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Efficacy of β-lactam/β-lactamase inhibitors to treat extended-spectrum beta-lactamase-producing *Enterobacterales* bacteremia secondary to urinary tract infection in kidney transplant recipients (INCREMENT-SOT Project)

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Abbreviations: auROC, area under the receiving operator characteristics curve; BC, blood culture; BLBLI, β-lactam/β-lactamase inhibitors; BSI, bloodstream infection; CCI, age-adjusted Charlson comorbidity index; CI, confidence interval; CLSI, Clinical and Laboratory Standards Institute; CMV, cytomegalovirus; CRE, carbapenem-resistant Enterobacterales; ESBL, extended-spectrum β-lactamase; ESBL-E, extended-spectrum β-lactamase-producing Enterobacterales; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IQR, interquartile range; KTRs, kidney transplant recipients; MDR, multidrug-resistant; MIC, minimum inhibitory concentrations; OR, odds ratio; PCR, polymerase chain reaction; PS, propensity score; SD, standard deviation; UTI, urinary tract infection; VIF, variance inflation factor.

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Abstract

Background: Whether active therapy with β-lactam/β-lactamase inhibitors (BLBLI) is as affective as carbapenems for extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL-E) bloodstream infection (BSI) secondary to urinary tract infection (UTI) in kidney transplant recipients (KTRs) remains unclear.

Methods: We retrospectively evaluated 306 KTR admitted to 30 centers from January 2014 to October 2016. Therapeutic failure (lack of cure or clinical improvement and/or death from any cause) at days 7 and 30 from ESBL-E BSI onset was the primary and secondary study outcomes, respectively.

Results: Therapeutic failure at days 7 and 30 occurred in 8.2% (25/306) and 13.4% (41/306) of patients. Hospital-acquired BSI (adjusted OR [aOR]: 4.10; 95% confidence interval [CI]: 1.50-11.20) and Pitt score (aOR: 1.47; 95% CI: 1.21-1.77) were independently associated with therapeutic failure at day 7. Age-adjusted Charlson Index (aOR: 1.25; 95% CI: 1.05-1.48), Pitt score (aOR: 1.72; 95% CI: 1.35-2.17), and lymphocyte count ≤500 cells/μL at presentation (aOR: 3.16; 95% CI: 1.42-7.06) predicted therapeutic failure at day 30. Carbapenem monotherapy (68.6%, primarily meropenem) was the most frequent active therapy, followed by BLBLI monotherapy (10.8%,

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mostly piperacillin-tazobactam). Propensity score (PS)-adjusted models revealed no significant impact of the choice of active therapy (carbapenem-containing vs any other regimen, BLBLI- vs carbapenem-based monotherapy) within the first 72 hours on any of the study outcomes.

Conclusions: Our data suggest that active therapy based on BLBLI may be as effective as carbapenem-containing regimens for ESBL-E BSI secondary to UTI in the specific population of KTR. Potential residual confounding and unpowered sample size cannot be excluded (ClinicalTrials.gov identifier: NCT02852902).

KEYWORDS

bloodstream infection, carbapenem-sparing regimen, extended-spectrum β-lactamase-producing *Enterobacterales*, kidney transplantation, outcomes, urinary tract infection

1 | INTRODUCTION

Bloodstream infections (BSI) represent a common complication after solid organ transplant (SOT), with an incidence higher than that expected in the general population.[1] Urinary tract infection (UTI) is the most common source of BSI in kidney transplant recipients (KTRs),[2-4] mainly as a result of the combined impact of invasive procedures on the urinary tract and underlying immunosuppression.[2,5] The increasing prevalence of infections caused by multidrug-resistant (MDR) gram-negative bacilli, such as extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* (ESBL-E), is of particular concern in the SOT setting.[6-9] Approximately 10% of KTR will develop an UTI caused by ESBL-E within the first year,[10] and these patients face a three times higher risk of recurrence compared to those infected with non-MDR bacteria.[10,11]

The management of infections caused by ESBL-E remains challenging, with limited antimicrobials available and scarce supporting evidence. Carbapenems have been considered as the front-line therapy both in the general population[12] and in immunocompromised patients, including KTR.[13] Observational studies conducted in the general population—such as the multinational INCREMENT cohort (ClinicalTrials.gov identifier: NCT01764490)—have shown that, for organisms showing in vitro susceptibility, β-lactam/β-lactamase inhibitors (BLBLI) may be a good alternative to carbapenems for the treatment of BSI caused by ESBL-E, particularly among non-critically ill patients with UTI.[14-17] On the contrary, other studies, including a recently published randomized trial, have reported a difference in mortality favoring carbapenems.[18-20] Interpretation of previous studies is further complicated by the lower reliability and reproducibility of in vitro susceptibility testing to piperacillin-tazobactam as compared to carbapenems when gradient methods, such as E-test, are used.[21] Whether these findings can be extrapolated to the SOT population remains to be assessed. The aim of the present study was to compare the impact of therapeutic regimens based on carbapenems versus BLBLI on the clinical outcome in a large multinational cohort of KTR with ESBL-E BSI secondary to UTI.

2 | MATERIALS AND METHODS

2.1 | Study population and setting

The INCREMENT-SOT project (ClinicalTrials.gov identifier NCT02852902) comprised a retrospective international cohort of SOT recipients diagnosed with clinically significant (ie, meeting criteria for systemic inflammatory response syndrome) BSI caused by ESBL-E or carbapenemase-producing *Enterobacterales* admitted to 40 tertiary hospitals in 16 countries from January 2004 to October 2016. For the present analysis, KTRs with monomicrobial ESBL-E BSI secondary to UTI were eligible. Patient data were collected at each site by review of microbiology reports and patients' charts until day 30 after incident blood cultures (BCs) were taken. Exclusion criteria were key missing data regarding therapeutic regimens and/or outcomes, death earlier than 24 hours after the index date (ie, that of BSI onset), and the administration of active therapy for at least 2 days prior to BC sampling. The study protocol was approved by the Spanish Agency of Medicines (code FIB-COL-2015-01) and by the Ethics Committee of the Hospital Universitario Reina Sofía (Act 243, code 2907), which waived the need to obtain written informed consent. Approval was also gained at participating centers according to local requirements.

