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Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

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Objectives: Infections caused by *Klebsiella pneumoniae* (Kp) carbapenemase (KPC)-producing strains of Kp have become a significant threat in recent years. To assess their outcomes and identify risk factors for 14 day mortality, we conducted a 4 year (2010–13) retrospective cohort study in five large Italian teaching hospitals.

Methods: The cohort included 661 adults with bloodstream infections (BSIs; $n=447$) or non-bacteraemic infections (lower respiratory tract, intra-abdominal structure, urinary tract or other sites) caused by a KPC-Kp isolate. All had received ≥48 h of therapy (empirical and/or non-empirical) with at least one drug to which the isolate was susceptible.

Results: Most deaths occurred within 2 weeks of infection onset (14 day mortality: 225/661, 34.1%). Logistic regression analysis identified BSI (OR, 2.09; 95% CI, 1.34–3.29), presentation with septic shock (OR, 2.45; 95% CI, 1.47–4.08), inadequate empirical antimicrobial therapy (OR, 1.48; 95% CI, 1.01–2.18), chronic renal failure (OR, 2.27; 95% CI, 1.44–3.58), high APACHE III score (OR, 1.05; 95% CI, 1.04–1.07) and colistin-resistant isolates (OR, 2.18; 95% CI, 1.37–3.46) as independent predictors of 14 day mortality. Combination therapy with at least two drugs displaying *in vitro* activity against the isolate was associated with lower mortality (OR, 0.52; 95% CI, 0.35–0.77), in particular in patients with BSIs, lung infections or high APACHE III scores and/or septic shock at infection onset. Combinations that included meropenem were associated with significantly higher survival rates when the KPC-Kp isolate had a meropenem MIC of ≤8 mg/L.

Conclusions: KPC-Kp infections are associated with high mortality. Treatment with two or more drugs displaying activity against the isolate improves survival, mainly in patients who are critically ill.

Keywords: carbapenemases, combination therapy, inadequate empirical therapy, colistin resistance, meropenem MICs, carbapenem resistance, treatment

Introduction

The production of *Klebsiella pneumoniae* (Kp) carbapenemases (KPCs) by Kp isolates has become a significant problem in recent years, both from epidemiological and clinical points of view. Substantial percentages of hospitalized patients are colonized by these microorganisms, which have caused several outbreaks of severe nosocomial infections, including bacteraemia and ventilator-associated pneumonia, since 2010. In some countries, KPC-producing Kp isolates (KPC-Kp) are now considered endemic.[1–12]

Reported rates of mortality associated with KPC-Kp infections vary widely from 22% to 72%.[5,8,9,13–15] The variability depends largely on differences involving the populations analysed in the various studies, including those related to age and underlying

disease/comorbidity profiles. It also could reflect the potential inclusion of patients with KPC-Kp colonization rather than true infections, which can obviously distort assessment of treatment success and case outcomes. For clinicians, selecting an effective treatment regimen for KPC-Kp infections is a major challenge. Nonetheless, published data suggest that survival benefits might be associated with regimens that include two or more drugs that display activity against the isolate and paradoxically the most pronounced improvement seems to be produced by combination regimens that include a carbapenem.[4,5,14,15] A randomized trial with more in-depth analysis of clinical characteristics and outcomes is needed to define the best antimicrobial regimen for management of these infections. In the meantime, we conducted a large multicentre retrospective study aimed at pinpointing risk factors for KPC-Kp infection-related mortality in subgroups of patients with different clinical and epidemiological profiles, with emphasis on factors related to antimicrobial drug therapy.

Methods

Study design, setting and patients

A retrospective cohort study was conducted between 1 January 2010 and 31 December 2013 in five large academic healthcare facilities in Italy. The cohort consisted of patients aged ≥18 years, who had been consecutively admitted to the facility during the study period and had developed a culture-confirmed infection caused by a KPC-Kp strain. A proportion of the patients included in this study (451/661, 68%) have been reported in previous articles from our group.[5,11,12]

Patients were classified as having KPC-Kp bloodstream infections (BSIs) if they had blood culture positivity for a KPC-Kp strain and clinical signs of systemic inflammatory response syndrome.[16] BSIs were further classified as low risk or high risk depending on the source of the bacteraemia (urinary tract versus all other identified and unidentified sources, respectively).[17] The criteria for classification as a *non-bacteraemic KPC-Kp infection* were: (i) documented recovery of a KPC-Kp isolate from cultures of intra-abdominal wounds, urine, respiratory tract specimens (sputum or bronchoalveolar lavage fluid) or other sites; (ii) no blood culture positivity for KPC-Kp for the duration of hospitalization; (iii) clinical signs of infection;[18] and (iv) post-antibiogram treatment with an antimicrobial regimen that was consistent with the isolate's *in vitro* susceptibility profile. Two infectious diseases specialists independently reviewed data available at the time of each patient's discharge or death to exclude cases representing KPC-Kp colonization rather than infection. The Research Ethics Committee of the coordinating centre (Catholic University of the Sacred Heart) approved the study and informed consent was waived because of the retrospective observational nature of the study.

