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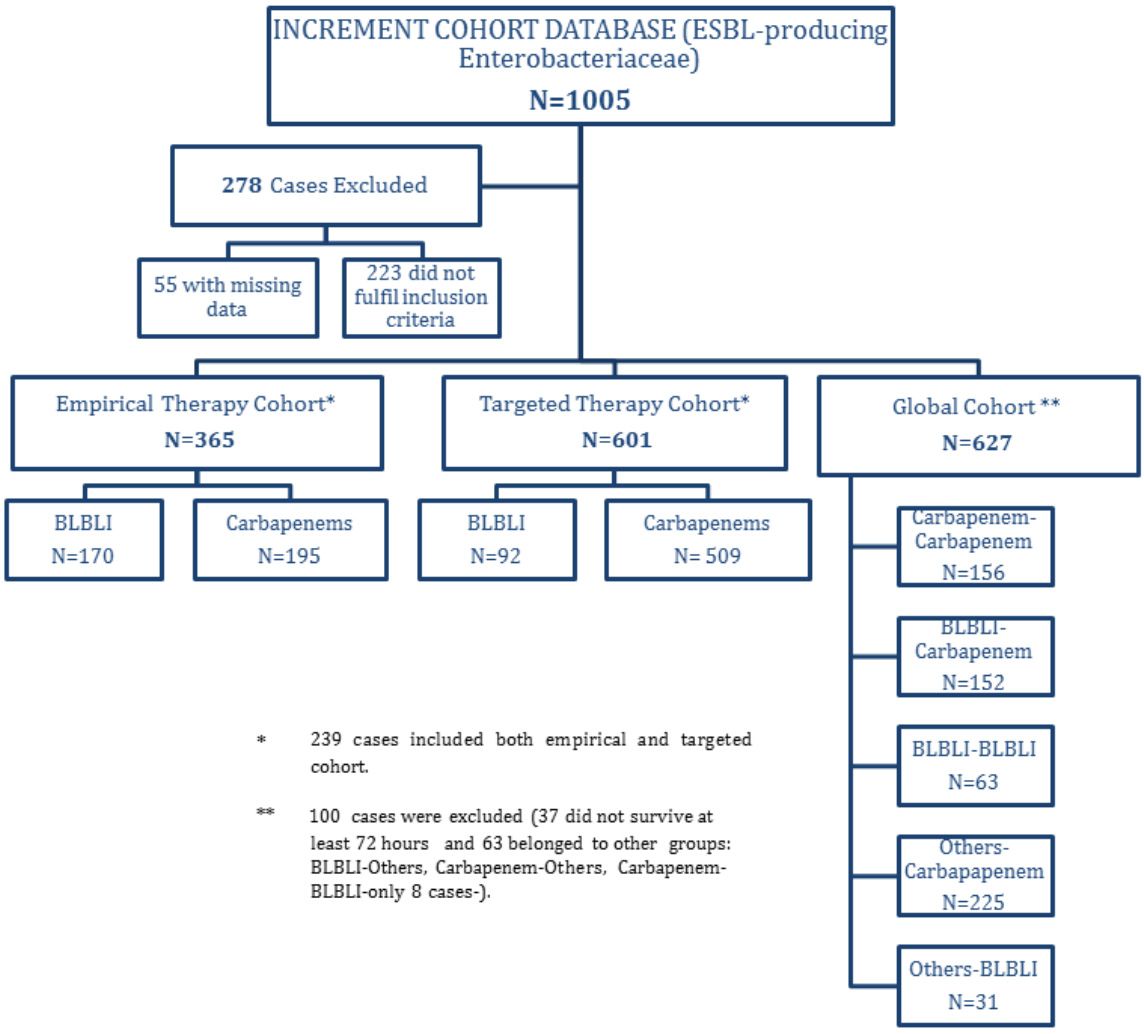


Supplementary Table S1. Checklist of items according to STROBE document.

