Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

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Summary

Background The best available treatment against carbapenemase-producing Enterobacteriaceae (CPE) is unknown. The objective of this study was to investigate the effect of appropriate therapy and of appropriate combination therapy on mortality of patients with bloodstream infections (BSIs) due to CPE.

Methods In this retrospective cohort study, we included patients with clinically significant monomicrobial BSIs due to CPE from the INCREMENT cohort, recruited from 26 tertiary hospitals in ten countries. Exclusion criteria were missing key data, death sooner than 24 h after the index date, therapy with an active antibiotic for at least 2 days when blood cultures were taken, and subsequent episodes in the same patient. We compared 30 day all-cause mortality between patients receiving appropriate (including an active drug against the blood isolate and started in the first 5 days after infection) or inappropriate therapy, and for patients receiving appropriate therapy, between those receiving active monotherapy (only one active drug) or combination therapy (more than one). We used a propensity score for receiving combination therapy and a validated mortality score (INCREMENT-CPE mortality score) to control for confounders in Cox regression analyses. We stratified analyses of combination therapy according to INCREMENT-CPE mortality score (0–7 [low mortality score] *vs* 8–15 [high mortality score]). INCREMENT is registered with ClinicalTrials.gov, number NCT01764490.

Findings Between Jan 1, 2004, and Dec 31, 2013, 480 patients with BSIs due to CPE were enrolled in the INCREMENT cohort, of whom we included 437 (91%) in this study. 343 (78%) patients received appropriate therapy compared with 94 (22%) who received inappropriate therapy. The most frequent organism was *Klebsiella pneumoniae* (375 [86%] of 437; 291 [85%] of 343 patients receiving appropriate therapy *vs* 84 [89%] of 94 receiving inappropriate therapy) and the most frequent carbapenemase was *K pneumoniae* carbapenemase (329 [75%]; 253 [74%] *vs* 76 [81%]). Appropriate therapy was associated with lower mortality than was inappropriate therapy (132 [38·5%] of 343 patients died *vs* 57 [60·6%] of 94; absolute difference 22·1% [95% CI 11·0–33·3]; adjusted hazard ratio [HR] 0·45 [95% CI 0·33–0·62]; p<0·0001). Among those receiving appropriate therapy, 135 (39%) received combination therapy and 208 (61%) received monotherapy. Overall mortality was not different between those receiving combination therapy or monotherapy (47 [35%] of 135 *vs* 85 [41%] of 208; adjusted HR 1·63 [95% CI 0·67–3·91]; p=0·28). However, combination therapy was associated with lower mortality than was monotherapy in the high-mortality-score stratum (30 [48%] of 63 *vs* 64 [62%] of 103; adjusted HR 0·56 [0·34–0·91]; p=0·02), but not in the low-mortality-score stratum (17 [24%] of 72 *vs* 21 [20%] of 105; adjusted odds ratio 1·21 [0·56–2·56]; p=0·62).

Interpretation Appropriate therapy was associated with a protective effect on mortality among patients with BSIs due to CPE. Combination therapy was associated with improved survival only in patients with a high mortality score. Patients with BSIs due to CPE should receive active therapy as soon as they are diagnosed, and monotherapy should be considered for those in the low-mortality-score stratum.

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Introduction

Among antibiotic-resistant organisms, carbapenemase-producing Enterobacteriaceae (CPE) are probably the most worrying threat because the therapeutic options against these bacteria are very few.[1] Most CPE are resistant to all first-line anti-Gram-negative antibiotics, such as cephalosporins, β-lactam–β-lactamase inhibitors, carbapenems, and fluoroquinolones. Alternative drugs,

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Research in context

Evidence before this study

We searched PubMed and Scopus from Jan 1, 2007, to Dec 31, 2016, using the terms "carbapenemase-producing", "fluoroquinolone-resistant Enterobacteriaceae", "colistin-resistant Enterobacteriaceae", "*Escherichia coli*", "*Klebsiella*", "*Enterobacter*", "*Serratia*", "therapy", "treatment", "bacteremia", "bloodstream infections", "sepsis", "pneumonia", "intraabdominal infections", "complicated UTI", "central nervous system infections", and "osteoarticular infections", with no language restrictions. We selected comparative cohort or case-control human studies with outcome analysis (eg, mortality or cure), including confounding control (multivariate analysis, stratified analysis, or similar) and randomised controlled trials. The best available treatment against carbapenemase-producing Enterobacteriaceae (CPE) is unknown. We did not find any randomised clinical trials comparing the potential benefit of combination therapy with that of monotherapy in patients with CPE infections. The existing data are mainly based on the results of retrospective studies and case series using small sample sizes. Findings from several cohort studies suggest that combination therapy with two or three active drugs including a carbapenem is better than monotherapy. Investigators of other studies did not find combination therapy to be better than monotherapy. Investigators of most previous studies did not find active initial therapy to be associated with mortality in bloodstream infections due to CPE, but a study done in Italy and including only *Klebsiella pneumoniae* carbapenemase-producing *K pneumoniae* cases found inappropriate empirical therapy to be independently associated with increased risk of death.

Added value of this study

We found that active therapy started 5 days or sooner after infection is associated with lower mortality than is inappropriate therapy. We found that combination therapy is protective of mortality only in patients with a high probability of death according to a previously validated mortality score (INCREMENT-CPE mortality score).