2.2 | Study outcomes and definitions

The *primary study outcome* was therapeutic failure, defined as the lack of cure or clinical improvement (ie, persistence or worsening

of fever, leukocytosis or other signs of infection, and/or persistently positive BC for the same microorganism), and/or death from any cause at day 7 from the onset of BSI. Therapeutic failure at day 30 was considered as *secondary outcome*. The *main explanatory variable* was the type of active therapy (according to the categories defined below) administered within the first 72 hours from BSI onset. Sensitivity analyses were also performed based on the regimen used during the first 24 hours and 7 days. The tested hypothesis (BLBLI are not associated with worse outcomes than carbapenem-containing regimens after controlling for potential confounders) was specified a priori in the study protocol. Because of the exploratory nature of the study and the expected low proportion of patients treated with BLBLI across participating institutions, no sample size estimation on the basis of the anticipated incidence of study outcomes was performed. In addition, the statistical analysis was not formally modeled on a non-inferiority assumption.

Episodes of ESBL-E BSI were considered *hospital-acquired* if symptoms started beyond the first 48 hours from hospital admission or within 48 hours from a previous hospital discharge. *Enterobacterales* were identified using standard microbiological techniques at each center. ESBL production was screened in all isolates with diminished susceptibility to third-generation cephalosporins—a key phenotypic property of ESBL enzymes—and confirmed by standard methods.[22] Susceptibility was studied 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.[23,24] Isolates were considered to be ESBL producers if at least one phenotypic confirmatory test was positive according to the corresponding CLSI or EUCAST criteria applicable at the time of testing, or if they had been characterized by PCR and DNA sequencing using established methods.

Active therapy was defined as administration of at least one antimicrobial agent to which the isolate showed susceptibility in vitro, at the standard dose and frequency.[12] Specifically, standard intravenous dosing regimens for the most common antimicrobials administered were as follows: piperacillin-tazobactam, 3/0.375 g to 4/0.5 g every 6-8 hours; meropenem, 1-2 g every 8 hours; ertapenem, 1 g every 24 hours; and imipenem-cilastatin, 500/500 mg to 1/1 g every 6-8 hours. All doses were adjusted to renal function. The therapy was considered to be inactive if the isolate was non-susceptible to the agent(s) administered or the dosing was inappropriate. *Monotherapy* was defined as the administration of a single active drug for at least 48 hours (except for patients who died in less than 48 hours, and who were included if they received at least one complete day of therapy). The definition criteria for *combination antibiotic therapy* (ie, simultaneous administration of two or more active drugs) varied according to the time elapsed since the initiation of treatment, in order to account for changes in antimicrobial therapy during the course of BSI (from empirical to targeted therapy). For the first 24 or 72 hours from the onset of BSI, combination therapy was defined as the administration of two or more active antimicrobial agents for at least 24 hours. For therapy administered within the first 7 days, the definition required the use of two or more active agents for at least 72 hours. *Source control* included at least one of the following measures: surgical debridement (eg, laparotomy for organ/space surgical site infection), non-surgical debridement (eg, imaging-guided drainage of perinephric abscess or infected kidney cyst), and/or removal or replacement of urinary catheter. To avoid confounding by indication bias, only those source control procedures performed before the time of outcome assessment (ie, days 7 and 30 for the primary and secondary outcomes, respectively) were taken into account. Severity of infection and comorbidity burden were assessed by means of the Pitt bacteremia score,[25] the age-adjusted Charlson comorbidity index (CCI),[26] and the McCabe score.[27] The diagnosis of *cytomegalovirus (CMV) infection* required the presence of laboratory-confirmed CMV replication by either pp65 antigenemia assay or PCR-based nucleic acid amplification testing. *CMV disease* was defined as evidence of CMV replication with attributable symptoms.[28]

2.3 | Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD) or the median with interquartile range (IQR). Categorical data were expressed as absolute and relative frequencies. The χ^2 test or Fisher's exact test were used to compare categorical variables, as appropriate. The Student's *t*-test or Mann-Whitney *U* test were applied for continuous variables. Univariate and multivariable logistic regression models were applied to identify factors predicting therapeutic failure. For analysis of therapeutic failure at days 7 and 30 (primary and secondary outcomes), we explored the impact of the antibiotic regimen administered within the first 72 hours from the onset of BSI. Further sensitivity analyses were performed according to the regimen used during the first 24 hours (for primary and secondary outcomes) and 7 days (for the secondary outcome only). At each of these windows, therapeutic regimens were classified into one of the following mutually exclusive categories: active versus inactive therapy; combination therapy versus monotherapy; carbapenem-containing versus other active regimens; and carbapenem versus BLBLI monotherapy. Absolute risk differences with 95% confidence intervals (CIs) were determined with the allegedly more effective regimen (ie, combination therapy, carbapenem-containing regimen, and carbapenem monotherapy) as the reference.

Associations were given as odds ratios (ORs) and 95% CIs. Multicollinearity among explanatory variables was analyzed using the variance inflation factor (VIF). The Hosmer-Lemeshow test was used to assess the goodness-of-fit of the models. Thirty-day survival curves were plotted by the Kaplan-Meier method and differences related to therapeutic regimens were compared with the log-rank test.

To partially overcome the limitation posed by the non-randomized design of the study, we calculated the propensity scores (PS) for receiving either the carbapenem-containing therapy (vs any other

active regimen) or the BLBLI-based (vs carbapenem-based) monotherapy, within the first 72 hours and given the patient's baseline characteristics and the clinical features at BSI presentation. Both scores were estimated by means of backward stepwise logistic regression models including variables with *P*-values < 0.1 in the univariate analysis (Tables S1 and S2), and the fit of the resulting models was assessed by means of the area under the receiving operator characteristics curve (auROC). PS were entered as a covariate in multivariable models to adjust for potential confounding by factors influencing the choice of therapy.

Statistical analysis was performed with SPSS version 20.0 (IBM Corp.) and graphs were generated with Prism version 6.0 (GraphPad Software Inc).

3 | RESULTS

3.1 | Characteristics of the study population

Overall, 306 episodes of ESBL-E BSI occurring in 306 KTRs were included from 30 centers in 14 countries. The clinical and microbiological features are shown in Table 1. The median interval from transplantation to BSI onset was 119 days, and 23.2% of the episodes occurred within the first month. The median length of stay was 16 days (9-33.5). Most patients were receiving triple maintenance immunosuppression consisting of corticosteroids, tacrolimus, and mycophenolic acid or mycophenolate mofetil. Regarding the ESBL-E identified, *Escherichia coli* (62.1%) and *Klebsiella* spp. (35.0%) accounted for the majority of cases.

