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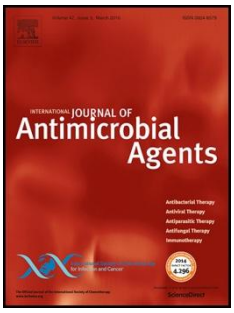

Title: Geographical variation in therapy for bloodstream infections due to multidrug-resistant *enterobacteriaceae*: a post hoc analysis of the INCREMENT study

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Geographical variation in therapy for bloodstream infections due to multidrug-resistant *Enterobacteriaceae*: a post hoc analysis of the INCREMENT study

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Highlights:

- Regional variation exists in therapy for BSI caused by ESBL-producers or CPE
- Location influenced the empirical use of BLBLIs or carbapenems
- BLBLI use for ESBL-producers or combination therapy for CPE also varied by location
- Variation by location remained after adjustment for clinical factors
- These data may help clinical trial design and antimicrobial stewardship efforts

Abstract

We aimed to describe regional differences in therapy for bloodstream infection (BSI) caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) or carbapenemase-producing Enterobacteriaceae (CPE). 1,482 patients in 12 countries were included from an observational study of BSI caused by ESBL-E or CPE. Multivariate logistic regression was used to calculate adjusted odds ratios (aORs) for the influence of country of recruitment on empirical use of β-lactam/β-lactamase inhibitors (BLBLI) or carbapenems, targeted use of BLBLI for ESBL-E and use of targeted combination therapy for CPE. The use of BLBLI for empirical therapy was least likely in sites from Israel (aOR 0.34, 95% CI 0.14-0.81), Greece (aOR 0.49, 95% CI 0.26-0.94) and Canada (aOR 0.31, 95% CI 0.11-0.88) but more likely in Italy (aOR 1.58, 95% CI 1.11-2.2) and Turkey (aOR 2.09, 95% CI 1.14-3.81), compared to Spain as a reference. Empirical carbapenems were more likely to be used in sites from Taiwan (aOR 1.73, 95% CI 1.03-2.92) and USA (aOR 1.89; 95% CI 1.05-3.39), and less likely in Italy (aOR 0.44, 95% CI 0.28-0.69) and Canada (aOR 0.10, 95% CI 0.01-0.74). Targeted BLBLI for ESBL-E was more likely in sites from Italy. Treatment at sites within Israel, Taiwan, Turkey and Brazil was associated with less combination therapy for CPE. Although this study does not provide precise data on the relative prevalence of ESBL-E or CPE, significant variation in therapy exists across countries even after adjustment for patient factors. A better

understanding of what influences therapeutic choices for these infections will aid antimicrobial stewardship efforts.

Keywords: extended-spectrum beta-lactamase, carbapenemase, carbapenems, beta-lactam/beta-lactamase inhibitors, *Escherichia coli*, *Klebsiella pneumoniae*

1. Introduction

Bloodstream infections (BSI) are an important cause of morbidity and mortality worldwide. Differences in population demography, risk factor distribution and microbiology influence the incidence of BSI within different countries. Enterobacteriaceae are a major cause of BSI, with *Escherichia coli* and *Klebsiella pneumoniae* as the two most common gram-negative species isolated from blood cultures both in the community and in health care setting.[1, 2] Extended-spectrum β-lactamase (ESBL) enzymes confer resistance to oxyiminocephalosporins and monobactams in additional to penicillins, and have become widespread among Enterobacteriaceae,[3, 4] with rising trends even in low-prevalence countries.[5, 6] ESBL-producing organisms often carry other resistance genes thus limiting choices for effective antimicrobial therapy.[7] Due to their stability to ESBLs, carbapenems have been considered the preferred agent for the treatment of serious infections caused by ESBL-producers,[3] but overuse of carbapenems may provide selection pressure for carbapenem resistance.[8] Carbapenem-resistant Enterobacteriaceae (CRE), often resulting from the acquisition of carbapenemase genes, is now an emerging global public health threat.[9, 10] Although geographical variation in the prevalence of ESBL-producing Enterobacteriaceae (ESBL-E) or carbapenemase-producing Enterobacteriaceae (CPE) causing

BSI is well known, it is less clear how this variation influences clinical practice in terms of selecting empirical or targeted treatment regimens.

