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22 **Title page**

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24 producing *Enterobacterales* bacteremia secondary to urinary tract infection in kidney transplant
25 recipients (INCREMENT-SOT Project).

26 **Running title:** BLBLI for ESBL-*Enterobacterales* in KT.

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183 **Abbreviations**

- 184 • auROC: area under the receiving operator characteristics curve
- 185 • BC: blood culture
- 186 • BLBLI: β -lactam/ β -lactamase inhibitors
- 187 • BSI: bloodstream infection
- 188 • CCI: age-adjusted Charlson comorbidity index
- 189 • CI: confidence interval
- 190 • CLSI: Clinical and Laboratory Standards Institute
- 191 • CMV: cytomegalovirus
- 192 • CRE: carbapenem-resistant *Enterobacterales*
- 193 • ESBL: extended-spectrum β -lactamase
- 194 • ESBL-E: extended-spectrum β -lactamase-producing *Enterobacterales*
- 195 • EUCAST: European Committee on Antimicrobial Susceptibility Testing
- 196 • IQR: interquartile range
- 197 • KTR: kidney transplant recipients
- 198 • MDR: multidrug-resistant
- 199 • MIC: minimum inhibitory concentrations
- 200 • OR: odds ratio
- 201 • PCR: polymerase chain reaction
- 202 • PS: propensity score
- 203 • SD: standard deviation
- 204 • UTI: urinary tract infection
- 205 • VIF: variance inflation factor

206 **Abstract** (250 words)

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

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

215 *Results:* Therapeutic failure at days 7 and 30 occurred in 8.2% (25/306) and 13.4% (41/306) of
216 patients. Hospital-acquired BSI (adjusted OR [aOR]: 4.10; 95% confidence interval [CI]: 1.50-11.20)
217 and Pitt score (aOR: 1.47; 95% CI: 1.21-1.77) were independently associated with therapeutic failure
218 at day 7. Age-adjusted Charlson Index (aOR: 1.25; 95% CI: 1.05-1.48), Pitt score (aOR: 1.72; 95% CI:
219 1.35-2.17) and lymphocyte count ≤ 500 cells/ μ L at presentation (aOR: 3.16; 95% CI: 1.42-7.06)
220 predicted therapeutic failure at day 30. Carbapenem monotherapy (68.6%, primarily meropenem)
221 was the most frequent active therapy, followed by BLBLI monotherapy (10.8%, mostly piperacillin-
222 tazobactam). Propensity score-adjusted models revealed no significant impact of the choice of active
223 therapy (carbapenem-containing versus any other regimen, BLBLI- versus carbapenem-based
224 monotherapy) within the first 72 hours on any of the study outcomes.

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

229
230 **Keywords:** kidney transplantation; extended-spectrum β -lactamase-producing *Enterobacterales*
231 (ESBL-E); urinary tract infection (UTI); bloodstream infection (BSI); outcomes; carbapenem-sparing
232 regimen.

233 INTRODUCTION

234 Bloodstream infections (BSI) represent a common complication after solid organ transplantation
235 (SOT), with an incidence higher than that expected in the general population¹. Urinary tract infection
236 (UTI) is the most common source of BSI in kidney transplant recipients (KTR)²⁻⁴, mainly due to the
237 combined impact of invasive procedures on the urinary tract and underlying immunosuppression^{2,5}.

238 The increasing prevalence of infections due to multidrug-resistant (MDR) gram-negative bacilli, such
239 as extended-spectrum β -lactamase (ESBL)-producing *Enterobacterales* (ESBL-E), is of particular
240 concern in the SOT setting⁶⁻⁹. Approximately 10% of KTR will develop an UTI caused by ESBL-E within
241 the first year¹⁰, and these patients face a three times higher risk of recurrence compared to those
242 infected with non-MDR bacteria^{10,11}.

243 The management of infections caused by ESBL-E remains challenging, with limited antimicrobials
244 available and scarce supporting evidence. Carbapenems have been considered as the front-line
245 therapy both in the general population¹² and in immunocompromised patients, including KTR¹³.

246 Observational studies conducted in the general population —such as the multinational INCREMENT
247 cohort (ClinicalTrials.gov identifier: NCT01764490)— have shown that, for organisms showing *in*
248 *vitro* susceptibility, β -lactam/ β -lactamase inhibitors (BLBLI) may be a good alternative to
249 carbapenems for the treatment of BSI due to ESBL-E, particularly among non-critically ill patients
250 with UTI¹⁴⁻¹⁷. On the contrary, other studies, including a recently published randomized trial, have
251 reported a difference in mortality favoring carbapenems¹⁸⁻²⁰. Interpretation of previous studies is
252 further complicated due to the lower reliability and reproducibility of *in vitro* susceptibility testing to
253 piperacillin-tazobactam as compared to carbapenems when gradient methods such as E-test are
254 used²¹. Whether these findings can be extrapolated to the SOT population remains to be assessed.

255 The aim of the present study was to compare the impact of therapeutic regimens based on
256 carbapenems versus BLBLI on the clinical outcome in a large multinational cohort of KTR with ESBL-E
257 BSI secondary to UTI.