Therapeutic failure at days 7 and 30 (primary and secondary outcomes) occurred in 8.2% (25/306) and 13.4% (41/306) of patients. All-cause mortality rates at days 7 and 30 were 1.0% (3/306) and 2.9% (9/306), respectively. All but one death were considered attributable to ESBL-E BSI. The rates of cure and clinical improvement were 2.6% (8/206) and 89.2% (273/306) by day 7, and 77.5% (237/306) and 9.2% (28/306) by day 30, respectively.

The therapeutic regimens given at different time intervals are detailed in Table 2. Most patients received active therapy with carbapenem monotherapy (144 [47.1%] for the first 24 hours, 210 [68.6%] for the first 72 hours, and 237 [77.5%] for the first 7 days from BSI onset), whereas BLBLI monotherapy (mostly piperacillin-tazobactam) was chosen in about 10% of cases. Piperacillin-tazobactam was most commonly administered at doses of 4/0.5 g every 8 hours (46.7% [14/30]) and 2/0.25 g every 8 hours (20.0% [6/30]). The use of combination antibiotic therapy was anecdotal. Twenty-one patients (6.8%) received during the first 72 hours an antibiotic that lacked in vitro activity against the isolate, which mainly included second- or third-generation cephalosporins (10 patients [47.6%]), piperacillin-tazobactam (eight patients [38.1%]), or quinolones (two patients [9.5%]). Within the subgroup of patients who received monotherapy during the first 72 hours from BSI onset, 5.0% (13/261) were subsequently transitioned to a second active antibiotic.

3.2 | Risk factors for therapeutic failure

Univariate and multivariable analyses of factors predicting therapeutic failure at day 7 (primary outcome) are shown in Table 3. At the univariate level, recipient gender, time interval from transplantation to BSI onset, use of trimethoprim-sulfamethoxazole prophylaxis, presence of urinary stenosis, hospital-acquired infection, acute rejection within the prior month, Pitt bacteremia score, and the degree of sepsis severity were associated with this outcome. Since the Pitt score and the presence of septic shock exhibited significant multicollinearity (VIF values > 1.5), only the former variable was included into the logistic regression model. The presence of hospital-acquired BSI (OR: 4.10; 95% CI: 1.50-11.20; *P*-value = 0.006) and the Pitt bacteremia score at BSI onset (OR [per one-point increase]: aOR: 1.47; 95% CI: 1.21-1.77; *P*-value < 0.0001) remained as independent predictors for therapeutic failure at day 7.

Age-adjusted CCI (OR [per one-point increase]: 1.25; 95% CI: 1.05-1.48; *P*-value = 0.010), Pitt score (OR [per one-point increase]: 1.72; 95% CI: 1.35-2.17; *P*-value <0.0001), and an absolute lymphocyte count ≤500 cells/μL at BSI onset (OR: 3.16; 95% CI: 1.42-7.06; *P*-value = 0.005) were independent predictors for therapeutic failure at day 30 (Table 4). There were no significant differences in 30-day survival between patients receiving or not receiving active therapy within the first 24 (98.3% vs 95.3%, respectively; log-rank test *P*-value = 0.365) or 72 hours (100.0% vs 95.9%; log-rank test *P*-value = 0.293) from the onset of BSI.

3.3 | Impact of different therapeutic regimes on study outcomes

The impact on study outcomes of different regimens was next investigated within the subgroup of participants who received active therapy. First, we compared the incidence of therapeutic failure at day 7 (primary outcome) in patients receiving combination therapy versus monotherapy during the first 72 hours from the onset of BSI, with no significant differences found between both groups (8.3% [1/12] vs 8.4% [22/261], respectively; risk difference: 0.06%; 95% CI: −0.15-0.16; unadjusted OR [uOR]: 0.99; 95% CI: 0.12-8.01; *P*-value = 0.991) (Figure 1A). There were no significant differences in the occurrence of therapeutic failure at day 30 (secondary outcome) either (16.7% [2/12] vs 13.0% [34/261]; risk difference: −3.63%; 95% CI: −0.23-0.16; uOR: 1.34; 95% CI: 0.28-6.36; *P*-value = 0.717) (Figure 1B). Next, we evaluated the impact of using a carbapenem-containing regimen versus any other active regimen during the first 72 hours. No significant differences were observed, either at day 7 (8.7% [19/219] vs 7.4% [4/54]; risk difference: −1.27%; 95% CI: −0.09-0.07; uOR: 1.18; 95% CI: 0.39-3.65; *P*-value = 0.764) (Figure 2A) or day 30 (13.7% [30/219] vs 11.1% [6/54]; risk difference: −2.59; 95% CI: −0.13-0.07; uOR: 1.27; 95% CI: 0.50-3.23; *P*-value = 0.615) (Figure 2B). Finally, we compared the risk of therapeutic failure between patients treated with carbapenem monotherapy versus BLBLI monotherapy. Once again, we observed no