Implications of all the available evidence

Our study provides new results that will inform important changes in clinical practice. First, because the importance of administration of active antimicrobial therapy might prompt implementation of active programmes to achieve this goal and second, because the data suggest that combination therapy (the standard at present) is only needed in patients with high pretreatment probability of death according to a previously validated mortality score. By avoiding the need to use combination therapy in many patients, a contribution to avoid the spread of antibiotic resistance (one of the greatest threats worldwide, as declared by the UN) is possible. Since randomised controlled trials of patients with these infections are difficult to do because of the different susceptibility profiles of carbapenemase producers, among other reasons, the information from well designed observational studies will form the basis of guidelines for many years.

such as colistin, tigecycline, fosfomycin, or amino glycosides, are frequently the only options, which might explain the higher mortality of patients with CPE infections than of those with infections from carbapenem-susceptible Enterobacteriaceae.[2,3]

The best available treatment against CPE infections is unknown. Results from several retrospective studies[4–6] suggest that combination therapy is better than monotherapy. These studies included only or mostly *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K pneumoniae* infections. Although KPC are the most frequent carbapenemases in some parts of the world, oxacillinase 48 or metallo-β-lactamases are predominant in other areas.[1] This difference might be important since their epidemiology, susceptibility, and bacterial clonal groups are different.[7,8] Investigators of other studies[9,10] did not find combination therapy to be better than monotherapy. Even if combination therapy is better than monotherapy, subsets of patients that can be treated with monotherapy would be important to know.[11]

To do randomised controlled trials of these infections is difficult because of the different susceptibility profiles of CPE, among other reasons; therefore, recommendations will be mostly based on observational studies during the next few years. Importantly, intrinsic challenges exist for observational studies in this population, including assignment of treatment groups when regimens are changed during the course of infection, avoidance of a survivor bias, and appropriate control for key confounders, such as the source of infection, severity of underlying conditions, and severity of response syndrome at presentation. The INCREMENT project, a retrospective international cohort study, was designed to try to overcome some of the limitations of previous studies, with the intention to provide useful additional information for treatment of patients with CPE. Our pre-registered hypothesis was that empirical and definitive appropriate combined therapy is associated with better outcomes than is monotherapy with carbapenems, colistin, or tigecycline in patients with bloodstream infections (BSIs) due to CPE. Because data published after registration of the INCREMENT project suggested that combination therapy might be beneficial only in patients with severe infections or conditions who therefore have an increased mortality risk,[6,11] we also analysed whether or not such association would occur in these patients.

Methods

Study design and patients

The INCREMENT project recruited a retrospective international cohort of patients with BSIs due to extended-spectrum β-lactamase-producing Enterobacteriaceae or

CPE consecutively admitted to 37 tertiary hospitals in 12 countries. Patients with BSIs due to CPE included in this study were recruited from 26 centres in ten countries. Participant sites were selected according to their experience in research into BSIs and CPE.

Patients were sought at each site by review of microbiology reports and bacteraemia databases. Data were collected by review of patients' charts until day 30 after blood cultures were taken; if needed, patients or relatives were contacted by telephone and mortality registers consulted. For this analysis, patients with clinically significant, monomicrobial BSIs due to CPE were eligible. Exclusion criteria were missing key data, death sooner than 24 h after the index date, therapy with an active antibiotic for at least 2 days when blood cultures were taken, and subsequent episodes in the same patient.

The study was approved by the Hospital Universitario Virgen Macarena institutional review board (code 1921), which waived the need to obtain written informed consent. Approval was also gained at participating centres according to local requirements. STROBE recommendations were followed (appendix pp 1–2).

Procedures

We did a two-step analysis: first, we analysed the effect of patients receiving appropriate therapy, and then second, within those receiving appropriate therapy only, we analysed the effect of combination therapy considering the mortality risk according to the INCREMENT-CPE mortality score.[12] The main outcome variable was 30 day all-cause mortality, measured from the day on which the blood cultures were taken (index date or day 0). We used mortality at day 30 instead of clinical cure at day 14 (as stated in the protocol) as the main outcome because all recent studies assessed mortality.[4–6,9,10] The main exposure variable was antimicrobial treatment. We considered antibiotic therapy appropriate if administered 5 days after infection or sooner and including an active drug against the blood isolate. If the active drug was started in 2 days or sooner, we considered it early appropriate therapy. We defined combination therapy as a regimen including more than one in-vitro active antimicrobial and monotherapy as including one active drug. If the regimen was changed during the course, we considered the antibiotic regimen as the one started in the 5 days or sooner period after infection and administered for at least half of the duration of therapy (for patients who died <48 h after the start of therapy, we required 1 complete day of therapy).

Other variables collected were demographics, nosocomial (if the onset of symptoms started >48 h after hospital admission or within 48 h of a previous hospital discharge) or community acquisition, hospital service, underlying conditions, Charlson comorbidity index score,[13] severity of acute condition at presentation according to the Pitt bacteraemia score,[14] source of BSI according to clinical and microbiological data, severity of systemic inflammatory response syndrome on day 0,[15] doses of antibiotics, Enterobacteriaceae species, and carbapenemase type. The data collected were centrally monitored for missing information, consistency, and coherence, and queries were sent to the respective sites.