Microbiology, KPC gene identification and antimicrobial susceptibility testing

The Vitek 2 system (bioMérieux, Marcy l'Étoile, France) was used in all participating centres for isolate identification and antimicrobial susceptibility testing. Vitek MICs were classified according to EUCAST breakpoints.[19] The presence of carbapenemase genes of bla_{KPC}, bla_{NDM}, bla_{VIM} and bla_{OXA-48} types was investigated by PCR and DNA sequencing analysis using the protocol described by Endimiani *et al*.[20]

Definitions

The following terms were defined prior to data analysis. *Hospital admission* was defined as the date the patient was admitted to the study facility. *Infection onset* was defined as the collection date of the *index culture* (i.e. the first culture that yielded the study isolate). *Septic shock* was defined as sepsis associated with organ dysfunction and persistent hypotension despite volume replacement.[21] Infections were considered *hospital acquired*, *healthcare associated* or *community acquired* as defined by the ECDC.[22]

An empirical antimicrobial treatment regimen was defined as *inadequate* unless it included at least one drug displaying *in vitro* activity against the KPC-Kp isolate. Regimens were classified as *monotherapy* or *combination therapy* depending on the number of active drugs they included.

Variables explored as possible predictors of mortality

The primary outcome measured was death within 14 days of infection onset. In-hospital mortality was assessed as a secondary outcome. Survivor and non-survivor subgroups were compared in order to identify predictors of 14 day mortality. The variables considered are listed in Table 1. Comorbidities were also collectively expressed on the basis of the Charlson index[23] and severity of illness was expressed by the APACHE III score.[24]

Statistical analysis

The results are expressed as the mean ± SD or median (IQR) (continuous variables) or as percentages of the group from which they were derived (categorical variables). Student's *t*-test and the Mann–Whitney *U*-test were used to compare normally and non-normally distributed continuous variables, respectively. Categorical variables were evaluated with the χ^2 or two-tailed Fisher's exact test. ORs and 95% CIs were calculated for all associations that emerged. Two-tailed tests were used to determine statistical significance; a *P* value of <0.05 was considered significant. Multivariate logistic regression analysis was used to identify independent risk factors for 14 day mortality. Variables emerging from univariate analysis with *P* values of <0.1 were included in the multivariate model in a backward stepwise manner. The discriminating ability of the model was assessed by estimating the area under the receiver operating characteristic (ROC) curve. Collinearity was assessed by generating a correlation coefficient matrix. A propensity score for receiving combination therapy was added to the model, in order to provide a means of balancing baseline covariates predictive of treatment, mitigating the unequal chance of receiving monotherapy versus combination therapy and to control for confounding. The propensity score was calculated using a bivariate logistic regression model in which the outcome variable was use of combination therapy. All statistical analyses were performed with the Intercooled Stata program (version 11).

Results

Figure 1 reports the flow chart of the patient inclusion process. The characteristics of the 661 patients who met the criteria for inclusion in our study are shown in Table 1. Approximately two-thirds of the patients had BSIs (447/661, 67.6%); in 159/447 (35.6%) of BSI cases, the primary source of the BSI was unknown. These 159 cases plus those with documented origins outside the urinary tract (respiratory tract in 51 cases, central venous catheter infection in 64 cases, surgical wound in 36 cases, pancreatico-biliary tract in 19 cases and other sources in 15 cases) were all classified as high-risk BSIs (344 cases). The remaining 103 BSIs originated in the urinary tract and were classified as low-risk BSIs. The non-bacteraemic infections included 85 involving the lower respiratory tract, 82 urinary tract infections, 42 abdominal wound infections and 5 infections at other sites.

Characteristics of KPC-producing isolates

Four hundred and ninety-seven out of 661 (75.2%) isolates harboured the bla_{KPC-3} gene; the other 164/661 (24.8%) carried the bla_{KPC-2} gene. Approximately half produced ESBLs (CTX-M in most cases). All 661 isolates were resistant to penicillins, cephalosporins,