	Recommendation	Assessment in article
Title and abstract	(*a*) Indicate the study design with a commonly used term in the title or abstract	Study design specified in title and abstract
	(*b*) Provide an informative and balanced summary in the abstract of what was done and what was found	Balanced summary included in the abstract
Background/ Rationale	Explain the scientific background and rationale for the investigation being reported	The scientific background and rationale is included in the Introduction
Objectives	State specific objectives, including any pre-specified hypotheses	Pre-specified hypothesis and objectives are stated in the Introduction
Study design	Present key elements of study design early in the paper	Study design described in the first part of Methods
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Described in Methods
Participants	(*a*) Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up	Described in Methods
	(*b*) For matched studies, give matching criteria and number of exposed and unexposed	This is not a matched study
Variables	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable	Defined in Methods
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Specified in Methods. The same methods for data collection of data were used in the groups.
Bias	Describe any efforts to address potential sources of bias	Selection bias: inclusion of consecutive cases. Information bias: use of well defined, standard, easy to collect variables (piloted). Use of soft and hard outcome variables.
Study size	Explain how the study size was arrived at	The attempted sample size was specified in Methods
Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Quantitative variables were handled as such. No groupings were made

Statistical methods	(*a*) Describe all statistical methods, including those used to control for confounding	Included in Methods
	(*b*) Describe any methods used to examine subgroups and interactions	Included in Methods
	(*c*) Explain how missing data were addressed	Patients with missing data were excluded
	(*d*) If applicable, explain how loss to follow-up was addressed	No patient was lost to follow-up
	(*e*) Describe any sensitivity analyses	Included in Methods
Participants	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Included in Results (Supplementary Figure 1)
	(b) Give reasons for non-participation at each stage	Specified in Supplementary Figure 1
	(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
	(b) Indicate number of participants with missing data for each variable of interest	Supplementary Figure 1
	(c) Summarise follow-up time (eg, average and total amount)	Information for 30 days was available from all patients
Outcome data	Report numbers of outcome events or summary measures over time	Table 1
Main results	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Specified in Results (Tables 2, 3; Supplementary Tables 2, 3, 4, 5, 6, 7, 8 and 9)
	(*b*) Report category boundaries when continuous variables were categorized	Continuous variables were not categorized
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Specified in Results
Key results	Summarise key results with reference to study objectives	Specified in Abstract and Discussion
Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included in Discussion
Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Included in Discussion

Generalisability	Discuss the generalisability (external validity) of the study results	Included in Discussion
Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included

Supplementary Table S2. Univariate analysis of the association between different variables and cure/improvement in the Empirical Therapy Cohort.

	Crude Analysis	
Variable	OR (95% CI)	p
Age (per unit)	0.99 (0.97-1.005)	0.17
Male sex	1.04 (0.62-1.74)	0.88
Enterobacteriaceae		
E. coli	Reference	
K. pneumoniae	0.55 (0.31-0.99)	0.044
Others	2.20 (0.61- 14.1)	0.30
Nosocomial acquisition	0.48 (0.28- 0.80)	0.005
Source		
Urinary	Reference	
Biliary tract	0.9 (0.38- 2.42)	0.83
Others (high risk source)	0.33 (0.19-0.58)	0.0002
ICU admission	0.53 (0.26-1.15)	0.10
McCabe classification, non fatal	3.15 (1.82-5.66)	<0.0001
Pitt score (per unit)	0.70 (0.62-0.78)	<0.0001
Severe sepsis or shock	0.13 (0.07-0.23)	<0.0001
Empirical therapy with BLBLI	1.06 (0.64-1.78)	0.81
Targeted therapy		
Carbapenems	Reference	
Others	0.85 (0.5-1.47)	0.55
Propensity score*	1.13 (0.41-3.16)	0.81

*Variables used for calculating the propensity score: center, age, gender, underlying conditions, McCabe, acquisition type, source, Pitt score, and presentation with severe sepsis or septic shock. The area under the ROC curve for the propensity score was 0.80.

Supplementary Table S3. Univariate analysis of the association between different variables and 30-day mortality in the Empirical Therapy Cohort.