258 MATERIALS AND METHODS

259 Study population and setting

260 The INCREMENT-SOT project (ClinicalTrials.gov identifier NCT02852902) comprised a retrospective
261 international cohort of SOT recipients diagnosed with clinically significant (i.e. meeting criteria for
262 systemic inflammatory response syndrome) BSI due to ESBL-E or carbapenemase-producing
263 *Enterobacterales* admitted to 40 tertiary hospitals in 16 countries from January 2004 to October
264 2016. For the present analysis, KTR with monomicrobial ESBL-E BSI secondary to UTI were eligible.
265 Patient data were collected at each site by review of microbiology reports and patients' charts until
266 day 30 after incident blood cultures (BCs) were taken. Exclusion criteria were key missing data
267 regarding therapeutic regimens and/or outcomes, death earlier than 24 hours after the index date
268 (i.e. that of BSI onset), and the administration of active therapy for at least 2 days prior to BC
269 sampling. The study protocol was approved by the Spanish Agency of Medicines (code FIB-COL-
270 2015-01) and by the Ethics Committee of the Hospital Universitario Reina Sofía (Act 243, code 2907),
271 which waived the need to obtain written informed consent. Approval was also gained at
272 participating centers according to local requirements.

273 Study outcomes and definitions

274 The *primary study outcome* was therapeutic failure, defined as the lack of cure or clinical
275 improvement (i.e. persistence or worsening of fever, leukocytosis or other signs of infection, and/or
276 persistently positive BC for the same microorganism) and/or death from any cause, at day 7 from
277 the onset of BSI. Therapeutic failure at day 30 was considered as *secondary outcome*. The *main*
278 *explanatory variable* was the type of active therapy (according to the categories defined below)
279 administered within the first 72 hours from BSI onset. Sensitivity analyses were also performed
280 based on the regimen used during the first 24 hours and 7 days. The tested hypothesis (BLBLI are not
281 associated with worse outcomes than carbapenem-containing regimens after controlling for
282 potential confounders) was specified *a priori* in the study protocol. Due to the exploratory nature of
283 the study and the expected low proportion of patients treated with BLBLI across participating
284 institutions, no sample size estimation on the basis of the anticipated incidence of study outcomes

285 was performed. In addition, the statistical analysis was not formally modelled on a non-inferiority
286 assumption.

287 Episodes of ESBL-E BSI were considered *hospital-acquired* if symptoms started beyond the first 48
288 hours from hospital admission or within 48 hours from a previous hospital discharge.
289 *Enterobacterales* were identified using standard microbiological techniques at each centre. ESBL
290 production was screened in all isolates with diminished susceptibility to third-generation
291 cephalosporins—a key phenotypic property of ESBL enzymes—and confirmed by standard
292 methods²². Susceptibility was studied using automated systems or disk diffusion and interpreted
293 according to the guidelines (Clinical and Laboratory Standards Institute [CLSI] or European
294 Committee on Antimicrobial Susceptibility Testing [EUCAST]) applied at each centre^{23,24}. Isolates
295 were considered to be ESBL producers if at least one phenotypic confirmatory test was positive
296 according to the corresponding CLSI or EUCAST criteria applicable at the time of testing, or if they
297 had been characterized by PCR and DNA sequencing using established methods.

298 *Active therapy* was defined as administration of at least one antimicrobial agent to which the isolate
299 showed susceptibility *in vitro*, at the standard dose and frequency¹². Specifically, standard
300 intravenous dosing regimens for the most common antimicrobials administered were as follows:
301 piperacillin-tazobactam, 3/0.375 g to 4/0.5 g every 6-8 hours; meropenem, 1-2 g every 8 hours;
302 ertapenem, 1 g every 24 hours; and imipenem-cilastatin, 500/500 mg to 1/1 g every 6-8 hours. All
303 doses were adjusted to renal function. The therapy was considered to be inactive if the isolate was
304 non-susceptible to the agent(s) administered or the dosing was inappropriate. *Monotherapy* was
305 defined as the administration of a single active drug for at least 48 hours (except for patients that
306 died in less than 48 hours, who were included if they received at least one complete day of therapy).
307 The definition criteria for *combination antibiotic therapy* (i.e. simultaneous administration of two or
308 more active drugs) varied according to the time elapsed since the initiation of treatment, in order to
309 account for changes in antimicrobial therapy during the course of BSI (from empirical to targeted
310 therapy). For the first 24 or 72 hours from the onset of BSI, combination therapy was defined as the
311 administration of two or more active antimicrobial agents for at least 24 hours. For therapy
312 administered within the first 7 days, the definition required the use of two or more active agents for

313 at least 72 hours. *Source control* included at least one of the following measures: surgical
314 debridement (e.g. laparotomy for organ/space surgical site infection), non-surgical debridement
315 (e.g. imaging-guided drainage of perinephric abscess or infected kidney cyst), and/or removal or
316 replacement of urinary catheter. To avoid confounding by indication bias, only those source control
317 procedures performed before the time of outcome assessment (i.e. days 7 and 30 for the primary
318 and secondary outcomes, respectively) were taken into account. Severity of infection and
319 comorbidity burden were assessed by means of the Pitt bacteremia score²⁵, the age-adjusted
320 Charlson Comorbidity Index (CCI)²⁶ and the McCabe score²⁷. The diagnosis of *cytomegalovirus (CMV)*
321 *infection* required the presence of laboratory-confirmed CMV replication by either pp65
322 antigenemia assay or PCR-based nucleic acid amplification testing. *CMV disease* was defined as
323 evidence of CMV replication with attributable symptoms²⁸.

324 **Statistical analysis**

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

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

345 To partially overcome the limitation posed by the non-randomized design of the study, we
346 calculated the propensity scores (PS) for receiving either carbapenem-containing therapy (versus
347 any other active regimen) or BLBLI-based (versus carbapenem-based) monotherapy, within the first
348 72 hours and given the patient's baseline characteristics and the clinical features at BSI presentation.
349 Both scores were estimated by means of backward stepwise logistic regression models including
350 variables with *P*-values <0.1 in the univariate analysis (**Tables S1** and **S2**), and the fit of the resulting
351 models were assessed by means of the area under the receiving operator characteristics curve
352 (auROC). PS were entered as a covariate in multivariable models to adjust for potential confounding
353 by factors influencing the choice of therapy.