TABLE 1 Clinical characteristics of the study cohort

Variable	(n = 306)
Patient-related variables	
Age, years [mean ± SD]	56.6 ± 13.9
Male gender [n (%)]	163 (53.3)
Geographic area [n (%)]	
Europe	190 (62.1)
Asia	56 (18.3)
South America	18 (5.9)
North America	17 (5.6)
Israel	25 (8.2)
McCabe score [n (%)]	
Non-fatal	230 (75.2)
Ultimately fatal	61 (19.9)
Rapidly fatal	15 (4.9)
Age-adjusted CCI [median (IQR)]	4 (3-6)
Major pre-transplant comorbidities [n (%)]	
Diabetes	152 (49.7)
Coronary heart disease	45 (14.7)
Congestive heart failure	37 (12.1)
Liver disease	31 (10.1)
Chronic pulmonary disease	25 (8.2)
Transplant-related variables	
Time from transplantation to BSI onset, days [median (IQR)]	119 (35.3-1.378)
BSI within the first post-transplant month [n (%)]	71 (23.2)
Simultaneous kidney-pancreas transplantation [n (%)]	5 (1.6)
Induction therapy [n (%)]	
Basiliximab	110 (35.9)
Anti-thymocyte globulin	82 (26.8)
Maintenance immunosuppression at BSI onset [n (%)]	
Corticosteroids	275 (89.9)
Tacrolimus	242 (79.1)
Cyclosporine	51 (16.7)
Mycophenolic acid/mycophenolate mofetil	244 (79.7)
Azathioprine	22 (7.2)
mTOR inhibitor	26 (8.5)
TMP/SMX prophylaxis within the prior month [n (%)]	163 (53.3)
Urinary stenosis at BSI onset [n (%)]	55 (18.0)
ICU admission within the prior month [n (%)]	37 (12.1)
Dialysis within the prior month [n (%)]	65 (21.2)
CMV infection within the prior month [n (%)]	31 (10.1)
CMV disease within the prior month [n (%)]	15 (4.9)
Acute graft rejection within the prior month [n (%)]	30 (9.8)
BSI episode-related variables	
Hospital-acquired BSI [n (%)]	127 (41.5)
Pitt bacteremia score [median (IQR)]	0 (0-2)
Hemodynamic severity [n (%)][a]	
Severe sepsis	36 (12.6)
Septic shock	13 (4.5)
Lymphocyte count at presentation ≤ 500 cells/μL [n (%)][b]	117 (39.9)
Microbiological results [n (%)]	
Escherichia coli	190 (62.1)
Klebsiella spp.	107 (35.0)
Enterobacter spp.	4 (1.3)
Other	5 (1.6)
Treatment-related variables and outcomes	
BSI source control [n (%)]	113 (36.9)
Surgical debridement	26 (8.5)
Non-surgical debridement	44 (14.4)
Removal/replacement of urinary catheter	67 (21.9)
Time to BSI source control, days [median (IQR)][c]	3 (0-9)
Overall duration of therapy, days [median (IQR)][d]	14 (12-21)
Duration of active therapy, days [median (IQR)][d]	14 (11-20)
Time to active therapy, days [median (IQR)]	0 (0-1)
Length of stay, days [median (IQR)]	16 (9-33.5)
Therapeutic failure [n (%)]	
At day 7 (primary outcome)	25 (8.2)
At day 30 (secondary outcome)	41 (13.4)
All-cause mortality [n (%)]	
At day 7 (primary outcome)	3 (1.0)
At day 30 (secondary outcome)	9 (2.9)

Note: BSI, bloodstream infection; CCI, age-adjusted Charlson comorbidity index; CI, confidence interval; CMV, cytomegalovirus; ICU, intensive care unit; IQR, interquartile range; mTOR; mammalian target of rapamycin; SD, standard deviation; TMP/SMX, trimethoprim-sulfamethoxazole.

[a]Data not available for 20 patients.

[b]Data not available for 13 patients.

[c]Data not available for 36 patients.

[d]Data not available for 3 patients.

(Continues)

significant differences at day 7 (9.0% [19/210] vs 3.0% [1/33]; risk difference: −6.01%; 95% CI: −0.16-0.04; uOR: 3.18; 95% CI: 0.41-24.62; *P*-value = 0.267) (Figure 2A) or day 30 (13.8% [29/210] vs 9.1% [3/33]; risk difference: −4.72%; 95% CI: −0.17-0.08; uOR: 1.60; 95% CI: 0.46-5.59; *P*-value = 0.459) (Figure 2B) between both therapeutic modalities. In addition, there were no significant differences in hospital stay between any of these therapeutic regimens (Table S3).

3.4 | Propensity score-adjusted analysis

Next, we applied a PS-based approach to investigate whether the therapeutic regimen administered within the first 72 hours from BSI onset influenced study outcomes. The following variables were included in the PS for the use of a carbapenem-containing regimen: geographical area (Europe or North America vs other sites), simultaneous kidney-pancreas transplantation, certain pre-transplant chronic conditions (diabetes, liver disease, congestive heart failure, and chronic pulmonary disease), CMV disease within the prior month, and presence of a rapidly or ultimately fatal disease according to the McCabe score (Table S1). The auROC of the resulting PS was 0.738 (95% CI: 0.664-0.812). The risk of therapeutic failure at day 7 (PS-adjusted OR: 4.66; 95% CI: 0.58-37.28; *P*-value = 0.147) or at day 30 (PS-adjusted OR: 2.13; 95% CI: 0.55-8.20; *P*-value = 0.274) was not found to be significantly affected by the use of a carbapenem-containing regimen versus any other active regimen. In addition, we further adjusted by the degree of sepsis severity (Pitt score and presence of septic shock) and comorbidity burden in different regression models, since the relatively low number of patients suffering from therapeutic failure at either point was insufficient to perform a single multivariable analysis without incurring in model overfitting. None of these adjustments suggested a risk difference according to the use of a carbapenem-containing therapy or an alternative regimen (Figure S1).

This methodological approach was also applied to compare the use of BLBLI versus carbapenem within the subgroup of patients treated with monotherapy in the first 72 hours from BSI onset. The variables included in the PS for the use of carbapenem-based monotherapy as compared to BLBLI-based monotherapy were: geographical area (Europe or North America vs other study sites), pre-transplant chronic conditions (congestive heart failure and chronic pulmonary disease), presence of a rapidly or ultimately fatal disease according to the McCabe score, and receipt of active therapy within the first 24 hours (Table S2). The auROC of the score was 0.794 (95% CI: 0.719-0.869). Again, neither the risk of therapeutic failure at day 7 (PS-adjusted OR: 4.36; 95% CI: 0.51-37.38; *P*-value = 0.179) or day 30 (PS-adjusted OR: 2.59; 95% CI: 0.66-10.21; *P*-value = 0.175) appeared to be influenced by the choice of carbapenem-based versus BLBLI-based monotherapy (Figure S2).

3.5 | Sensitivity analysis

Finally, to evaluate the consistency of these findings, we investigated the impact of therapy administered during time periods other than the 72-hour window. There were no significant differences in the incidence of 7-day and 30-day therapeutic failure among different therapeutic regimens administered within the first 24 hours from BSI (Figures S3 and S4, Table S4). No significant differences were found in 30-day therapeutic failure according to the type of therapy used within the first 7 days either (Figure S5, Table S4).