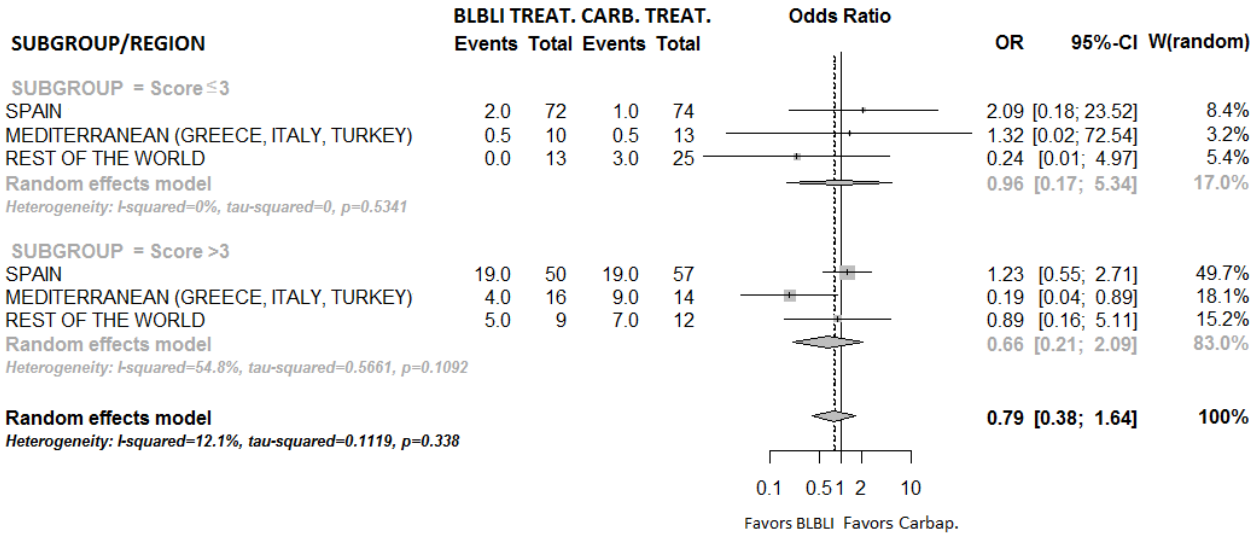
	Crude Analysis	
Variable	**OR (95% CI)**	**p**
Age (per unit)	1.025 (1.01-1.04)	0.008
Male sex	1.24 (0.73-2.15)	0.43
Enterobacteriaceae		
E. coli	Reference	
K. pneumoniae	2.30 (1.28-4.10)	0.005
Others	0.54 (0.08- 1.97)	0.43
Nosocomial acquisition	1.86 (1.1-3.18)	0.02
Source		
Urinary	Reference	
Biliary tract	1.03 (0.36-2.60)	0.95
Others (high risk source)	3.03 (1.71-5.54)	0.0002
ICU admission	2.43 (1.15-4.97)	0.016
McCabe classification, non fatal	0.29 (0.15-0.51)	<0.0001
Pitt score, per unit	1.49 (1.33-1.68)	<0.0001
Severe sepsis or shock	11.82 (6.22-24.17)	<0.0001
Empirical therapy with BLBLI	0.86 (0.5-1.45)	0.57
Targeted therapy		
Carbapenems	Reference	
Others	1.28(0.73-2.2)	0.38
Propensity score*	0.87 (0.3-2.5)	0.80

*Variables used for calculating the propensity score: center, age, gender, underlying conditions, acquisition type, source, Pitt score, and presentation with severe sepsis or septic shock. The area under the ROC curve for the propensity score was 0.80.

Supplementary Table S4. Number of BLBLI/carbapenem cases in the Empirical Therapy Cohort included according the center, country and region.

CENTER	COUNTRY	REGION	TOTAL BLBLI	TOTAL CARBAPENEM	TOTAL
2	SPAIN	SPAIN	25	11	36
3	ISRAEL	REST OF WORLD	3	4	7
4	USA	REST OF WORLD	6	7	13
5	ITALY	OTHER MEDITERR	7	0	7
7	GREECE	OTHER MEDITERR	1	8	9
9	ITALY	OTHER MEDITERR	0	2	2
12	SPAIN	SPAIN	11	13	24
16	SOUTH AFRICA	REST OF WORLD	0	5	5
17	TAIWAN	REST OF WORLD	0	2	2
18	SPAIN	SPAIN	3	1	4
20	SPAIN	SPAIN	1	15	16
21	SPAIN	SPAIN	10	11	21
22	SPAIN	SPAIN	7	0	7
23	ARGENTINA	REST OF WORLD	1	3	4
24	SPAIN	SPAIN	8	14	22
25	SPAIN	SPAIN	4	17	21
26	SPAIN	SPAIN	2	8	10
27	SPAIN	SPAIN	0	5	5
28	SPAIN	SPAIN	4	8	12
31	GREECE	OTHER MEDITERR	1	0	1
32	CANADA	REST OF WORLD	2	2	4
35	SPAIN	SPAIN	0	5	5
38	TURKEY	OTHER MEDITERR	5	10	15
40	GERMANY	REST OF WORLD	4	12	16
42	SPAIN	SPAIN	6	7	13
43	SPAIN	SPAIN	17	6	23
45	ITALY	OTHER MEDITERR	12	7	19
47	GERMANY	REST OF WORLD	6	2	8
49	SPAIN	SPAIN	8	3	11
51	SPAIN	SPAIN	16	7	23
		TOTAL	**170**	**195**	**365**

