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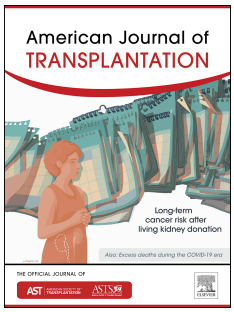

Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae*.

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Title page

Title: Efficacy of ceftazidime-avibactam in solid organ transplant recipients with bloodstream infections caused by carbapenemase-producing *Klebsiella pneumoniae.*

Running title: CAZ-AVI for CPE-BSI in SOT recipients.

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Keywords: ceftazidime-avibactam; carbapenem-resistant *Klebsiella pneumoniae*; solid organ transplantation; bloodstream infections; INCREMENT-SOT Project.

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Abbreviations

AE, adverse event; AST, antimicrobial susceptibility testing; AUROC, area under the receiver operating characteristic curve; BAT, best available therapy; BC, blood culture; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; CPE, carbapenemase-producing Enterobacterales; CPKP, carbapenemase-producing *Klebsiella pneumoniae;* CRE, carbapenem-resistant Enterobacterales; ESBL, extended-spectrum β-lactamase; GBRT, Gradient Boosted Regression Tree; HR, hazard ratio; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamases; MIC, minimum inhibitory concentration; OR, odds ratio; OXA, oxacillinase; SOT, solid organ transplantation.

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Abstract (words = 200)

We aimed to compare the efficacy of ceftazidime-avibactam (CAZ-AVI) versus the best available therapy (BAT) in solid organ transplant (SOT) recipients with bloodstream infection caused by carbapenemase-producing *Klebsiella pneumoniae* (CPKP-BSI). A retrospective (2016-2021) observational cohort study was performed in 14 INCREMENT-SOT centers (ClinicalTrials.gov identifier: NCT02852902). Outcomes were 14-day and 30-day clinical success (complete resolution of attributable manifestations, adequate source control and negative follow-up blood cultures) and 30-day all-cause mortality. Multivariable logistic and Cox regression analyses adjusted for the propensity score to receive CAZ-AVI were constructed. Among 210 SOT recipients with CPKP-BSI, 149 received active primary therapy with CAZ-AVI (66/149) or BAT (83/149). Patients treated with CAZ-AVI had higher 14-day (80.7% versus 60.6%, *P*=0.011) and 30-day (83.1% versus 60.6%, *P*=0.004) clinical success and lower 30-day mortality (13.25%-versus 27.3%, *P*=0.053) than those receiving BAT. In the adjusted analysis, CAZ-AVI increased the probability of 14-day (adjusted odds ratio [aOR]: 2.65; 95% confidence interval [95%CI]: 1.03-6.84, *P*=0.044) and 30-day clinical success (aOR: 3.14; 95%CI: 1.17-8.40; *P*=0.023). In contrast, CAZ-AVI therapy was not independently associated with 30-day mortality. In the CAZ-AVI group, combination therapy was not associated with better outcomes. In conclusion, CAZ-AVI may be considered a first-line treatment in SOT recipients with CPKP-BSI.

Summary sentence

We retrospectively analyzed a cohort of 210 SOT recipients with bloodstream infection due to carbapenemase-producing *Klebsiella pneumoniae*. Among 149 patients receiving active therapy, 83 were treated with CAZ-AVI and 66 with other regimens. CAZ-AVI was an independent predictor of 14-day and 30-day clinical success.

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1. Introduction

Solid organ transplant (SOT) recipients are at particular risk of developing infectious complications due to carbapenem-resistant Enterobacterales (CRE)[1,2]. Infections caused by these multidrug-resistant bacteria are associated with high mortality[3]. In addition, therapeutic options are limited and often associated with adverse events (AEs)[1,4].

Recently, ceftazidime-avibactam (CAZ-AVI) —a combination of a third-generation cephalosporin and a novel β-lactamase inhibitor— has been approved for the treatment of complicated urinary tract infections, intraabdominal infections and nosocomial pneumonia [1,3]. CAZ-AVI is active *in vitro* against organisms producing class A (TEM, SHV, CTX-M), class C (AmpC) and some class D (i.e. OXA-48 and related enzymes) β-lactamases. Furthermore, this is the first agent within the β-lactam family to retain activity against *Klebsiella pneumoniae* carbapenemase (KPC)-producing isolates [4,5].

Available experience in real-world clinical practice with CAZ-AVI in SOT recipients with CRE infections is limited to some case reports[6–10] and small case series[11,12]. Most of them are restricted to lung transplant (LuT) recipients with cystic fibrosis treated for respiratory tract infections due to carbapenemase-producing *Klebsiella pneumoniae* (CPKP). A single-center small series has compared the clinical efficacy of CAZ-AVI and that of other antibiotic regimens in a cohort of kidney transplant (KT) recipients infected with CPKP[13]. In view of this literature gap, and taking into account the increasing trend over the last years in the prevalence of multidrug-resistant bacteria in transplant centers worldwide, our objective was to investigate the efficacy of CAZ-AVI compared to the best available therapy (BAT) in a retrospective, multicenter, international cohort of SOT recipients with bloodstream infection (BSI) caused by CPKP.

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2. Materials and Methods

2.1 Study setting and population.

The INCREMENT-SOT Project (ClinicalTrials.gov identifier NCT02852902) aims to investigate the associations between specific antimicrobial therapies, antimicrobial susceptibility testing (AST) and clinical outcomes in SOT recipients diagnosed with BSI due to extended-spectrum β-lactamase-producing or carbapenemase-producing Enterobacterales (CPE)[14]. The original INCREMENT-SOT cohort was a retrospective, international (38 centers in 16 countries), observational cohort over a 12-year period (2004-2016). In the present work, this period was extended to cover from January 2016 to December 2021 in 14 centers from the consortium (6 in Spain, 5 in Italy, 2 in Brazil, 1 in USA) with clinical access to CAZ-AVI. Inclusion criteria were consecutive BSI episodes caused by KPC- or OXA-48-producing *K. pneumoniae* in SOT recipients with a functioning graft. Patient data were collected at each site by reviewing microbiology laboratory reports and patients' charts until day 30 from the incident (i.e. first) blood culture (BC). The choice of antibiotic therapy was at the discretion of the attending clinician. An electronic centralized database was curated, and queries were sent to participating centres for missing or inconsistent data. Follow-up was censored at day 30 from the incident BC or death (whichever occurred first). Exclusion criteria were the unavailability of relevant data relative to therapeutic regimen administered and/or outcome, and death within the first 48 hours since incident BCs were obtained (**Figure 1**).