354 Statistical analysis was performed with SPSS version 20.0 (IBM Corp., Armonk, NY) and graphs were
355 generated with Prism version 6.0 (GraphPad Software Inc., La Jolla, CA).

356 RESULTS

357 Characteristics of the study population

358 Overall, 306 episodes of ESBL-E BSI occurring in 306 KTR were included from 30 centers in 14
359 countries. The clinical and microbiological features are shown in **Table 1**. The median interval from
360 transplantation to BSI onset was 119 days, and 23.2% of the episodes occurred within the first
361 month. The median length of stay was 16 days (9 – 33.5). Most patients were receiving triple
362 maintenance immunosuppression consisting of corticosteroids, tacrolimus and mycophenolic acid or
363 mycophenolate mofetil. Regarding the ESBL-E identified, *Escherichia coli* (62.1%) and *Klebsiella* spp.
364 (35.0%) accounted for the majority of cases.

365 Therapeutic failure at days 7 and 30 (primary and secondary outcomes) occurred in 8.2% (25/306)
366 and 13.4% (41/306) of patients. All-cause mortality rates at days 7 and 30 were 1.0% (3/306) and
367 2.9% (9/306), respectively. All but one death were considered attributable to ESBL-E BSI. The rates of
368 cure and clinical improvement were 2.6% (8/206) and 89.2% (273/306) by day 7, and 77.5%
369 (237/306) and 9.2% (28/306) by day 30, respectively.

370 The therapeutic regimens given at different time intervals are detailed in **Table 2**. Most patients
371 received active therapy with carbapenem monotherapy (144 [47.1%] for the first 24 hours, 210
372 [68.6%] %] for the first 72 hours, and 237 [77.5%] for the first 7 days from BSI onset), whereas BLBLI
373 monotherapy (mostly piperacillin-tazobactam) was chosen in about 10% of cases. Piperacillin-
374 tazobactam was most commonly administered at doses of 4/0.5 g every 8 hours (46.7% [14/30]) and
375 2/0.25 g every 8 hours (20.0% [6/30]). The use of combination antibiotic therapy was anecdotal.
376 Twenty-one patients (6.8%) received during the first 72 hours an antibiotic that lacked *in vitro*
377 activity against the isolate, which mainly included second- or third-generation cephalosporins (10
378 patients [47.6%]), piperacillin-tazobactam (8 patients [38.1%]) or quinolones (2 patients [9.5%]).
379 Within the subgroup of patients that received monotherapy during the first 72 hours from BSI onset,
380 5.0% (13/261) were subsequently transitioned to a second active antibiotic.

381 Risk factors for therapeutic failure

382 Univariate and multivariable analyses of factors predicting therapeutic failure at day 7 (primary

383 outcome) are shown in **Table 3**. At the univariate level, recipient gender, time interval from
384 transplantation to BSI onset, use of trimethoprim-sulfamethoxazole prophylaxis, presence of urinary
385 stenosis, hospital-acquired infection, acute rejection within the prior month, Pitt bacteremia score,
386 and the degree of sepsis severity were associated with this outcome. Since the Pitt score and the
387 presence of septic shock exhibited significant multicollinearity (VIF values >1.5), only the former
388 variable was included into the logistic regression model. The presence of hospital-acquired BSI (OR:
389 4.10; 95% CI: 1.50 – 11.20; *P*-value = 0.006) and the Pitt bacteremia score at BSI onset (OR [per one-
390 point increase]: aOR: 1.47; 95% CI: 1.21 – 1.77; *P*-value <0.0001) remained as independent
391 predictors for therapeutic failure at day 7.

392 Age-adjusted CCI (OR [per one-point increase]: 1.25; 95% CI: 1.05 – 1.48; *P*-value = 0.010), Pitt score
393 (OR [per one-point increase]: 1.72; 95% CI: 1.35 – 2.17; *P*-value <0.0001) and an absolute
394 lymphocyte count ≤ 500 cells/ μL at BSI onset (OR: 3.16; 95% CI: 1.42 – 7.06; *P*-value = 0.005) were
395 independent predictors for therapeutic failure at day 30 (**Table 4**). There were no significant
396 differences in 30-day survival between patients receiving or not receiving active therapy within the
397 first 24 (98.3% versus 95.3%, respectively; log-rank test *P*-value = 0.365) or 72 hours (100.0% versus
398 95.9%; log-rank test *P*-value = 0.293) from the onset of BSI.

399 **Impact of different therapeutic regimes on study outcomes**

400 The impact on study outcomes of different regimens was next investigated within the subgroup of
401 participants that received active therapy. First, we compared the incidence of therapeutic failure at
402 day 7 (primary outcome) in patients receiving combination therapy versus monotherapy during the
403 first 72 hours from the onset of BSI, with no significant differences found between both groups
404 (8.3% [1/12] versus 8.4% [22/261], respectively; risk difference: 0.06%; 95% CI: -0.15 – 0.16;
405 unadjusted OR [uOR]: 0.99; 95% CI: 0.12 – 8.01; *P*-value = 0.991) (**Figure 1a**). There were no
406 significant differences in the occurrence of therapeutic failure at day 30 (secondary outcome) either
407 (16.7% [2/12] versus 13.0% [34/261]; risk difference: -3.63%; 95% CI: -0.23 – 0.16; uOR: 1.34; 95% CI:
408 0.28 – 6.36; *P*-value = 0.717) (**Figure 1b**). Next, we evaluated the impact of using a carbapenem-
409 containing regimen versus any other active regimen during the first 72 hours. No significant

