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MECHANISMS OF RESISTANCE

Propensity Score and Desirability of Outcome Ranking Analysis of Ertapenem for Treatment of Nonsevere Bacteremic Urinary Tract Infections Due to Extended-Spectrum-Beta-Lactamase-Producing *Enterobacterales* in Kidney Transplant Recipients

Belén Gutiérrez-Gutiérrez,[a,b] Elena Pérez-Nadales,[a,c] Salvador Pérez-Galera,[d] Mario Fernández-Ruiz,[a,e] Jordi Carratalà,[f] Isabel Oriol,[f] Elisa Cordero,[g] José Antonio Lepe,[g] Ban Hock Tan,[h] Laura Corbella,[i] Mical Paul,[j] Alejandra M. Natera,[a,c] Miruna D. David,[k] Miguel Montejo,[l] Ranganathan N. Iyer,[m] Ligia Camera Pierrotti,[n] Esperanza Merino,[o] Seema Mehta Steinke,[p] Meenakshi M. Rana,[q] Patricia Muñoz,[r] Alessandra Mularoni,[s] Christian van Delden,[t] Paolo Antonio Grossi,[u] Elena María Seminari,[v] Filiz Gunseren,[w] Erika D. Lease,[x] Emmanuel Roilides,[y] Jesús Fortún,[z] Hande Arslan,[aa] Julien Coussement,[bb] Zeliha Koçak Tufan,[cc] Benoit Pilmis,[dd] Marco Rizzi,[ee] Belén Loeches,[ff] Britt Marie Eriksson,[gg] Edson Abdala,[hh] Fabio Soldani,[ii] Warren Lowman,[jj] Wanessa Trindade Clemente,[kk] Marta Bodro,[ll] María Carmen Fariñas,[mm] Esra Kazak,[nn] Luis Martínez-Martínez,[a,oo] José María Aguado,[a,e] Julián Torre-Cisneros,[a,pp] Álvaro Pascual,[a,b] Jesús Rodríguez-Baño,[a,b] Investigators from the REIPI/ESGICH/ESGBIS/INCREMENT-SOT Group

[a]Spanish Network for Research in Infectious Diseases (REIPI)
[b]Clinical Unit of Infectious Diseases and Microbiology, Virgen Macarena University Hospital, Institute of Biomedicine of Seville, University of Seville, Seville, Spain
[c]Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain
[d]Clinical Unit of Internal Medicine, Virgen Macarena University Hospital, Seville, Spain
[e]Unit of Infectious Diseases, "12 de Octubre" University Hospital, Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12), Universidad Complutense, Madrid, Spain
[f]Department of Infectious Diseases, Bellvitge University Hospital, Bellvitge Biomedicine Research Institute (IDIBELL), University of Barcelona, Barcelona, Spain
[g]Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Virgen del Rocío University Hospital, Seville, Spain
[h]Department of Infectious Diseases, Singapore General Hospital, Singapore
[i]Unit of Infectious Diseases, "12 de Octubre" University Hospital, Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12), Universidad Complutense, Madrid, Spain
[j]Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel
[k]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom
[l]Infectious Diseases Unit, Cruces University Hospital, Bilbao, Spain
[m]Clinical Microbiology Identification and Infection Control, Global Hospitals, Hyderabad, India
[n]Infectious Diseases Division, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil
[o]Unit of Infectious Diseases, General University Hospital of Alicante, ISABIAL, Alicante, Spain
[p]Johns Hopkins University, School of Medicine, Baltimore, USA
[q]Icahn School of Medicine at Mount Sinai, New York, New York, USA
[r]Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[s]IRCCS ISMETT, Palermo, Italy
[t]Unit for Transplant Infectious Diseases, University Hospitals of Geneva and the Swiss Transplant Cohort Study (STCS), Geneva, Switzerland
[u]Infectious Diseases Section, Department of Medicine and Surgery, University of Insubria, Varese. National Center for Transplantation, Rome, Italy
[v]Division of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo Pavia, Pavia, Italy
[w]Department of Infectious Diseases and Clinical Microbiology, Akdeniz University Faculty of Medicine, Antalya, Turkey
[x]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, Washington, USA
[y]Infectious Diseases Unit and 3rd Department of Pediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Hippokration General Hospital, Thessaloniki, Greece
[z]Ramón y Cajal University Hospital, Madrid, Spain

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Address correspondence to Julián Torre-Cisneros, julian.torre.sspa@juntadeandalucia.es.