The study protocol was approved by the Spanish Agency for Medicines and Health Products (AEMPS code FIB-COL-2015-01) and by the Ethics Committee of Reina Sofia University Hospital-IMIBIC (code 2907), which waived the requirement for informed consent given the retrospective nature of the research. Approval of the Ethical Committees of the participating centers was also obtained, following local requirements. This report follows STROBE recommendations (**Table S1**)

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2.2 Study design and definitions

BSI was defined as the isolation of CPKP in BCs in a patient fulfilling criteria for systemic inflammatory response (defined by the presence of ≥2 of the following features: respiratory rate ≥22/min, altered mental status, or systolic blood pressure ≤100 mmHg)[15]. Primary outcome variables were 14-day and 30-day clinical success and 30-day all-cause mortality. The variables registered in the INCREMENT-SOT cohort have been previously described[14,16]. Clinical success required the achievement of clinical cure, defined by the resolution of all signs and symptoms attributable to the infection, adequate surgical control of the source (when applicable) and negative follow-up BCs (when obtained), and the absence of relapse or death. Clinical status by days 14 and 30 was assessed by the local investigator at each participating center. In addition, the investigator's adjudication was reviewed and validated by two coordinating investigators (EPN and JTC). When necessary, queries were performed to clarify the classification.

The INCREMENT-SOT-CPE mortality risk score at the time of BSI onset included the following variables: INCREMENT-CPE score ≥8 (8 points), cytomegalovirus (CMV) disease in the previous 30 days (7 points), absolute lymphocyte count ≤600 mm^3 (4 points), no source control (3 points), inappropriate empirical therapy (2 points), and the interaction INCREMENT-CPE score ≥8 x previous CMV disease (-7 points)[14]. In the overall cohort the INCREMENT-CPE-SOT score exhibited an area under the receiver operating characteristic curve (AUROC) of 0.76 (95% confidence interval [CI]: 0.69-0.82) for predicting 30-day all-cause mortality, with an optimal cut-off value of 8, which yielded a sensitivity of 93.9% and a negative predictive value (NPV) of 96.6% but only moderate specificity (52.8%) and PPV (37.7%) (**Figure S1** and **Table S2**). Based on these results and our previous study[14], a cut-off value of 8 was selected to classify patients as having low (INCREMENT-CPE-SOT score <8) or high mortality risk (score ≥8).

Treatment was considered empirical when administered before the results of AST became available, whereas targeted therapy was defined as that initiated thereafter. Targeted

therapy was classified as monotherapy if it included one single *in vitro* active agent and combination therapy if two or more active agents were used. The use of CAZ-AVI was considered as combination therapy if it was administered with other active agents. The activity of carbapenems was redefined based on the minimum inhibitory concentration (MIC) values provided by the centers and taking into consideration pharmacokinetics/pharmacodynamics considerations. In detail, meropenem was considered active when the CPKP isolate had a MIC value ≤4 mg/L and maximum doses were used (2 g every 8 hours in a 3-hour extended perfusion). Tigecycline was considered active for intraabdominal BSI only provided that the focus was properly controlled. Of note, tigecycline was always considered inactive when the BSI had a urinary tract source, regardless of the MIC values. In cases of tigecycline-containing combination therapy for a urinary tract BSI, tigecycline was not considered and the regimen was classified as monotherapy. Cephalosporins were considered active when the CPKP (mostly an OXA-48-producer) did not have an associated extended-spectrum β-lactamase (ESBL) or AmpC, showed *in vitro* sensitivity and the patient had an INCREMENT-SOT-CPE score <8. Aminoglycosides were considered active in the presence of *in vitro* sensitivity, an INCREMENT-SOT-CPE score <8, and the source of BSI was the urinary tract source or intravascular catheter. Fosfomycin was considered active when the isolate exhibited *in vitro* susceptibility, the source of BSI was the urinary tract and the INCREMENT-SOT-CPE score <8. Colistin was considered active when the CPE isolate showed *in vitro* sensitivity, the source of BSI was other than the lung, and the patient had an INCREMENT-SOT-CPE score <8.

The global cohort included all reported BSI cases in SOT recipients that fulfilled inclusion criteria (**Figure 1**). To assess the efficacy of CAZ-AVI as compared to BAT, we defined a "treatment cohort", which included all patients that received CAZ-AVI-based or BAT regimens as first-line targeted therapy within the first 5 days from BSI onset. For analysis purposes, day 0 was defined as the date in which active therapy was initiated. Patients were excluded from the treatment cohort (**Figure 1**): (a) if they did not receive an active therapy; (b) if they had been

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receiving an active agent for ≥2 days before the sampling of incident BCs; (c) if they received a first active therapy beyond 5 days from incident BCs; and (d) if they received CAZ-AVI-based salvage therapy (defined by the initiation of CAZ-AVI ≥7 days from incident BCs).

2.3 Microbiological studies and antimicrobial susceptibility testing

Klebsiella isolates were locally identified by standard microbiological techniques. AST was investigated using automated systems or disk diffusion and interpreted according to the guidelines (Clinical and Laboratory Standards Institute [CLSI] or European Committee on Antimicrobial Susceptibility Testing [EUCAST]) applied at each center[17,18]. Investigators were requested to record both susceptibility rates for the CPKP isolates according to the clinical breakpoints established by the respective committees and MIC values if available. All CPKP isolates were confirmed to be carbapenemase producers according to PCR and DNA sequencing of carbapenemase genes *(bla*$_{KPC}$, *bla*$_{OXA-48}$, *bla*$_{VIM}$, *bla*$_{IMP}$ and *bla*$_{NDM}$) using established methods at each participating center.