The objectives of this study were to investigate variation across countries in antibiotic regimens used as empirical or targeted therapy for resistant gram-negative BSI, with the following hypotheses: (1) regional variation exists in the choice of empirical or targeted therapy for BSI caused by ESBL-E or CPE; (2) Regional variation exists in the use of β-lactam/β-lactamase inhibitor (BLBLI) agents as targeted therapy for bacteraemia caused by ESBL-E; and (3) regional variation exists in the use of combination therapy for bacteraemia caused by CPE.

2. Material and Methods

2.1 Study design and participants

This was a sub-study of a retrospective international cohort study (INCREMENT project; ClinicalTrials.gov identifier: NCT01764490) investigating the outcome impact of different antimicrobial regimens in the empirical and targeted therapy in BSI caused by ESBL-E or CPE from January 2004 to December 2013.[11] Thirty-seven hospitals from twelve countries (Spain, Italy, Greece, Taiwan, Turkey, Israel, USA, Argentina, Canada, Germany, Brazil and South Africa) participated in the INCREMENT project. Consecutive patients were included if they had a clinically significant monomicrobial BSI due to either ESBL-E or CPE. Sites were encouraged to limit inclusion of only 50 ESBL-E cases, but had no limit to CPE cases. Canada and Germany only contributed ESBL-E cases, Brazil only submitted CPE cases, whereas all other sites included both ESBL-E and CPE.

2.2 Variables and definitions

We defined as "empirical" therapies administrated before the availability of any microbiological result; among the empirical therapies we considered the first antimicrobial agent used regardless of later additions or changes. Antibiotic regimens were incorporated into the following classes: aminoglycosides (amikacin, gentamicin, tobramycin), BLBLIs (amoxicillin-clavulanate, piperacillin-tazobactam, ticarcillin-clavulanate, ampicillin-sulbactam), cephalosporins (cefepime, cefotaxime, cefuroxime, ceftriaxone, ceftazidime, cephalothin, cefixime), carbapenems (imipenem, doripenem, meropenem, ertapenem), colistin or tigecycline-based regimens. Targeted therapy was defined as the agent selected once susceptibility results were available; this therapy had to be commenced within 5 days of the initial positive blood culture and administered for at least 50% of the total treatment duration. Monotherapy was defined if no other drug with activity against gram-negative organisms was co-administered, irrespective of isolate susceptibility. We defined as inadequate those regimens against which the corresponding bloodstream isolates displayed a resistant or intermediate profile, using Clinical and Laboratory Standards Institute (CLSI) guidelines from 2012.[12] ESBL production was screened and confirmed according to CLSI recommendations;[12] selected ESBLs and all carbapenemases were characterised by polymerase chain reaction (PCR) and DNA sequencing using established methods at each local laboratory. Nosocomial acquisition was defined as occurring when symptoms associated with bacteraemia occurred >48 hours after admission, or within 48 hours of discharge. Otherwise, acquisition was considered to be community-onset. Additional demographic and clinical data were collected for all patients, including age, sex, Charlson co-morbidity score[13], Pitt bacteraemia score[14], the presence of severe sepsis or shock[15], diabetes mellitus, liver cirrhosis, malignancy or renal insufficiency.

2.3 Statistical analysis

Categorical variables were expressed as proportions and compared using Pearson's χ^2 test. For normally distributed scale variables, means and standard deviations were calculated and compared by two-sample t-test. For non-parametric data, median and interquartile ranges (IQR) were calculated and compared using the Wilcoxon rank-sum test. Potential predictors for antibiotic choice as the dependent variable were included in a univariate logistic regression model, with country of recruitment used as the main predictor. Patients who died before empirical or targeted therapy could be administered or those missing data describing antibiotic therapy were excluded. Variables with a p-value of <0.2 and/or with large effect estimates (Odds Ratios > 2 or < 0.5) in the univariate analysis were included in the multivariate model (using fixed effects). Odds ratios (ORs) with 95% confidence intervals were calculated for predictors of empirical carbapenem or BLBLI use, use of BLBLI for targeted treatment of ESBL-E and for targeted combination therapy of CPE. The multivariate model was optimized using a stepwise approach, beginning with the univariate model most strongly associated with choice of antibiotic therapy. The goodness-of-fit of the model before and after each step was compared using the likelihood ratio test and Akaike's information criterion. Variables that did not significantly improve the model fit were not added to the model. Statistical analysis was performed using Stata 13.1 (StataCorp; TX, USA) and figures produced using Prism 6 (GraphPad Software; CA, USA). A P-value <0.05 was considered significant.