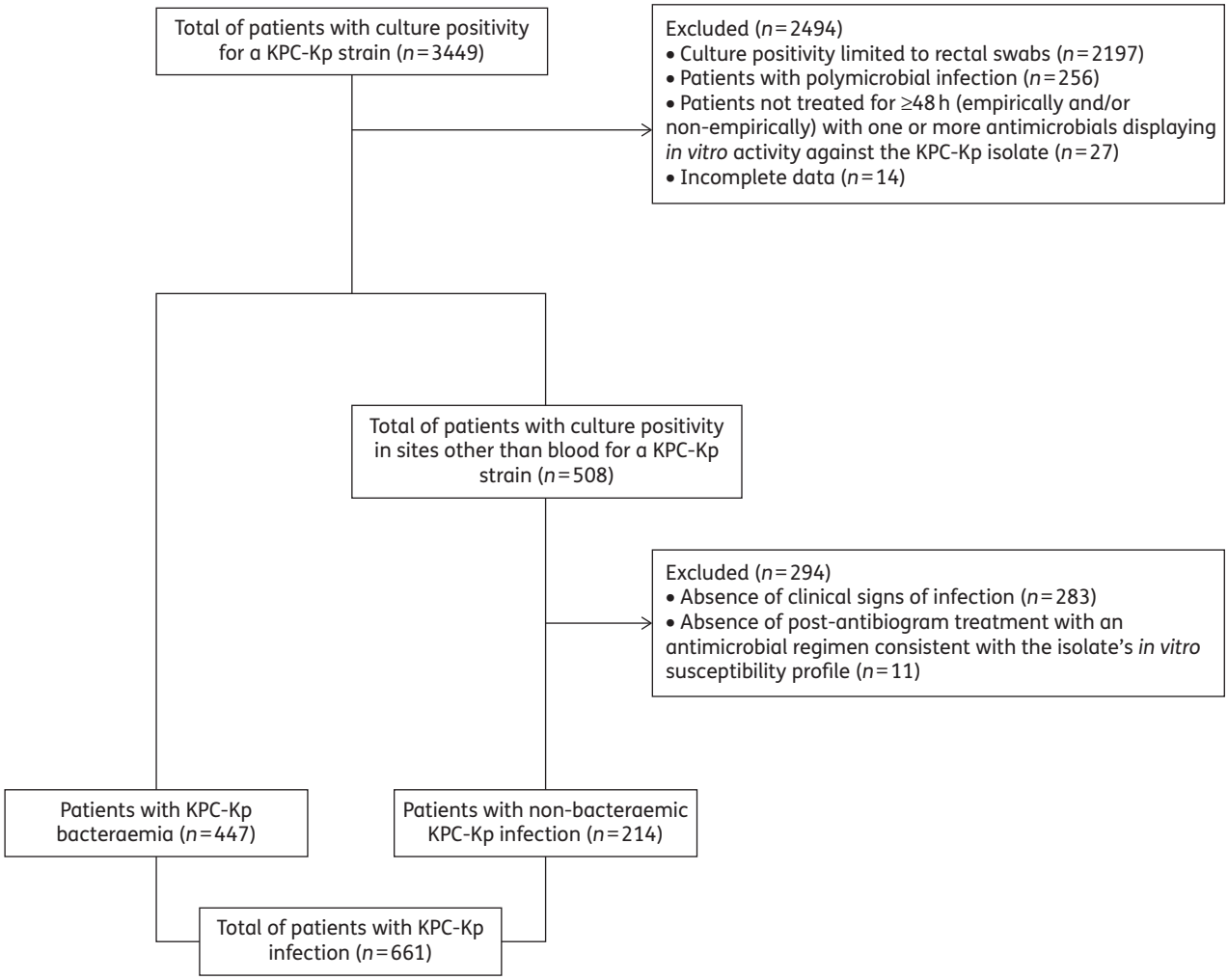

Figure 1. Flow chart of the patient inclusion process.

ertapenem, ciprofloxacin, amikacin, co-trimoxazole and chloramphenicol. Meropenem MICs were often ≥16 mg/L (418/661, 63.2%); 233/661 (35.2%) isolates were intermediate to meropenem (MIC, 4–8 mg/L) and only 10/661 (1.5%) isolates were susceptible (MIC, ≤2 mg/L). The vast majority of isolates were susceptible to gentamicin (543/661, 82.1%), colistin (529/661, 80%) or tigecycline (509/661, 77%) and in 84/661 cases (12.7%) susceptibility was confined to only one of these drugs [gentamicin in 19/661 strains (2.9%), colistin in 49/661 (7.4%) and tigecycline in 16/661 (2.4%)]. During the study period, rates of non-susceptibility to each of these drugs increased alarmingly among study isolates: from 6% (gentamicin), 11% (colistin) and 9% (tigecycline) in 2010 to 21%, 27% and 25%, respectively, in 2013.

Antimicrobial treatment

All patients were empirically treated with currently standard doses of drugs with known Gram-negative activity (alone or with other antibiotics). Over half (365/661, 55.2%) proved to be inadequate in light of *in vitro* susceptibility data. Single-drug regimens (colistin in 121 patients, tigecycline in 116 and gentamicin in the remaining 70) were prescribed for 307/661 (46.4%) patients. As shown in Table 1, most patients (354/661, 53.5%) received two or more drugs with *in vitro* activity against the KPC-Kp isolate. Most combinations included at least one carbapenem (meropenem in all cases; meropenem and ertapenem in 8) and in 12 cases the regimen also included rifampicin. In Table 2, characteristics of patients according to treatment with mono- or combination therapy are reported. Colistin, gentamicin, tigecycline and meropenem in definitive regimens were administered as previously reported.[5]

Outcomes of infections

Most deaths occurred within 14 days after KPC-Kp infection onset (225/661 patients, 34.1%) while the in-hospital mortality rate was 41.1% (272/661 patients). As shown in Table 3, a significantly higher 14 day mortality rate was observed in the BSI subgroup [173/447 (38.7%) versus 52/214 (24.3%) in the group with non-bacteraemic infections; $P<0.001$]. The 225 patients who died within this interval included 118/307 (38.4%) of those placed on single-drug post-antibiogram regimens and 107/354 (30.2%)

Table 1. Characteristics of patients with BSIs and non-bacteraemic infections caused by KPC-Kp