2.4 Statistical analysis

Outcome comparisons between groups were made using the Mann-Whitney test (continuous variables) and the χ^2 test or Fisher's exact tests (categorical variables). The propensity score (PS) for the use of CAZ-AVI (versus BAT) or CAZ-AVI monotherapy (versus CAZ-AVI-based combination therapy) was calculated using a non-parsimonious logistic regression model. This PS included the following variables: age, gender, biliary stenosis, previous CMV disease, chronic kidney disease, post-transplant dialysis, Charlson comorbidity index (CCI)[19], diabetes mellitus, chronic lung disease, myocardial infarct, hospital-acquired infection, severe sepsis or septic shock, Pitt bacteremia score[20], lower respiratory tract as source of infection, urinary tract as source of infection, source control, non-surgical debridement, removal/replacement of vascular line, and KPC carbapenemase. In addition, to further control for the potential center effect on the probability of CAZ-AVI administration, we performed a

partial dependence analysis using a Gradient Boosted Regression Tree (GBRT) model including the following five predictors: age, gender, study period (2018-2021 versus 2016-2017), INCREMENT-SOT-CPE score, and centre. The GBRT model, discussed in detail in **Table S4,** highlighted that the probability to receive CAZ-AVI-based therapy was mostly influenced by CAZ-AVI availability across the study period (with 2018 representing a turning point in most centers) rather than by a given participating center. Based on this GBT model, centers were dichotomized into those with "high CAZ-AVI availability" versus "low/neutral CAZ-AVI availability", and this variable was entered into the multivariable models. The variable "high CAZ-AVI availability", however, showed high collinearity with the variable "CAZ-AVI therapy" (i.e. receiving targeted therapy with CAZ-AVI). Therefore, it was not possible to simultaneously include both variables in the final models.

Non-parsimonious logistic regression models were used to analyze the association of CAZ-AVI therapy with clinical success at days 14 and 30. The prediction ability of these models was examined by the corresponding AUROCs. We assumed lack of multicollinearity if all variables had a variance inflation factor <2. In addition, Cox proportional-hazards models were constructed to determine the influence of CAZ-AVI therapy on 30-day all-cause mortality. Covariates with a two-sided P <0.05 were considered statistically significant. Finally, the impact of CAZ-AVI combination therapy on study outcomes was also studied, adjusting by the PS and other potential confounders. Patients with missing data for each specific analysis were excluded from the multivariate models. The analyses were carried out using R software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25.0 (IBM Corp., Armonk, NY).

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3. Results

3.1. Characteristics of the study cohort

Fourteen participating centers contributed with 216 episodes of post-transplant CPKP-BSI, 210 and 149 of which were included in the global and treatment cohorts, respectively (**Figure 1**). Clinical characteristics are summarized in **Table S2. Table 1** compares the clinical characteristics of patients receiving CAZ-AVI (83/149, 55.7%) or BAT (66/149, 44.3%) as primary targeted therapy in the treatment cohort. Both groups were well balanced, since there were no significant differences in variables potentially related to study outcomes such as type of transplant, urinary stenosis, previous CMV disease, type of immunosuppression, severity of sepsis, source of infection, and risk of mortality according to INCREMENT-SOT-CPE and Pitt bacteremia scores. In contrast, we observed that patients allocated to the CAZ-AVI ~~BAT~~ group were more likely to have diabetes (89.2% versus 74.2%), chronic lung disease (20.1% versus 7.6%), and to undergo non-surgical debridement of the infection source (27.7% versus 7.7%) as compared to those in the BAT group.

3.2. Characteristics of the antibiotic treatment

Active antibiotic treatments defined as primary targeted regimes in the treatment cohort are summarized in **Table S3**. In the BAT group, monotherapy and combination therapy was administered to 59 (89.4%) and 12 (18.2%) patients, respectively. Monotherapy included colistin (N=30), meropenem (N=9), cephalosporins (N=1), aminoglycosides (N=4), fosfomycin (N=1) and tigecycline (N=9). Combination therapy included double-carbapenem therapy with meropenem and ertapenem (N=5), colistin and tigecycline (N=2), colistin and aminoglycosides (N=2), meropenem and tigecycline (N=2), and fosfomycin and aminoglycosides (N=1). In the CAZ-AVI group, on the other hand, monotherapy was administered to 67 (80.7%) patients and combination therapy to 16 (19.3%). The latter regimens were based on the combination CAZ-

AVI with tigecycline (N=10), colistin (N=2), colistin and tigecycline (N=2), fosfomycin (N=1), and tigecycline and ciprofloxacin (N=1).

In addition to these treatment definitions, we performed a descriptive analysis of the full course of antibiotic therapy given in both the CAZ-AVI and BAT groups from the date of the incident BC to the end of therapy, including those periods in which no antibiotic therapy or non-active agents were administered (**Figure 2**). We estimated differences in the length of treatment, frequency of treatment switching, and number of antibiotics administered in those patients that remained alive at the end of follow-up, to minimize the risk of bias due to early death (**Table S6**). The **Figure 2** highlights the large heterogeneity in regimens administered in the BAT group, as compared to the more homogeneous therapy in the CAZ-AVI group. No significant differences were found in the length of treatment across different groups (CAZ-AVI-based versus carbapenem-containing, polymyxin-containing, tigecycline-containing or aminoglycoside-containing regimens) (**Table S6**). There were no significant differences in the rate of switching between CAZ-AVI-based versus carbapenem-containing or polymyxin-containing regimens either. In contrast, patients in the CAZ-AVI group experienced a lower median number of sequential antibiotic changes than those treated with tigecycline-including or aminoglycoside-including regimens (**Table S6**). The median number of antibiotics administered per patient was significantly lower in the CAZ-AVI group as compared to other regimes (**Table S6**).

3.3. Association of CAZ-AVI with clinical outcomes

The crude rates of 14-day and 30-day clinical success and 30-day all-cause mortality in the treatment cohort according to INCREMENT-CPE-SOT and type of treatment (CAZ-AVI versus BAT) are shown in **Table S7.** Patients treated with CAZ-AVI had a significantly higher rate of clinical success at day 14 than those treated with BAT (80.7% versus 60.6%, *P*=0.011). This significant difference was also observed in the high mortality risk stratum of the treatment cohort (71.1% versus 38.9%, *P*=0.007), but not in the low mortality risk stratum (94.7% versus

86.7%, *P*=0.463) according to the INCREMENT-SOT-CPE score. The same trend was observed for clinical success at day 30, with significant differences observed between patients receiving CAZ-AVI versus BAT in the treatment cohort (97.4% versus 60.6%, *P*=0.004) and in the high mortality risk stratum (71.1% versus 38.9%, *P*=0.007), but not in the low mortality risk stratum (97.4% versus 86.7%, *P*=0.463). Finally, all-cause mortality in the treatment cohort was significantly lower in the CAZ-AVI group (13.3% versus 27.3%, *P*=0.053), although the differences did not remain statistically relevant when the analysis was stratified according to low (0% versus 6.7%, *P*=0.372) and high mortality risk (24.4% versus 44.4%, *P*=0.010) **(Table S7).**

Univariate logistic and regression analyses for study outcomes are shown in **Tables S8** (clinical success at day 14), **S9** (clinical success at day 30) and **S10** (30-day all-cause mortality). In the PS-adjusted model, the variables independently associated with 14-day clinical success were male gender (adjusted odds ratio [aOR]: 2.62; 95% CI: 1.01-6.82; *P*=0.048), the INCREMENT-CPE-SOT score (aOR [per unitary increment]: 0.81; 95% CI 0.74-0.90; *P*<0.001), and targeted therapy with CAZ-AVI (aOR: 5.65; 95% CI 1.03-6.84; *P*=0.044) (**Table 2A**). The independent association of CAZ-AVI therapy with 14-day clinical success was confirmed in the high mortality risk stratum (aOR: 4.13; 95% CI 1.27-13.41; *P*=0.018) (**Table 2B**). The same variables were independently associated with 30-day clinical success in the treatment cohort (**Table 3A**) and in the high risk stratum (**Table 3B**), respectively.