4 | DISCUSSION

In the present study, we were not able to detect significant differences in the risk of therapeutic failure (lack of cure or clinical improvement and/or death from any cause) among KTRs with ESBL-E BSI secondary to UTI that were treated with carbapenem- or BLBLI-based regimens. Absolute risk differences observed were small (ranging from −6.01% to 0.06%) and of questionable relevance from a clinical perspective. Although current consensus statements favor BLBLI-based regimens for non-severe ESBL infections,[29,30] such recommendations are supported by limited data. Our research would reinforce previous studies suggesting that BLBLI monotherapy may be as effective as a carbapenem to treat ESBL-E BSI, particularly for low-inoculum infections in non-critically ill patients.[14-17]

The very low number of KTRs within the BLBLI group that received amoxicillin-clavulanic acid (n = 2) imply that our results are mostly applicable to piperacillin-tazobactam, in line with other studies performed in the non-transplant population.[16,17] Whether both BLBLIs are equally effective for treating ESBL-E remains debatable, although a potential "inoculum effect" has been proposed for piperacillin-tazobactam but not for amoxicillin-clavulanic acid.[31] In addition, variations have been reported in the rates of susceptibility to piperacillin-tazobactam according to the specific ESBL enzyme involved, with higher activity for CTX-M-14-like enzymes as compared to other β-lactamases (such as CTX-M-15-like, CMY-like, OXA-1, or SHV enzymes).[32] It should be noted that the CLSI and EUCAST guidelines differ in the interpretative criteria for categorizing an isolate as susceptible to piperacillin-tazobactam, with minimum inhibitory concentration (MIC) breakpoints set at ≤16 mg/L and ≤8 mg/L, respectively. Given the retrospective design of the study, such a discrepancy complicates data aggregation across centers. Indeed, if we focused on episodes treated with piperacillin-tazobactam monotherapy during the first 72 hours, 67.7% (21/31) and 32.3% (10/31) of the isolates had been tested by the CLSI and EUCAST methods.

To our knowledge, this is the first study to compare the efficacy of carbapenems and BLBLI for ESBL-E BSI in the specific setting of SOT. Immunocompromised individuals were included in a systematic review and meta-analysis that demonstrated comparable mortality rates for patients with ESBL-E BSI treated with carbapenems or other regimens.[14] Nonetheless, most of them were diagnosed with malignancy and neutropenia, with only a low number of SOT recipients.[33] In line with these findings, a recent international study in neutropenic hematological patients with ESBL-E BSI also failed to demonstrate differences between carbapenems and BLBLI.[34]

In contrast with our results and most of the previously reported studies, results from a multicenter, open-label, randomized non-inferiority trial of piperacillin-tazobactam versus meropenem for the definitive treatment of BSI caused by ceftriaxone-resistant *E. coli* or *K. pneumoniae* did not support the use of BLBLI as a carbapenem-sparing option.[20] In contrast to the present study, about

TABLE 2 Description of therapeutic regimens administered

Therapeutic regimen [n (%)]	Time interval from BSI onset		
	24 hours	72 hours	7 days
Active therapy	190 (62.1)	273 (89.2)	298 (97.4)
Monotherapy	179 (58.5)	261 (85.3)	287 (93.8)
Carbapenem	144 (47.1)	210 (68.6)	237 (77.5)
Meropenem	76 (24.8)	105 (34.3)	109 (35.6)
Ertapenem	46 (15.0)	72 (23.5)	94 (30.7)
Imipenem-cilastatin	22 (7.2)	33 (10.8)	32 (10.5)
BLBLI	22 (7.2)	33 (10.8)	32 (10.5)
Piperacillin-tazobactam[a]	20 (6.5)	31 (10.1)	30 (9.8)
Amoxicillin-clavulanic acid	2 (0.7)	2 (0.7)	2 (0.7)
Quinolone	5 (1.6)	9 (2.9)	10 (3.3)
Aminoglycoside	3 (1.0)	3 (1.0)	1 (0.3)
Other[b]	5 (1.6)	6 (2.0)	6 (2.0)
Combined therapy	10 (3.3)	12 (3.9)	11 (3.6)
Carbapenem-containing	7 (2.3)	9 (2.9)	9 (2.9)
Other combinations[c]	3 (1.0)	3 (1.0)	2 (0.7)
Inactive therapy	116 (37.9)	33 (10.8)	8 (2.6)
Inactive agent in vitro	59 (19.3)	21 (6.8)	3 (1.0)
No antibiotic administered	57 (18.6)	12 (3.9)	5 (1.6)

Note: BLBLI, β-lactam/β-lactamase inhibitor; BSI, bloodstream infection.

[a]Piperacillin-tazobactam was administered at the following doses: 4/0.5 g every 8 hours (n = 14), 2/0.25 g every 8 hours (n = 6), 2/0.5 g every 6 hours (n = 3), 4/0.5 g every 12 hours (n = 2), 3/0.375 g every 6 hours (n = 2), 4/0.5 g every 24 hours (n = 1), unknown (n = 2).

[b]Other monotherapy regimens used within the first 24 hours included cefepime (n = 3), trimethoprim-sulfamethoxazole (n = 2), and tigecycline (n = 1).

[c]Other combination regimens used within the first 24 hours included BLBLI plus aminoglycoside (n = 1) or quinolone (n = 1), and ceftazidime plus quinolone (n = 1).

one third of the participants in the MERINO trial had non-urinary sources, and the risk difference for 30-day mortality in this subgroup was sensibly higher than that observed among patients with BSI from urinary source (14.1% vs 3.7%, respectively). Previous studies have demonstrated poorer outcomes in infections from non-urinary sources treated with piperacillin-tazobactam-based regimens.[35,36]

The absence of demonstrable differences in the rates of therapeutic failure at days 7 and 30 among patients receiving BLIBL versus carbapenems must be interpreted with particular caution, given the low number of patients treated with BLBLI and the subsequent risk of inadequate power to reject the null hypothesis. Alternative carbapenem-sparing active regimens other than BLBLI were used in a small proportion of patients, which precludes conclusions about their potential efficacy for the treatment of post-transplant ESBL-E BSI of urinary origin. In addition, we found no differences in the rates of therapeutic failure between patients treated with combination therapy or monotherapy, regardless of the time elapsed from the onset of BSI to the initiation of an in vitro active agent.

The low mortality rates observed (1.0% at day 7 and 2.9% at day 30) were consistent with those previously published among KTRs, which ranged from 2.5% to 11%,[36,37] and would have contributed to the quite unexpected lack of apparent impact in terms of worse outcomes of not receiving active therapy. The improved outcomes reported for BSI from urinary source may be explained by the presence of a lower inflammatory response and the higher antibiotic concentration typically reached in the urinary tract. Although the development of septic shock represents a major predictor of mortality,[36] Kalil et al showed that mortality was actually lower in SOT recipients with bacteremic sepsis compared with non-transplant patients, suggesting that post-transplant immunosuppression may provide a survival advantage through modulation of the inflammatory response.[38] On the other hand, the overall favorable outcomes found in our study may reflect the occurrence of a less severe infection, consistent with the low age-adjusted CCI (median of 4) and Pitt bacteremia (median of 0) score values, and the small proportion of patients with rapidly fatal disease (4.9%).