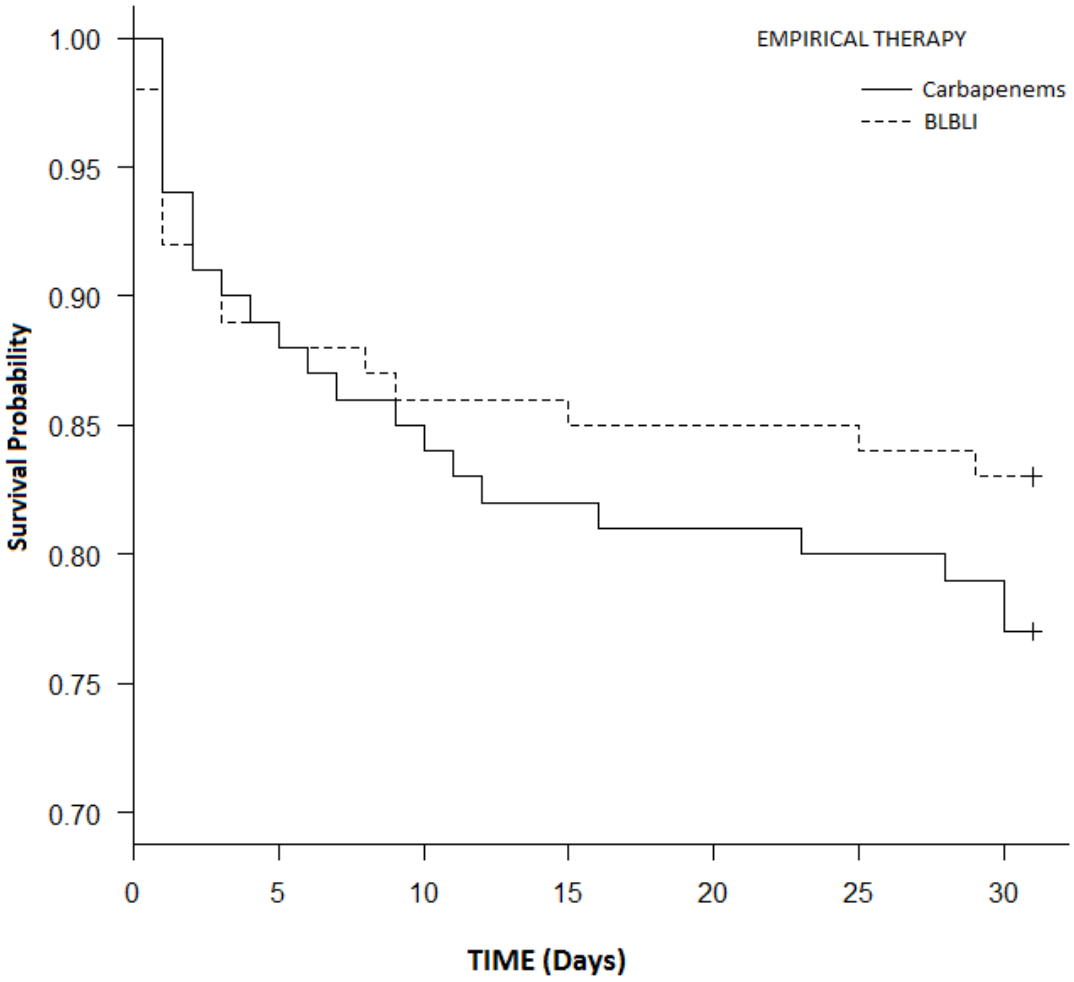
Supplementary Figure S2. Meta-regression analysis of mortality at Day 30 grouping by regions in the Empirical Therapy Cohort.



Supplementary Table S5. Features of patients matched according to the propensity score from the Empirical Therapy Cohort.