3. Results

A total of 1,482 patients (1,003 with ESBL-E and 479 with CPE) were enrolled from 12 countries, with most cases recruited from sites in Spain (47.2%) (Figure 1). The baseline patient characteristics are presented in Table 1. Overall CPE accounted for 32.3% (479/1482) of cases, and were most frequently submitted from Italy (n=115), Spain (n=99), Greece (n=89) and Taiwan (n=60), whereas Canada and Germany contributed no CPE cases (Figure 1). It should be noted that these proportions reflect case selection and should not be interpreted as reflecting the true prevalence of resistance in each country. Empirical antibiotic choices for both ESBL-E and CPE cases and the proportions of isolates testing susceptible to the chosen regimen are shown in Figures 2A-D. Use of empirical therapy for ESBL-E and CPE BSI according to source of infection and acquisition status (community vs. nosocomial) is shown in Figures 3A-D. The use of BLBLI for the targeted treatment of ESBL-E or targeted combination therapy CPE also varied across countries (Figures 4A-D). For targeted therapy of ESBL-E, carbapenems were used most commonly across all countries (478/993, 48.1%), with BLBLIs used less frequently (101/993, 10.1%) (Figure 4A). Italy showed the highest use of BLBLIs for ESBL-E (29/132, 22.0%), whereas these were never used in Germany, Canada, Taiwan or South Africa. Targeted combination therapy was used in 44.1% of CPE cases (211/479) (Figure 4B). Carbapenem-based combination therapy of CPE (i.e. any targeted regimen that included a carbapenem in combination with at least one other agent) was used in 17.1% (82/479) of cases, and occurred most commonly in Italy (31/115, 27.0%), Greece (16/89, 18.0%) and Turkey (5/27, 18.5%) but was never used in Argentina or South Africa, although the total number of CPE treated in these countries was low (Supplementary Table 1). Details of agents used in targeted combination therapy for CPE are presented in Supplementary Table 2.

In a multivariate logistic regression model, using Spain as the reference category (as the group with the largest number of cases), patients were less likely to receive empirical BLBLI therapy if they were from Israel (aOR 0.34, 95% CI 0.14-0.81; p=0.015), Canada (aOR 0.31, 95% CI 0.11-0.88; p=0.028) or Greece (aOR 0.49, 95% CI 0.26-0.94; p=0.033), but more likely in Italy (aOR 1.58, 95% CI 1.11-2.25; p=0.012) or Turkey (aOR 2.09, 95% CI 1.14-3.81; p=0.016) after adjustment for age, ICU admission, infecting species, acquisition status and Pitt bacteraemia score (Figure 5A; Supplementary table 3). Empirical carbapenem use was more likely for sites within Taiwan (aOR 1.73, 95% CI 1.03-2.92; p=0.038) and the USA (aOR 1.89, 95% CI 1.05-3.39; p=0.032), but less likely in Italy (aOR 0.44, 95% CI 0.28-0.69; p<0.001) and Canada (aOR 0.10, 95% CI 0.01-0.74; p=0.024) after adjustment for age, ICU admission, infecting organism, acquisition status and Pitt score (Figure 5B; Supplementary Table 4). The use of a BLBLI for targeted therapy of ESBL-E was significantly more likely in patients treated at Italian sites (aOR 3.46, 95% CI 2.00-6.00; p<0.001) after adjustment for age, ICU admission, infecting genus, acquisition status, the presence of severe sepsis and Pitt score (Figure 5C; Supplementary table 5). It is worth noting that use of BLBLI as targeted therapy was less likely with higher Pitt scores, although the effect was modest (aOR 0.88; 95% CI 0.77-0.99; p=0.038) (Supplementary table 5). For the use of targeted combination therapy against CPE, the effect of location was seen for Israel (aOR 0.14; 95% CI 0.04-0.44; p=0.001), Taiwan (aOR 0.09; 95% CI 0.03-0.24; p<0.001), Brazil (aOR 0.14, 95% CI 0.04-0.45; p=0.001) and Turkey (aOR 0.26; 95% CI 0.10-0.69; p=0.007) where combination therapy was significantly less likely to be used after adjustment for source, acquisition status, presence of liver disease and infecting genus (Figure 5D; Supplementary table 6).

