Efficacy of β-Lactam/β-Lactamase Inhibitor Combinations for the Treatment of Bloodstream Infection Due to Extended-Spectrum-β-Lactamase-Producing *Enterobacteriaceae* in Hematological Patients with Neutropenia

Carlota Gudiol,[a,b,y] Cristina Royo-Cebrecos,[a,y] Edson Abdala,[c] Murat Akova,[d] Rocío Álvarez,[e] Guillermo Maestro-de la Calle,[f] Angela Cano,[g,y] Carlos Cervera,[h] Wanessa T. Clemente,[i] Pilar Martín-Dávila,[j] Alison Freifeld,[k] Lucía Gómez,[l] Thomas Gottlieb,[m] Mercè Gurguí,[n] Fabián Herrera,[o] Adriana Manzur,[p] Georg Maschmeyer,[q] Yolanda Meije,[r,y] Miguel Montejo,[s,y] Maddalena Peghin,[t] Jesús Rodríguez-Baño,[u,y] Isabel Ruiz-Camps,[v,y] Teresa C. Sukiennik,[w] Cristian Tebe,[x] Jordi Carratalà,[a,y] for the BICAR Study Group

Infectious Diseases Department, Bellvitge University Hospital, IDIBELL, University of Barcelona, Spain[a]; Duran i Reynals Hospital, ICO, Barcelona, Spain[b]; Instituto do Câncer do Estado de São Paulo, Faculty of Medicine, University of São Paulo, São Paulo, Brazil[c]; Hacettepe University School of Medicine, Ankara, Turkey[d]; Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Infectious Diseases Research Group, Institute of Biomedicine of Seville (IBiS), University of Seville/CSIC/University Hospitals Virgen del Rocio and Virgen Macarena, Seville, Spain[e]; Infectious Diseases Unit, Instituto de Investigación Hospital 12 de Octubre (i+12), 12 de Octubre University Hospital, School of Medicine, Universidad Complutense, Madrid, Spain[f]; Reina Sofía University Hospital-IMIBIC-UCO, Córdoba, Spain[g]; University Hospital of Alberta, Alberta, Canada[h]; Digestive Transplant Service, Hospital das Clínicas, Universidade Federal Minas Gerais, Belo Horizonte, Brazil[i]; Infectious Diseases Department, Ramon y Cajal Hospital, Madrid, Spain[j]; Internal Medicine, Infectious Diseases Section, University of Nebraska Medical Center, Omaha, Nebraska, USA[k]; Internal Medicine, University Hospital Mútua de Terrassa, Barcelona, Spain[l]; Department of Microbiology & Infectious Diseases, Concord Hospital, Concord, NSW, Australia[m]; Infectious Diseases Unit, Hospital de la Santa Creu i Sant Pau and Instituto de Investigación Biomédica Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain[n]; Infectious Diseases Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina[o]; Infectious Diseases, Hospital Rawson, San Juan, Argentina[p]; Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann, Academic Teaching Hospital of Charité University Medical School, Berlin, Germany[q]; Infectious Disease Unit, Internal Medicine Department, Barcelona Hospital, SCIAS, Barcelona, Spain[r]; Infectious Diseases Unit, Cruces University Hospital, Bilbao, Spain[s]; Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy[t]; Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, University Hospitals Virgen Macarena and Virgen del Rocío—IBiS, Department of Medicine, University of Seville, Seville, Spain[u]; Infectious Diseases Department, Vall d'Hebron University Hospital, Barcelona, Spain[v]; Hospital Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil[w]; Statistics Advisory Service, Institute of Biomedical Research of Bellvitge, Rovira i Virgili University, Tarragona, Spain[x]; REIPI (Spanish Network for Research in Infectious Disease), Instituto de Salud Carlos III, Madrid, Spain[y]

Address correspondence to Carlota Gudiol, cgudiol@iconcologia.net.

C.G. and J.C. contributed equally to this article.