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[aa]Başkent University School of Medicine, Ankara, Turkey
[bb]Division of Infectious Diseases, CUB-Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium
[cc]Infectious Diseases and Clinical Microbiology Department, Medical School of Ankara Yildirim Beyazit University, Ankara, Turkey
[dd]Paris Descartes University, Necker-Enfants Malades University Hospital, Department of Infectious Diseases and Tropical Medicine, Centre d'Infectiologie Necker-Pasteur, Institut Imagine, AP-HP, Paris, France
[ee]Infectious Diseases Unit, ASST Papa Giovanni XXIII, Bergamo, Italy
[ff]Infectious Diseases Unit, Hospital La Paz, Madrid, Spain
[gg]Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala, Sweden
[hh]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[ii]Department of Medicine, Infectious Diseases Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy
[jj]Wits Donald Gordon Medical Centre, Pathcare/Vermaak, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[kk]Faculdade de Medicina, UFMG, Grupo de Transplante de Fígado, Instituto Alfa de Gastroenterologia, Hospital da Clínicas, Universidad de Federal Minas Gerais (HC-UFMG), Minas Gerais, Brazil
[ll]Infectious Diseases Department, Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, Spain
[mm]Infectious Diseases Unit, Hospital Universitario Marqués de Valdecilla, University of Cantabria, Santander, Spain
[nn]Uludag University, Bursa, Turkey
[oo]Clinical Unit of Microbiology, Reina Sofía University Hospital, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Department of Microbiology, University of Cordoba, Córdoba, Spain
[pp]Clinical Unit of Infectious Diseases, Reina Sofía University Hospital, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), University of Cordoba, Córdoba, Spain

ABSTRACT There are scarce data on the efficacy of ertapenem in the treatment of bacteremia due to extended-spectrum-beta-lactamase (ESBL)-producing *Enterobacterales* (ESBL-E) in kidney transplant (KT) recipients. We evaluated the association between treatment with ertapenem or meropenem and clinical cure in KT recipients with nonsevere bacteremic urinary tract infections (B-UTI) caused by ESBL-E. We performed a registered, retrospective, international (29 centers in 14 countries) cohort study (INCREMENT-SOT, NCT02852902). The association between targeted therapy with ertapenem versus meropenem and clinical cure at day 14 (the principal outcome) was studied by logistic regression. Propensity score matching and desirability of outcome ranking (DOOR) analyses were also performed. A total of 201 patients were included; only 1 patient (treated with meropenem) in the cohort died. Clinical cure at day 14 was reached in 45/100 (45%) and 51/101 (50.5%) of patients treated with ertapenem and meropenem, respectively (adjusted OR 1.29; 95% CI 0.51 to 3.22; $P = 0.76$); the propensity score-matched cohort included 55 pairs (adjusted OR for clinical cure at day 14, 1.18; 95% CI 0.43 to 3.29; $P = 0.74$). In this cohort, the proportion of cases treated with ertapenem with better DOOR than with meropenem was 49.7% (95% CI, 40.4 to 59.1%) when hospital stay was considered. It ranged from 59 to 67% in different scenarios of a modified (weights-based) DOOR sensitivity analysis when potential ecological advantage or cost was considered in addition to outcome. In conclusion, targeted therapy with ertapenem appears as effective as meropenem to treat nonsevere B-UTI due to ESBL-E in KT recipients and may have some advantages.

KEYWORDS ertapenem, extended-spectrum-β-lactamase-producing *Enterobacterales*, ESBL-E, urinary tract infection, UTI, bloodstream infection, BSI, kidney transplant

Carbapenems are considered the drugs of choice for the treatment of bloodstream infections caused by extended-spectrum beta-lactamase producing *Enterobacterales* (ESBL-E) (1–4), in particular for immunosuppressed patients such as solid organ transplant (SOT) recipients (5). This has caused an increase in the consumption of carbapenems (6) that may have contributed to the spread of carbapenem-resistant *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (7, 8). This phenomenon has been overwhelming in the setting of SOT (9).

Ertapenem is active *in vitro* against ESBL-E (10) and lacks significant activity against *P. aeruginosa* or *A. baumannii*, thus exerting a lower selective pressure than that of imipenem or meropenem on these bacteria (11, 12). It is also convenient as outpatient therapy. Therefore, ertapenem could be an adequate alternative to other carbapenems (13). However, the higher MIC of ESBL-E, the lower daily dose, and its high binding to