410 differences were observed, either at day 7 (8.7% [19/219] versus 7.4% [4/54]; risk difference: -
411 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
412 (13.7% [30/219] versus 11.1% [6/54]; risk difference: -2.59; 95% CI: -0.13 – 0.07; uOR: 1.27; 95% CI:
413 0.50 – 3.23; *P*-value = 0.615) (**Figure 2b**). Finally, we compared the risk of therapeutic failure
414 between patients treated with carbapenem monotherapy versus BLBLI monotherapy. Once again,
415 we observed no significant differences at day 7 (9.0% [19/210] versus 3.0% [1/33]; risk difference: -
416 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
417 (13.8% [29/210] versus 9.1% [3/33]; risk difference: -4.72%; 95% CI: -0.17 – 0.08; uOR: 1.60; 95% CI:
418 0.46 – 5.59; *P*-value = 0.459) (**Figure 2b**) between both therapeutic modalities. In addition, there
419 were no significant differences in hospital stay between any of these therapeutic regimens (**Table**
420 **S3**).

421 **Propensity score-adjusted analysis**

422 Next, we applied a PS-based approach to investigate whether the therapeutic regimen administered
423 within the first 72 hours from BSI onset influenced study outcomes. The following variables were
424 included in the PS for the use of a carbapenem-containing regimen: geographical area (Europe or
425 North America versus other sites), simultaneous kidney-pancreas transplantation, certain pre-
426 transplant chronic conditions (diabetes, liver disease, congestive heart failure and chronic
427 pulmonary disease), CMV disease within the prior month, and presence of a rapidly or ultimately
428 fatal disease according to the McCabe score (**Table S1**). The auROC of the resulting PS was 0.738
429 (95% CI: 0.664 – 0.812). The risk of therapeutic failure at day 7 (PS-adjusted OR: 4.66; 95% CI: 0.58 –
430 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) were
431 not found to be significantly affected by the use of a carbapenem-containing regimen versus any
432 other active regimen. In addition, we further adjusted by the degree of sepsis severity (Pitt score and
433 presence of septic shock) and comorbidity burden in different regression models, since the relatively
434 low number of patients suffering from therapeutic failure at either point was insufficient to perform
435 a single multivariable analysis without incurring in model overfitting. None of these adjustments
436 suggested a risk difference according to the use of a carbapenem-containing therapy or an

437 alternative regimen (**Figure S1**).

438 This methodological approach was also applied to compare the use of BLBLI versus carbapenem
439 within the subgroup of patients treated with monotherapy in the first 72 hours from BSI onset. The
440 variables included in the PS for the use of carbapenem-based monotherapy as compared to BLBLI-
441 based monotherapy were: geographical area (Europe or North America versus other study sites),
442 pre-transplant chronic conditions (congestive heart failure and chronic pulmonary disease),
443 presence of a rapidly or ultimately fatal disease according to the McCabe score, and receipt of active
444 therapy within the first 24 hours (**Table S2**). The auROC of the score was 0.794 (95% CI: 0.719 –
445 0.869). Again, neither the risk of therapeutic failure at day 7 (PS-adjusted OR: 4.36; 95% CI: 0.51 –
446 37.38; *P*-value = 0.179) or day 30 (PS-adjusted OR: 2.59; 95% CI: 0.66 – 10.21; *P*-value = 0.175)
447 appeared to be influenced by the choice of carbapenem-based versus BLBLI-based monotherapy
448 (**Figure S2**).

449 **Sensitivity analysis**

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

456 DISCUSSION

457 In the present study we were not able to detect significant differences in the risk of therapeutic
458 failure (lack of cure or clinical improvement and/or death from any cause) among KTR with ESBL-E
459 BSI secondary to UTI that were treated with carbapenem- or BLBLI-based regimens. Absolute risk
460 differences observed were small (ranging from -6.01% to 0.06%) and of questionable relevance from
461 a clinical perspective. Although current consensus statements favor BLBLI-based regimens for non-
462 severe ESBL infections^{29,30}, such recommendations are supported by limited data. Our research
463 would reinforce previous studies suggesting that BLBLI monotherapy may be as effective as a
464 carbapenem to treat ESBL-E BSI, particularly for low-inoculum infections in non-critically ill
465 patients¹⁴⁻¹⁷.

466 Due to the very low number of KTR within the BLBLI group that received amoxicillin-clavulanic acid
467 (n = 2), our results are mostly applicable to piperacillin-tazobactam, in line with other studies
468 performed in the non-transplant population^{16,17}. Whether both BLBLIs are equally effective for
469 treating ESBL-E remains debatable, although a potential “inoculum effect” has been proposed for
470 piperacillin-tazobactam but not amoxicillin-clavulanic acid³¹. In addition, variations have been
471 reported in the rates of susceptibility to piperacillin-tazobactam according to the specific ESBL
472 enzyme involved, with higher activity for CTX-M-14-like enzymes as compared to other β -lactamases
473 (such as CTX-M-15-like, CMY-like, OXA-1 or SHV enzymes)³². It should be noted that the CLSI and
474 EUCAST guidelines differ in the interpretative criteria for categorizing an isolate as susceptible to
475 piperacillin-tazobactam, with minimum inhibitory concentration (MIC) breakpoints set at ≤ 16 mg/L
476 and ≤ 8 mg/L, respectively. Given the retrospective design of the study, such a discrepancy
477 complicates data aggregation across centers. Indeed, if we focused on episodes treated with
478 piperacillin-tazobactam monotherapy during the first 72 hours, 67.7% (21/31) and 32.3% (10/31) of
479 the isolates had been tested by the CLSI and EUCAST methods.