For the assessment of the effect of combination therapy, we used the INCREMENT-CPE mortality score, already validated in the cohort.[12] The score includes severe sepsis or shock at presentation (five points), a Pitt bacteraemia score of at least 6 (four points), a Charlson comorbidity index score of at least 2 (three points), a source of BSI other than urinary or biliary tract (three points), and inappropriate empirical and early targeted therapy (two points; we did not consider this factor since we specifically assessed therapy as a predictor).

Identification of microorganisms and susceptibility testing were done at each participating centre. We studied susceptibility using automated systems or disk diffusion and interpreted it using the 2012 Clinical and Laboratory Standards Institute breakpoints.[16] For isolates obtained before 2012, we assigned the susceptibility category according to the minimum inhibitory concentration (MIC) and, if unavailable, as reported by the local laboratory. We considered antibiotics to which the bacteria were classified as susceptible or intermediate active. We considered imipenem and meropenem active if the MIC was 8 mg/L or lower, according to previous studies.[1,4,6,17,18] We investigated isolates with reduced susceptibility to carbapenems for carbapenemase production; we did phenotypic tests according to local protocols and characterised carbapenemases with PCR for KPC, Verona integron-encoded metallo-β-lactamase, and imipenemase, and from 2011, New Delhi metallo-β-lactamase and oxacillinase 48.

Statistical analysis

We compared continuous variables with Mann-Whitney *U* tests and categorical variables with χ^2 or Fisher's exact tests as appropriate. We compared Kaplan-Meier curves using log-rank tests. We dichotomised the study period according to a classification and regression tree analysis. We did a Breslow test of homogeneity between centres; however, to control for the site effect, we classified centres into those with low (low-mortality-risk centres) and high (high-mortality-risk centres) mortality using TreeNet considering all other variables; therefore, sites classified as high-risk centres were those with high mortality after consideration of patients' features. We did multivariate analyses using Cox regression after assessing the proportional hazards assumption. We included variables with a univariate p of 0·2 or less for mortality and manually selected them in a backward stepwise manner according to their association and biological value. We calculated the variance inflation factor value for every variable included to control for the potential occurrence of collinearity between the propensity score and other potential confounders. We selected the best model according to the likelihood ratio test.

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See **Online** for appendix

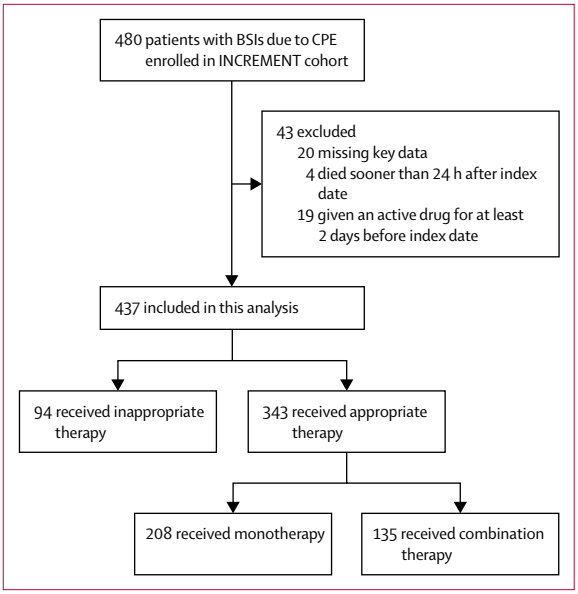

Figure 1: **Flow chart of included patients with BSIs due to CPE**
BSI=bloodstream infection. CPE=carbapenemase-producing Enterobacteriaceae.

For the analyses of combination therapy, we calculated a propensity score for receiving of combination therapy using a non-parsimonious logistic regression model in which the outcome variable was combination therapy. We investigated the INCREMENT-CPE mortality score as an effect modifier. We did stratified analyses according to the INCREMENT-CPE mortality score (0–7 [low mortality score] *vs* 8–15 [high mortality score]) because we found a significant interaction of combination therapy and INCREMENT-CPE mortality score (this analysis had not been planned when the study was registered). We did sensitivity analyses in subgroups and using different definitions (considering as active only antibiotics for which the bacteria were susceptible; classifying therapy into only one active drug, one active plus at least one inactive drug, and more than one active drug; and considering only combinations including a carbapenem). Finally, we matched patients given monotherapy and combination therapy (1:1) using calipers of 0·2 width of the SD of the logit of the propensity score and the INCREMENT mortality score strata. We compared mortality in matched pairs with a Cox regression analysis using a robust variance estimator (approximate jack-knife estimator of the variance) and with conditional logistic regression. We did analyses using R software (version 3.0.1), SPSS 15.0, Classification and Regression Tree software 7.0, and TreeNet version 7.0.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. BG-G and JR-B had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