In the adjusted Cox regression model the variables predicting 30-day mortality were male gender (adjusted hazard ratio [aHR]: 0.42; 95% CI 0.19-0.94; *P*=0.034) and the INCREMENT-CPE-SOT score (aHR [per unitary increment]: 1.18; 95% CI 1.08-1.29; *P*<0.001) (**Table 4A**). Male gender did not remain as an independent predictor of 30-day mortality in the adjusted Cox model restricted to the high mortality risk stratum (**Table 4B**). Finally, we did not find evidence of an independent association between CAZ-AVI-including combination therapy (versus CAZ-AVI monotherapy) with study outcomes (**Tables S11** and **S12**). Kaplan-Meier survival curves in the

treatment cohort (CAZ-AVI versus BAT, log-rank test *P*=0.020) and the CAZ-AVI cohort (CAZ-AVI-including combination versus monotherapy, log-rank test *P*=0.870) are shown in **Figure S2**.

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4. Discussion

In this study we analyzed a retrospective cohort of 210 SOT recipients with BSI due to CPKP recruited in 14 transplant centers from multiple sites, 149 of whom received an active primary therapy with either CAZ-AVI or best available therapy (BAT) and were included in the treatment cohort. As compared to BAT, the rates of clinical success by days 14 and 30 were significantly higher and the 30-day all-cause mortality was significantly lower in patients that received CAZ-AVI. In the multivariate logistic regression model, and after adjusting for the PS for the choice of treatment, receiving CAZ-AVI was found to act as an independent predictor of clinical success but not of all-cause mortality by day 30. In addition, the clinical benefit of CAZ-AVI was greater among recipients with an increased baseline risk of poor outcome according to the INCREMENT-CPE-SOT score.

The experience to date with CAZ-AVI in the SOT setting has been mostly limited to case reports and a small non-comparative series[6–12]. Most of this experience was restricted to LuT recipients with respiratory tract infection or KT recipients. The only previous comparative series was recently published and included 54 KT recipients with CPKP infection mainly in form of surgical site infection and BSI, 22 of which received CAZ-AVI[13]. The rates of clinical cure by day 14 with CAZ-AVI and BAT (64.8% and 53.1%, respectively) were consistent with our results. In contrast, the overall 30-day mortality rate of 34.5% (13.6% with CAZ-AVI and 43.8% with BAT) was higher than that observed in our experience, which could be explained by the fact that a third of patients in the study by Zhang *et al.* received CAZ-AVI as salvage therapy, whereas our cohort only included the use of CAZ-AVI as first-line regimen. Moreover, Zhang *et al*. reported that CAZ-AVI was an independent protective factor for 30-day mortality. In addition to the potential confounder derived from the use of CAZ-AVI as salvage therapy, confounding by indication may have also led to a biased estimate of the treatment effect in that study, which we aimed to control for by means of a PS-based approach. On the other side, the inclusion of

INCREMENT-SOT-CPE score in our adjusted model, and the relatively low mortality rate in our cohort may explain the lack of apparent association between CAZ-AVI and 30-day survival..

An association between the use of CAZ-AVI and 30-day survival has been reported in studies carried out in the general population, which included variable proportions of SOT recipients and other immunocompromised patients[21–24]. The CAVICOR study is the largest series to date assessing the impact on mortality of CAZ-AVI in CPE infections, although only 13.3% of the 339 patients included were SOT recipients. In the multivariate analysis, CAZ-AVI therapy was associated with an increased survival, and this effect was particularly evident for those patients with an INCREMENT-CPE score ≥8 points[21]. In contrast, we did not find evidence of an independent association between the use of CAZ-AVI and 30-day survival, either in the global cohort or in the subgroup of patients with high mortality risk. In the CAVICOR study, the 30-day crude mortality was 17.4%, a figure that was close to ours (19.5%). The differences observed in the CAVICOR study according to the treatment group arose from the significantly higher 30-day crude mortality in patients with ≥8 points in the INCREMENT-CPE score treated with BAT compared with CAZ-AVI (46.9% versus 21.9%). However, the differences observed in the high mortality risk stratum of our cohort did not achieve statistical significance, which could be due to the relatively small sample size in the BAT group.

According to the literature, CAZ-AVI has activity against most KPC- and OXA-48-like-producing CPE[21,25]. In the univariable analyses, we observed that OXA-48-producing (versus KPC-producing) *K. pneumoniae* was associated with increased odds of 14-day (**Table S8**, OR 3.45, 95% CI 1.24-9.55, p=0.017) and 30-day clinical success (**Table S9**, OR 3.17, 95% CI 1.14-8.81, p=0.027). In an explorative analysis restricted to the KPC group (N = 100, data not shown), we observed that CAZ-AVI was significantly associated in univariable analysis with clinical success at day 14 (OR: 2.35, 95% CI: 1.05-5.30, p=0.039) and day 30 (OR: 2.88, 95% CI: 1.24-6.64, p=0.013) and also showed a non-significant trend towards a protective effect on 30-day mortality (HR 0.49, 95% CI 0.22 - 1.12, p=0.091). In contrast, we did not observe any significant association between

CAZ-AVI therapy and clinical outcomes in the subgroup of episodes due to OXA-48-producing CPE (N=49, data not shown). It should be noted, however, that the limited sample size of the OXA-48 group and the large heterogeneity of BAT regimens preclude any firm conclusion on the potential differences of CAZ-AVI therapy in terms of clinical outcomes according to the type of carbapenemase involved.