In the multivariable analysis, hospital-acquired infection and Pitt score were associated with an increased odds of therapeutic failure at day 7. On the other hand, age-adjusted CCI, Pitt score, and the presence of lymphopenia (≤500 cells/μL) at presentation were associated with therapeutic failure at day 30. Surprisingly, despite the high rate of inadequate (non-active) initial empiric antimicrobial therapy within the first 24 and 72 hours (37.9% and 10.8%, respectively), this variable was not associated with a worse outcome in either univariate or multivariable models. Previous studies have also reported high rates of inadequate initial antimicrobial therapy to treat ESBL-E BSI in the overall population,[39-41] which may reach up to 60% in studies targeting the SOT population.[6] Some previous studies reported that, following multivariate adjustment, inappropriate initial empiric therapy was not associated with increased mortality after SOT,[6] although inadequately treated UTI episodes exerted a deleterious impact on graft function and patient survival among KTRs.[3,5] Again, such a low mortality rate may be related to the lower inflammatory response in these patients compared to non-transplant patients. Unfortunately, we lack data on the medium- and long-term evolution of renal graft function between patients receiving and not receiving adequate therapy, although no significant differences were found in the overall length of stay (which may serve as a proxy for the development of acute kidney injury or the requirement of renal replacement therapy during the incident hospitalization).

Carbapenem monotherapy (primarily meropenem) was the most frequent active therapy used, followed by BLBLI (mostly piperacillin-tazobactam). To overcome the limitation posed by the non-randomized retrospective design, PS-adjusted analyses for receiving the front-line and intuitively "more potent" therapy (carbapenem-containing or carbapenem-based regimens) versus the "alternative" less

TABLE 3 Univariate and multivariable analyses of factors for therapeutic failure at day 7 (primary outcome)

	Therapeutic failure at day 7 (n = 25)	No therapeutic failure at day 7 (n = 281)	Univariate[f]			Multivariable[g]		
			OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age, years [mean ± SD]	57.2 ± 17.3	56.6 ± 13.7						
Male gender [n (%)]	18 (72.0)	145 (51.6)	2.41	0.98-5.96	0.056			
Time interval from transplantation, days [median (IQR)]	68 (23-194)	133 (36-1,543)	1.00	0.99-1.00	0.073			
BSI within the first post-transplant month [n (%)]	7 (28.0)	64 (22.8)						
Induction therapy with anti-thymocyte globulin [n (%)]	9 (36.0)	73 (26.0)						
TMP/SMX prophylaxis within the prior month [n (%)]	18 (72.0)	145 (51.6)	2.41	0.98-5.96	0.056			
Urinary stenosis [n (%)]	9 (36.0)	46 (16.4)	**2.87**	**1.19-6.89**	**0.018**	-	-	-
ICU admission within the prior month [n (%)]	6 (24.0)	31 (11.0)						
Dialysis within the prior month [n (%)]	9 (36.0)	56 (19.9)						
CMV infection within the prior month [n (%)]	5 (20.0)	26 (9.3)						
CMV disease within the prior month [n (%)]	3 (12.0)	12 (4.3)						
Hospital-acquired BSI [n (%)]	19 (76.0)	108 (38.4)	**5.07**	**1.96-13.10**	**0.001**	4.10	1.50-11.20	0.006
Acute graft rejection within the prior month [n (%)]	6 (24.0)	24 (8.5)	**3.38**	**1.23-9.27**	**0.018**	-	-	-
Age-adjusted CCI [median (IQR)]	5 (3-6)	4 (2-6)						
Rapidly or ultimately fatal McCabe scores [n (%)]	10 (40.0)	66 (23.5)						
Pitt bacteremia score at BSI onset [median (IQR)]	2 (0-4.5)	0 (0-1)	**1.50**[d]	**1.24-1.82**	**<0.0001**	1.47[d]	1.21-1.77	<0.0001
Septic shock at BSI onset [n (%)][a]	6 (24.0)	7 (2.6)	11.82[e]	3.61-38.69	<0.0001			
Lymphocyte count ≤ 500 cells/μL at BSI onset [n (%)][b]	14 (56.0)	103 (38.4)						
Surgical debridement within the first 7 days [n (%)]	2 (8.0)	11 (3.9)						
Non-surgical debridement [n (%)]	6 (24.0)	38 (13.5)						

(Continues)

TABLE 3 (Continued)

	Therapeutic failure at day 7 (n = 25)	No therapeutic failure at day 7 (n = 281)	Univariate[f]			Multivariable[g]		
			OR	95% CI	*P*-value	OR	95% CI	*P*-value
Removal/replacement of urinary catheter [n (%)]	7 (28.0)	60 (21.4)						
Time to BSI source control [median (IQR)][c]	9.5 (0.3-20)	2.5 (0-7)						
Time to active therapy [median (IQR)]	0 (0-1)	0 (0-1)						
Active therapy within the first 24 hours [n (%)]	15 (60.0)	175 (62.3)						
Active therapy within the first 72 hours [n (%)]	23 (92.0)	250 (89.0)						

Note: BSI, bloodstream infection; CCI, age-adjusted Charlson comorbidity index; CI, confidence interval; CMV, cytomegalovirus; ESBL, extended spectrum beta-lactamase; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; SD, standard deviation; TMP/SMX, trimethoprim-sulfamethoxazole.

[a]Data not available for 12 patients.

[b]Data not available for 13 patients.

[c]Data not available for 36 patients.

[d]Hazard ratio estimated per one-point increase in the score.

[e]The variable "septic shock" was not entered into the model based on the existence of significant collinearity with the Pitt bacteremia score.

[f]Variables entered into the multivariable model are highlighted in bold characters.

[g]Hosmer-Lemeshow *P*-value = 0.799.