	Appropriate therapy (n=343)	Inappropriate therapy (n=94)	p value
Age (years)	66 (55·5–76·0)	66 (50–77)	0·76
Male sex	197 (57%)	58 (62%)	0·46
Enterobacteriaceae	..	..	0·27
Klebsiella pneumoniae	291 (85%)	84 (89%)	..
Other	52 (15%)	10 (11%)	..
Enterobacter cloacae	24 (7%)	4 (4%)	..
Escherichia coli	14 (4%)	3 (3%)	..
Enterobacter aerogenes	10 (3%)	3 (3%)	..
Citrobacter spp	3 (1%)	0	..
Serratia marcescens	1 (<1%)	0	..
Type of carbapenemase	..	..	0·64
OXA-48	57 (17%)	12 (13%)	..
KPC	253 (74%)	76 (81%)	..
Metallo-β-lactamases	33 (10%)	6 (6%)	..
VIM	30 (9%)	6 (6%)	..
Other	3 (1%)	0	..
Nosocomial acquisition	298 (87%)	87 (93%)	0·13
Source other than urinary or biliary tract	272 (79%)	76 (81%)	0·74
Vascular catheter	87 (25%)	13 (14%)	..
Pneumonia	34 (10%)	9 (10%)	..
Intra-abdominal	37 (11%)	7 (7%)	..
Skin and skin structures	11 (3%)	5 (5%)	..
Other	10 (3%)	3 (3%)	..
Unknown	93 (27%)	39 (41%)	..
ICU admission	123 (36%)	36 (38%)	0·66
Charlson comorbidity index score	2 (1–4)	2 (2–4)	0·74
Pitt bacteraemia score	2 (1–5)	3 (0–5)	0·50
Severe sepsis or septic shock	172 (50%)	57 (61%)	0·07
Mental status: not alert	156 (45%)	43 (46%)	0·96
Leukaemia or metastatic cancer	52(15%)	13 (14%)	0·75
Chronic liver disease	41 (12%)	16 (17%)	0·20
Chronic kidney disease	80 (23%)	18 (19%)	0·39
High-mortality-risk centre	105 (31%)	41 (44%)	0·02
Study period 2004–11 (reference 2012–13)	237 (69%)	67 (71%)	0·68
30 day mortality	132 (38%)	57 (61%)	0·0001

Data are n (%) or median (IQR). OXA=oxacillinase. KPC=*Klebsiella pneumoniae* carbapenemase. VIM=Verona integron-encoded metallo-β-lactamase. ICU=intensive care unit.

Table 1: **Characteristics of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae**

Results

Between Jan 1, 2004, and Dec 31, 2013, 480 patients with BSIs due to CPE were included in the INCREMENT cohort. After application of the exclusion criteria, we included 437 (91%) in this study (figure 1). The number of patients per site ranged from two (<1%) to 56 (13%); the highest numbers of patients were from Italy

	Crude analysis		Adjusted analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per year)	1·00 (1·00–1·01)	0·32	..	..
Male sex	0·93 (0·70–1·24)	0·62	..	..
Klebsiella pneumoniae	1·29 (0·83–2·02)	0·25	..	..
OXA-type carbapenemase	1·43 (1·00- 2·05)	0·05	..	..
Nosocomial acquisition	1·83 (1·06- 3·16)	0·03	..	..
Source other than urinary or biliary tracts†	2·12 (1·37- 3·29)	0·0009	1·72 (1·09–2·72)	0·02
ICU admission	1·55 (1·16–2·08)	0·003	..	..
Charlson comorbidity index score (per unit)	1·10 (1·05–1·16)	<0·0001	1·13 (1·07–1·20)	<0·0001
Mechanical ventilation	1·76 (1·32–2·34)	<0·0001	..	..
Mental status: not alert	2·45 (1·82–3·29)	<0·0001	..	..
Chronic kidney disease	1·33 (0·97–1·84)	0·08	..	..
Chronic liver disease	1·58 (1·08–2·31)	0·02	..	..
Leukaemia or metastatic cancer	1·61 (1·12–2·31)	0·009	..	..
Pitt bacteraemia score (per unit)	1·17 (1·13–1·22)	<0·0001	1·09 (1·04–1·15)	0·0003
Severe sepsis or septic shock	3·87 (2·78–5·39)	<0·0001	3·11 (2·14–4·51)	<0·0001
Early appropriate therapy (started in ≤2 days after infection)	0·84 (0·59–1·21)	0·35	..	..
Appropriate therapy (started in ≤5 days after infection)	0·44 (0·33–0·61)	<0·0001	0·45 (0·33–0·62)	<0·0001
High-mortality-risk centre	2·25 (1·69–2·99)	<0·0001	2·37 (1·74–3·22)	<0·0001
Study period 2004–11 (reference 2012–13)	1·52 (1·09–2·13)	0·01	1·43 (1·02–2·01)	0·04

HR=hazard ratio. OXA=oxacillinase. ICU=intensive care unit. *All variance inflation factor values of the variables included in the final multivariate model were less than 1·4. We included variables with a univariate p value of 0·2 or less for mortality in the initial model. †Biliary tract infections included cholecystitis and cholangitis.

Table 2: **Univariate and multivariate Cox regression analyses for mortality of patients with bacteraemia due to carbapenemase-producing Enterobacteriaceae**

(109 [25%]), Spain (94 [22%]), Greece (81 [19%]), and Taiwan (56 [13%]).

We considered antibiotic therapy appropriate in 343 (78%) patients compared with 94 (22%) who received inappropriate therapy. Characteristics of patients who received inappropriate and appropriate therapy are compared in table 1. 57 (60·6%) of 94 patients receiving inappropriate therapy died of all causes by day 30 compared with 132 (38·5%) of 343 receiving appropriate therapy (absolute difference 22·1% [95% CI 11·0–33·3]; p<0·0001). The Kaplan-Meier curve for survival is shown in the appendix (p 10; hazard ratio [HR] 0·44 [95% CI 0·33–0·61]; log-rank p<0·0001). Univariate and multivariate analyses of 30 day mortality are shown in table 2. Appropriate therapy was independently associated with a protective effect (adjusted HR 0·45 [0·33–0·62]; p<0·0001), but early appropriate therapy was not (HR 0·84 [0·59–1·21]; p=0·35).