Previous studies in the non-transplant population have reported a greater benefit derived from CAZ-AVI therapy among patients with higher disease severity. In a retrospective study from Greece, CAZ-AVI was found to be more effective than other therapeutic options in critically ill patients with CPE infection and presence of shock or higher Sequential Organ Failure Assessment (SOFA) score[26]. Gu *et al.* also reported that CAZ-AVI may be of more value for severe, rather than mild, infections due to CPKP on the basis of the presence of septic shock, higher SOFA and CCI scores, and mechanical ventilation[27]. We have previously shown that the INCREMENT-CPE and INCREMENT-SOT-CPE scores can be used to define subgroups of patients with BSI by CPE with high-risk of mortality in the general and SOT populations, respectively, for whom more aggressive management strategies may be targeted[3,14,28,29]. A recent study in the general population reported that the performance of widely used tools such as the Pitt bacteremia score or the INCREMENT-CPE score to predict outcomes in patients with CPE infection was variable in the new era of novel antibiotics[30]. In our present experience the INCREMENT-SOT-CPE score was independently associated in the treatment cohort with the probability of achieving clinical success by days 14 and 30 and with 30-day mortality. Overall, our study provides an external validation of the clinical value of the INCREMENT-SOT-CPE to predict clinical outcomes in this complex patient population.

The role of CAZ-AVI as combination therapy remains under discussion. The combination treatment of various agents with *in vitro* activity has been recommended for those patients at high baseline risk of poor outcome[29]. In previous studies conducted in the general population, however, CAZ-AVI monotherapy was comparable to combination therapy based on other

agents[22–24,31]. Of note, some authors have reported the risk of emergence of resistance to CAZ-AVI, especially in high-inoculum infections (pneumonia) and when renal replacement therapies are used[32]. We found a similar 30-day mortality rate between patients treated with CAZ-AVI as single agent or combination therapy (14.9% versus 6.3%, respectively, *P*=0.611). Similarly, no significant differences were found between the two groups in the probability of 14-day or 30-day clinical success. These results are consistent with three recent metanalyses reviewing studies in the general population which found no difference in mortality or the rate of microbiological cure between patients receiving CAZ-AVI combination therapy compared to monotherapy for treatment of severe infections, mostly CPE BSI[33–35].

Our study has important limitations, including those inherent to any retrospective design, i.e. the treatment groups were not randomly assigned. Therefore, a PS for receiving CAZ-AVI was constructed to control for potential confounding by indication. In addition, no specific information on the differential impact of the therapeutic regimens on graft function was collected. A second major limitation is posed by the lack of data regarding treatment-emergent AEs. As per study protocol, only those AEs that led to the discontinuation of therapy were initially intended to be collected. Unfortunately, the reporting was not consistent across centers and, therefore, we chose not to include any information on this point. Finally, test-of-cure BCs were not systematically obtained provided that the patient experienced resolution of symptoms and signs and the clearance of bacteremia was demonstrated at 48-72 hours since the initiation of adequate therapy. In our opinion, however, this “pragmatic” approach is consistent with the retrospective nature of our study and reflects the usual practice in cases of BSI due to Enterobacterales.

On the other hand, participating centers included all consecutive CPKP BSI episodes diagnosed in SOT recipients during the study period that fulfilled study criteria in order to minimize any risk of inclusion bias. Therefore, the apparent heterogeneity in the number of cases per center would be explained by differences in local epidemiology. Fourteen centers from

four countries (Spain, Italy, Brazil and US) contributed to the study, further contributing to the representativeness of the sample, which would accurately reflect real-life practice in the SOT setting. Another potential source of bias would have arisen from comparing patients that were already receiving adequate treatment at BSI onset and those in which CPKP involvement was not clinically suspected. To control for this confounder, we restricted inclusion to those cases that were receiving inadequate therapy —or no antibiotics— at the time of BC sampling or that had previously received adequate empirical treatment for less than 48 hours.

Our study represents the largest comparative study to analyze the role of CAZ-AVI in the specific SOT setting. As compared to BAT, the use of this novel β-lactam/β-lactamase inhibitor was independently associated with 14-day and 30-day clinical success, and thus CAZ-AVI may be considered as a first-line therapeutic option for post-transplant CPKP BSI, particularly in SOT recipients with an INCREMENT-SOT-CPE score ≥8. Our findings should be ideally confirmed by controlled studies.

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Funding

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. JTC has served as scientific advisor for a research/consensus project for Pfizer, Marck, Shionogy and Menarini, as an expert in a consensus document for InfectoPharm and has received payment for lectures, including service on speakers' bureaus and the development of educational presentations for Pfizer, AstraZeneca and Merck. LMM has been a consultant for MSD and Shionogi, has served as speaker for Merck, Astra-Zeneca, Astellas, and Becton Dickinson and has received research support from Merck, Shionogi, Janssen-Cilag and

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

- **Figure 1.** Study flowchart.
- **Figure 2.** Graphical illustration of the rate of treatment switching, defined as number of antibiotic regime changes (Y-axis) per patient (X-axis) in patients from the BAT **(A)** and CAZ-AVI **(B)** groups of the treatment cohort. Patients are ordered from left to right according to the rate of treatment switching. In the Y-axis, each column square represents a new sequential change in the antibiotic regime in a single patient (see insert treatment line as an example; BC, date of blood culture; AB, date of the antibiotic susceptibility testing results). Results of *in vitro* antimicrobial susceptibility testing for the carbapenemase-producing *Klebsiella pneumoniae* isolate were coded according to the data provided by participating centers in the clinical database. A colour code was assigned to the following distinct antibiotic categories: no antibiotic ("none", light grey), inactive antibiotic (dark grey), and active antibiotics (one different colour per antibiotic, as indicated in the figure legend). Thus, monotherapy is depicted as a single-colour square and combination therapy as a multi-colour square in a column.

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Supporting Information statement

Additional Supporting Information may be found online in the supporting information tab for this article.

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Table 1. Clinical characteristics and outcomes of 149 solid organ transplant recipients with bloodstream infections by carbapenem-resistant *Klebsiella pneumoniae* who received primary therapy with ceftazidime-avibactam (CAZ-AVI) or best available therapy (BAT).