	BLBLI (n=100)	**Carbapenem (n=100)**	**P**
Age, median (IQR)	69.5 (54.8-77.3)	68.5 (57.8-78)	0.92
Male sex	53 (53.0)	57 (57)	0.57
Enterobacteriaceae			
E. coli	76 (76.0)	68 (68.0)	0.21
K. pneumoniae	21 (21.0)	26 (26.0)	0.40
Others	3 (3.0)	6 (6.0)	0.31
Nosocomial acquisition	47 (47.0)	45 (45.0)	0.78
Source			
Urinary	44 (44.0)	50 (50.0)	0.40
Biliary tract	18 (18.0)	12 (12.0)	0.23
Others (high risk source)	38 (38.0)	38 (38.0)	1.00
ICU admission	9 (9.0)	6 (6.0)	0.43
McCabe classification, non fatal	45 (45.0)	45 (45.0)	1.00
Pitt score, median (IQR)	1 (0-3)	1 (0-3)	0.86
Severe sepsis or shock	41 (41.0)	41 (41.0)	1.00
Cancer	38 (38.0)	36 (36.0)	0.77
Targeted therapy			
Carbapenem	52 (52.0)	85 (85.0)	<0.0001
BLBLI	34 (34.0)	3 (3.0)	<0.0001
Others	14 (14.0)	12 (12.0)	0.67
Cure/improvement	78 (78.0)	77 (77.0)	0.87
30-day mortality	17 (17.0)	23 (23.0)	0.29

Supplementary Figure S3. Kaplan-Meier curves for mortality in empirical therapy propensity score-matched cohorts of patients treated with BLBLI versus carbapenems.



P= 0.33 (log-rank test)

Supplementary Table S6. Univariate analysis of the association between different variables and cure/improvement in the Targeted Therapy Cohort.

	Crude Analysis	
Variable	**OR (95% CI)**	**p**
Age (per unit)	0.99 (0.98-1.01)	0.83
Male sex	1.14 (0.71-1.82)	0.58
Enterobacteriaceae		
E. coli	Reference	
K. pneumonie	0.45 (0.26-0.77)	0.003
Others	0.54 (0.25-1.25)	0.12
Nosocomial acquisition	0.62 (0.39-0.99)	0.05
Source		
Urinary	Reference	
Biliary tract	0.82 (0.35-2.14)	0.66
Others (high risk source)	0.33 (0.19-0.55)	<0.0001
ICU admission	0.3 (0.17-0.55)	<0.0001
McCabe classification, non fatal	3.92 (2.33-6.84)	<0.0001
Pitt score, per unit	0.73 (0.66-0.80)	<0.0001
Severe sepsis or shock	0.18 (0.11-0.30)	<0.0001
Empirical therapy		
Active	Reference	
Inactive/no drug	0.74(0.46-1.20)	0.22
Empirical therapy continued as targeted therapy	1.08 (0.64-1.91)	0.76
Targeted therapy with BLBLI	1.57 (0.79-3.47)	0.23
Propensity score*	1.56 (0.57-4.9)	0.41

*Variables used for calculating the propensity score: center, age, gender, underlying conditions, McCabe, acquisition type, source, Pitt score, presentation with severe sepsis or septic shock, and empirical treatment. The area under the ROC curve for the propensity score was 0.84.

Supplementary Table S7. Univariate analysis of the association between different variables and 30-day mortality in the Targeted Therapy Cohort.