We built two additional multivariate Cox logistic regression models. In the first model, we used the variable time to appropriate treatment instead of appropriate or inappropriate therapy, selecting the same variables. The adjusted HR per day of delay in administration of appropriate therapy was 1·02 (95% CI 1·01–1·04; p<0·0001; appendix p 3). In the second model, we reclassified the variable therapy into inappropriate therapy (reference), active monotherapy, and active combination therapy. Monotherapy (adjusted HR 0·52 [95% CI 0·37–0·74]; p=0·0002) and combination therapy (0·35 [0·23–0·52]; p<0·0001) had a protective effect on mortality.

Of the 343 patients who received appropriate therapy, 208 (61%) received monotherapy and 135 (39%) received combination therapy. Their characteristics are shown in the appendix (p 4). 85 (40·9%) of 208 patients receiving monotherapy died of all causes by day 30 compared with 47 (34·8%) of 135 receiving combination therapy (absolute difference 6·1% [95% CI –4·4 to 16·5]; p=0·26; figure 2).

We did a multivariate Cox regression analysis including INCREMENT-CPE mortality score (table 3). Combination therapy was not associated with mortality (adjusted HR 1·63 [95% CI 0·67–3·91]; p=0·28), but its interaction with the score was protective, meaning that combination therapy was protective only in patients with a high mortality score. We checked the effect of the individual components of the score; severe sepsis or shock and the Pitt bactaeremia score also showed a modifying effect, but the resulting models were less fitted to the data than was the model with the mortality score (data not shown).

To analyse this interaction in detail, we dichotomised the INCREMENT-CPE mortality score using TreeNet into 0–7 (low mortality score) and 8–15 (high mortality score) points (appendix p 11). 30 day mortality in the low-mortality-score stratum was shown by 21 (20%) of 105 patients receiving