TABLE 4 Univariate and multivariable analyses of factors for therapeutic failure at day 30 (secondary outcome)

	Therapeutic failure at day 30 (n = 41)	No therapeutic failure at day 30 (n = 265)	Univariate[f]			Multivariable[g]		
			OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age, years [mean ± SD]	60.4 ± 12.3	56.1 ± 14.1						
Male gender [n (%)]	23 (56.1)	140 (52.8)						
Time interval from transplantation, days [median (IQR)]	97 (51.5-1688)	124 (35-1366)						
BSI within the first post-transplant month [n (%)]	7 (17.1)	64 (24.2)						
Induction therapy with anti-thymocyte globulin [n (%)]	13 (31.7)	69 (26.0)						
TMP/SMX prophylaxis within the prior month [n (%)]	27 (65.9)	136 (51.3)						
Urinary stenosis [n (%)]	7 (17.1)	48 (18.1)						
ICU admission within the prior month [n (%)]	7 (17.1)	30 (11.3)						
Dialysis within the prior month [n (%)]	12 (29.3)	53 (20.0)						
CMV infection within the prior month [n (%)]	7 (17.1)	24 (9.1)						
CMV disease within the prior month [n (%)]	2 (4.9)	13 (4.9)						
Hospital-acquired BSI [n (%)]	25 (61.0)	102 (38.5)	**2.49**	**1.27-4.90**	**0.008**	-	-	-
Acute graft rejection within the prior month [n (%)]	7 (17.1)	23 (8.7)						
Age-adjusted CCI [median (IQR)]	6 (4-7)	4 (2-6)	**1.24**[d]	**1.08-1.43**	**0.003**	1.25[d]	1.05-1.48	0.010
Rapidly or ultimately fatal McCabe scores [n (%)]	15 (36.6)	61 (23.0)						
Pitt bacteremia score at BSI onset [median (IQR)]	1 (0-4)	0 (0-1)	**1.62**[d]	**1.32-1.99**	**<0.0001**	1.72[d]	1.35-2.17	<0.0001
Septic shock at BSI onset [n (%)][a]	9 (24.3)	4 (1.6)	20.33[e]	5.88-70.31	<0.0001			
Lymphocyte count ≤ 500 cells/μL at BSI onset [n (%)][b]	24 (64.9)	93 (36.3)	**3.24**	**1.57-6.66**	**0.001**	3.16	1.42-7.06	0.005
Surgical debridement within the first 7 days [n (%)]	6 (14.6)	20 (7.5)						

(Continues)

TABLE 4 (Continued)

	Therapeutic failure at day 30 (n = 41)	No therapeutic failure at day 30 (n = 265)	Univariate[f]			Multivariable[g]		
			OR	95% CI	*P*-value	OR	95% CI	*P*-value
Non-surgical debridement [n (%)]	3 (7.3)	41 (15.5)						
Removal/replacement of urinary catheter [n (%)]	8 (19.5)	59 (22.3)						
Time to BSI source control [median (IQR)][c]	1 (−1-9)	3 (0-9)						
Time to active therapy [median (IQR)]	0 (0-1)	0 (0-1)						
Active therapy within the first 24 hours [n (%)]	27 (65.9)	163 (61.5)						
Active therapy within the first 72 hours [n (%)]	36 (87.8)	237 (89.4)						
Active therapy within the first 7 days [n (%)]	41 (100.0)	257 (97.0)						

Note: BSI, bloodstream infection; CCI, age-adjusted Charlson comorbidity index; CI, confidence interval; CMV, cytomegalovirus; ESBL, extended spectrum beta-lactamase; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; SD, standard deviation; TMP/SMX, trimethoprim-sulfamethoxazole.

[a]Data not available for 12 patients.

[b]Data not available for 13 patients.

[c]Data not available for 36 patients.

[d]Hazard ratio estimated per one-point increase in the score.

[e]This variable was not entered into the model based on the existence of significant collinearity with the Pitt bacteremia score.

[f]Variables entered into the multivariable model are highlighted in bold characters.

[g]Hosmer-Lemeshow *P*-value = 0.260.

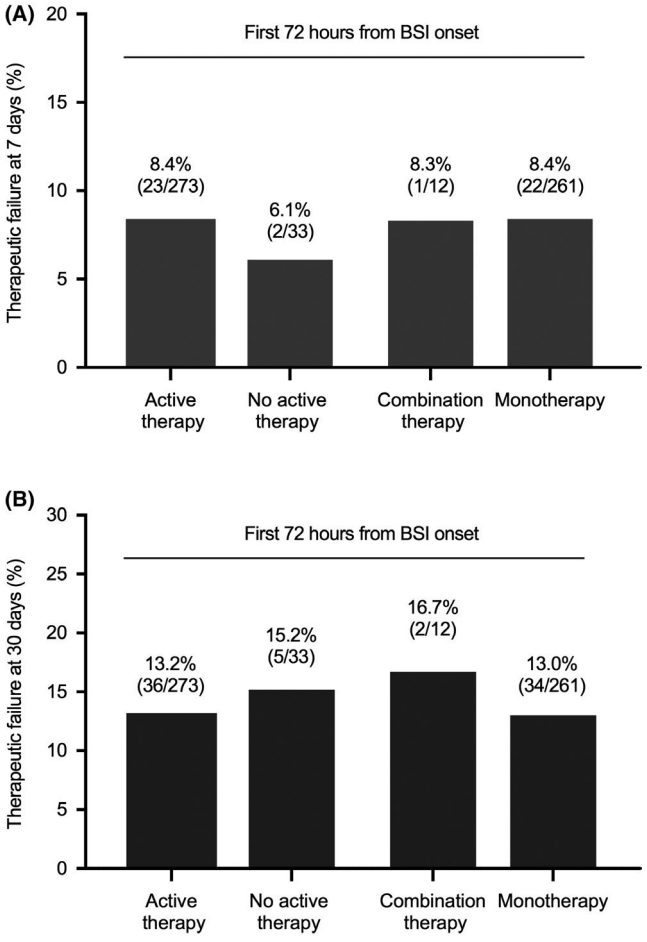

FIGURE 1 Primary (therapeutic failure at day 7) (A) and secondary (therapeutic failure at day 30) (B) study outcomes according to the administration of active (vs inactive) therapeutic regimens or combination therapy (vs monotherapy) within the first 72 hours. BSI, bloodstream infection