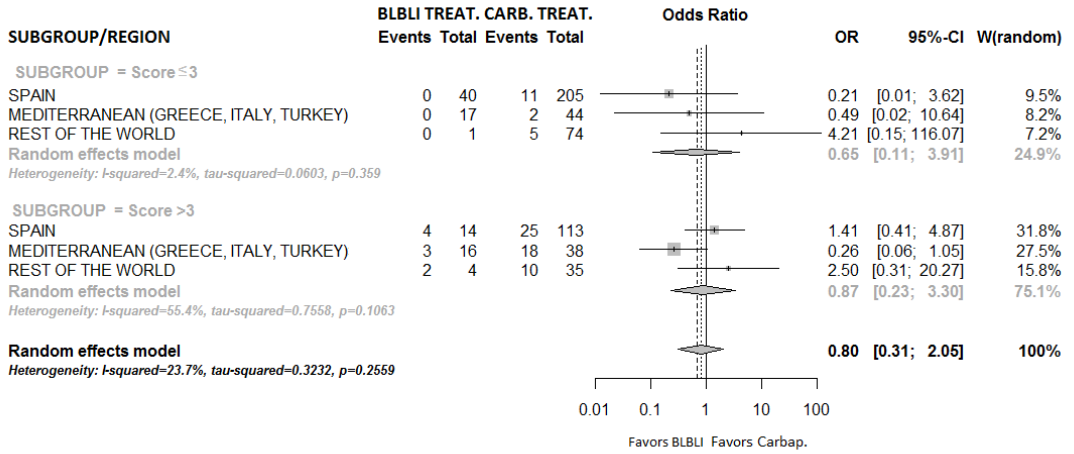
	Crude Analysis	
Variable	**OR (95% CI)**	**p**
Age (per unit)	1.02 (1.00-1.04)	0.018
Male sex	1.15 (0.72-1.89)	0.56
Enterobacteriaceae		
E. coli	Reference	
K. pneumonie	2.58 (1.50-4.39)	0.0005
Others	2.02 (0.87-4.28)	0.08
Nosocomial acquisition	1.31 (0.82-2.11)	0.26
Source		
Urinary	Reference	
Biliary tract	1.03 (0.37-2.51)	0.95
Others (high risk source)	2.88 (1.71-4.99)	<0.0001
ICU admission	3.5 (1.91-6.28)	<0.0001
McCabe classification, non fatal	0.23 (0.13-0.40)	<0.0001
Pitt score, per unit	1.38 (1.26-1.51)	<0.0001
Severe sepsis or shock	5.70 (3.46-9.64)	<0.0001
Empirical therapy continued as targeted therapy	0.83 (0.46-1.43)	0.31
Empirical Therapy		
Active	Ref	
No active/no empirical therapy	1.56 (0.97-2.51)	0.07
Targeted Therapy with BLBLI	0.67 (0.30-1.32)	0.28
Propensity score*	0.75 (0.24-2.01)	0.59

*Variables used for calculating the propensity score: center, age, gender, underlying conditions, McCabe, acquisition type, source, Pitt score, presentation with severe sepsis or septic shock, and empirical treatmet. The area under the ROC curve for the propensity score was 0.84.

Supplementary Table S8. Number of BLBLI/carbapenem cases in the Targeted Therapy Cohort included according the center, country and region.

CENTER	COUNTRY	REGION	TOTAL BLBLI	TOTAL CARBAPENEM	TOTAL
2	SPAIN	SPAIN	14	33	47
3	ISRAEL	REST OF WORLD	2	10	12
4	USA	REST OF WORLD	1	12	13
5	ITALY	OTHER MEDITERR	11	11	22
7	GREECE	OTHER MEDITERR	4	10	14
9	ITALY	OTHER MEDITERR	0	19	19
12	SPAIN	SPAIN	6	18	24
16	SOUTH AFRICA	REST OF WORLD	0	9	9
17	TAIWAN	REST OF WORLD	0	9	9
18	SPAIN	SPAIN	0	20	20
20	SPAIN	SPAIN	0	19	19
21	SPAIN	SPAIN	0	27	27
22	SPAIN	SPAIN	12	12	24
23	ARGENTINA	REST OF WORLD	1	9	10
24	SPAIN	SPAIN	2	26	28
25	SPAIN	SPAIN	0	26	26
26	SPAIN	SPAIN	0	14	14
27	SPAIN	SPAIN	0	4	4
28	SPAIN	SPAIN	0	26	26
31	GREECE	OTHER MEDITERR	0	1	1
32	CANADA	REST OF WORLD	1	27	28
35	SPAIN	SPAIN	0	5	5
38	TURKEY	OTHER MEDITERR	2	24	26
40	GERMANY	REST OF WORLD	0	16	16
42	SPAIN	SPAIN	0	17	17
43	SPAIN	SPAIN	7	22	29
45	ITALY	OTHER MEDITERR	16	17	33
47	GERMANY	REST OF WORLD	0	17	17
49	SPAIN	SPAIN	7	29	36
51	SPAIN	SPAIN	6	20	26
		TOTAL	**92**	**509**	**601**