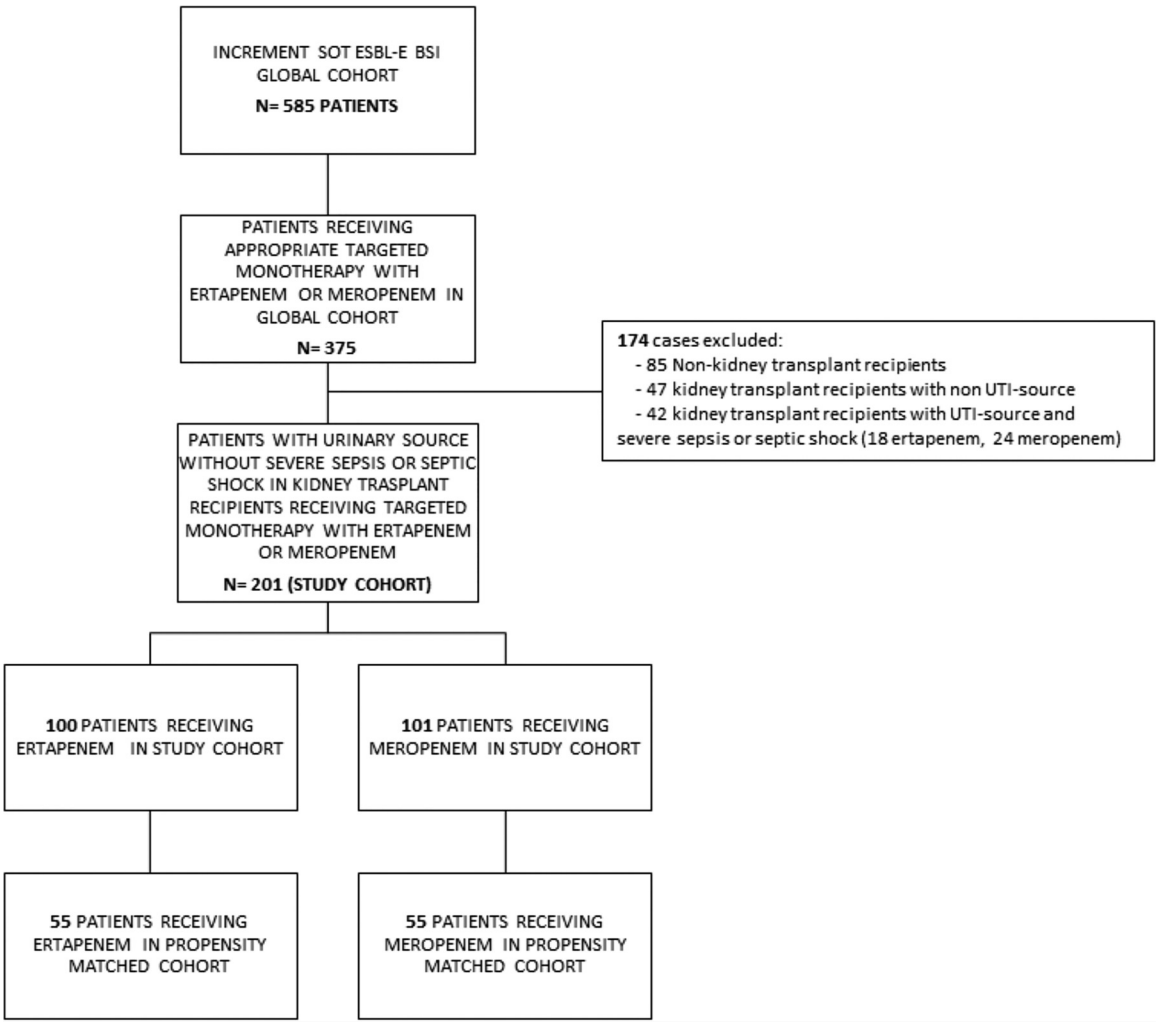

FIG 1 Flow chart of study.

proteins raise some concerns about its efficacy in complex patients. To our knowledge, there are no specific studies in immunosuppressed patients, and specifically in kidney transplant (KT) recipients (5), who are at high risk for urinary tract infections (UTI) due to ESBL-E (5); in fact, approximately 10% of them develop a UTI caused by ESBL-E within the first year, which are frequently bacteremic (14, 15).

Therapeutic decisions for infections caused by multidrug-resistant pathogens frequently need to be individualized. Performing randomized trials for every specific situation is difficult and, therefore, well-performed observational studies may provide useful information. The objective of this study was to evaluate whether ertapenem is associated with similar outcomes to meropenem as a targeted treatment of bacteremic-UTI (B-UTI) in KT recipients.

RESULTS

Characteristics of the study cohort. Overall, 585 episodes of bacteremia due to ESBL-E from 29 centers in 14 countries were included in the INCREMENT-SOT cohort; in this analysis, we included 201 KT recipients with B-UTI receiving targeted monotherapy with ertapenem (100 patients) or meropenem (101 patients) (Fig. 1). The clinical and microbiological features of the patients are shown in Table 1. The median interval from transplantation to bloodstream infection (BSI) onset was 117 days (interquartile range [IQR], 36 to 1,543). Most patients were receiving triple maintenance immunosuppression consisting of tacrolimus, mycophenolic acid/mycophenolate mofetil, and corticosteroids.

TABLE 1 Clinical characteristics of kidney transplant recipients with bloodstream infection of urinary source due to ESBL-*Enterobacterales* treated with ertapenem or meropenem in the global cohort (201 cases) and in the propensity-matched cohort (110 cases, 55 pairs)