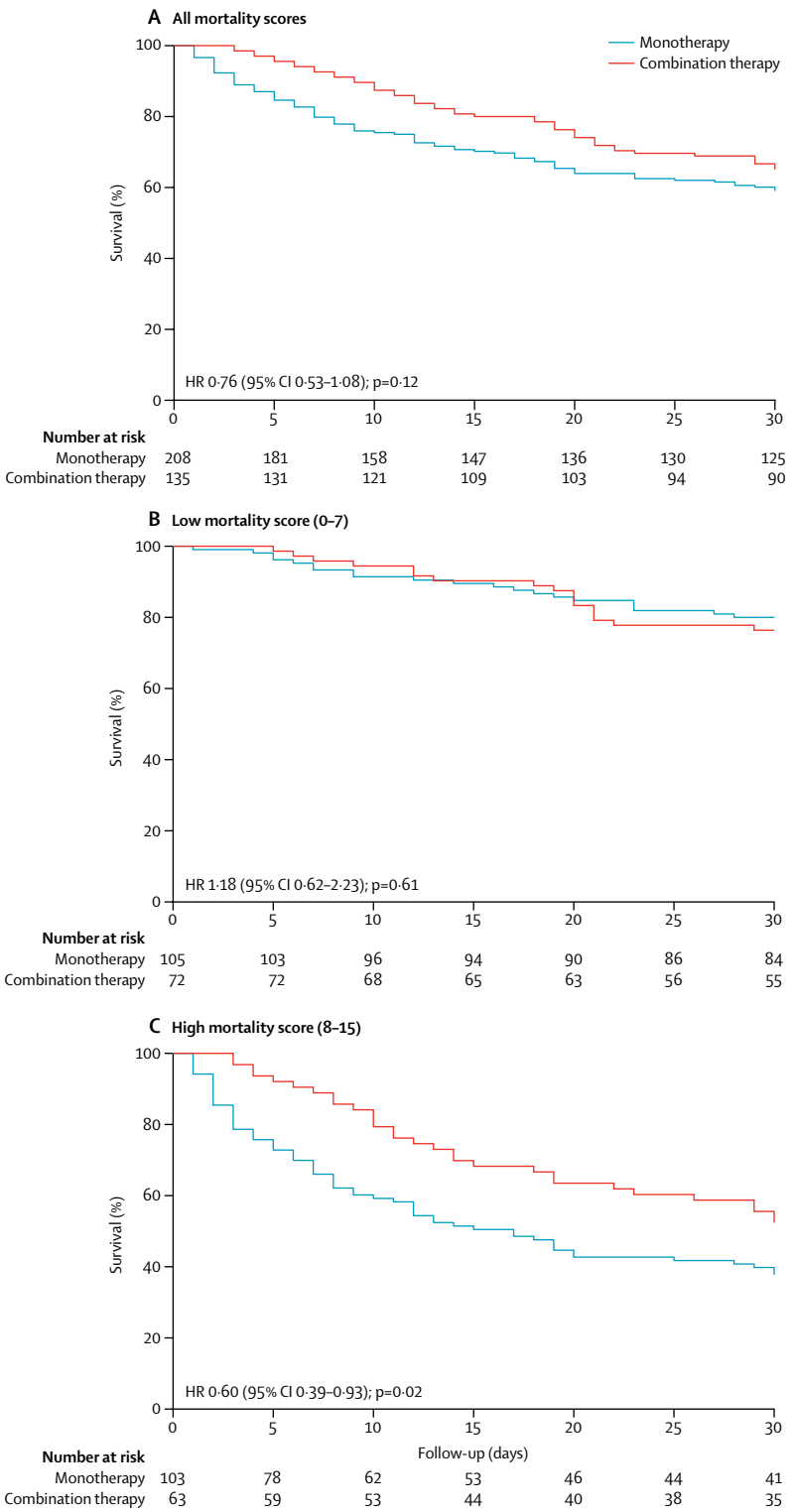

Figure 2: **Monotherapy versus combination therapy**
HR=hazard ratio.

monotherapy dying compared with 17 (24%) of 72 receiving combination therapy, and in the high-mortality-score stratum was shown by 64 (62%) of 103 dying with monotherapy and 30 (48%) of 63 dying with combination therapy (figure 2, appendix p 5). For multivariate analyses, in the low-mortality-score stratum, the proportional hazards assumptions were not fulfilled (figure 2), so we used logistic regression. Combination therapy was not significantly associated with 30 day mortality in the low-mortality-score stratum (adjusted odds ratio [OR] 1·21 [95% CI 0·56–2·56]; p=0·62; table 4). In the high-mortality-score stratum, combination therapy showed a protective effect (adjusted HR 0·56 [95% CI 0·34–0·91]; p=0·02). The distribution of patients according to the score variables and mortality is shown in the appendix (p 6). According to the Breslow test, however, neither in the high-mortality-score stratum (p=0·07) nor in the low-mortality-score stratum (p=0·14) could we rule out the hypothesis of homogeneity of results between centres; we used the variable centre (dichotomised) to control for unmeasured site-associated variables in the analysis.

In sensitivity analyses, results were similar when we considered isolates classified as intermediate non-active (the proportion of intermediate isolates is shown in the appendix [p 7]), although the OR was rendered insignificant in the high-mortality-score stratum: in the low-mortality-score stratum, the adjusted OR was 1·22 (95% CI 0·56–2·62; p=0·62), whereas in the high-mortality-score stratum, the adjusted HR was 0·61 (0·37–1·00; p=0·05). When we reclassified the variable therapy as only one active drug, one active drug plus at least one inactive drug, and more than one active drug to check for potential synergistic effects of inactive drugs, only more than one active drug showed a protective effect on mortality in the high-mortality-score stratum (HR 0·54 [95% CI 0·32–0·89]; p=0·01; appendix p 8). We estimated the specific effect of combination regimens including carbapenems in the low-mortality-score stratum; the adjusted OR was 1·21 (0·31–3·90; p=0·75).

We could match 202 (59%) patients (101 pairs) receiving monotherapy or combination therapy using the propensity score in the mortality score strata (appendix p 9). Mortality for matched patients in the low-mortality-score stratum was nine (16%) of 55 patients receiving monotherapy versus 16 (29%) of 55 receiving combination therapy (OR 2·00 [95% CI 0·81–4·96]; p=0·13) and in the high-mortality-score stratum was 32 (70%) of 46 versus 23 (50%) of 46 (0·47 [0·20–1·09]; p=0·07).

The antimicrobials administered and their associated mortality are shown in table 5. The most frequent drugs used in monotherapy were colistin, meropenem or imipenem (carbapenems), and tigecycline. In combination regimens, tigecycline, colistin, and aminoglycosides were the most common. The proportion of patients receiving high doses of specific antimicrobials is shown in the appendix (p 9). We compared different combinations of antimicrobials with colistin monotherapy in the

high-mortality-score stratum. The propensity and mortality score-adjusted HR obtained for tigecycline included in a combination compared with colistin monotherapy was 0·45 (95% CI 0·23–0·86; p=0·02), for colistin was 0·47 (0·24–0·92; p=0·03), for aminoglycosides was 0·42 (0·20–0·88; p=0·02), and for carbapenems was 0·56 (0·26–1·23; p=0·15; appendix p 12).

Discussion

Results from this study showed that delayed active treatment after 5 days is associated with increased mortality in patients with BSIs due to CPE and that combination therapy is associated with lower mortality than is monotherapy only in patients with a high mortality score. BSIs due to CPE frequently affect patients who are severely ill; therefore, the effect of the underlying conditions in mortality is important[12,19] and might mask the influence of antibiotic therapy. Investigators of previous studies[5,6,10,20] except for those of one study[4] could not find that active initial therapy is associated with mortality. In this study, the negative effect of mortality per day of delay was small. This finding, together with the fact that administration of active therapy in the first 5 days (but not in the first 2) was associated with lower mortality than was therapy administered after the first 5 days or inactive therapy, suggests that the deleterious effect occurs after the second day. This finding reinforces the importance of timely reporting of the susceptibility results and provision of specialised advice.