4. Discussion

In the present study we sought to understand the different therapeutic approaches to BSI caused by multidrug-resistant Enterobacteriaceae across participant sites according to the country of recruitment. Considerable geographical variation was seen in choice of therapy, either when selected empirically or targeted against a known pathogen. While much of this might be explained by the background prevalence of resistance, this may not account for all the variation seen.

Historical differences in clinical practice or local guidelines across countries are likely to be strong drivers in routine selection of empirical therapy. A survey conducted in Europe between 1997-2009 showed significant variation in total outpatient antibiotic use, highest in Greece (38.6 defined daily doses per 1000 inhabitants per day [DID]) and lowest in Romania (10.6 DID).[16] Penicillins were the most frequently prescribed class due mainly to an increase in the use of combinations with β-lactamase inhibitors.[17] Notably, Italy was the country with the highest use of penicillins followed by Greece.[17]

A key question of interest was how frequently BLBLIs were used as therapy for BSI caused by ESBL-E. After adjustment for potential confounding factors, recruitment from sites in Israel, Canada and Greece was independently associated with less use of BLBLI for empirical therapy of patients with ESBL-E. In the participant hospitals from Italy and Turkey empirical BLBLI use was significantly more likely to be used for ESBL-E, even after adjustment. Not surprisingly, BSI caused by CPE was associated with less empirical BLBLI use. This may either reflect prior knowledge of colonisation with multi-resistant organisms, or recognition of relevant clinical risk factors. Indeed CPE was significantly more likely to be seen in

nosocomial infection than ESBL-E (88.9% vs 50.1%, p<0.001; χ^2 test). Empirical carbapenem use was also less likely in older patients, although this effect size was small (aOR 0.99, 95% CI 0.98-1.00; p=0.029). No other clinical factors, apart from geographical location, were significantly associated with empirical carbapenem use on univariate or multivariate analyses. This is perhaps surprising, given that one might expect carbapenem use to be more likely in patients with high acuity infections or with greater burden of disease, but this was not associated with the objective markers of infection severity or co-morbidity that were measured in this cohort (i.e. Pitt, Charlson scores, co-morbid disease or the presence of severe sepsis or septic shock). However, it is possible that additional clinical factors could influence empirical carbapenem use, which were not measured (e.g. presence of significant immunosuppression, organ transplant, background rate or antibiotic resistance).

The burden of CPE and ESBL-E seen in this cohort broadly reflects existing prevalence data from these countries, but should not be considered an accurate description of national prevalence data. Within the European Union/European Economic Area (EU/EAA), Greece and Italy were the two countries with the majority of CPE cases included (see Figure 1). From 2009 to 2014 there has been an increasing trend of the EU/EAA population weighted mean percentage for carbapenem resistance in *K. pneumoniae* with the highest rates in Italy, Greece and Romania.[18] Carbapenem resistance in *E. coli* in Europe remains generally low (<0.1%), however a rising trend in resistance to third-generation cephalosporins has been observed in more than a third of countries.[18] Taiwan, which still has a low prevalence of CPE,[19] detected carbapenemase genes in 6% of 100 isolates in 2010 and 22.3% of 247 isolates in 2012 in a national surveillance study on carbapenem non-susceptible *K. pneumoniae*.[20] In the USA, CDC surveillance systems have reported an increase in the