	Study cohort			Propensity-matched cohort		
Parameter[d]	Ertapenem (*n* = 100)	Meropenem (*n* = 101)	*P*[c]	Ertapenem (*n* = 55)	Meropenem (*n* = 55)	*P*
Female gender, no. (%)	49 (49)	48 (47.5)	0.83	29 (52.7)	26 (47.3)	0.54
Age, median yrs (IQR)	59.0 (48.8–66.0)	60.0 (50.0–67.0)	0.79[a]	57 (45–64)	59 (46.5–64.5)	0.96[a]
McCabe classification, no. (%)			<0.001[b]			0.54[b]
Nonfatal	91 (91)	72 (71.3)		49 (89.1)	45 (81.8)	
Rapidly fatal	4 (4)	2 (2)		1 (1.8)	2 (3.6)	
Ultimately fatal	5 (5)	27 (26.7)		5 (9.1)	8 (14.5)	
Age-adjusted Charlson index (IQR)	5 (3–8)	6 (4–8)	0.19[a]	5 (3–8)	5 (4–7)	0.83[a]
Diabetes mellitus	48 (48)	50 (49.5)	0.83	24 (43.6)	26 (47.3)	0.70
Transplant-related variables						
Induction therapy, no. (%)	52 (52)	68 (67.3)	0.03	38 (69.1)	35 (63.6)	0.78
Basiliximab	28 (28)	45 (44.6)	0.01	21 (38.2)	23 (41.8)	0.70
Antithymocyte globulin	26 (26)	27 (26.7)	0.91	19 (34.5)	15 (27.3)	0.41
Maintenance immunosuppression, no. (%)						
Tacrolimus	74 (74)	80 (79.2)	0.38	45 (81.8)	40 (72.7)	0.26
Cyclosporine	17 (17)	17 (16.8)	0.97	8 (14.5)	10 (18.2)	0.61
Mycophenolic acid/mycophenolate mofetil	71 (71)	86 (85.1)	0.01	45 (81.8)	47 (85.5)	0.61
Azathioprine	12 (12)	5 (5)	0.08[b]	5 (9.1)	2 (3.6)	0.44[b]
Corticosteroids	89 (89)	94 (93.1)	0.31	51 (92.7)	49 (89.1)	0.51
mTOR inhibitor	6 (6)	10 (9.9)	0.43[b]	2 (3.6)	5 (9.1)	0.44[b]
Acute graft rejection (previous 30 days), no. (%)	8 (8)	12 (11.9)	0.36[b]	5 (9.1)	7 (12.7)	0.76[b]
Simultaneous kidney-pancreas transplant, no. (%)	3 (3)	1 (1)	0.37[b]	3 (5.5)	1 (1.8)	0.62[b]
Chronic kidney disease, no. (%)	61 (61)	71 (70.3)	0.16	40 (72.7)	36 (65.5)	0.41
Dialysis (previous 30 days), no. (%)	16 (16)	23 (22.8)	0.22	13 (23.6)	8 (15.4)	0.28
Urinary stenosis at BSI onset, no. (%)	11 (11)	25 (24.8)	0.01	8 (14.5)	11 (20.0)	0.45
TMP/SMX prophylaxis (previous 30 days), no. (%)	45 (45)	59 (58.4)	0.06	34 (61.8)	33 (60)	0.84
ICU stay (previous 30 days), no. (%)	7 (7)	10 (9.9)	0.46	4 (7.3)	4 (7.3)	1[b]
CMV replication (previous 30 days), no. (%)	9 (9)	10 (9.9)	0.83	7 (12.7)	4 (7.3)	0.54[b]
CMV disease (previous 30 days), no. (%)	2 (2)	8 (7.9)	0.10[b]	2 (3.6)	4 (7.3)	0.68[b]
Lymphocyte count at BSI presentation, median cells/μL (IQR)	700 (400–1,020)	620 (340–1,080)	0.33[a]	600 (400–1,000)	600 (330–1,005)	0.46[a]
BSI episode-related variables						
Time from transplantation to BSI, median days (IQR)	408 (54.3–2,230)	78 (28–890)	0.003[a]	98 (31–802)	60 (21.5–1,136)	0.38[a]
BSI within the first post-transplant mo, no. (%)	16 (16)	30 (29.7)	0.02	14 (25.5)	18 (32.7)	0.40
BSI after mo 12 post-transplant, no. (%)	51 (51)	31 (30.7)	0.003	21 (38.2)	20 (36.4)	0.84
Nosocomial acquisition, no. (%)	30 (30)	52 (51.5)	0.002	25 (45.5)	26 (47.3)	0.85
Pitt bacteremia score, median (IQR)	0 (0–1)	0 (0–2)	0.11[a]	0 (0–1)	0 (0–1)	0.88[a]
Mental status (not alert), no. (%)	7 (7)	18 (17.8)	0.02	6 (10.9)	5 (9.1)	1[b]
Source control, no. (%)	31 (31)	40 (39.6)	0.20	21 (38.2)	17 (30.9)	0.42
Center with higher chance for cure at day 14, no. (%)	39 (39)	42 (41.6)	0.67	19 (34.5)	23 (41.8)	0.43
Period prior to 2013 (higher chance for cure at day 14), no. (%)	44 (44)	48 (47.5)	0.62	29 (52.7)	25 (45.5)	0.45

(Continued on next page)

TABLE 1 (Continued)

Parameter[d]	Study cohort			Propensity-matched cohort		
	Ertapenem (n = 100)	Meropenem (n = 101)	P[c]	Ertapenem (n = 55)	Meropenem (n = 55)	P
Microbiology						
Enterobacteriaceae			0.57			0.60
Escherichia coli, no. (%)	65 (65)	64 (63.4)		36 (65.5)	36 (65.5)	
Klebsiella spp., no. (%)	33 (33)	34 (33.7)		19 (34.5)	18 (32.7)	
Enterobacter spp., no. (%)	1 (1)	0		0	0	
Others, no. (%)	1 (1)	3 (3)		0	1 (1.8)	
Antibiotic treatment						
Appropriate empirical therapy, no. (%)	67 (67)	73 (73)	0.35	40 (72.7)	37 (67.3)	0.53
Time to active treatment, median days (IQR)	1 (0–2)	0 (0–2)	0.12	0 (0–2)	0 (0–2)	0.81
Overall duration of active treatment, median days (IQR)	14 (11.8–20)	13 (10–17)	0.23	14 (11–21)	13 (10–17)	0.10[a]
Outcome						
Improvement at day 14, no. (%)	53 (53)	45 (44.6)	0.23	27 (49.1)	26 (47.3)	0.85
Clinical cure at day 14, no. (%)	45 (45)	51 (50.5)	0.43	27(49.1)	27 (49.1)	1
Not improvement or deterioration at day 14, no. (%)	2 (2)	4 (3.9)	0.68[b]	1 (1.8)	2 (3.6)	1[b]
Hospital stay, median days (IQR)	10.5 (7–15)	14 (8.8–20)	0.008[a]	11 (7–14)	12 (8–19)	0.15
All-cause mortality at day 30, no. (%)	0 (0)	1 (1)	1[b]	0 (0)	0 (0)	1[b]
UTI recurrence after cure, no. (%)	6 (6)	5 (5)	0.74	4 (7.3)	3 (5.5)	0.74[b]