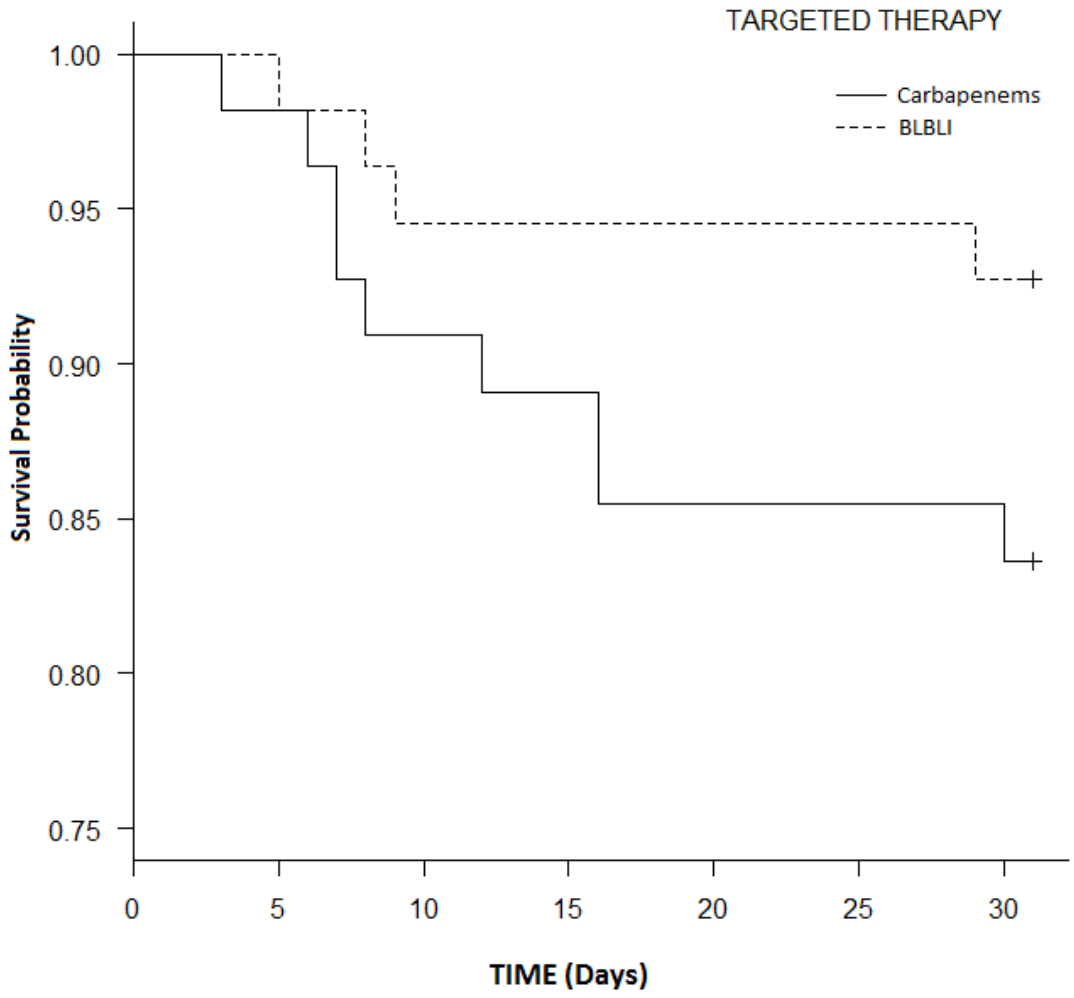
Supplementary Figure S4. Meta-regression analysis of mortality at Day 30 grouping by regions in the Targeted Therapy Cohort.



Supplementary Table S9. Features of patients matched according to the propensity score from the Targeted Therapy Cohort.