ABSTRACT β-Lactam/β-lactamase inhibitors (BLBLIs) were compared to carbapenems in two cohorts of hematological neutropenic patients with extended-spectrum-β-lactamase (ESBL) bloodstream infection (BSI): the empirical therapy cohort (174 patients) and the definitive therapy cohort (251 patients). The 30-day case fatality rates and other secondary outcomes were similar in the two therapy groups of the two cohorts and also in the propensity-matched cohorts. BLBLIs might be carbapenem-sparing alternatives for the treatment of BSI due to ESBLs in these patients.

Bloodstream infection (BSI) due to extended-spectrum-β-lactamases (ESBLs) is increasingly being identified among patients with hematological malignancies (1–5). This is of special concern because a delay in initiating adequate antibiotic therapy may impair their outcomes (1, 6). Carbapenems are increasingly used for treating severe infections caused by ESBL producers. This is particularly worrisome in a scenario in which carbapenem-resistant *Enterobacteriaceae* (CRE) are spreading rapidly and are adversely compromising patients' outcomes (7–12). While recent investigations have suggested that β-lactam/β-lactamase inhibitors (BLBLIs) may be reliable options for the treatment of BSI due to ESBL-producing Gram-negative bacilli (ESBL-GNB), especially in nonimmunocompromised patients (13–19), other studies have found contrasting data (20, 21). To date, the efficacy of BLBLIs for the treatment of BSI due to ESBL-GNB in high-risk hematological patients has not been established. In this regard, assessing the usefulness of BLBLIs as carbapenem-sparing antibiotic regimens may be a key step in the efforts to minimize the spread of CRE. This study aimed to assess the efficacy of BLBLIs compared with carbapenems for the treatment of hematological neutropenic patients with BSI due to ESBL-GNB.

The study comprised hematological neutropenic patients, including hematopoietic stem cell transplant (HSCT) recipients, who had had at least one episode of BSI due to an ESBL-GNB and who had received carbapenems or BLBLIs for >24 h as the empirical or definitive antibiotic therapy. Patients were recruited retrospectively at 22 centers from nine different countries (Argentina, Australia, Brazil, Canada, Germany, Italy, Spain, Turkey, and the United States) from 1 January 2006 to 31 March 2015.

The primary endpoint was the case fatality rate at 30 days from onset of BSI. Secondary outcomes included the following: (i) 7-day and (ii) 14-day case fatality rates; (iii) persistent BSI; (iv) relapse of BSI; (v) colonization/infection by bacteria resistant to the antibiotics under study; and (vi) superinfection due to any bacteria. The protocol of the study has been published elsewhere (22). Antimicrobial therapy administered before susceptibility results were available was considered empirical therapy, and antibiotic therapy administered afterward was considered definitive therapy. Initial empirical antibiotic therapy was considered inadequate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism. (See additional information regarding methodology in Text S1 in the supplemental material).

The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The protocol of the study was approved by all appropriate regulatory agencies and the local Research Ethics Committees, with the following local reference number: EPA020/15. The need for informed consent and information sheets was waived by the ethics committees because of the retrospective nature of the study.

Clinical samples were processed at the microbiology laboratories of each participating center in accordance with standard operating procedures. *Enterobacteriaceae* species were identified using standard microbiological techniques at each center. ESBL production was screened in all isolates with diminished susceptibility to cephalosporins and confirmed using standard procedures and phenotypic methods, such as disk-diffusion or Etest, or molecular characterization by PCR, depending on the participating center. The following β-lactams were used for confirmation by testing their synergistic effect with amoxicillin-clavulanate: cefepime, ceftazidime, cefotaxime, cefuroxime, and aztreonam. *In vitro* susceptibility was determined according to CLSI recommendations (23).