percentage of Enterobacteriaceae with non-susceptibility to carbapenems.[21] In 2001 approximately 1.2% of the most common Enterobacteriaceae reported to the Nosocomial Infection Surveillance system were non-susceptible to at least one of the 3 carbapenems; in 2011 that percentage had risen to 4.2% with the greatest increase observed among *K. pneumoniae* (from 1.6% to 10.4%).[22] A retrospective cohort study among community hospitals throughout the south-eastern United States has found an increase in the incidence of ESBL–*E. coli* infections (from 5.3% in 2009 to 10.5% in 2014) while ESBL-*K. pneumoniae* remained stable.[23] Among South American countries, Argentina, along with Brazil, has experienced a statistical significant trend for carbapenem-resistant *K. pneumoniae*.[24, 25] According to the SENTRY study results from Latin America (2008-2010) rates of ESBL production were 24.7% among *E. coli* and 52.7% among *K. pneumoniae*.[25]

In our cohort, BLBLIs, carbapenems and cephalosporins were the most frequently prescribed antibiotic classes for empirical monotherapy. A significant proportion of empirical regimens were inadequate (50.6% of empirical regimens for ESBL-E and 76.4% for CPE; see Figure 2C and 2D), underscoring the difficulty in selecting appropriate empirical antimicrobial therapy in the context of MDR infections. However, it should be noted that some agents may still have some clinical efficacy (e.g. carbapenems against CPE) despite being categorised as 'non-susceptible' according to clinical breakpoints, particularly if used in combination.

Empirical combination therapy partially matches epidemiological data (i.e. countries with a high rate of carbapenem resistance are those which tend to use more combination therapies) but also with clinical presentation. Considering severity of disease at clinical presentation, the participant sites from Greece, Brazil, Argentina, Turkey and Italy were

302 countries with >50% of patients presented with severe sepsis or septic shock, which may
303 influence the use of combination empirical regimens. Combination therapy is recommended
304 by some for the treatment of serious infection due to MDR organisms, particularly for
305 CPE[26] and inadequate empirical treatment has been shown to be associated with higher
306 mortality.[27]
307
308 The variation in BLBLI use for ESBL-E bacteraemia is notable. Despite some observational
309 data suggesting that BLBLI may be non-inferior to carbapenems in this context,[11, 28] it is
310 clear that this practice was not widespread during the period of study in these countries.
311 This may suggest that if robust clinical evidence emerges that indicates equivalent clinical
312 efficacy for BLBLIs against ESBL-E, there may be considerable scope to reduce carbapenem
313 use against these infections. Studies have been conflicting in this area, with some
314 observational data to suggest that empirical BLBLI is associated with increased mortality,[29]
315 although this finding does not reflect the experience in other settings.[28] Given these
316 uncertainties, the standard of care has relied upon carbapenems for serious ESBL-E
317 infections.[3] However, with the international drive for improved antimicrobial stewardship,
318 there is considerable interest to seek carbapenem-sparing options for ESBL-E infections.
319 Use of targeted combination therapy for ESBL-E was relatively infrequent (21%, range 0 to
320 31.6%) but may reflect lack of data suggesting benefit for such infections. However,
321 targeted combination therapy for CPE was more common (used in 44.1% overall, range
322 13.3% [Taiwan] to 66.7% [Argentina]), probably reflecting limited effective treatment
323 options, and some evidence that combination therapy may be of benefit.[30] However,
324 when directed combination therapy was used for CPE, carbapenem-based regimens were

less common than non-carbapenem-based options (17.3% vs 26.7%) (Supplementary Table 1).

Knowledge of historical clinical practice and the prevalence of MDR bacteria at a local level are both important when selecting antibiotic therapy. Scoring systems[31] have been studied to assess risk prediction for ESBL-E or CPE BSI.[32, 33] Factors such as poor functional status, recent antibiotic therapy or hospitalization and the severity of clinical presentation should be taken into account when assessing such risks. This can be challenging, especially in clinical settings where consultation with an infectious disease specialist is not readily available. Clinical risk-prediction scores also need to be adapted based on local prevalence. Hence, effective antimicrobial stewardship and the development of local guidelines, based on surveillance at an institutional and national level, are helpful to guide a prudent use of antimicrobials. In particular, the use of BLBLIs and carbapenems, two of the most frequently used classes for gram-negative BSI, has to be carefully balanced in an era where carbapenemases are increasingly encountered and alternatives therapies are currently limited.