	ALL N=149	BAT N=66	CAZ-AVI N=83	*P*-value
Age [median (IQR)]	58 (50-65)	58 (52-65)	58 (50-67)	0.986[d]
Male gender [n (%)]	106 (71.10)	44 (66.67)	62 (74.70)	0.372
SOT-related variables				
Type of SOT [n (%)]				
Liver[a]	66 (44.30)	29 (43.94)	37 (44.58)	1.000
Kidney[b]	61 (40.90)	28 (42.42)	33 (39.76)	0.872
Heart	14 (9.40)	4 (6.06)	10 (12.05)	0.336
Lung	6 (4.00)	4 (6.06)	2 (2.42)	0.480[e]
Other multiorgan	2 (1.30)	1 (1.52)	1 (1.20)	1.000[e]
Time interval from SOT to positive blood culture [n (%)]				
≤30 days	44 (29.50)	18 (27.27)	26 (31.33)	0.720
31-180 days	40 (26.80)	16 (24.24)	24 (28.92)	0.650
≥ 181 days	65 (43.60)	32 (48.48)	33 (39.76)	0.368
Absolute lymphocyte count, cells/mm^3 [median (IQR)]	600 (300-905)	600 (310-890)	595 (268-915)	0.563[d]
TMP / SMX prophylaxis (previous 30 days) [n (%)]	94 (64.40)	41 (63.08)	53 (65.43)	0.903
Urinary stenosis [n (%)]	12 (8.10)	4 (6.06)	8 (9.64)	0.621
Biliary stenosis [n (%)]	30 (20.10)	9 (13.64)	21 (25.30)	0.119
Post-transplant dialysis (previous 30 days) [n (%)]	36 (24.30)	15 (23.08)	21 (25.30)	0.904
CMV replication (previous 30 days) [n (%)]	29 (19.50)	10 (15.15)	19 (22.89)	0.329
CMV disease (previous 30 days) [n (%)]	14 (9.40)	4 (6.06)	10 (12.05)	0.336
Baseline immunosuppression (previous 30 days) [n (%)]	111 (75.00)	43 (65.15)	68 (82.93)	0.022
Tacrolimus	130 (87.20)	58 (87.88)	72 (86.75)	1.000
Corticosteroids	85 (57.00)	34 (51.52)	51 (61.45)	0.294
Mycophenolic acid / mycophenolate mofetil	64 (43.00)	23 (34.85)	41 (49.40)	0.106
Cyclosporine	8 (5.40)	3 (4.55)	5 (6.02)	0.975
Everolimus	14 (9.40)	7 (10.61)	7 (8.43)	0.866
Azathioprine	10 (6.70)	4 (6.06)	6 (7.23)	1.000[e]
Inducction therapy [n (%)]	70 (47.30)	28 (42.42)	42 (51.22)	0.368
Basiliximab	43 (28.90)	14 (21.21)	29 (34.94)	0.098
Thymoglobulin	29 (19.60)	14 (21.21)	15 (18.29)	0.813
Acute rejection (previous 30 days) [n (%)]	8 (5.40)	5 (7.58)	3 (3.61)	0.484[e]
Comorbidities [n (%)]				
Charlson comorbidiy index [median (IQR)]	6 (4-8)	5 (4-7)	6 (5-8)	0.064[d]
Diabetes	123 (82.60)	49 (74.24)	74 (89.16)	**0.030**
Liver disease	126 (85.10)	52 (80.00)	74 (89.16)	0.186
Cronic kidney disease[c]	88 (59.1)	36 (54.6)	52 (62.7)	0.406
Congestive heart failure	16 (10.70)	6 (9.09)	10 (12.05)	0.754
Chronic lung disease	22 (14.80)	5 (7.58)	17 (20.48)	**0.048**

Metastatic solid tumor	3 (2.00)	0 (0.00)	3 (3.61)	0.330[e]
Any non-metastatic solid tumor	11 (7.40)	3 (4.55)	8 (9.64)	0.387
Characteristics of the BSI episode				
ICU admission [n (%)]	76 (51.00)	32 (48.48)	44 (53.01)	0.701
Hospital-acquired infection [n (%)]	121 (81.20)	50 (75.76)	71 (85.54)	0.191
Mechanical ventilation [n (%)]	42 (28.20)	21 (31.82)	21 (25.30)	0.487
Source of BSI [n (%)]				
Intrabdominal	28 (18.80)	13 (19.70)	15 (18.07)	0.967
Urinary tract	37 (24.80)	15 (22.73)	22 (26.51)	0.734
Biliary tract	26 (17.40)	11 (16.67)	15 (18.07)	0.994
Respiratory tract	14 (9.40)	7 (10.61)	7 (8.43)	0.866
Vascular access	25 (16.80)	16 (24.24)	9 (10.84)	0.051
Skin and soft tissue	6 (4.00)	1 (1.52)	5 (6.02)	0.33[e]
Unknown	7 (4.70)	3 (4.55)	4 (4.82)	1.000[e]
Control of the source of infection [n (%)]				
Surgical debridement	16 (10.70)	5 (7.58)	11 (13.25)	0.398
Non-surgical debridement	28 (18.90)	5 (7.69)	23 (27.71)	**0.004**
Removal/replacement of vascular line	44 (29.90)	25 (38.46)	19 (23.17)	0.067
Removal/replacement of urinary catheter	27 (18.50)	10 (15.62)	17 (20.73)	0.566
BSI severity				
Severe sepsis or septic shock [n (%)]	71 (47.70)	31 (46.97)	40 (48.19)	1.000
Pitt bacteriemia score [median (IQR)]	2 (0-5)	3 (1-6)	1 (0-5)	0.287[d]
INCREMENT-SOT-CPE score [median (IQR)][f]	8 (3-12)	8 (3-12)	8 (4-12)	0.587[d]
Type of carbapenemase [n (%)]				
KPC	110 (73.80)	53 (80.30)	57 (68.67)	0.157
OXA-48	39 (26.20)	13 (19.70)	26 (31.33)	0.157
Antibiotic therapy				
Time to active therapy [median (IQR)]	1 (0-2)	1 (0-3)	1 (0-2)	0.058
Active therapy in ≤24 hours	97 (65.10)	37 (56.06)	60 (72.29)	0.059
Active therapy in ≤3 days	134 (89.90)	57 (86.36)	77 (92.77)	0.309
Clinical outcomes [n (%)]				
Clinical success at 14 days	107 (71.80)	40 (60.61)	67 (80.72)	**0.011**
Clinical success at 30 days	109 (73.20)	40 (60.61)	69 (83.13)	**0.004**
All-cause mortality at 30 days	29 (19.50)	18 (27.27)	11 (13.25)	0.053

BAT, best available therapy; BSI, bloodstream infection; CAZ-AVI: ceftazidime-avibactam; CMV, cytomegalovirus; CPKP: carbapenemase-producing Klebsiella *pneumoniae*; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; OXA, oxacillinase; IQR, interquartile range; SOT, solid organ transplant; TMP/SMX, trimethoprim-sulfamethoxazole; ICU, intensive care unit,

[a] Including liver-kidney.