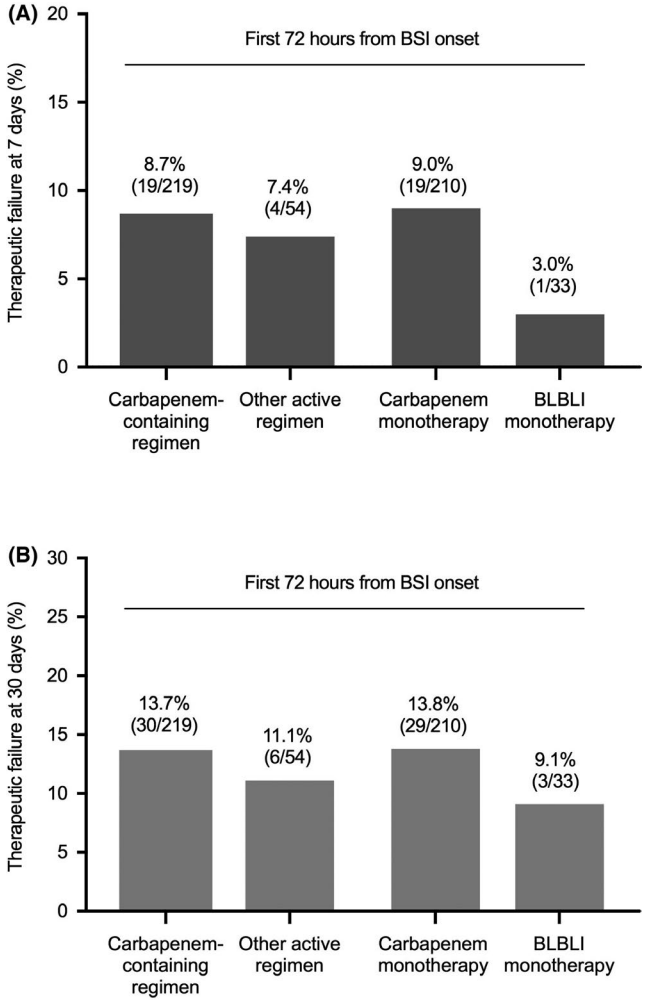

FIGURE 2 Primary (therapeutic failure at day 7) (A) and secondary (therapeutic failure at day 30) (B) study outcomes according to the administration of a carbapenem-containing regimen (vs any other active therapy) or BLBLI-based (vs carbapenem-based) monotherapy within the first 72 hours. BLBLI, β-lactam/β-lactamase inhibitor; BSI, bloodstream infection

potent regimen were carried out. The PS-adjusted risk of therapeutic failure at days 7 and 30 did not significantly differ between patients treated with a carbapenem-containing regimen within the first 72 hours and those receiving any other active regimens. No impact was demonstrated for the choice of BLBLI-based versus carbapenem-based monotherapy either, although these subgroup analyses must be taken with particular caution, considering the small sample sizes. In addition, a small proportion of patients were transitioned to a different active antibiotic beyond the first 72 hours, posing a potential risk of misclassification bias.

This study has several limitations. Firstly and most importantly, statistical power may be insufficient given the low number of patients who received some specific regimens (such as BLBLI or combination therapy) and the low rates of therapeutic failure and death, as discussed above. In other words, only large absolute risk differences between therapeutic groups would have been detected with the present sample size. Secondly, we have included cases of ESBL-E BSI based only on the phenotypic profile of resistance. Although ceftriaxone non-susceptibility is often used as a simple surrogate marker for ESBL production, not all *Enterobacterales* with a ceftriaxone MIC greater than 1 mg/L are ESBL producers.[42] Thirdly, we were not able to examine the potential impact of the MICs of the reported antibiotic agents on therapeutic failure, since these data were not always provided by the participating centers; rather, we assumed this limitation and used the informed category of susceptibility or resistance as reported by local investigators. Previous studies have shown that infections caused by *Enterobacterales* with higher MIC values for piperacillin-tazobactam have an increased risk for non-favorable outcome compared to isolates with lower MIC values.[42,43] Fourthly, while we considered data regarding BLBLI dose, frequency of administration, and duration of treatment in order to assess the adequacy of therapy, the low number of patients precluded any further analyses regarding the potential impact of the different treatment schemes used. High-dose and/or continuous infusion regimens have been associated with higher probability of therapeutic success.[15,44] Fifthly, no specific information on the differential impact of the therapeutic regimens analyzed on graft function was collected. Finally,

potential overfitting of multivariable models (with associated instability) cannot be ruled out given the relatively low number of patients, particularly for therapeutic failure at day 7.

How the present findings can inform decision-making process in clinical practice? While the empirical use of a carbapenem-containing regimen should be always considered in a given recipient with sepsis from a presumed urinary source, considering the high proportion of infections caused by ESBL-E in this population (estimated at 33% in the abovementioned meta-analysis, with large geographical variations[10]), early de-escalation to an alternative carbapenem-sparing regimen may be safely implemented once in vitro susceptibility has been demonstrated, with preference given to piperacillin-tazobactam monotherapy. On the other hand, the switch to a carbapenem before antimicrobial susceptibility testing become available would not be mandatory for those recipients who have been already initiated on BLBLI and are experiencing good clinical evolution during the first hours from BSI onset. This strategy would contribute to minimize the spread of carbapenem-resistant *Enterobacterales* in the transplant setting. The ongoing PETERPEN (NCT03671967) and MERINO-3 (NCT04238390) trials, which are exploring the role of piperacillin-tazobactam and ceftolozane-tazobactam for infections caused by third-generation cephalosporin-resistant *Enterobacterales* in non-transplant patients, will hopefully shed light on this question.

In conclusion, although preliminary in nature, our results would support previous evidence from non-immunocompromised patients suggesting that BLBLI (namely piperacillin-tazobactam) may be as effective as carbapenem-containing regimens to treat ESBL-E BSI secondary to UTI in KTRs, provided the isolate is susceptible in vitro. The present findings can inform that the design of pragmatic, non-inferiority randomized clinical trials confirm the role of carbapenem-sparing approaches in the specific KTR population.

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CONFLICT OF INTEREST

All authors report no conflict of interest relevant to this article.

AUTHOR CONTRIBUTIONS

JTC, JRB, JMA, LMM, AP, BGG, and EPN conceived and designed the study. JMA and LMM obtained funding. EPN and BGG were involved in study coordination and data curation. JTC and JRB supervised the global study. JMA coordinated and supervised the present analysis.

LCP, EPN, MFR, JTC, and JMA analyzed and interpreted the data. EPN and MFR did the statistical analysis. LCP, EPN, MFR, JTC, and JMA drafted the manuscript. All other heading authors were directly involved in investigation and study supervision at each of the participating centers. All other authors acknowledged as Investigators from the REIPI/INCREMENT-SOT Group participated in data collection at their respective institutions.

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SUPPORTING INFORMATION

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