Patients who were given BLBLIs were compared with those treated with carbapenems as empirical and/or definitive therapy. Two non-mutually exclusive cohorts were constructed and analyzed separately. The empirical therapy cohort (ETC) included patients who received empirical therapy with BLBLI or carbapenem and whose isolates were susceptible to the empirical antimicrobial administered. The definitive therapy cohort (DTC) comprised patients who received definitive therapy with an active BLBLI or carbapenem. We used an uncorrected chi-square statistic to evaluate the primary
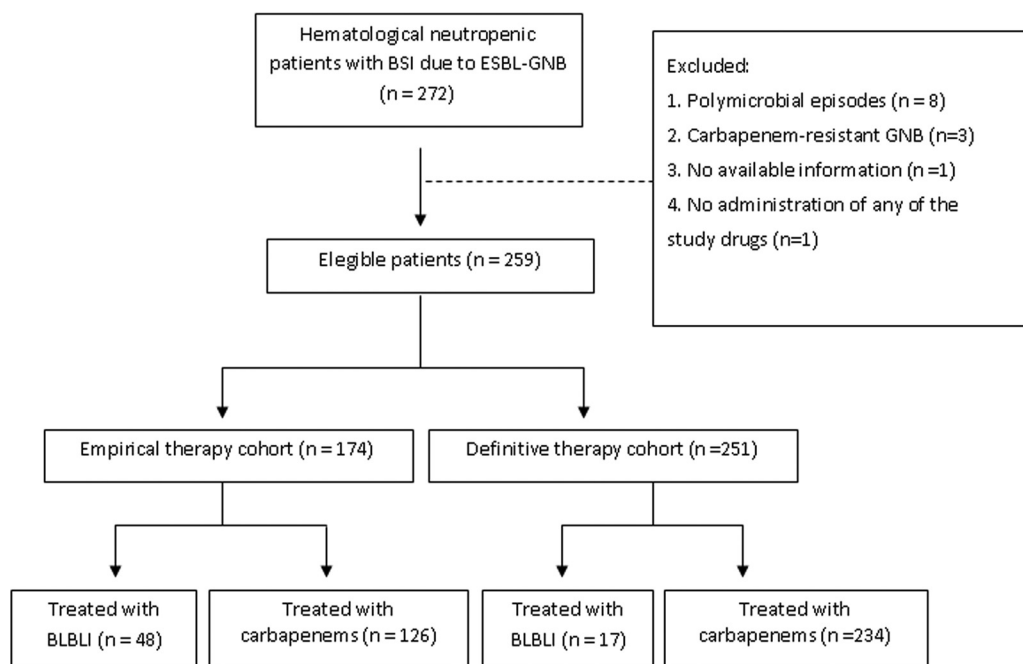
FIG 1 Flow chart of patients included in the study.

endpoint under the null hypothesis of the 30-day case fatality rate between study groups. Survival functions were estimated using Kaplan-Meier curves and compared using the log rank test. The adjusted mortality odds ratio (OR) at 30 days was estimated in both cohorts by a multivariate logistic regression model. A propensity score (PS)—the probability of receiving BLBLIs as empirical and/or targeted therapy—was calculated in both cohorts (ETC and DTC), using a nonparsimonious multivariate logistic regression model in which the outcome variable was the use of BLBLI as empirical and/or definitive therapy. Each patient of each therapy group in the two cohorts was later matched to another patient using the nearest-matching method. This analysis allowed the identification of pairs of patients who had very close PS values but differed in terms of the therapy received. The final data set matched only pairs of patients on carbapenems and BLBLIs. The analysis was performed using R software (R v. 3.2.5).

Figure 1 shows the flow chart of patients included in the study. A total of 259 episodes of BSI due to ESBL-GNB in 253 patients were eligible for analysis. The ETC comprised 174 patients and the DTC 251. Characteristics of patients are detailed in Table 1. The most frequent source of BSI was an endogenous source (52.8%), followed by catheter-related BSI (18.1%), neutropenic enterocolitis (8.1%), and urinary tract and perianal infections (6.9% each). The most frequently isolated ESBL-GNB species was *Escherichia coli* (73.7%), followed by *Klebsiella pneumoniae* (23.1%) and *Klebsiella oxytoca* and *Enterobacter cloacae* (1.5% each). (See additional information regarding the results in Text S1).