Variable	All infections ($n=661$)	BSIs ($n=447$)	Non-bacteraemic infections ($n=214$)	*P* value
Patient variables				
male	417 (63.1)	281 (62.9)	136 (63.5)	0.86
age (years), median (IQR)	68 (55–76)	65 (52–75)	72 (60–80)	<0.001
comorbidities				
COPD	106 (16.0)	56 (12.5)	50 (23.4)	<0.001
cardiovascular disease	275 (41.6)	159 (35.6)	116 (54.2)	<0.001
cerebrovascular disease or dementia	81 (12.2)	47 (10.5)	34 (15.9)	0.049
solid tumour	147 (22.2)	83 (18.6)	64 (29.9)	0.001
haematological malignancy	89 (13.5)	75 (16.8)	14 (6.5)	<0.001
liver disease	72 (10.9)	51 (11.4)	21 (9.8)	0.54
HIV infection/immunodeficiency	20 (3.0)	16 (3.6)	4 (1.9)	0.23
solid organ transplantation	52 (7.9)	41 (9.2)	11 (5.1)	0.07
chronic renal failure	122 (18.4)	73 (16.3)	49 (22.9)	0.04
diabetes	168 (25.4)	115 (25.7)	53 (24.8)	0.79
neutropenia	70 (10.6)	61 (13.6)	9 (4.2)	<0.001
Charlson comorbidity index ≥3	339 (51.3)	241 (53.9)	98 (45.8)	0.05
Characteristics of index hospitalization				
admission from another healthcare facility	39 (5.9)	20 (5.2)	19 (8.8)	0.06
time at risk (days), median (IQR)	21 (10–36)	23 (12–38)	19 (7–35)	0.003
ward submitting index culture				
medical (all)	272 (41.1)	183 (40.9)	89 (41.6)	0.87
haematology	59 (8.9)	50 (11.2)	9 (4.2)	0.003
surgical (all)	159 (24.0)	98 (21.9)	61 (28.5)	0.06
transplants	18 (2.7)	12 (2.7)	6 (2.8)	0.93
ICU	230 (34.8)	166 (37.1)	64 (29.9)	0.07
Pre-infection healthcare interventions				
hospitalization[a]	419 (63.4)	279 (62.4)	140 (65.4)	0.45
surgery[b]	292 (44.2)	189 (42.3)	103 (48.1)	0.16
dialysis[b]	82 (12.4)	56 (12.5)	26 (12.1)	0.89
endoscopy[c]	107 (16.2)	64 (14.3)	43 (20.1)	0.06
mechanical ventilation[c]	185 (28.0)	133 (29.7)	52 (24.3)	0.14
indwelling invasive devices				
central venous catheter	389 (58.8)	268 (60.0)	121 (56.5)	0.40
bladder catheter	385 (58.2)	235 (52.6)	150 (70.1)	<0.001
nasogastric tube[c]	159 (24.0)	83 (18.6)	76 (35.5)	<0.001
surgical drain[c]	148 (22.4)	82 (18.3)	66 (30.8)	<0.001
treatments administered[b]				
corticosteroids	161 (24.3)	104 (23.3)	57 (26.6)	0.34
chemotherapy or radiotherapy	89 (13.5)	73 (16.3)	16 (7.5)	0.002
antibiotic therapy	566 (85.6)	387 (86.6)	179 (83.6)	0.31
Infection variables				
epidemiology				
healthcare associated	62 (9.4)	40 (8.9)	22 (10.3)	0.58
hospital acquired	585 (88.5)	399 (89.3)	186 (86.9)	0.38
clinical presentation				
presentation with septic shock	100 (15.1)	83 (18.6)	17 (7.9)	<0.001
APACHE III score >15	481 (72.7)	352 (78.7)	129 (60.3)	<0.001
Treatment variables				
inadequate empirical antimicrobial treatment	365 (55.2)	279 (62.4)	86 (40.2)	<0.001
post-antibiogram antimicrobial therapy				
monotherapy	307 (46.4)	156 (34.9)	151 (70.6)	<0.001
combination therapy	354 (53.5)	291 (65.1)	63 (29.4)	<0.001
two-drug combination	134 (20.3)	93 (20.8)	41 (19.2)	0.62

Continued

Table 1. *Continued*

Variable	All infections ($n=661$)	BSIs ($n=447$)	Non-bacteraemic infections ($n=214$)	*P* value
three-drug combination	217 (32.8)	196 (43.8)	21 (9.8)	<0.001
combination including a carbapenem[d]	205 (31.0)	177 (39.6)	28 (13.1)	<0.001
double-carbapenem combination	8 (1.2)	8 (1.8)	0	0.049
combination without a carbapenem	149 (22.5)	114 (25.5)	35 (16.4)	0.008
combination plus rifampicin	12 (1.8)	6 (1.3)	6 (2.8)	0.19

Data are expressed as *n* (%), unless otherwise stated.
[a]During the 12 months preceding infection onset.
[b]During the 30 days preceding infection onset.
[c]During the 72 h preceding infection onset.
[d]All carbapenem-containing regimens included meropenem; double-carbapenem regimens included meropenem and ertapenem.

Table 2. Characteristics of patients with infections caused by KPC-Kp, according to type of antibiotic regimen

Characteristic	Number (%) of patients		*P* value
	monotherapy ($n=307$)	combination therapy ($n=354$)	
Patient variables			
male	189 (61.6)	228 (64.4)	0.45
age (years), median (IQR)	71 (60–78)	64 (51–75)	<0.001
comorbidities			
COPD	58 (18.9)	48 (13.6)	0.06
cardiovascular disease	140 (45.6)	135 (38.1)	0.05
cerebrovascular disease or dementia	46 (15.0)	35 (9.9)	0.04
solid tumour	78 (25.4)	69 (19.5)	0.07
haematological malignancy	25 (8.1)	64 (18.1)	<0.001
liver disease	35 (11.4)	37 (10.4)	0.70
HIV infection/immunodeficiency	5 (1.6)	15 (4.2)	0.05
solid organ transplantation	14 (4.6)	38 (10.7)	0.003
chronic renal failure	55 (17.9)	67 (18.9)	0.74
diabetes	78 (25.4)	90 (25.4)	0.99
neutropenia	18 (5.9)	52 (14.7)	<0.001
Charlson comorbidity index ≥3	158 (51.5)	181 (51.1)	0.93
Characteristics of index hospitalization			
ward submitting index culture			
medical (all)	140 (45.6)	132 (37.3)	0.03
surgical (all)	78 (25.4)	81 (22.9)	0.45
ICU	89 (29.0)	141 (39.8)	0.003
Infection variables			
BSI	156 (50.8)	291 (82.2)	<0.001
low-risk BSI	29 (9.4)	74 (20.9)	<0.001
high-risk BSI	127 (41.4)	217 (61.3)	<0.001
non-bacteraemic infections	151 (49.1)	63 (17.8)	<0.001
lower respiratory tract	53 (17.3)	32 (9.0)	0.02
intra-abdominal	25 (8.1)	17 (4.8)	0.08
urinary tract	71 (23.1)	11 (3.1)	<0.001
other	2 (0.6)	3 (0.8)	0.77
Clinical presentation			
shock	33 (10.7)	67 (18.9)	0.003
APACHE III score ≥15	214 (69.7)	267 (75.4)	0.10