[a]Mann-Whitney U test.
[b]Fisher's exact test.
[c]P values were calculated by $\chi 2$ test, except where otherwise specified.
[d]Abbreviations: IQR, interquartile range; TMP/SMX, Trimethoprim/Sulfamethoxazole; ICU, intensive care unit; BSI, bloodstream infection.

TABLE 2 Summary of crude and adjusted associations between targeted therapy with ertapenem versus meropenem and cure at day 14

Association	Odds ratio (95% CI)	*P*
Targeted therapy study cohort		
Crude[a]	0.80 (0.46–1.40)	0.44
Adjusted (logistic regression)[a,b,c]	1.29 (0.51–3.22)	0.76
IPTW cohort		
Crude	1.07 (0.72–1.59)	0.75
Adjusted (logistic regression)[d]	1.06 (0.66–1.69)	0.81
Targeted therapy propensity score-matched cohort		
Crude	1.00 (0.59–1.71)	1.00
Adjusted (conditional logistic regression)[e]	1.18 (0.43–3.29)	0.74

[a]The complete model is shown in Supplementary Table S1.
[b]The variables used to calculate the propensity score for receiving targeted therapy with meropenem were: center; age; gender; appropriate empirical therapy, TMP/SMX prophylaxis, CMV replication (previous 30 days), CMV disease (previous 30 days), time from transplant to BSI, lymphocyte count at BSI presentation, maintenance of immunosuppression, kidney disease, induction therapy, acute graft rejection (previous 30 days), McCabe classification, Charlson index, diabetes, any tumor, *Klebsiella* spp., ICU previous BSI, acquisition, Pitt score, mental status, PTZ resistance, cefepime resistance and source control. The model showed a *P* value of 0.45 for the Hosmer-Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0.80 (95% CI: 0.74–0.86). CI, confidence interval.
[c]All the variables included in the adjusted analysis showed a VIF $\leq$1.4.
[d]The complete model is shown in Supplementary Table S2.
[e]The complete adjusted model is shown in Supplementary Table S3.

The most frequent ESLB-E identified were *Escherichia coli* (64.2%) and *Klebsiella* spp. (33.3%). Patients receiving targeted treatment with meropenem more frequently had an ultimately fatal underlying condition (26.7%) and a shorter time from transplantation to infection (median, 78 days) compared to those treated with ertapenem (5.0% and 408 days, respectively). The most frequent dose regimens (including those adjusted based on the patient's renal function) were as follows: for meropenem, 1 g every 8 h (32%), 0.5 g every 6 h (28%), or 0.5 g every 12 h (25%); and for ertapenem, 1 g every 24 h (74%) or 500 mg every 24 h (26%).

Clinical cure rate at day 14 occurred in 45% (45/100) patients treated with ertapenem and 50.5% (51/101) treated with meropenem (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.46 to 1.39; *P* = 0.43). Hospital stay was shorter in patients receiving ertapenem than meropenem (median 10.5 days, IQR 7 to 15 versus median 14 days, IQR 8.8 to 20; *P* = 0.008). Median hospital stay of the patients was >10 days in 51.7% (15/29) of the participating centers. Only 1 patient treated with meropenem (none treated with ertapenem) died within 30 days after index culture.

Adjusted analysis of the association of targeted treatment with ertapenem versus meropenem with clinical cure at day 14. A propensity score for receiving meropenem was calculated; the model showed a *P* value of 0.45 for the Hosmer-Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0.80 (95% CI: 0.74 to 0.86) (Fig. S1 in supplemental material). The univariable and multivariable logistic regression analyses of variables associated with clinical cure at day 14 are shown in Table S1. In multivariable analysis, including the propensity score as a covariate, targeted therapy with ertapenem was not shown to be significantly associated with lower risk of clinical cure compared with meropenem, but the precision of the estimate was low (OR, 1.29; 95% CI, 0.51 to 3.22; *P* = 0.76) (Table 2). A sensitivity analysis was performed considering cure or improvement at day 14 as the outcome; targeted therapy with ertapenem was also not significantly associated with lower probability compared with meropenem (OR, 0.89; 95% CI, 0.13 to 6.03, *P* = 0.91).