Our study has some limitations. As a *post hoc* analysis of a previously completed retrospective study, the original design was not intended to analyse epidemiological trends or variation in practice across countries. The great majority of cases occurred in Spain, with relatively small numbers of cases and sites from other countries, which may introduce sampling bias. Given the retrospective nature of the study, data were missing for some patients. For some countries, the low proportion of CPE BSI reported did not reflect the known background prevalence of resistance, which may reflect sampling bias. For countries

with few CPE cases, the study would be underpowered to detect regional differences in treatment selection. We did not look at the impact on mortality of different regimens between the countries as this question has been addressed elsewhere.[11]

5. Conclusions

In this international observational cohort of patients with bloodstream infections caused by multi-drug resistant Enterobacteriaceae, we observed a preference to treat ESBL-E BSI with carbapenems and CPE BSI with alternatives to carbapenems or combination therapy. In some countries, such as Italy and Turkey, the likelihood of using empirical BLBLI for ESBL-E is significantly higher than in recruiting sites in other countries such as Israel, Greece and Canada. Being treated in the participant sites from USA or Taiwan was independently associated with an increased likelihood of receiving empirical carbapenem therapy, whereas this strategy was used less in Canadian or Italian participating hospitals. It should be noted that, although this study does not provide accurate data on the relative prevalence of ESBL-E or CPE across countries, it does offer some insight into the antibiotic strategies used for these infections. Despite variation across countries in the prevalence of ESBL-E or CPE, which may drive antibiotic selection, additional factors beyond clinical presentation and illness severity influence selection of empirical and targeted therapy in multi-drug resistant gram-negative bloodstream BSI. Knowledge of regional differences in therapy for these infections will help design international clinical trials aiming to compare new treatment options for gram-negative BSI. Further research is needed to better understand the reasons for these differences in order to target antimicrobial stewardship efforts.

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Declarations

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Competing Interests: Dr. Rodríguez-Baño reports grants and personal fees from Merck, personal fees from AstraZeneca and personal fees from InfectoPharm, outside the submitted work. Dr. Pascual reports personal fees from Merck, grants and personal fees from B. Braun, personal fees from Astra Zeneca, outside the submitted work. Dr. Bonomo reports grants from Allergan, grants from Merck, grants from Entasis, grants from the NIH and grants from Merit Review VA, outside the submitted work. Dr. Doi reports personal fees from Meiji, personal fees from Shionogi, personal fees from Tetraphase, personal fees from Achaogen, personal fees from Allergan, grants and personal fees from The Medicines Company, personal fees from Curetis, personal fees from Roche, grants and personal fees from Merck, outside the submitted work. Dr. Perez reports grants from Pfizer, outside the submitted work. Dr. Canton reports personal fees from AstraZeneca, MSD and personal fees from Bayer, outside the submitted work. Dr. Tuon reports personal fees from Astra-

Zeneca, personal fees from Pfizer, personal fees from TEVA, grants and personal fees from MSD, personal fees from Bayer, during the conduct of the study. Dr Daikos reports grants and personal fees from Pfizer, personal fees from Achaogen, personal fees from MSD, grants from GILEAD and personal fees from REMPEX, during the conduct of the study. Dr. Paterson has received personal fees from Merck, grants from Merck, and nonfinancial support from Allergen, Shionogi, and Achaogen. Dr. Harris has received travel and accommodation support to speak at an educational event sponsored by Pfizer. All other authors declare no conflicts of interest

Ethical Approval: The INCREMENT project was approved by the Spanish Agency of Medicines (AEMPS; code JRB-ANT-2012-01) and the Hospital Universitario Virgen Macarena Institutional Review Board (code 1921); the need to obtain written informed consent was waived. Approval was also obtained at participating centres according to local requirements.