Table 3. Impact of combination therapy versus monotherapy on 14 day mortality in patients with infections caused by KPC-Kp

	Numbers (%) of non-survivors				
	all	those who received combination therapy	those who received monotherapy	OR (95% CI)	*P*
Patient characteristics					
total	225/661 (34.0)	107/354 (30.2)	118/307 (38.4)	0.69 (0.49–0.97)	0.03
male	151/417 (36.2)	76/228 (33.3)	75/189 (39.7)	0.76 (0.50–1.16)	0.18
age >65 years	131/362 (36.2)	49/165 (29.7)	82/197 (41.6)	0.59 (0.37–0.94)	0.02
comorbidities					
COPD	57/106 (53.8)	24/48 (50.0)	33/58 (56.9)	0.76 (0.33–1.75)	0.48
cardiovascular disease	117/275 (42.5)	56/135 (41.5)	61/140 (43.6)	0.92 (0.55–1.52)	0.73
cerebrovascular disease or dementia	30/81 (37.0)	13/35 (37.1)	17/46 (37.0)	1.01 (0.36–2.75)	0.99
solid tumour	38/147 (25.8)	16/69 (23.2)	22/78 (28.2)	0.77 (0.34–1.72)	0.49
haematological malignancy	36/89 (40.4)	22/64 (34.4)	14/25 (56.0)	0.41 (0.14–1.17)	0.06
liver disease	30/72 (41.7)	13/37 (35.1)	17/35 (48.6)	0.57 (0.20–1.63)	0.25
solid organ transplantation	24/52 (46.1)	19/38 (50.0)	5/14 (35.7)	1.8 (0.43–8.10)	0.36
chronic renal failure	56/122 (45.9)	29/67 (43.3)	27/55 (49.1)	0.79 (0.36–1.72)	0.52
HIV infection or immunodeficiency	8/20 (40.0)	5/15 (33.3)	3/5 (60.0)	0.33 (0.02–4.17)	0.29
diabetes	70/168 (41.7)	39/90 (43.3)	31/78 (39.7)	1.16 (0.60–2.25)	0.64
neutropenia	26/70 (37.1)	17/52 (32.7)	9/18 (50.0)	0.48 (0.14–1.68)	0.19
Charlson comorbidity index ≥3	155/339 (45.7)	78/181 (43.1)	77/158 (48.7)	0.80 (0.51–1.25)	0.30
ward submitting index culture					
medical (all)	86/272 (31.6)	43/132 (32.6)	43/140 (30.7)	1.09 (0.63–1.88)	0.74
haematology	25/59 (42.4)	14/43 (32.6)	11/16 (68.7)	0.22 (0.05–0.87)	0.01
surgical (all)	50/159 (31.4)	22/81 (27.2)	28/78 (35.9)	0.66 (0.32–1.38)	0.23
transplants	7/18 (38.9)	3/10 (30.0)	4/8 (50.0)	0.43 (0.04–4.28)	0.39
ICU	89/230 (38.7)	42/141 (29.8)	47/89 (52.8)	0.38 (0.21–0.68)	<0.001
Infection characteristics					
BSI	173/447 (38.7)	93/291 (32.0)	80/156 (51.3)	0.45 (0.29–0.68)	<0.001
low-risk BSI	32/103 (31.1)	19/74 (25.7)	13/29 (44.8)	0.42 (0.16–1.16)	0.06
high-risk BSI	141/344 (41.0)	74/217 (34.1)	67/127 (52.8)	0.46 (0.29–0.74)	<0.001
non-bacteraemic infections (all)	52/214 (24.3)	14/63 (22.2)	38/151 (25.2)	0.85 (0.39–1.78)	0.65
lower respiratory tract	34/85 (40.0)	8/32 (25.0)	26/53 (49.1)	0.35 (0.11–0.99)	0.03
intra-abdominal	12/42 (28.6)	4/17 (23.5)	8/25 (32.0)	0.65 (0.12–3.16)	0.55
urinary tract	4/82 (4.9)	1/11 (9.1)	3/71 (4.2)	2.27 (0.04–31.22)	0.48
other	2/5 (40.0)	1/3 (33.3)	1/2 (50.0)	0.50 (0.004–78.17)	0.71
clinical presentation					
septic shock	57/100 (57.0)	30/67 (44.8)	27/33 (81.8)	0.18 (0.05–0.53)	<0.001
APACHE III score ≥15	208/481 (43.2)	98/267 (36.7)	110/214 (51.4)	0.55 (0.37–0.80)	0.001
KPC-Kp isolate characteristics					
colistin resistant	62/132 (47.0)	23/54 (42.6)	39/78 (50.0)	0.74 (0.35–1.58)	0.40
tigecycline resistant	51/152 (33.5)	29/91 (31.9)	22/61 (36.1)	0.83 (0.40–1.74)	0.59
gentamicin resistant	47/118 (39.8)	25/69 (36.2)	22/49 (44.9)	0.70 (0.31–1.57)	0.34
meropenem MIC ≤8 mg/L	79/243 (32.5)	43/154 (27.9)	36/89 (40.4)	0.57 (0.32–1.03)	0.04
meropenem MIC ≥16 mg/L	146/418 (34.9)	64/200 (32.0)	82/218 (37.6)	0.78 (0.51–1.19)	0.22
Inadequate empirical antibiotic therapy	144/365 (39.4)	71/212 (33.5)	73/153 (47.7)	0.55 (0.35–0.86)	0.006

