinical isolate was fully susceptible to both meropenem (MIC = 0.25 mg/L; clinical breakpoint [CB] = 2 mg/L) and ceftazidime-avibactam (MIC = 0.5 mg/L; CB = 8 mg/L). Treatment with CI ceftazidime-avibactam (2.5g LD followed by 2.5g q8h over 8h) was started according to evidence showing higher clinical cure and lower mortality rate with ceftazidime-avibactam monotherapy compared with carbapenem-based regimens for carbapenem-susceptible OXA–48–producing Kp infections [2]. Ceftazidime-avibactam exposure was optimized by means of real-time attainment of an optimal joint pharmacokinetic/pharmacodynamic (PK/PD) target at the infection site. For this purpose, ceftazidime and avibactam steady-state concentrations (C_{ss}) were simultaneously measured in serum and in peritoneal fluid by means of a validated liquid chromatography-tandem mass spectrometry method [3]. The joint PK/PD target at the infection site was considered optimal when, in the peritoneal fluid, both the C_{ss}/MIC ratio for ceftazidime was 4 to 8 and the C_{ss}/C_T ratio for avibactam was >1 (where C_T is the fixed concentration threshold of 4 mg/L adopted by the EUCAST for avibactam when testing ceftazidime-avibactam susceptibility) [4]. Ceftazidime-avibactam C_{ss} were measured every 48 to 72 hours (namely on days 10, 12, 15, 17, 19, 22, and 25) for a total of seven assessments and each result was made available within 8 hours of sampling. During overall treatment, optimal joint pharmacokinetic/pharmacodynamic targets were attained in both peritoneal fluid (average ceftazidime C_{ss}/MIC ratio of 39.6 and avibactam C_{ss}/C_T ratio of 4.93) and serum (average ceftazidime C_{ss}/MIC ratio of 40.5 and avibactam C_{ss}/C_T ratio of 4.81). The mean peritoneal fluid-to-serum ratio was 0.98 for ceftazidime (range 0.78–1.14) and 1.03 for avibactam (range 0.84–1.33; Fig. 1). On day 10, the ceftazidime-avibactam dosing regimen was halved to 1.25 g q8h CI based on the finding of a joint PK/PD target attainment that was more than optimal in the presence of moderate renal dysfunction. On day 15, continuous venovenous haemodiafiltration (CVVHDF) was applied and the dosage was increased up to 2.5 g q8h CI; on day 19, the confirmatory attainment of a more than optimal joint PK/PD target allowed it to decrease to 1.25 g q8h CI. Clinical improvement occurred and microbiological eradication with persistent negativization of follow-up cultures was achieved, both in blood (first collected at 48 h from the start of therapy and then depending on clinical conditions) and in peritoneal fluid samples (collected at least once weekly during surgical revisions). On day 25, ceftazidime-avibactam treatment was stopped.

Unfortunately, the patient experienced a subsequent duodenal perforation associated with haemodynamic instability and the need for CVVHDF. A difficult-to-treat (DTR) *Pseudomonas aeruginosa* strain resistant to almost all the beta lactams [cefepime (MIC>8 mg/L), ceftazidime (MIC>32 mg/L), piperacillin-tazobactam (MIC>16 mg/L), ceftolozane-tazobactam (MIC>4 mg/L), ceftazidime-avibactam (MIC>8 mg/L), and meropenem (MIC = 8 mg/L)] was isolated from the peritoneal fluid on day 26. Given the permissible MIC of meropenem, treatment with high-dose CI meropenem (2g LD followed by 1.5g q6h over 6h) was started on day 28 and a TDM-guided dosing optimization was implemented every 48 to 72 h for attaining a C_{ss}/MIC ratio of 4 to 8. Overall, the average serum meropenem C_{ss}/MIC ratio was optimal during treatment (6.31, ranging from 3.01–15.6), leading to documented microbiological eradication. After positioning an abdominal prosthesis and applying vacuum-assisted closure (VAC) therapy for promoting closure of the abdominal wall, meropenem treatment was stopped on day 43.

On day 45, the OXA-181-producing Kp strain (MIC of 0.5 mg/L and 0.25 mg/L for ceftazidime-avibactam and meropenem, respec-