[b] Including kidney-pancreas.

[c] Defined by an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for at least 3 months.

[d] Mann-Whitney U test.

[e] Fisher's Exact Test

[f] INCREMENT-SOT-CPE score at the time of BSI onset included the following variables: INCREMENT-CPE score ≥8 (8 points), cytomegalovirus disease in the previous 30 days (7 points), lymphocytes ≤ 600 mm^3 (4 points), no source control (3 points), inappropriate empirical therapy (2 points), and the interaction INCREMENT-CPE score ≥ 8 x Cytomegalovirus disease in the previous 30 days (-7 points) (Pérez-Nadales et al., 2020).

Table 2. Multivariable logistic regression analyses for 14-day clinical success in the treatment cohort (**A**) and in the subgroup of patients from the treatment cohort with high mortality risk according to the INCREMENT-SOT-CPE score (**B**).

A. Treatment cohort

	aOR (95% CI)	***P* value**
Male sex	2.62 (1.01-6.82)	**0.048**
INCREMENT-SOT-CPE score [per unitary increment]	0.81 (0.74-0.90)	**<0.001**
CAZ-AVI therapy	2.65 (1.03-6.84)	**0.044**
Propensity score to receive CAZ-AVI[a]	1.63(0.21-12.43)	0.639

aOR, adjusted odds ratio; auROC, area under the receiver operating characteristic curve; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Nine patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

auROC 0.79 (95% CI 0.70-0.88).

B. High mortality risk group (INCREMENT-SOT-CPE score ≥8)

	aOR (95% CI)	***P* value**
Male gender	4.60 (1.36-15.57)	**0.014**
CAZ-AVI therapy	4.13 (1.27-13.41)	**0.018**
Propensity score to receive CAZ-AVI[a]	1.87 (0.16-21.43)	0.615

aOR, adjusted odds ratio; auROC, area under the receiver operating characteristic curve; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Five patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

auROC 0.75 (95% CI 0.63-0.87).

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Table 3. Multivariable logistic regression analyses for 30-day clinical success in the treatment cohort (**A**) and in the subgroup of patients from the treatment cohort with high INCREMENT-SOT-CPE mortality risk score (**B**).

A. Targeted therapy cohort

	aOR (95% CI)	***P* value**
Male sex	3.08 (1.14-8.33)	**0.027**
INCREMENT-SOT-CPE score [per unitary increment]	0.80 (0.72-0.89)	**<0.001**
CAZ-AVI therapy	3.14 (1.17-8.40)	**0.023**
Propensity score to receive CAZ-AVI[a]	1.93 (0.23-15.96)	0.543

aOR, adjusted odds ratio; auROC, area under the receiver operating characteristic curve; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Nine patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

auROC 0.81 (95% CI 0.72-0.90).

B. High mortality risk group (INCREMENT-SOT-CPE score ≥8)

	aOR (95% CI)	***P* value**
Male sex	4.99 (1.44-17.31)	**0.011**
CAZ-AVI therapy	4.47 (1.35-14.81)	**0.014**
Propensity score to receive CAZ-AVI[a]	2.67 (0.22-32.10)	0.440

aOR, adjusted odds ratio; auROC, area under the receiver operating characteristic curve; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Five patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

auROC 0.78 (95% CI 0.66-0.89).

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Table 4. Multivariable Cox regression analyses for 30-day all-cause mortality in the treatment cohort (**A**) and in the subgroup of patients from the treatment cohort with high INCREMENT-SOT-CPE mortality risk score (**B**).

A. Targeted therapy cohort

	aHR (95% CI)	***P* value**
Age [per one-year increment]	0.99 (0.95-1.03)	0.567
Male sex	0.43 (0.19-0.94)	**0.036**
INCREMENT-SOT-CPE score [per unitary increment]	1.18 (1.08-1.28)	**<0.001**
CAZ-AVI therapy	0.60 (0.23-1.56)	0.298
Propensity score to receive CAZ-AVI[a]	0.71 (0.10-5.15)	0.732

aHR, adjusted hazard ratio; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Nine patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

Concordance = 0.760.

B. High mortality risk group (INCREMENT-SOT-CPE score ≥8)

	aHR (95% CI)	***P* value**
Age [per one-year increment]	1.00 (0.96-1.04)	0.861
Male sex	0.46 (0.20-1.05)	0.065
CAZ-AVI therapy	0.58 (0.22-1.52)	0.264
Propensity score to receive CAZ-AVI[b]	0.58 (0.08-4.42)	0.603

aHR, adjusted hazard ratio; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval.

[a] Five patients had missing data in one or more of the variables included in the propensity score and thus were excluded from the final model.

Concordance = 0.656.

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Figure 1. Study flowchart.