of those who were on combination regimens ($P=0.03$). The protective effects of combination therapy were highly significant in the most critically ill patients of the cohort (those in the ICU, those with APACHE III scores ≥15 and those whose infections presented with septic shock) and those who had received inadequate empirical therapy. The association between 14 day survival and combination therapy was also strong among patients with BSIs, excluding those classified as low-risk infections. In patients with non-bacteraemic KPC-Kp infections, the positive impact of combination therapy on survival was significant only in the subgroup with lower respiratory tract infections.

Figures 2 and 3 show the 14 day mortality rates associated with more-specific antimicrobial drug regimen categories. For patients whose combination regimens included meropenem,

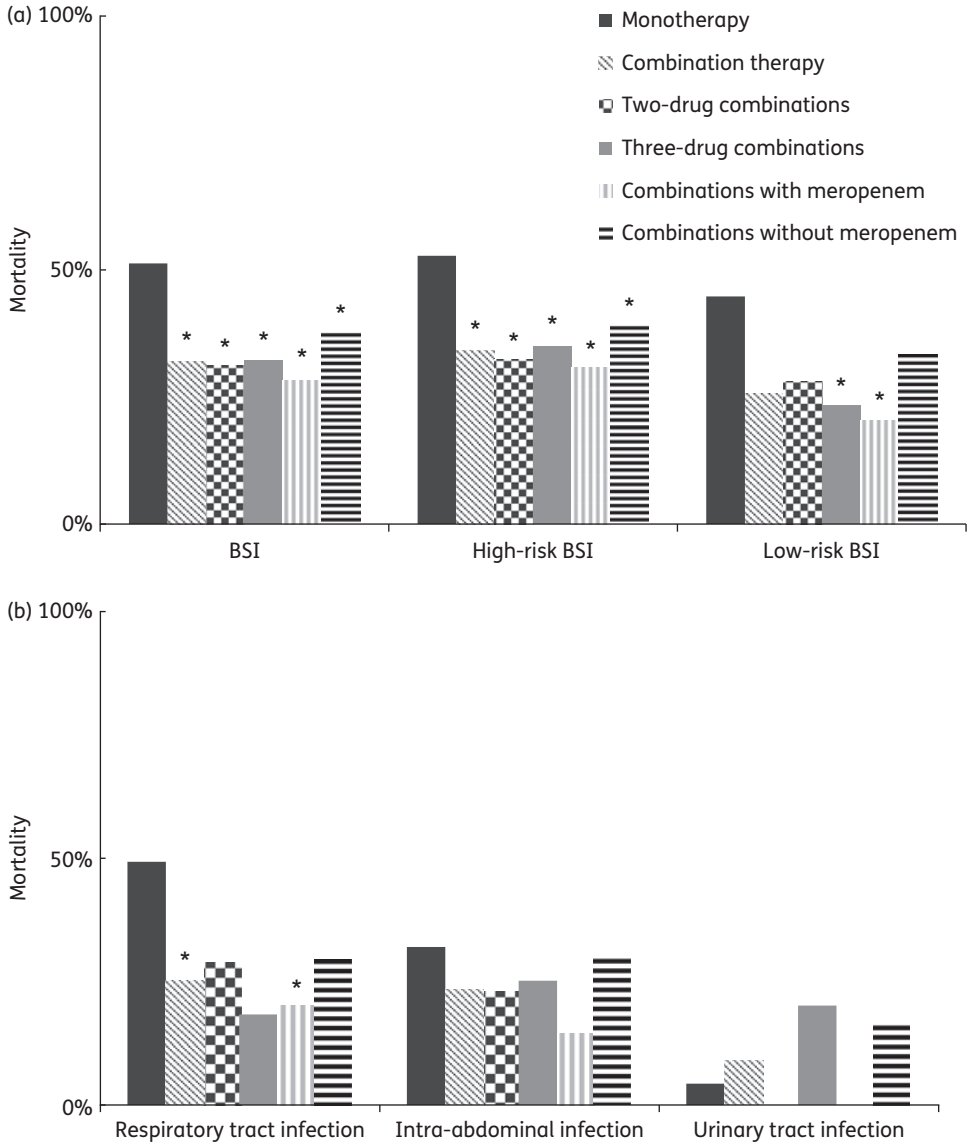

Figure 2. Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs (a) or non-bacteraemic infections (b). *Statistically significant differences ($P<0.05$) among different types of combination therapy and monotherapy.

14 day mortality rates were significantly lower than those associated with monotherapy only when the meropenem MICs for the KPC-Kp isolates were ≤8 mg/L.