Of the 174 patients included in the ETC, 126 received a carbapenem (93 received meropenem, 31 imipenem, and 2 ertapenem) and 48 a BLBLI (44 received PTZ, 2 amoxicillin-clavulanate [AMC], and 2 cefoperazone-sulbactam). In the DTC, 234 patients received carbapenems (130 received meropenem, 79 imipenem, and 25 ertapenem) and 17 were given BLBLIs (12 received PTZ and 5 AMC).

As shown in Table 2, in the ETC there were no significant differences in the 30-day case fatality rate between the patients treated with carbapenems and those who received BLBLIs. Similarly, there were no significant differences between any of the secondary endpoints, including 7-day and 14-day case fatality rates. Figure 2 shows the Kaplan-Meier survival curves in the ETC. After applying the PS-based matched analysis, we were able to match 35 pairs of patients treated empirically with BLBLIs or carbap-

TABLE 1 Characteristics of patients with bloodstream infection caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae* according to therapy

| Patient characteristic | Value(s) | | | | | |
| | Empirical therapy cohort (n = 174) | | | Definitive therapy cohort (n = 251) | | |
	Carbapenem; n = 126	BLBLI; n = 48	P	Carbapenem; n = 234	BLBLI; n = 17	P
No. (%) of males	76 (60.3)	32 (66.6)	0.55	154 (65.8)	7 (41.1)	0.07
Median age in yrs (IQR[a])	50 (34–61)	55 (40–63)	0.10	52 (36–63)	57 (37–60)	0.71
No. (%) of patients with:						
Acute leukemia	70 (55.5)	25 (52)	0.99	137 (58.5)	9 (52.9)	0.69
Comorbidities	18 (14.2)	17 (35.4)	0.003	49 (20.9)	5 (29.4)	0.37
Hematopoietic stem cell transplant	49 (38.8)	15 (31.25)	0.44	77 (32.9)	6 (35.2)	0.99
Graft vs host disease	13 (10.3)	2 (4.1)	0.72	17 (7.2)	2 (11.76)	0.87
Corticosteroid therapy	73 (57.9)	25 (52)	0.58	115 (49.1)	11 (64.7)	0.35
Profound neutropenia (<100 neutrophils/mm³)	17 (13.4)	9 (18.7)	0.48	37 (15.8)	3 (17.6)	0.72
Median no. of days of previous neutropenia (IQR)	6 (3–12)	5.5 (4–9)	0.65	6 (3–12)	7.5 (5.7–9)	0.68
No. (%) of patients with:						
Previous antibiotics (1 mo)	107 (84.9)	33 (68.7)	0.01	187 (79.9)	12 (70.5)	0.61
Previous hospital admission (1 mo)	90 (71.4)	36 (75)	0.67	167 (71.3)	9 (52.9)	0.09
Previous episode of BSI	19 (15)	6 (12.5)	0.84	34 (14.5)	2 (11.7)	0.99
Concomitant infection	25 (19.8)	7 (14.5)	0.51	51 (21.7)	4 (23.5)	0.99
MASCC index score < 21	57 (45.2)	22 (45.8)	0.99	102 (43.5)	7 (41.1)	0.63
Complex bloodstream infection	25 (19.8)	14 (29.1)	0.26	48 (20.5)	7 (41.1)	0.064
Septic shock at presentation	36 (28.5)	10 (20.8)	0.38	53 (22.6)	2 (11.7)	0.7
Granulocyte colony-stimulating factor	79 (62.7)	23 (47.9)	0.075	129 (55.1)	6 (35.2)	0.14
Active combination antibiotic therapy	42 (33.3)	12 (25)	0.37	22 (9.4)	1 (5.8)	0.99
Adequate initial empirical antibiotic therapy				179 (76.5)	15 (88.2)	0.37
Enterobacteriaceae species infection						
Escherichia coli	91 (72.2)	37 (77)		174 (74.3)	14 (82.3)	
Klebsiella pneumoniae	31 (24.6)	11 (22.9)	0.77	54 (23)	3 (17.6)	0.84
Enterobacter cloacae	1 (0.79)	0		3 (1.2)	0	
Klebsiella oxytoca	3 (2.38)	0		3 (1.2)	0	