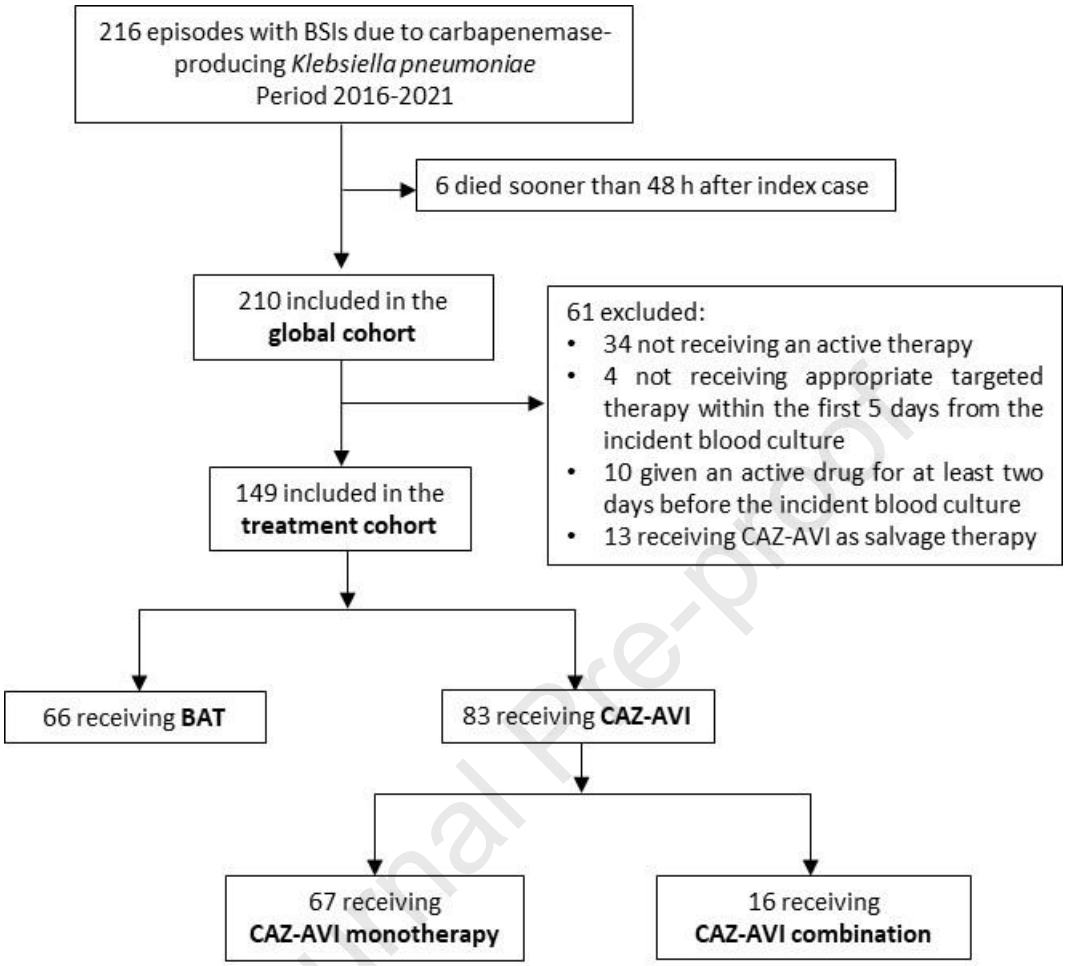

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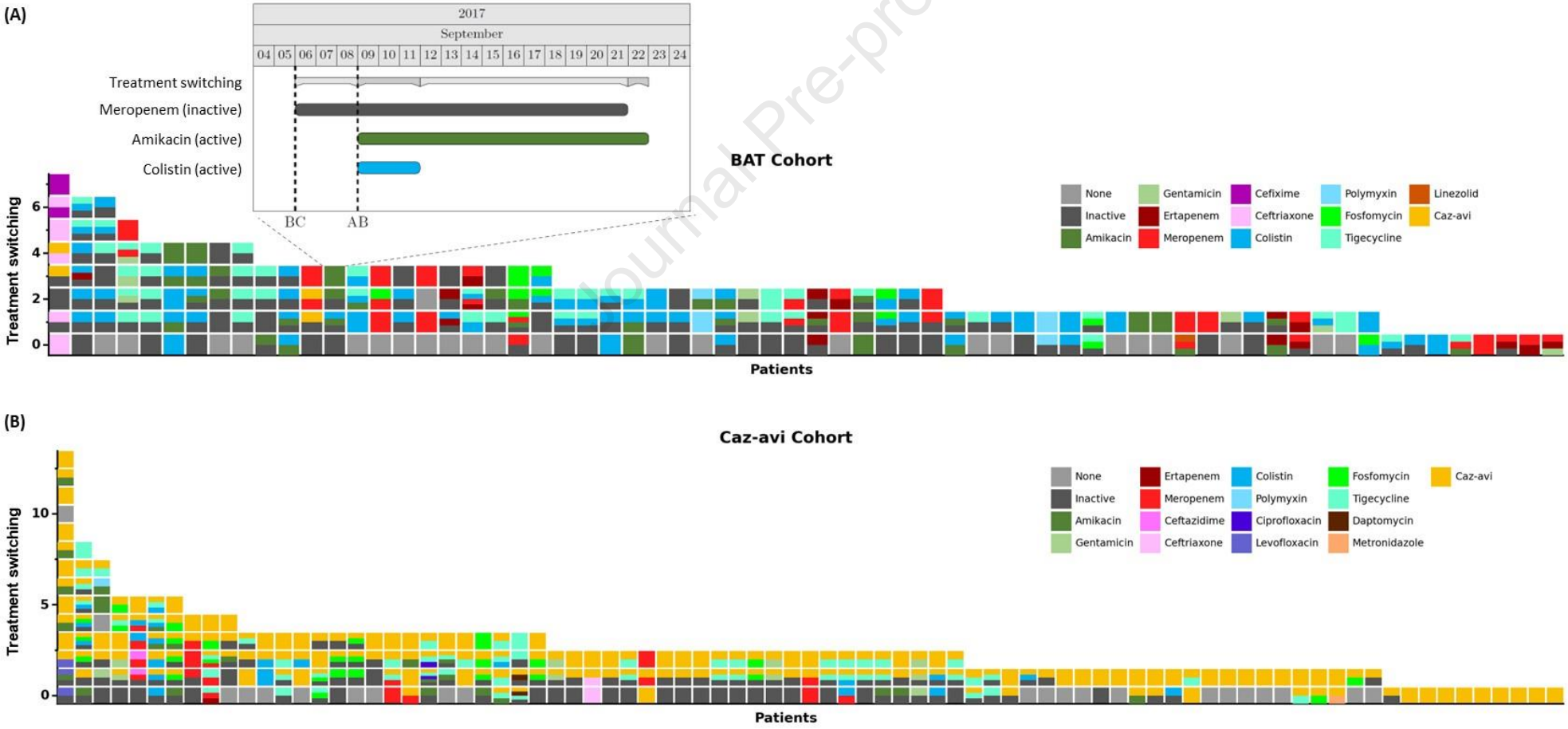
Figure 2. Graphical illustration of the rate of treatment switching, defined as number of antibiotic regime changes (Y-axis) per patient (X-axis) in patients from the BAT **(A)** and CAZ-AVI **(B)** groups of the treatment cohort. Patients are ordered from left to right according to the rate of treatment switching. In the Y-axis, each column square represents a new sequential change in the antibiotic regime in a single patient (see insert treatment line as an example; BC, date of blood culture; AB, date of antibiotic susceptibility testing results). Results of *in vitro* antimicrobial susceptibility testing for the carbapenemase-producing *Klebsiella pneumoniae* isolate were coded according to the data provided by participating centers in the clinical database. A colour code was assigned to the following distinct antibiotic categories: no antibiotic ("none", light grey), inactive antibiotic (dark grey), and active antibiotics (one different colour per antibiotic, as indicated in the figure legend). Thus, monotherapy is depicted as a single-colour square and combination therapy as a multi-colour square in a column.



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Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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