Whether or not combination therapy is associated with improved survival is controversial. Although investigators of most previous studies[4–6,21] found a protective effect, some others[10,20] did not. In some,[4,6] inclusion of a carbapenem in the combination was associated with improved survival if the meropenem MIC was 8 mg/L or lower (for which a high probability of attaining of the pharmacodynamic target exists if meropenem is used at high doses).[18] However, carbapenems might not be free of adverse effects, including an ecological negative effect.[9,11] In a study by Daikos and colleagues,[6] an (unadjusted) association between combination therapy and mortality was only apparent in patients with septic shock or severe chronic conditions. Investigators of another study found an unadjusted benefit of combination therapy only in patients with lung infections and high Acute Physiology and Chronic Health Evaluation III scores.[17]

Results of this study suggest that combination therapy is only associated with improved survival among patients with a high probability of death as measured by the INCREMENT-CPE mortality score.[12] Although a benefit of combination therapy in the low-mortality-score stratum cannot be totally discarded, the sample size in this stratum (177 patients) is large enough to suggest an absence of a clinically relevant effect. This finding is important for antibiotic stewardship programmes to reduce consumption of some drugs and, potentially, adverse events.

	Crude analysis		Adjusted analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per year)	1·01 (1·00–1·02)	0·09	..	..
Male sex	0·96 (0·68–1·36)	0·81	..	..
Klebsiella pneumoniae	1·33 (0·79–2·24)	0·29	..	..
OXA-type carbapenemase	1·47 (0·97- 2·23)	0·07	..	..
Nosocomial acquisition	1·53 (0·84- 2·77)	0·16	..	..
ICU admission	1·26 (0·88–1·80)	0·20	..	..
Mechanical ventilation	1·95 (1·38–2·74)	0·0001	..	..
Mental status: not alert	2·73 (1·91–3·90)	<0·0001	..	..
Chronic kidney disease	1·55 (1·07–2·25)	0·02	..	..
Chronic liver disease	1·38 (0·85–2·24)	0·19	..	..
Leukaemia or metastatic cancer	1·53 (1·00–2·35)	0·05	..	..
INCREMENT-CPE mortality score (per unit)	1·20 (1·15–1·25)	<0·0001	1·23 (1·16–1·31)	<0·0001
Combination therapy	0·76 (0·53–1·08)	0·13	1·63 (0·67–3·91)	0·28
Delay to first active treatment (per day)	1·07 (0·99–1·14)	0·08	..	..
High-mortality-risk centre	2·28 (1·61–3·22)	<0·0001	2·00 (1·40–2·85)	0·0001
Study period 2004–11 (reference 2012–13)	1·44 (0·97–2·13)	0·07	1·46 (0·98–2·18)	0·06
Propensity score†	1·86 (1·04–3·34)	0·04	1·20 (0·61–2·35)	0·60
Interaction of INCREMENT-CPE mortality score (per unit) with combination therapy	..	..	0·92 (0·84–0·99)	0·04

HR=hazard ratio. OXA=oxacillinase. ICU=intensive care unit. *We included variables with a univariate p value of 0·2 or smaller for mortality. †The variables used to calculate the propensity score for combination therapy were centre, age, sex, acquisition, hospital service, Pitt bacteraemia score, Charlson comorbidity index score, cancer, chronic renal insufficiency, liver disease, mechanical ventilation, source of bloodstream infection, severe sepsis or septic shock, and appropriate early therapy. The model showed a p value of 0·98 for the Hosmer-Lemeshow goodness-of-fit test and an area under the receiver operating characteristic curve of 0·85.

Table 3: **Univariate and multivariate Cox regression analyses of variables associated with mortality in patients receiving active therapy, including the INCREMENT-CPE mortality score and its interaction with combination therapy**

	OR or HR (95% CI)	p value
Low mortality score (0–7)*†		
Combination therapy	1·21 (0·56–2·56)	0·62
High-mortality-risk centre	2·95 (1·37–6·32)	0·005
Study period 2004–11 (reference 2012–13)	1·62 (0·73–3·85)	0·25
Propensity score	0·86 (0·20–3·38)	0·84
High mortality score (8–15)‡		
Combination therapy	0·56 (0·34–0·91)	0·02
High-mortality-risk centre	1·94 (1·27–2·96)	0·002
Study period 2004–11 (reference 2012–13)	1·61 (1·00–2·61)	0·05
Propensity score	1·98 (0·85–4·62)	0·11

OR=odds ratio. HR=hazard ratio. *Proportional hazards assumptions not fulfilled for low mortality score, so we used logistic regression. †ORs presented. ‡HRs presented.

Table 4: **Multivariate analysis of mortality-associated variables according to INCREMENT-CPE mortality score strata**

	All patients (n=343)	Low-mortality score (0–7; n=177)	High-mortality score (8–15; n=166)
Monotherapy			
Any	85/208 (41%)	21/105 (20%)	64/103 (62%)
Colistin	40/74 (54%)	12/32 (38%)	28/42 (67%)
Meropenem or imipenem	16/43 (37%)	5/25 (20%)	11/18 (61%)
Other active β-lactams	3/19 (16%)	2/17 (12%)	1/2 (50%)
Cefepime	1/13 (8%)	0/11	1/2 (50%)
Aztreonam	1/4 (25%)	1/4 (25%)	0/0
Ceftazadime	1/2	1/2	0/0
Tigecycline	14/37 (38%)	0/15	14/22 (64%)
Aminoglycosides	11/27 (41%)	1/9 (11%)	10/18 (56%)
Others	1/8 (13%)	1/7 (14%)	0/1
Cloramphenicol	1/1 (100%)	1/1 (100%)	0/0
Ciprofloxacin	0/4	0/3	0/1
Fosfomycin	0/1	0/1	0/0
Levofloxacin	0/2	0/2	0/0
Combination therapy*†			
Any	47/135 (35%)	17/72 (24%)	30/63 (48%)
Tigecycline included	29/82 (35%)	10/45 (22%)	19/37 (51%)
Colistin included	28/74 (38%)	11/36 (31%)	17/38 (45%)
Aminoglycosides included	19/56 (34%)	4/27 (15%)	15/29 (52%)
Carbapenem included	14/37 (38%)	4/19 (21%)	10/18 (56%)
Fosfomycin included	3/9 (33%)	1/4 (25%)	2/5 (40%)
Others	6/17 (35%)	3/11 (27%)	3/6 (50%)