We then performed an inverse probability of treatment weighting (IPTW)-adjusted analysis using the propensity score. The estimated OR for clinical cure at day 14 with ertapenem versus meropenem in the IPTW cohort was similar, but more precise: 1.06 (95% CI, 0.66 to 1.69; *P* = 0.81) (Table 2) (the whole multivariate model is shown in Table S2 in supplemental material).

TABLE 3 Classification of cases in the three categories considered for desirability of outcome ranking (DOOR) analysis in the IPTW and propensity score-matched cohorts

DOOR rank[a]	Category	IPTW cohort[a]		Propensity-matched cohort	
		Ertapenem (198 cases)	Meropenem (190 cases)	Ertapenem (55 cases)	Meropenem (55 cases)
1	Cure at day 14, no.	96	89	25	27
2	Not cure at day 14 or recurrence after cure, no.	102	101	30	28
3	Dead at day 30, no.	0	0	0	0

[a]For those cases that cured at day 14, length of hospital stay was used to break a tie. DOOR, desirability of outcome ranking; IPTW, inverse probability of treatment weighting.

Finally, we compared the clinical cure rates in the 55 pairs of patients that could be matched by the propensity score (PS). As shown in Table 1, exposure to all baseline features was similar between the matched patients, confirming the improvement of the balance and the correct performance of the selected PS model. The conditional multivariable logistic regression analysis of variables associated with clinical response at day 14 days is shown in Table S3 in supplemental material; targeted therapy with ertapenem was not associated with lower risk of clinical cure at day 14 (adjusted OR, 1.18; 95% CI, 0.43 to 3.29; $P = 0.74$) compared with targeted therapy with meropenem (Table 2).

DOOR analysis in the IPTW and in the propensity score-matched cohorts. Table 3 shows the classification of patients in the three DOOR categories. The proportion of cases with better DOOR among those treated with ertapenem was 50.8% (95% CI 45.8 to 55.8%) and 48.2% (95% CI 38.8 to 57.5%) in the IPTW and the propensity score-matched cohorts, respectively. When hospital length of stay was applied to break a tie for those cases that cured at day 14, the proportion of cases treated with ertapenem with better DOOR was 52.6% (47.7 to 57.6%) and 49.7% (40.4 to 59.1%) in each cohort, respectively.

For the modified weight-based DOOR analysis (only in propensity score-matched cohort), the weights assigned to the outcome categories in the different scenarios are specified in Table 4. Overall, the proportion of patients treated with ertapenem having a better DOOR ranged from 59% to 67% (with a lower value of the 95% confidence interval always >50%) (Table 4, Table S5 and Fig. S2 in supplemental material).

DISCUSSION

The results of this study strongly suggest that treatment with ertapenem of KT recipients with nonsevere bacteremia B-UTI due to ESBL-E is not associated with worse outcomes than treatment with meropenem, and might have some advantages according to the DOOR analysis (including only once-daily administration, potential lower ecological impact, and the possibility of outpatient treatment).

TABLE 4 Weights-based desirability of outcome ranking (DOOR) analysis in the subcohort of patients matched for propensity score of receiving meropenem

Category[a]		Assigned weights					
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
A	All-cause death at day 30	65	70	75	75	75	80
B	No death at day 30 and no clinical cure at day 14 (including improvement and no improvement or deterioration)	25	25	35	35	31	50
C	Clinical cure at day 14, (points per day of hospitalization)[b]	1.3	1.3	1.4	1.8	1.4	2.8
D	Recurrent UTI at day 30	30	25	20	20	20	15
E	Daily antibiotic cost >45 €	2	3	5	0	3	0
F	Stewardship criteria[c]	3	2	0	5	2	5
DOOR							
	Proportion of cases treated with ertapenem with a better modified DOOR than those treated with meropenem (95% CI)	67 (58–75)	66 (57–75)	59 (51–67)	67 (59–76)	66 (57–75)	67 (58–76)

[a]Previous conditions for the weight-assignment criteria in the different scenarios considered are shown in Supplementary Table S4.
[b]The maximum weight assigned to this category is 18 points for Scenarios 1 and 2; 20 points for scenarios 3 and 5; 25 points for Scenario 4; and 40 points for Scenario 6.
[c]Considerations for stewardship criteria favoring any cases treated with ertapenem: once-daily dosing and lower selection pressure for carbapenem-resistant Gram-negative bacilli.

Meropenem or imipenem are currently considered to be the gold standard for the treatment of BSI due to ESBL-E (1–4). In the general population, previous observational studies suggested that ertapenem would be as effective as meropenem, particularly in patients with low mortality risk (e.g., urinary source, absence of septic shock) (16, 17). However, there are scarce data of the efficacy of ertapenem in the treatment of ESBL-E BSI in the SOT setting (5). In fact, SOT recipients are underrepresented in studies evaluating treatment options for ESBL-E BSI (1). In this study, the different analyses used to control for confounding could not show an association or trend of ertapenem with worse outcomes.