Predictors of mortality

Univariate analysis revealed significant differences between the 14 day outcome-based subgroups (Table 4). As shown in Table 5, BSI, septic shock at infection onset, inadequate empirical antimicrobial therapy, chronic renal failure, high APACHE III score and colistin-resistant isolates emerged as independent predictors of 14 day mortality. Post-antibiogram combination therapy was associated with a lower risk of mortality. The model had an area under the ROC curve of 0.79, indicating good predictive ability, and absence of multicollinearity. After adjustment for the propensity score in the logistic regression model evaluating risk factors for mortality, treatment with combination therapy showed an OR of 0.64 (95% CI, 0.45–0.90; $P=0.01$).

Discussion

Our findings in the 661 patient cohort described above—the largest sample of patients with infections caused KPC-Kp analysed to date—confirm the high mortality associated with these infections in previous studies.[5,15,25,26] Deaths were significantly more common in patients with BSIs or lower respiratory tract infections than in those with infections at other sites. This finding probably reflects the severity of these infections and/or the relatively poor overall condition of the patients who contract them. This conclusion is supported by the fact that mortality in our cohort was independently predicted by septic shock and high APACHE III score at infection onset and it is also in line with previous reports.[5,15,26,27]

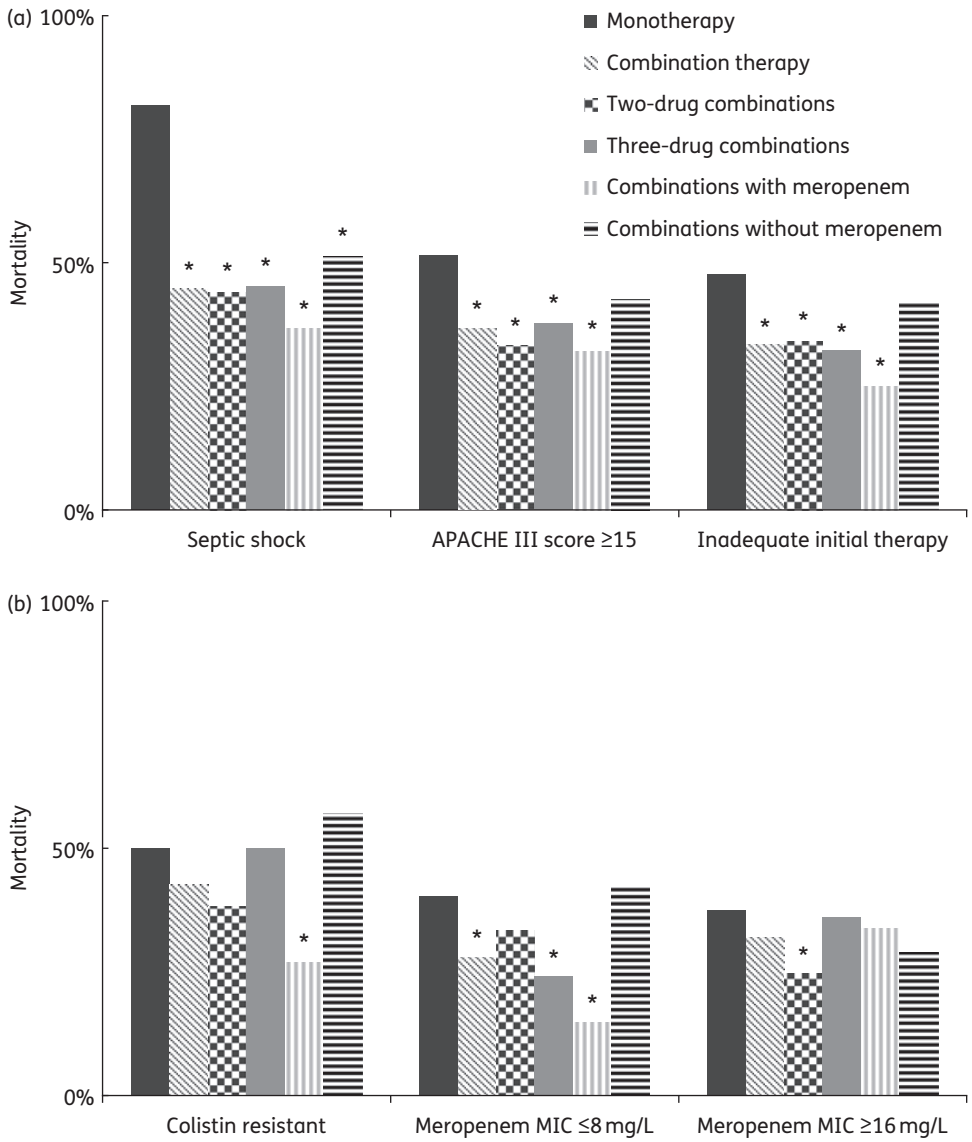

Figure 3. Mortality rates associated with different antimicrobial drug regimen categories in patients with different presenting features (a) or in patients with different KPC-Kp isolate characteristics (b). *Statistically significant differences ($P < 0.05$) among different types of combination therapy and monotherapy.

As for the non-empirical phase of treatment, our findings confirm previous reports on the mortality-limiting effects of regimens containing two or more drugs with activity against the isolate.[4,5,8,15,27–29] A more detailed analysis of this protective effect revealed that, in general, the benefits of multidrug therapy are more pronounced in patients who are critically ill. These findings are consistent with those that recently emerged from a smaller study that was limited to patients with KPC-Kp BSIs.[15] The impact on survival of combination drug therapy also varied *within* the subset of KPC-Kp BSIs: in most cases the mortality risk reduction was quite strong, but the benefits declined (and became statistically non-significant) when the urinary tract was the source of the BSI. This finding tends to support the view that combination therapy is particularly important for clinically severe infections caused by KPC-Kp.