Data are n/N (%). *The most common combination therapies used were colistin plus tigecycline (10/32 [31%]), aminoglycoside plus tigecycline (7/20 [35%]), and colistin plus carbapenem (7/16 [44%]). †Drugs listed are not mutually exclusive with each other.

Table 5: **Mortality of patients receiving appropriate therapy according to antimicrobials administered and INCREMENT-CPE mortality score strata**

Regarding which combinations should be used, those including colistin, tigecycline, and aminoglycosides were associated with lower mortality than was monotherapy with colistin. We could not show that inclusion of a carbapenem provides a beneficial effect, but this finding should be interpreted with caution because of the low numbers of patients in this subgroup.

This study has limitations, including its observational nature, so that an effect of unmeasured variables and residual confounding cannot be discarded. Also, despite being, to our knowledge, the biggest cohort to date, the statistical power in some strata was low. We could not provide estimations of the efficacy of specific combinations, an intrinsic problem in CPE since the scarce available options might be heterogeneous among isolates. We did not collect information about timing of source control. We included patients until December, 2013; therefore, subsequent changes in management should be considered. Finally, local laboratories might have used different procedures despite all of them being experienced in detection of carbapenemases. Some strengths of this analysis are inclusion of patients from different countries, the large number of patients, inclusion of different Enterobacteriaceae and carbapenemases, and use of strict definitions and advanced methods in controlling for confounders.

At present, a prospective multinational cohort study is being done trying to identify the best alternative therapy for different types of CPE infections (the EU Resource Efficiency Coordination Action project [NCT02709408]). A randomised controlled trial comparing colistin with colistin-meropenem in treatment of severe infections caused by carbapenem-resistant Gram-negative infections is recruiting.[22] Pending the results of these studies, our data suggest that active antimicrobials should be administered within 3–5 days of infection to patients with BSIs due to CPE and that combination therapy should be used only in patients with a high pretreatment probability of death according to the INCREMENT-CPE mortality score.

Contributors

AP and JR-B conceived the study. BG-G, ES, RAB, YC, DLP, AP, and JR-B designed the study. RAB, AP, JR-B, and JRP-P obtained funding. RAB, DLP, YC, AP, and JR-B supervised the study. ES, MdC, P-RH, PV, JRP-P, MV, MT, GD, RC, YD, FFT, IK, EP-N, MJS, ÖKA, MS, ER, SP, MA, FP, JB, AO, MA, WL, and BA acquired the data. BG-G, ES, MdC, RAB, YC, DLP, AP, and JR-B analysed and interpreted the data. BG-G and JR-B did the statistical analysis. BG-G, ES, AP, and JR-B drafted the manuscript. MdC, P-RH, PV, JRP-P, MV, MT, GD, RC, YD, FFT, IK, EP-N, MJS, ÖKA, MS, ER, SP, MA, FP, JB, AO, MA, WL, and BA critically revised the manuscript for important intellectual content. MS, ER, SP, MA, FP, JB, AP, MA, WL, and BA provided administrative support.

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Declaration of interests
JR-B has been a scientific adviser for AstraZeneca, Merck, and InfectoPharm and a speaker at accredited educational courses funded by unrestricted grants from Merck. RAB received grants for research from the National Institutes of Health, Veteran Affairs, Allergan, Merck, and Entasis. DLP has received honoraria for advisory board participation from Merck, AstraZeneca, Cubist, Pfizer, and Novartis. YC received grants, honoraria, travel support, consulting fees, and other forms of financial support from Achaogen, Allecra Therapeutics, AstraZeneca, Basilea Pharmaceutica, Biomerieux, Cepheid, DaVolterra, Durata Therapeutics, Intercell, Merck, Pharmaceutical Product Development, Proteologics, Rempex Pharmaceuticals, Rib-X Pharmaceuticals, Syntezza Bioscience, and Takeda Pharmaceutical. AP has been a speaker for Merck and B Braun, has been scientific adviser for Merck, and has received unrestricted research grants from B Braun and AstraZeneca. RC received research grants from AstraZeneca, Merck Sharp & Dohme (MSD), and Bayer. FFT reports personal fees from AstraZeneca, Pfizer, Teva, and Bayer and grants and personal fees from MSD. FP reports grants from Pfizer. GD reports grants and personal fees from Pfizer, personal fees from Achaogen, MSD, and Rempex, and grants from Gilead. YD reports personal fees from Meiji, Shionogi, Tetraphase, Achaogen, Curestis, Roche, and Allergan and grants and personal fees from The Medicines Company and Merck. All other authors declare no competing interests.

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