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Figure 1: Frequency of ESBL-E and CPE cases submitted by country

Figure 2: Selection of empirical therapy for BSI by country. **2A**| Empirical therapy for BSI caused by ESBL-E. **2B** | Empirical therapy for BSI caused by CPE. **2C** | Proportions of ESBL-E testing susceptible to the empirical regimen. **2D** | Proportions of CPE testing susceptible to the empirical regimen

Figure 3: Selection of empirical therapy for BSI caused by ESBL-E or CPE by source or acquisition status. **3A** | Empirical therapy for ESBL-E by source of infections. **3B** | Empirical therapy for CPE by source of infection. **3C** | Empirical therapy for ESBL-E by acquisition status. **3D** | Empirical therapy for CPE by acquisition status.

Figure 4: Selection of targeted therapy for ESBL-E or CPE by country. **4A**| Targeted therapy for BSI caused by ESBL-E. **4B** | Targeted therapy for BSI caused by CPE. **4C** | Proportions of ESBL-E cases treated with targeted combination therapy. **4D** | Proportions of CPE cases treated with targeted combination therapy

Figure 5: Forest plots of adjusted odd ratios (aOR) and 95% confidence intervals (95% CIs) for antibiotic selection by participating sites in each country. **5A** | aORs for empirical use of BLBLI. **5B** | aORs for empirical use of carbapenems. **5C** | aORs for targeted use of BLBLI for ESBL-E. **5D** | aORs for targeted use of combination therapy for CPE. **Note**: Spain used as a reference (full data in Supplementary tables 3-6)

561 **Table 1:** Baseline variables for patients with ESBL-E and CPE

Variable		ESBL	CPE	P
Gender	Female	441 (44.0%)	200 (41.8%)	0.42¶
	Male	562 (56.0%)	279 (58.2%)	
Age, mean (SD)		65.8 (17.8)	62.9 (17.5)	0.003*
Admission type	Medical	465 (46.9%)	196 (41.6%)	<0.001¶
	Surgical	138 (13.9%)	56 (11.9%)	
	ED	260 (26.2%)	51 (10.8%)	
	ICU	128 (12.9%)	168 (35.7%)	
Charlson score, median (IQR)		2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	0.022§
Pitt score, median (IQR)		1.0 (0.0, 3.0)	3.0 (0.0, 5.0)	<0.001§
Severe sepsis or shock	Absent	605 (62.2%)	212 (46.6%)	<0.001¶
	Present	367 (37.8%)	243 (53.4%)	
Acquisition	Nosocomial	492 (50.1%)	426 (88.9%)	<0.001¶
	Community	491 (49.9%)	53 (11.1%)	
Source	Urinary	421 (42.1%)	73 (15.6%)	<0.001¶
	Biliary	109 (10.9%)	21 (4.5%)	
	Intra-abdominal	115 (11.5%)	49 (10.4%)	
	Pneumonia	72 (7.2%)	52 (11.1%)	
	Osteoarticular	5 (0.5%)	0	
	Vascular	66 (6.6%)	105 (22.4%)	
	Skin / soft tissue	27 (2.7%)	16 (3.4%)	
	Central nervous system	2 (0.2%)	1 (0.2%)	
	Unknown	166 (16.6%)	135 (28.8%)	
	Others	16 (1.6%)	17 (3.6%)	
Species	*E. coli*	693 (69.1%)	17 (3.5%)	<0.001¶
	Klebsiella spp.	233 (23.2%)	415 (86.6%)	
	Others	77 (7.7%)	47 (9.8%)	
Diabetes	Absent	661 (66.5%)	314 (67.7%)	0.66¶
	Present	333 (33.5%)	150 (32.3%)	
Liver disease	Absent	857 (87.1%)	409 (86.8%)	0.89¶
	Present	127 (12.9%)	62 (13.2%)	
Malignancy	Absent	594 (60.9%)	302 (64.3%)	0.22¶
	Present	381 (39.1%)	168 (35.7%)	
Renal dysfunction	Absent	753 (78.6%)	348 (76.0%)	0.27¶
	Present	205 (21.4%)	110 (24.0%)	
Total		**1003**	**479**	

562 ***2-sample t-test §Wilcoxon rank-sum test ¶ Pearson's χ^2 test**

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