Some studies have questioned the efficacy of ertapenem in BSI due to ESBLE-E other than *E. coli* (13), as ertapenem MICs are usually higher (18). However, we did not find lower clinical cure rate in episodes due to *Klebsiella* spp. (Table S1), which may be due to the high probability of attaining the pharmacokinetic-pharmacodynamic (PK-PD) target with ertapenem in UTI (19). Another controversial issue is whether the conventional dose of ertapenem (1 g/day) is sufficient to treat severe infections (13). These doubts refer to the lower probability of attaining the PK-PD target in patients with a high volume of distribution (such as septic shock), especially if the strain has borderline sensitivity. Because ertapenem use in patients with septic shock in our cohort was infrequent, we could not analyze this aspect. However, our data support the use of standard dosing in B-UTI in KT recipients without septic shock.

Clinical studies that compare the efficacy of antibiotics may be limited by analyzing only a specific outcome. Ranking patients with respect to a DOOR allows the assessment of a ranking of outcomes (20). However, providing a hierarchical classification of outcomes to establish the categories may become too subjective and complex when the number of outcomes considered is high, particularly when the desirability between some outcomes is not clear. In addition, it may also be of interest to take into account other factors in the comparison, such as ecological advantage or cost. Therefore, we propose the use of a weight-based modified DOOR analysis.

In this methodology, we assign to each case previously established weights according to the presence of one or more categories (including both outcomes and other factors), in order to be able to next rank each patient in the study and then calculate the proportion of patients with a better DOOR for each study drug. In addition, it allows us to analyze the robustness of the results by evaluating different scenarios, which, always fulfilling previously established conditions, allows the weights assigned to each category to be varied. This methodology is therefore different from the one described by Evans and Follmann (22), since in that study the previously established categories and their ranking do not change, directly assigning to each category a relative importance (partial credits) that varies with respect to its hierarchically superior and inferior categories. Further, other variables to compare both treatments, such as cost or stewardship criteria, cannot be included in a partial credits methodology.

Our study has the intrinsic limitations of observational studies, including the potential effects of unmeasured variables and residual confounding due to lack of randomization. We were also unable to compare treatment with ertapenem and meropenem in patients with severe sepsis or septic shock because of the very low number of patients presenting with them. Only (recommended) phenotypic methods were required to consider the isolates as ESBL producers. Finally, the precision of some of the estimates is low. Some strengths of the study include a multinational inclusion of patients, reflecting real practice, the use of strict exposure definitions, and advanced methods for controlling confounding.

In conclusion, our data support the use of ertapenem in kidney transplant recipients with nonsevere bacteremia from urinary sources due to ESBL-E.

MATERIALS AND METHODS

Study design and population. The INCREMENT-SOT project (ClinicalTrials.gov identifier NCT02852902) is a retrospective, multicenter and multinational cohort of SOT recipients with clinically significant monomicrobial bacteremia due to ESBL-E or carbapenemase-producing *Enterobacterales* between 2004 and 2016. In this analysis, kidney transplant (KT) recipients with a functioning graft and bacteremic urinary tract

infections caused by ESBL-E and receiving targeted monotherapy with ertapenem or meropenem were eligible. Patients were included if targeted treatment was started in ≤5 days after the blood cultures (BC) had been obtained (or, if used empirically, was continued for at least 50% of the total duration of treatment unless changed because of failure) and the isolate was susceptible to carbapenems. Patients with severe sepsis or shock (23), those who died within 24 h of the first dose of the study drug, and patients with missing data regarding therapeutic regimens and/or outcomes were excluded. The study was approved by the Ethics Committee of Hospital Universitario Reina Sofia (Act 243, code 2907) and waived the need to obtain written informed consent due to the observational and retrospective nature of the study. Approvals were also obtained at participating centers according to local requirements. This report follows STROBE recommendations (24) (Table S6).

Study outcomes, variables, and definitions. Clinical outcome was collected as cure, improvement, not improvement, or deterioration and death. The primary outcome was clinical cure rate at day 14, defined as resolution of all new signs and symptoms related to the infection with no further need for antibiotic therapy. Secondary outcomes were duration of hospitalization after bacteremia, all-cause mortality, and UTI recurrence until day 30. The main explanatory variable was targeted monotherapy with ertapenem or meropenem. Improvement was defined as partial control or resolution of signs and symptoms related to the infection, or resolution but antibiotic therapy was still necessary. Not improvement or deterioration was defined as clinical situation qualified as similar or worse, respectively, in comparison to that at the point of diagnosis of bacteremia.

Data collected included the following seven types of variables: (i) demographics; (ii) age-adjusted Charlson comorbidity index (25); (iii) McCabe classification (26); (iv) transplant-related variables, including baseline and induction immunosuppression, simultaneous kidney-pancreas transplantation, urinary tract stenosis, lymphocyte count at the time of BSI, and clinical variables within the 30 days prior to the BSI episode, i.e., acute graft rejection, dialysis, trimethoprim-sulfamethoxazole prophylaxis, intensive care unit (ICU) stay, and cytomegalovirus (CMV) replication/disease; (v) bacteremia-related variables, including time from transplantation to BSI, nosocomial acquisition, severity of acute condition at presentation according to the Pitt bacteremia score (27), and sepsis criteria at day 0 [23]; (vi) microbiological variables, including *Enterobacterales* species, ESBL-type, and antimicrobial susceptibility data; and (vii) treatment-related variables, including the drug(s) administered, dosing, and source control interventions.