480 To our knowledge, this is the first study to compare the efficacy of carbapenems and BLBLI for ESBL-
481 E BSI in the specific setting of SOT. Immunocompromised individuals were included in a systematic
482 review and meta-analysis that demonstrated comparable mortality rates for patients with ESBL-E BSI

483 treated with carbapenems or other regimens¹⁴. Nonetheless, most of them were diagnosed with
484 malignancy and neutropenia, with only a low number of SOT recipients³³. In line with these findings,
485 a recent international study in neutropenic hematological patients with ESBL-E BSI also failed to
486 demonstrate differences between carbapenems and BLBLI³⁴.

487 In contrast with our results and most of the previously reported studies, results from a multicenter,
488 open-label, randomized non-inferiority trial of piperacillin-tazobactam versus meropenem for the
489 definitive treatment of BSI due to ceftriaxone-resistant *E. coli* or *K. pneumoniae* did not support the
490 use of BLBLI as a carbapenem-sparing option²⁰. In contrast to the present study, about one third of
491 the participants in the MERINO trial had non-urinary sources, and the risk difference for 30-day
492 mortality in this subgroup was sensibly higher than that observed among patients with BSI from
493 urinary source (14.1% versus 3.7%, respectively). Previous studies have demonstrated poorer
494 outcomes in infections from non-urinary sources treated with piperacillin-tazobactam-based
495 regimens^{35,36}.

496 The absence of demonstrable differences in the rates of therapeutic failure at days 7 and 30 among
497 patients receiving BLBLI versus carbapenems must be interpreted with particular caution, given the
498 low number of patients treated with BLBLI and the subsequent risk of inadequate power to reject
499 the null hypothesis. Alternative carbapenem-sparing active regimens other than BLBLI were used in
500 a small proportion of patients, which precludes conclusions about their potential efficacy for the
501 treatment of post-transplant ESBL-E BSI of urinary origin. The lack of *a priori* sample size calculation
502 renders our study hypothesis-generating rather than confirmatory. In addition, we found no
503 differences in the rates of therapeutic failure between patients treated with combination therapy or
504 monotherapy, regardless of the time elapsed from the onset of BSI to the initiation of an *in vitro*
505 active agent.

506 The low mortality rates observed (1.0% at day 7 and 2.9% at day 30) were consistent with those
507 previously published among KTR, which ranged from 2.5% to 11%^{36,37}, and would have contributed
508 to the quite unexpected lack of apparent impact in terms of worse outcomes of not receiving active
509 therapy. The improved outcomes reported for BSI from urinary source may be explained by the
510 presence of a lower inflammatory response and the higher antibiotic concentration typically reached

511 in the urinary tract. Although the development of septic shock represents a major predictor of
512 mortality³⁶, Kalil et al. showed that mortality was actually lower in SOT recipients with bacteremic
513 sepsis compared with non-transplant patients, suggesting that post-transplant immunosuppression
514 may provide a survival advantage through modulation of the inflammatory response³⁸. On the other
515 hand, the overall favorable outcomes found in our study may reflect the occurrence of a less severe
516 infection, consistent with the low age-adjusted CCI (median of 4) and Pitt bacteremia (median of 0)
517 score values, and the small proportion of patients with rapidly fatal disease (4.9%).

518 In the multivariable analysis, hospital-acquired infection and Pitt score were associated with an
519 increased odds of therapeutic failure at day 7. On the other hand, age-adjusted CCI, Pitt score and
520 the presence of lymphopenia (≤ 500 cells/ μ L) at presentation were associated with therapeutic
521 failure at day 30. Surprisingly, despite the high rate of inadequate (non-active) initial empiric
522 antimicrobial therapy within the first 24 and 72 hours (37.9% and 10.8%, respectively), this variable
523 was not associated with a worse outcome in either univariate or multivariable models. Previous
524 studies have also reported high rates of inadequate initial antimicrobial therapy to treat ESBL-E BSI
525 in the overall population^{39–41}, which may reach up to 60% in studies targeting the SOT population⁶.
526 Some previous studies reported that, following multivariate adjustment, inappropriate initial empiric
527 therapy was not associated with increased mortality after SOT⁶, although inadequately treated UTI
528 episodes exerted a deleterious impact on graft function and patient survival among KTR^{3,5}. Again,
529 such a low mortality rate may be related to the lower inflammatory response in these patients
530 compared to non-transplant patients. Unfortunately, we lack data on the medium- and long-term
531 evolution of renal graft function between patients receiving or not adequate therapy, although no
532 significant differences were found in the overall length of stay (which may serve as a proxy for the
533 development of acute kidney injury or the requirement of renal replacement therapy during the
534 incident hospitalization).

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

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

546 This study has several limitations. Firstly and most importantly, statistical power may be insufficient
547 given the low number of patients that received some specific regimens (such as BLBLI or
548 combination therapy) and the low rates of therapeutic failure and death, as discussed above. In
549 other words, only large absolute risk differences between therapeutic groups would have been
550 detected with the present sample size. Secondly, we have included cases of ESBL-E BSI based only on
551 the phenotypic profile of resistance. Although ceftriaxone non-susceptibility is often used as a simple
552 surrogate marker for ESBL production, not all *Enterobacterales* with a ceftriaxone MIC greater than 1
553 mg/L are ESBL producers⁴². Thirdly, we were not able to examine the potential impact of the MICs of
554 the reported antibiotic agents on therapeutic failure, since these data were not always provided by
555 the participating centers; rather, we assumed this limitation and used the informed category of
556 susceptibility or resistance as reported by local investigators. Previous studies have shown that
557 infections caused by *Enterobacterales* with higher MIC values for piperacillin-tazobactam have an
558 increased risk for non-favorable outcome compared to isolates with lower MIC values^{42,43}. Fourthly,
559 while we considered data regarding BLBLI dose, frequency of administration, and duration of
560 treatment in order to assess the adequacy of therapy, the low number of patients precluded any
561 further analyses regarding the potential impact of the different treatment schemes used. High-dose
562 and/or continuous infusion regimens have been associated with higher probability of therapeutic
563 success^{15,44}. Fifthly, no specific information on the differential impact of the therapeutic regimens
564 analyzed on graft function was collected. Finally, potential overfitting of multivariable models (with
565 associated instability) cannot be ruled out due to the relatively low number of patients, particularly
566 for therapeutic failure at day 7.