	BLBLI (n=55)	**Carbapenem (n=55)**	**p**
Age, median (IQR)	71 (55.5-81)	71 (63.5-78.5)	0.98
Male sex	29 (52.7)	36 (65.5)	0.17
Enterobacteriaceae			
E. coli	43 (78.2)	40 (72.7)	0.51
K. pneumoniae	11 (20.0)	11 (20.0)	1.00
Others	1 (1.8)	4 (7.3)	0.17
Nosocomial acquisition	22 (40.0)	24 (43.6)	0.70
Source			
Urinary tract	27 (49.1)	22 (40.0)	0.34
Biliary tract	6 (10.9)	10 (18.2)	0.28
Other	22[e] (40.0)	23[f] (41.8)	0.85
ICU admission	4 (7.3)	3 (5.5)	0.70
McCabe classification, non fatal	23 (41.8)	26 (47.3)	0.56
Pitt score, median (IQR)	1 (0-2)	0 (0-2)	0.52
Severe sepsis or shock	15 (27.3)	11 (20.0)	0.37
Cancer	29 (52.7)	25 (45.5)	0.45
Empirical therapy			
Carbapenem	4 (7.3)	21 (38.2)	0.0001
BLBLI	27 (49.1)	9 (16.4)	0.0002
Others	24 (43.6)	25 (45.4)	0.85
Active empirical therapy	35 (63.6)	29 (54.7)	0.35
Cure/improvement	49 (89.1)	46 (83.6)	0.40
30-day mortality	4 (7.3)	9 (16.4)	0.14

Supplementary Figure S5. Kaplan-Meier curves for mortality in targeted therapy propensity score-matched cohorts of patients treated with BLBLI versus carbapenems.



P= 0.14 (log-rank test)

Supplementary Table S10. Univariate analysis of the association between different variables and cure/improvement in the Global Therapy Cohort.

	Crude Analysis	
Variable	**OR (95% CI)**	**p**
Age (per unit)	0.99 (0.98-1.01)	0.48
Male sex	1.17 (0.74-1.85)	0.49
Enterobacteriaceae		
E. coli	Reference	
K. pneumoniae	0.55 (0.32-0.96)	0.03
Others	0.67 (0.31- 1.62)	0.34
Nosocomial acquisition	0.60 (0.38-0.95)	0.03
Source		
Urinary tract	Reference	
Biliary tract	0.57 (0.28-1.20)	0.13
Others (high risk source)	0.37 (0.21- 0.62)	0.0002
ICU admission	0.37 (0.21- 0.69)	0.001
McCabe classification, non fatal	4.26 (2.53- 7.50)	<0.0001
Pitt score, per unit	0.75 (0.69- 0.82)	<0.0001
Severe sepsis or shock	0.17 (0.10-0.28)	<0.0001
Appropriate empirical therapy	0.17 (0.72-1.87)	0.52
Empirical-Targeted therapy		
Carbapenem-Carbapenem	Reference	
BLBLI-Carbapenem	0.82 (0.42- 1.58)	0.55
BLBLI-BLBLI	0.95 (0.40- 2.42)	0.92
Others-Carbapenem	0.78 (0.42-1.41)	0.42
Others-BLBLI	1.29 (0.4-5.77)	0.69
Propensity score	1.41 (0.66-3.20)	0.39

Supplementary Table S11. Univariate analysis of the association between different variables and 30-day mortality in the Global Therapy Cohort.

	Crude Analysis	
Variable	**OR (95% CI)**	**p**
Age (per unit)	1.023 (1.01-1.04)	0.004
Male sex	1.19 (0.74-1.94)	0.47
Enterobacteriaceae		
E. coli	Reference	
K. pneumoniae	2.17 (1.25-3.69)	0.005
Others	1.68 (0.70-3.64)	0.21
Nosocomial acquisition	1.38 (0.86-2.21)	0.18
Source		
Urinary tract	Reference	
Biliary tract	1.29 (0.57-2.75)	0.51
Others (high risk source)	2.54 (1.52-4.35)	0.0005
ICU admission	2.95 (1.58- 5.31)	0.0004
McCabe classification, non fatal	0.20 (0.11-0.35)	<0.0001
Pitt score, per unit	1.34 (1.23-1.47)	<0.0001
Severe sepsis or shock	6.82 (4.1-11.74)	<0.0001
Appropriate empirical therapy	0.71 (0.44-1.15)	0.16
Empirical therapy continued in D.T	0.89 (0.50- 1.51)	0.67
Empirical Therapy-Targeted Therapy		
Carbapenem- Carbapenem	Ref	
BLBLI- Carbapenem	1.17 (0.58- 2.36)	0.66
BLBLI- BLBLI	1.19 (0.46- 2.84)	0.71
Others- Carbapenem	1.51 (0.82-2.86)	0.20
Others- BLBLI	0.56 (0.09-2.11)	0.46
Propensity score	0.44 (0.18-1.00)	0.06