[a]IQR, interquartile range.

enems according to the PS. In this PS-matched cohort, the 30-day case fatality rates did not differ significantly between groups (11.4% versus 20%, P = 0.32). Similar results were obtained in analyzing the 14-day case fatality rates (11.4% versus 14.2%, P = 0.99) and the 7-day case fatality rates (2.8% versus 2.8%, P = 0.99). The only independent risk factor for 30-day case fatality rate was a Multinational Association for Supportive Care in Cancer (MASCC) score of <21 (OR, 3.61; 95% confidence interval [95% CI], 1.19 to 12.72; P = 0.03). Neither therapy with carbapenems nor therapy with BLBLIs was found to be an independent risk factor for 30-day case fatality.

TABLE 2 Outcomes of patients with bloodstream infection caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae* according to therapy[a]

| Characteristic | No. (%) of patients with indicated treatment | | | | | |
| | Empirical therapy cohort (n = 174) | | | Definitive therapy cohort (n = 251) | | |
	Carbapenem; n = 126	BLBLI; n = 48	P	Carbapenem; n = 234	BLBLI; n = 17	P
ICU admission	30 (23.8)	7 (14.5)	0.25	44 (18.8)	2 (11.7)	0.74
30-day case fatality rate	17 (13.4)	10 (20.8)	0.33	37 (15.8)	1 (5.8)	0.99
14-day case fatality rate	12 (9.5)	7 (14.5)	0.49	23 (9.8)	1 (5.8)	0.99
7-day case fatality rate	6 (4.7)	2 (4.1)	0.99	11 (4.7)	0	NA
Relapse of bloodstream infection	0	2 (4.1)	NA	4 (1.7)	0	NA
Persistent bloodstream infection	5 (3.9)	5 (10.4)	0.13	11 (4.7)	3 (17.6)	0.059
Colonization/infection by resistant bacteria	8 (6.3)	1 (2)	0.28	15 (6.4)	1 (5.8)	0.99
Superinfection	11 (8.7)	2 (4.1)	0.51	21 (8.9)	2 (11.1)	0.68

[a]ICU, intensive care unit; NA, not applicable.
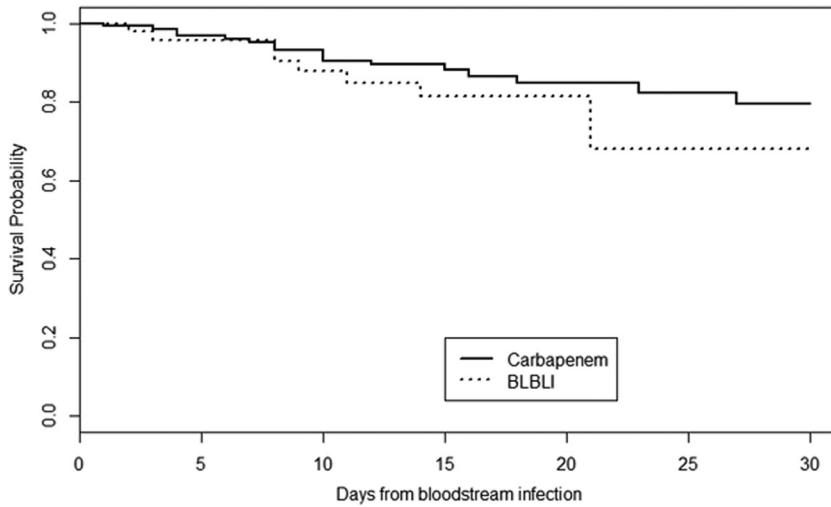
FIG 2 Kaplan-Meier survival curves in the empirical therapy cohort.