567 How the present findings can inform decision-making process in clinical practice? While the
568 empirical use of a carbapenem-containing regimen should be always considered in a given recipient
569 with sepsis from a presumed urinary source due to the high proportion of infections due to ESBL-E in
570 this population (estimated at 33% in the above-mentioned meta-analysis, with large geographical
571 variations¹⁰), early de-escalation to an alternative carbapenem-sparing regimen may be safely
572 implemented once *in vitro* susceptibility has been demonstrated, with preference given to
573 piperacillin-tazobactam monotherapy. On the other hand, the switch to a carbapenem before
574 antimicrobial susceptibility testing become available would not be mandatory for those recipients
575 that have been already initiated on BLBLI and are experiencing good clinical evolution during the first
576 hours from BSI onset. This strategy would contribute to minimize the spread of carbapenem-
577 resistant *Enterobacterales* in the transplant setting. The ongoing PETERPEN (NCT03671967) and
578 MERINO-3 (NCT04238390) trials, which are exploring the role of piperacillin-tazobactam and
579 ceftolozane-tazobactam for infections due to third-generation cephalosporin-resistant
580 *Enterobacterales* in non-transplant patients, will hopefully shed light on this question.

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

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<i>Variable</i>	<i>(n = 306)</i>
<i>Patient-related variables</i>	
Age, years [mean \pm SD]	56.6 \pm 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)
<i>Transplant-related variables</i>	

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)
Antithymocyte 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)
<i>BSI episode-related variables</i>	
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/ μ L [n (%)] ^b	117 (39.9)
Microbiological results [n (%)]	
<i>Escherichia coli</i>	190 (62.1)
<i>Klebsiella</i> spp.	107 (35.0)
<i>Enterobacter</i> spp.	4 (1.3)
Other	5 (1.6)
<hr/>	
<i>Treatment-related variables and outcomes</i>	
<hr/>	
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)

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.

731 **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 <i>in vitro</i>	59 (19.3)	21 (6.8)	3 (1.0)
No antibiotic administered	57 (18.6)	12 (3.9)	5 (1.6)

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).

TABLE 3. Univariate and multivariable analysis 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 antithymocyte 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)						
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)						

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.

^cData not available for 36 patients.

^dHazard ratio estimated per one-point increase in the score.

^eThe variable “septic shock” was not entered into the model due to the existence of significant collinearity with the Pitt bacteremia score.

^fVariables entered into the multivariable model are highlighted in bold characters.

^gHosmer-Lemeshow *P*-value = 0.799.

TABLE 4. Univariate and multivariable analysis 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 – 1,688)	124 (35 – 1,366)						
BSI within the first post-transplant month [n (%)]	7 (17.1)	64 (24.2)						
Induction therapy with antithymocyte 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 \leq 500 cells/ μ L 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)						
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)						

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 due to 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.