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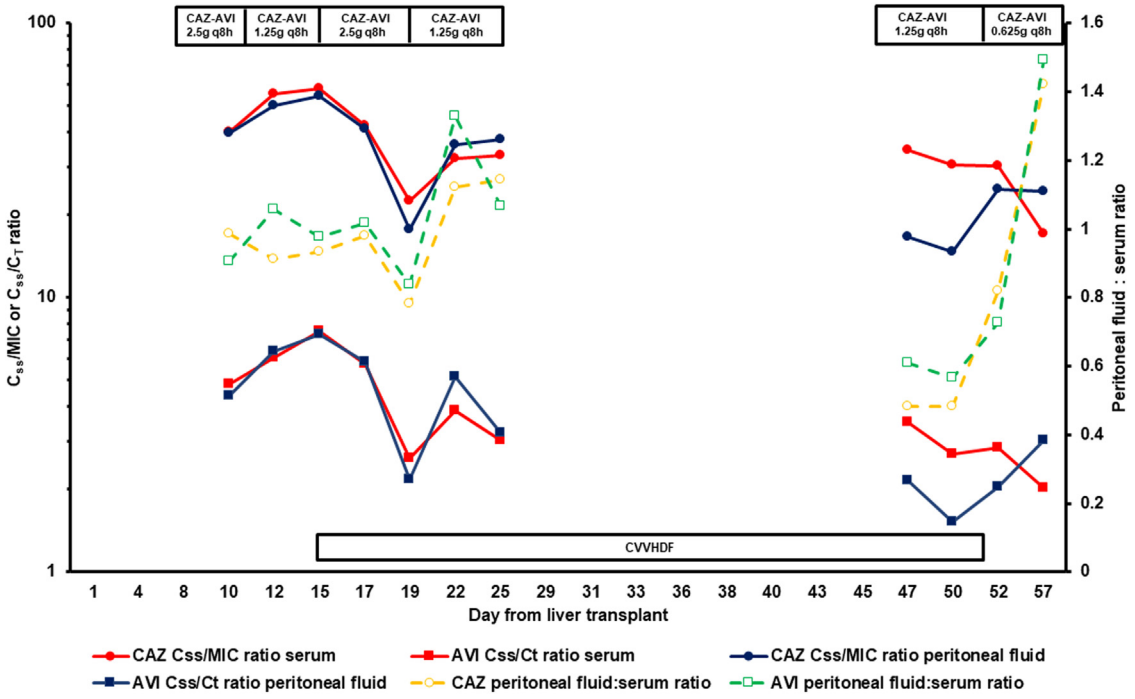

Fig. 1. Temporal trends of steady-state serum and peritoneal fluid concentrations and of peritoneal fluid/serum ratio of ceftazidime/avibactam. AVI, avibactam; CAZ, ceftazidime; C_{ss}, steady-state concentration; C_T, threshold concentration; CVVHDF, continuous venovenous haemodiafiltration; MIC, minimum inhibitory concentration.

tively) was isolated again from both surgical wound swabs and the VAC cultures; cautiously, ceftazidime-avibactam therapy was restarted. However, clinical conditions remained stable, renal function progressively improved, and CVVHDF was discontinued. During the second course of treatment, ceftazidime-avibactam C_{ss} were measured on days 47, 50, 52, and 57 for a total of four assessments. Optimal joint pharmacokinetic/pharmacodynamic targets were attained in both peritoneal fluid (average ceftazidime C_{ss}/MIC ratio of 20.1 and avibactam C_{ss}/C_T ratio of 2.19) and serum (average ceftazidime C_{ss}/MIC ratio of 28.1 and avibactam C_{ss}/C_T ratio of 2.77). The mean peritoneal fluid-to-serum ratios were 0.80 and 0.85 for ceftazidime and avibactam, respectively. On day 50, CVVHDF was withdrawn, and the ceftazidime-avibactam dosage was halved to 0.625 g q8h CI. Microbiological eradication was documented, ceftazidime-avibactam treatment was successfully completed on day 58, and no further relapses occurred at follow-up.

This case documented a very high penetration rate of ceftazidime-avibactam in the peritoneal fluid, with concentrations of both ceftazidime and avibactam quite similar to those observed in serum. Notably, the penetration rate in the peritoneal fluid was ca. 20% higher during the first course of treatment, likely due to conditions of septic shock that may have enhanced vascular permeability at the peritoneal level. In our patient, we found a higher ceftazidime peritoneal penetration rate than those found among 12 non-OLT patients receiving CI ceftazidime for severe cIAI (0.56–0.64) [5]; this may be associated with increased intestinal permeability in OLT recipients. Regarding avibactam, a preclinical peritonitis rat model treated with aztreonam-avibactam demonstrated an avibactam peritoneal penetration rate that was consistent (0.94) with our findings [6].

In conclusion, real-time attainment of optimal joint PK/PD targets of ceftazidime-avibactam in the peritoneal fluid may have favoured successful treatment with CI ceftazidime-avibactam monotherapy of OXA-181-producing Kp cIAI. Prompt dosing adaptation in relation to the evolving pathophysiological and/or iatrogenic conditions was fundamental for avoiding clinically unnecessarily high ceftazidime-avibactam concentrations. Further prospective studies are warranted for testing this hypothesis and providing more data on the peritoneal penetration rates of ceftazidime-avibactam in critical patients.

Declaration Competing Interest

MG received personal fees from Angelini and Shionogi outside of the submitted work. PV has served as a consultant for bioMérieux, Gilead, Merck Sharp and Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the speaker's bureaus for Correvio, Gilead, Merck Sharp and Dohme, Nordic Pharma, and Pfizer, outside the submitted work. FP has participated in speaker's bureau for Advanz Pharma,gelini, BeiGene, Gilead, InfectoPharm, MSD, Pfizer, and Shionogi, and acted as a consultant for Advanz Pharma, BeiGene, bioMerieux, Gilead, MSD, Pfizer, and Shionogi outside of the submitted work. The other authors report no potential conflicts of interest for this work.

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Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee [No. EM 232–2022_308/2021/Oss/AOUBo on 16 March 2022]. Informed written consent was collected.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2023.05.007.

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