The urinary tract was considered the source of BSI if there were urinary signs or symptoms or, in the case of isolation of the same organism in urine culture, in the absence of other evident source. A BSI was considered nosocomial if symptoms started after 48 h of hospital admission or within 48 h from a previous hospital discharge; otherwise, they were considered community onset. Antimicrobials administered before susceptibility results became available were considered empirical (typically, within 48 h of blood cultures obtainment) and targeted thereafter. Appropriate therapy was defined as administration of *in vitro* active drugs recommended for UTI. Monotherapy was defined as the administration of a single *in vitro* active drug. Source control included release of urinary tract obstruction, drainage of perinephric abscess or infected kidney cyst, and/or removal or replacement of urinary catheter. CMV disease was defined as evidence of CMV replication with attributable symptoms (28). Recurrence was considered when clinical symptoms and positive urine culture yielding the same uropathogen (i.e., identical species and antimicrobial susceptibility pattern) appeared after clinical cure. Daily cost of the antibiotics was based on the dose used and its official sales price in Spain (29).

Patient data were collected at each site by reviewing the microbiology reports and patients' charts until day 30 after incident BCs were taken. All time-dependent variables were measured with regard to the day when the incident BCs were drawn (considered as day 0).

Microbiology methods. *Enterobacterales* were identified using standard microbiological procedures at each center. Susceptibility was studied using automated systems or disk diffusion at each local laboratory and interpreted using the 2015 CLSI breakpoints (30). For isolates obtained before 2015, MICs were reviewed and the susceptibility category was assigned accordingly; when the MIC was not available or the available data had a MIC less than or equal to the older susceptibility breakpoint, these were considered as susceptible if so reported by the local laboratory.

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 a molecular method. The diagnosis of CMV replication required the presence of laboratory-confirmed CMV replication by either pp65 antigenemia assay or PCR-based nucleic acid amplification testing.

Statistical analysis. Either a χ^2 test or Fisher's exact test was used to compare categorical variables, as appropriate, and the Mann-Whitney U test was applied for continuous variables. Multivariable analyses were performed using logistic regression. A propensity score for receiving therapy with meropenem was calculated using a nonparsimonious multivariable logistic regression model in which all potential predictors of meropenem use were included. The performance of the PS was assessed by examining density plots. The propensity score was used in three ways: (i) as a covariate in a multivariable logistic analysis; (ii) to form an inverse probability of treatment weighting (IPTW) cohort; and (iii) to match patients (1:1) treated with meropenem or ertapenem using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. Potential interactions between therapy with ertapenem or meropenem and other variables were explored using TreeNet (Salford Predictive Modeler software) and included if they caused a significant modifying effect. The variance inflation factor (VIF) value for every covariable was calculated to evaluate collinearity. We assumed lack of collinearity if all variables had a VIF value <2. Variables were selected using a backward stepwise process; propensity score (when used as a covariate) and treatment arm were forced into the final models. The Akaike Information Criterion

(AIC) was used to select the final logistic models. The models chosen were those that minimized the Kullback-Leibler divergence between the model and the actual data.

To control for the site effect, we classified the centers according to their association with clinical cure at day 14 using TreeNet and considering all other variables into centers with higher and lower chance for cure at day 14. The period to which the cases belong at the time of inclusion was categorized as either "before 2013" (higher chance for cure at day 14) or "from 2013 onward" (lower chance) according to classification and regression tree analysis (CART). Also, lymphocyte count was classified into 3 categories: $<900/mm^3$, 900 to 1,300/mm^3, and $>1,300/mm^3$ using CART (Fig. S3).

Finally, a desirability of outcome ranking (DOOR) analysis (20) comparing ertapenem and meropenem was performed in the IPTW and in the propensity score-matched cohorts. The following three mutually exclusive hierarchical levels, in descending order of desirability, were stablished (the lower the DOOR rank, the more desirable outcome): (i) cure at day 14; (ii) no cure at day 14 or recurrence after cure; and (iii) death at day 30. For cases that cured at day 14, hospital stay was considered to break a tie. We calculated the proportion and 95% CI of cases who were treated with ertapenem showing a better DOOR than those treated with meropenem.

In addition, because developing a hierarchical order of categories to classify the patients using the "classic" DOOR approach may become too subjective and complex when the number of outcomes considered is high, we developed a new analysis method based on the DOOR concept. In this outcome-weight DOOR method, each considered outcome is given a specific weight based on conditions that should be transparently explained; because the weights provided to each outcome are arguable, data on several scenarios with different weights assignment may be provided. Patients in the study were classified according to the punctuation provided by the weighted categories and ranked to calculate the proportion of patients with better DOOR for each study drug in the same way as the DOOR standard methodology. In this study, the conditions for assigning weights to the outcomes are explained in Table S4 in supplemental material, and the weights provided to the different outcomes are shown in Table 4. We assessed six different scenarios according to different weight distributions in order to evaluate the robustness of the results. Further, Table S5 in the supplemental material is provided as an example, including a summary table for the calculation of the proportion of cases treated with ertapenem with a better-modified DOOR than those treated with meropenem in scenario 1 in the propensity matched cohort.

The analyses were carried out using R software (version 3.0.1), SPSS 25.0 (SPSS Inc.), and Salford Predictive Modeler software 8.2 (includes CART and TreeNet).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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