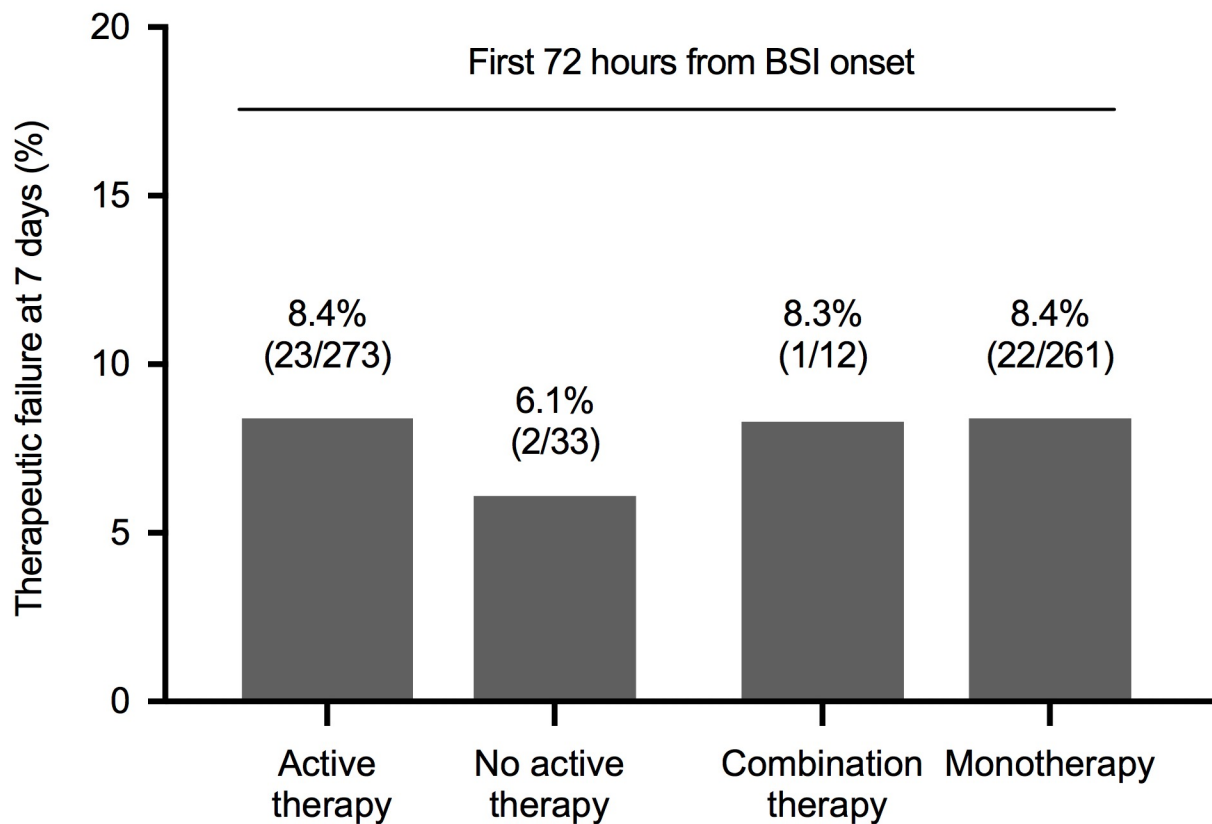
FIGURE LEGENDS

- **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 (versus inactive) therapeutic regimens or combination therapy (versus 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 (versus any other active therapy) or BLBLI-based (versus carbapenem-based) monotherapy within the first 72 hours. BLBLI: β -lactam/ β -lactamase inhibitor. BSI: bloodstream infection.