As shown in Table 2, in the DTC there were no significant differences in the 30-day case fatality rates between the patients treated with carbapenems and those who received BLBLIs. Similar results were obtained regarding all the secondary endpoints. Figure 3 shows the Kaplan-Meier curves of survival in the DTC. After applying the nearest-matching method, we were able to match 15 pairs of patients treated definitively with BLBLIs or carbapenems according to the PS. In this cohort, there were no significant differences regarding 30-day and 14-day case fatality rates between the patients treated with carbapenems and those who received BLBLIs (6.5% versus 12.5% [$P = 0.99$] and 6.25% versus 12.5% [$P = 0.99$], respectively). No patient died from BSI within the first 7 days in any group. Neither therapy with carbapenems nor BLBLIs was found to be an independent risk factor for 30-day case fatality.

In our study, there were no significant differences in the 30-day case fatality rates between the patients treated with carbapenems and those who received BLBLIs. Interestingly, the 30-day case fatality rates in the two groups were also similar in the propensity-matched cohorts. Furthermore, neither therapy with a carbapenem nor therapy with a BLBLI was found to be an independent risk factor for 30-day case fatality in either therapy cohort. It should also be stressed that the nonsignificant differences in the 30-day case fatality rates found in the ETC were not observed in the analysis of
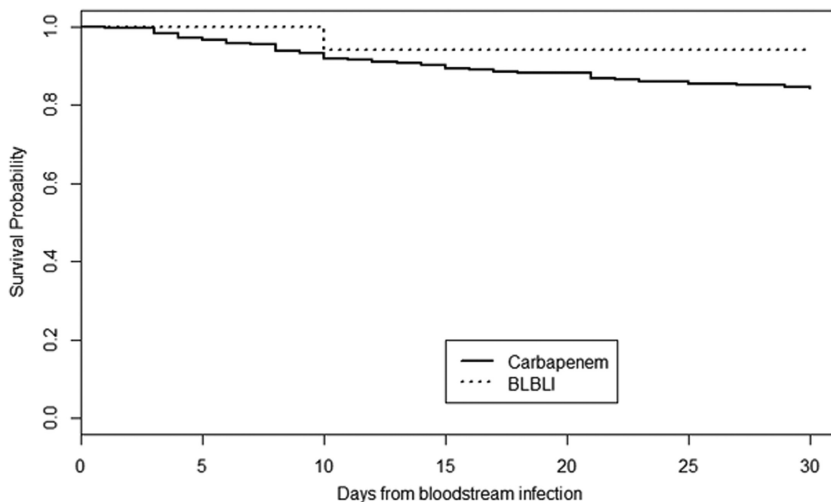
FIG 3 Kaplan-Meier survival curves in the definitive therapy cohort.

the 7-day case fatality rates. The impact of an empirical antibiotic regimen on outcomes is probably better assessed by taking early mortality into consideration. Also, the nonsignificantly higher 30-day mortality rate in the DTC in patients receiving carbapenems was probably due to the larger number of patients treated with this regimen. We found that secondary outcomes differed little between therapy groups in both cohorts. However, persistent BSI was more frequent in patients who received BLBLIs as a definitive therapy, although the difference did not reach statistical significance. Nevertheless, given the low number of patients receiving targeted BLBLI therapy, we cannot draw any firm conclusion. To date, the published data on the use of BLBLIs for the treatment of infections caused by ESBL-GNB are conflicting and mainly refer to nonimmunocompromised patients (13–21). Our study was the first to assess the usefulness of BLBLIs for the treatment of ESBL-BSI in a severely immunosuppressed cohort of hematological patients with neutropenia. This issue is of great concern due to the fact that hematological patients often receive repeated cycles of broad-spectrum antibiotics and are at a high risk of developing infections due to resistant bacteria, including carbapenem-resistant organisms. In this regard, the use of BLBLIs as carbapenem-sparing alternatives to treat suspected or documented ESBL infections may be a useful strategy to avoid the spread of CRE.

Our multicenter study has some limitations. First, this was a retrospective study, and so the typical limitations of this design applied. However, randomized trials comparing empirical and definitive antibiotic regimens are difficult to perform in severely immunosuppressed patients. Second, as carbapenems are the drugs recommended for the treatment of severe infections by ESBL-GNB, it was difficult to enroll a large number of patients treated with BLBLIs in both cohorts, but especially in the DTC. This led to a lack of the power required to assess mortality and detect true differences. Finally, the BLBLI MICs were not available for all the strains, and data regarding molecular characterization of ESBLs could not be obtained.

We conclude that BLBLIs, if active *in vitro*, might be carbapenem-sparing alternatives for the treatment of BSI due to ESBLs in high-risk hematological patients. Physicians dealing with these patients should consider using BLBLIs for the treatment of infections due to ESBL-producing *Enterobacteriaceae*. This strategy may prove useful in limiting the spread of carbapenem resistance in this high-risk population.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC .00164-17.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

REFERENCES

1. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, Fadda G, Leone G, Cauda R, Pagano L. 2009. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies. J Infect 58: 299–307. https://doi.org/10.1016/j.jinf.2009.02.002.

2. Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R, Arnan M, Marin M, Carratalà J, Gudiol F. 2010. Bacteraemia due to extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 65:333–341. https://doi.org/10.1093/jac/dkp411.

3. Kim SH, Kwon JC, Choi SM, Lee DG, Park SH, Choi JH, Yoo JH, Cho BS, Eom KS, Kim YJ, Kim HJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS. 2013. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: factors associated with extended-spectrum β-lactamase production and its impact on outcome. Ann Hematol 92: 533–541. https://doi.org/10.1007/s00277-012-1631-y.

4. Ha YE, Kang CI, Cha MK, Park SY, Wi YM, Chung DR, Peck KR, Lee NY, Song JH. 2013. Epidemiology and clinical outcomes of bloodstream infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli in patients with cancer. Int J Antimicrob Agents 42: 403–409. https://doi.org/10.1016/j.ijantimicag.2013.07.018.

5. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, Duarte R, Calvo M, Carratalà J. 2011. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother 66:657–663. https://doi.org/10.1093/jac/dkq494.

6. Lin MY, Weinstein RA, Hota B. 2008. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. Antimicrob Agents Chemother 52:3188–3194. https://doi.org/10.1128/AAC.01553-07.

7. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL; European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group. 2015. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill 20:pii=30062. https://doi.org/10.2807/1560-7917.ES.2015.20.45.30062.

8. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, Woodford N. 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 10:597–602. https://doi.org/10.1016/S1473-3099(10)70143-2.

9. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, Watkins RR, Scalera NM, Doi Y, Kaye KS, Evans S, Fowler VG, Jr, Bonomo RA, van Duin D; Antibacterial Resistance Leadership Group. 2016. Spectrum of excess mortality due to carbapenem-resistant Klebsiella pneumonia infections. Clin Microbiol Infect 22:513–519. https://doi.org/10.1016/j.cmi.2016.01.023.

10. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, Spanu T, Ambretti S, Ginocchio F, Cristini F, Losito AR, Tedeschi S, Cauda R, Bassetti M. 2012. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis 55: 943–950. https://doi.org/10.1093/cid/cis588.

11. Satlin MJ, Cohen N, Ma KC, Gedrimaite Z, Soave R, Askin G, Chen L, Kreiswirth BN, Walsh TJ, Seo SK. 2016. Bacteremia due to carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic malignancies. J Infect 73:336–345. https://doi.org/10.1016/j.jinf.2016.07.002.

12. Satlin MJ, Calfee DP, Chen L, Fauntleroy KA, Wilson SJ, Jenkins SG, Feldman EJ, Roboz GJ, Shore TB, Helfgott DC, Soave R, Kreiswirth BN, Walsh TJ. 2013. Emergence of carbapenem-resistant Enterobacteriaceae as causes of bloodstream infections in patients with hematologic malignancies. Leuk Lymphoma 54:799–806. https://doi.org/10.3109/10428194.2012.723210.