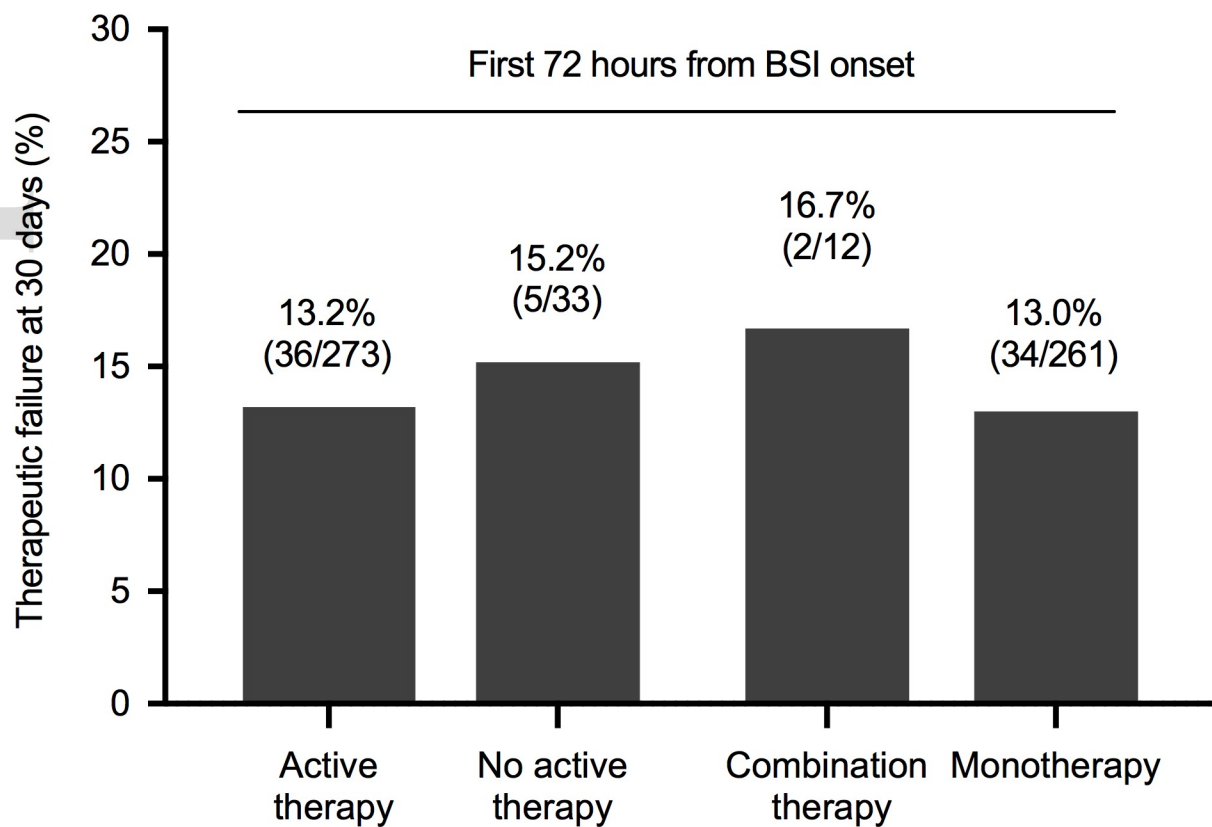
Supplemental Material

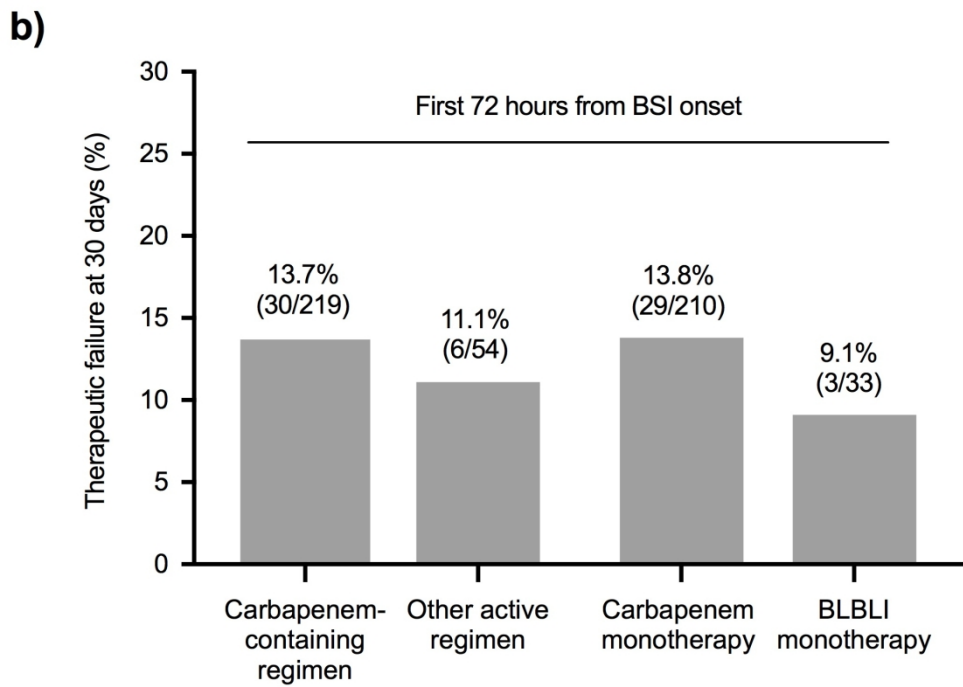
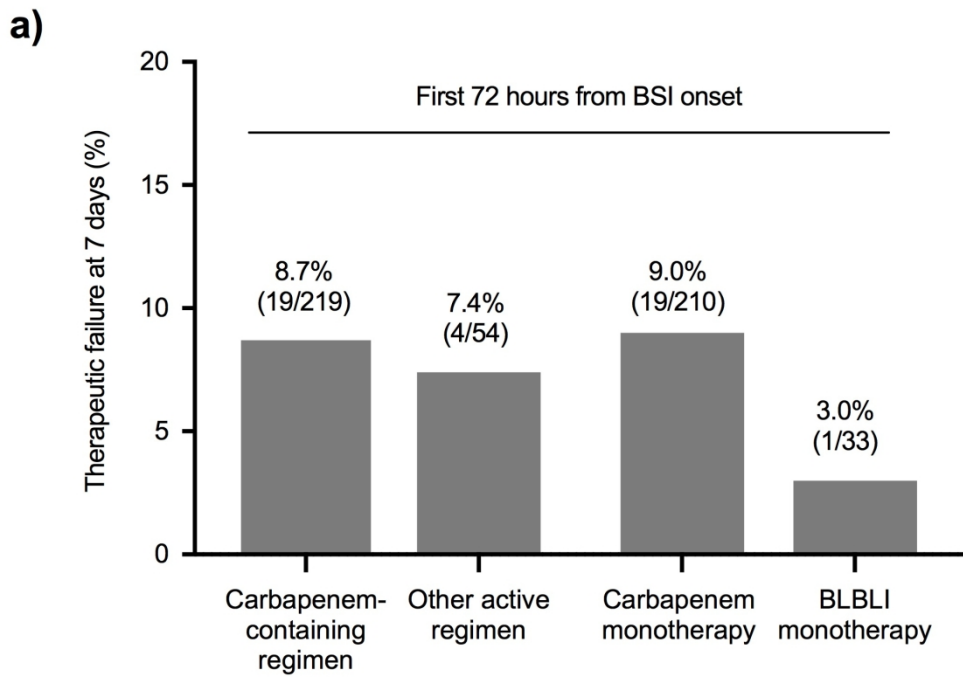
- **Table S1.** *Propensity score modelling:* Comparison of baseline characteristics between patients receiving a carbapenem-containing regimen or any other active regimen within the first 72 hours from the onset of bloodstream infection.
- **Table S2.** *Propensity score modelling:* Comparison of baseline characteristics between patients receiving β -lactam/ β -lactamase inhibitor- or carbapenem-based monotherapy during the first 72 hours from the onset of bloodstream infection.
- **Table S3.** Length of hospital stay according to different therapeutic regimens administered during the first 72 hours from the onset of bloodstream infection.
- **Table S4.** *Sensitivity analysis:* Effect on primary and secondary study outcomes of different therapeutic regimens administered within the first 24 hours and 7 days from the onset of bloodstream infection.
- **Figure S1.** Odds ratios (circles) with 95% confidence intervals (whiskers) for therapeutic failure at 7 (a) and 30 days (b) according to the use of carbapenem-containing regimen (versus any other active therapy) during the first 72 hours from the onset of bloodstream infection.
- **Figure S2.** Odds ratios (circles) with 95% confidence intervals (whiskers) for therapeutic failure at 7 (a) and 30 days (b) according to the use of carbapenem-based (versus β -lactam/ β -lactamase inhibitor-based) monotherapy during the first 72 hours from the onset of bloodstream infection.
- **Figure S3.** *Sensitivity analysis:* Primary (therapeutic failure at day 7) (a) and secondary (therapeutic failure at day 30) (b) study outcomes according to the administration of active (versus inactive) therapeutic regimens or combination therapy (versus monotherapy) within the first 24 hours from the onset of bloodstream infection.
- **Figure S4.** *Sensitivity analysis:* 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 (versus any other active therapy) or β -lactam/ β -lactamase inhibitor-based (versus carbapenem-based) monotherapy within the first 24 hours from the onset of bloodstream infection.
- **Figure S5.** *Sensitivity analysis:* Secondary study outcome (therapeutic failure at day 30) according to the administration of (a) active (versus inactive) therapeutic regimens or combination therapy (versus monotherapy), or (b) carbapenem-containing regimen (versus any other active therapy) or β -lactam/ β -lactamase inhibitor-based (versus carbapenem-based) monotherapy within the first 7 days from the onset of bloodstream infection.

a)



b)





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