13. Shiber S, Yahav D, Avni T, Leibovici L, Paul M. 2015. β-Lactam/β-lactamase inhibitors versus carbapenems for the treatment of sepsis: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 70:41–47. https://doi.org/10.1093/jac/dku351.

14. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. 2012. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother 67:2793–2803. https://doi.org/10.1093/jac/dks301.

15. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á; Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. 2012. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. Clin Infect Dis 54: 167–174. https://doi.org/10.1093/cid/cir790.

16. Harris PN, Yin M, Jureen R, Chew J, Ali J, Paynter S, Paterson DL, Tambyah PA. 2015. Comparable outcomes for β-lactam/β-lactamase inhibitor combinations and carbapenems in definitive treatment of bloodstream infections caused by cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*. Antimicrob Resist Infect Control 4:14. https://doi.org/10.1186/s13756-015-0055-6.

17. Ng TM, Khong WX, Harris PN, De PP, Chow A, Tambyah PA, Lye DC. 2016. Empiric piperacillin-tazobactam versus carbapenems in the treatment of bacteremia due to extended-spectrum beta-lactamase-producing Enterobacteriaceae. PLoS One 11:e0153696. https://doi.org/10.1371/journal.pone.0153696.

18. Tsai HY, Chen YH, Tang HJ, Huang CC, Liao CH, Chu FY, Chuang YC, Sheng WH, Ko WC, Hsueh PR. 2014. Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum β-lactamase-producing Proteus mirabilis. Diagn Microbiol Infect Dis 80:222–226. https://doi.org/10.1016/j.diagmicrobio.2014.07.006.

19. Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, Viale P, Oliver A, Pintado V, Gasch O, Martínez-Martínez L, Pitout J, Akova M, Peña C, Molina J, Hernández A, Venditti M, Prim N, Origüen J, Bou G, Tacconelli E, Tumbarello M, Hamprecht A, Giamarellou H, Almela M, Pérez F, Schwaber MJ, Bermejo J, Lowman W, Hsueh PR, Mora-Rillo M, Natera C, Souli M, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodríguez-Baño J, the REIPI/ESGBIS/INCREMENT Group. 2016. A multinational, preregistered cohort study of β-lactam/β-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-β-lactamase-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 60:4159–4169. https://doi.org/10.1128/AAC .00365-16.

20. Tamma PD, Han JH, Rock C, Harris AD, Lautenbach E, Hsu AJ, Avdic E, Cosgrove SE; Antibacterial Resistance Leadership Group. 2015. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis 60:1319–1325.

21. Ofer-Friedman H, Shefler C, Sharma S, Tirosh A, Tal-Jasper R, Kandipalli D, Sharma S, Bathina P, Kaplansky T, Maskit M, Azouri T, Lazarovitch T, Zaidenstein R, Kaye KS, Marchaim D. 2015. Carbapenems versus piperacillin-tazobactam for bloodstream infections of nonurinary source caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae*. Infect Control Hosp Epidemiol 36:981–985. https://doi.org/10.1017/ice .2015.101.

22. Gudiol C, Royo-Cebrecos C, Tebe C, Abdala E, Akova M, Álvarez R, Maestro-de la Calle G, Cano A, Cervera C, Clemente WT, Martín-Dávila P, Freifeld A, Gómez L, Gottlieb T, Gurguí M, Herrera F, Manzur A, Maschmeyer G, Meije Y, Montejo M, Peghin M, Rodríguez-Baño J, Ruiz-Camps I, Sukiennik TC, Carratalà J; for the BICAR study group. Clinical efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum β-lactamase-producing *Enterobacteriaceae* in hematological patients with neutropenia: study protocol for a retrospective observational study (BICAR). BMJ Open, in press.

23. Clinical and Laboratory Standards Institute (CLSI). 2016. Performance standards for antimicrobial susceptibility testing; approved standard, 26th ed. CLSI supplement M100S. Clinical and Laboratory Standards Institute, Wayne, PA.