In several studies, drug combinations that included carbapenems have performed better than other multidrug regimens, leading some groups to suggest that carbapenems are an important component in the treatment of KPC-Kp infections, especially BSIs.[5,14,15] This assertion is somewhat surprising since KPC enzymes hydrolyse carbapenems. Data from the present study indicate that the favourable impact on survival of active drug combinations that include at least one carbapenem is significant only when the meropenem MIC for the KPC-Kp isolate is ≤8 mg/L. Identical results have recently been reported by Daikos *et al*.,[15] who noted that their findings were also consistent with the human pharmacokinetic/pharmacodynamic data they had previously reviewed.[9] Possible explanations for this observation may be found in *in vitro*/*in vivo* animal model studies, which showed that carbapenems, alone or combined with different drugs commonly

Table 4. Univariate analysis of factors associated with 14 day mortality in patients with infections caused by KPC-Kp

Variable	Non-survivors, $n=225$ (34.1%)	Survivors, $n=436$ (65.9%)	*P* value	OR (95% CI)
Patient variables				
male	151 (67.1)	266 (61.0)	0.12	1.30 (0.92–1.86)
age (years), median (IQR)	69 (58–76)	66.5 (54.5–76)	0.08	—
comorbidities				
COPD	57 (25.3)	49 (11.2)	<0.001	2.68 (1.72–4.18)
cardiovascular disease	117 (52.0)	158 (36.2)	<0.001	1.91 (1.36–2.68)
cerebrovascular disease or dementia	30 (13.3)	51 (11.7)	0.54	1.16 (0.69–1.93)
solid tumour	38 (16.9)	109 (25.0)	0.02	0.61 (0.39–0.93)
haematological malignancy	36 (16.0)	53 (12.2)	0.17	1.38 (0.84–2.22)
liver disease	30 (13.3)	42 (9.6)	0.15	1.44 (0.84–2.44)
HIV infection/immunodeficiency	8 (3.6)	12 (2.7)	0.57	1.30 (0.45–3.52)
solid organ transplantation	24 (10.7)	28 (6.4)	0.05	1.74 (0.94–3.20)
chronic renal failure	56 (24.9)	66 (15.1)	0.002	1.86 (1.22–2.82)
diabetes	70 (31.1)	98 (22.5)	0.01	1.56 (1.07–2.27)
neutropenia	26 (11.6)	44 (10.1)	0.56	1.16 (0.67–2.00)
Charlson comorbidity index, median (IQR)	4 (2–6)	2 (2–4)	<0.001	—
Charlson comorbidity index ≥3	155 (68.8)	184 (42.2)	<0.001	2.94 (2.05–4.24)
Characteristics of index hospitalization				
admission from another healthcare facility	7 (3.1)	32 (7.3)	0.03	0.40 (0.15–0.96)
time at risk (days), median (IQR)	23 (12–36)	21 (9–36.5)	0.22	—
ward submitting index culture				
medical (all)	86 (38.2)	186 (42.7)	0.27	0.83 (0.59–1.17)
haematology	25 (11.1)	34 (7.8)	0.16	1.48 (0.82–2.63)
surgical (all)	50 (22.2)	109 (25.0)	0.43	0.86 (0.57–1.27)
transplants	7 (3.1)	11 (2.5)	0.66	1.24 (0.40–3.56)
ICU	89 (39.6)	141 (32.3)	0.06	1.37 (0.96–1.94)
Pre-infection healthcare interventions				
hospitalization[a]	151 (67.1)	268 (61.5)	0.15	1.28 (0.90–1.82)
surgery[b]	91 (40.4)	201 (46.1)	0.16	0.79 (0.56–1.11)
dialysis[b]	43 (19.1)	39 (8.9)	<0.001	2.40 (1.46–3.95)
endoscopy[c]	36 (16.0)	71 (16.3)	0.92	0.98 (0.61–1.54)
mechanical ventilation[c]	73 (32.4)	112 (25.7)	0.07	1.39 (0.96–2.00)
indwelling invasive devices				
central venous catheter	151 (67.1)	238 (54.6)	0.002	1.70 (1.20–2.41)
bladder catheter	138 (61.3)	247 (56.6)	0.25	1.21 (0.86–1.71)
nasogastric tube[c]	57 (25.3)	102 (23.4)	0.58	1.11 (0.75–1.64)
surgical drain[c]	49 (21.8)	99 (22.7)	0.79	0.95 (0.63–1.42)
treatments administered[b]				
corticosteroids	67 (29.8)	94 (21.6)	0.02	1.54 (1.05–2.26)
chemotherapy or radiotherapy	29 (12.9)	60 (13.8)	0.75	0.93 (0.55–1.52)
antibiotic therapy	195 (86.7)	371 (85.1)	0.58	1.14 (0.70–1.88)
Infection variables				
epidemiology				
healthcare associated	9 (4.0)	53 (12.2)	<0.001	0.30 (0.13–0.63)
hospital acquired	213 (94.7)	372 (85.3)	<0.001	3.05 (1.58–6.35)
BSI	173 (76.9)	274 (62.8)	<0.001	1.97 (1.35–2.89)
clinical presentation				
presentation with septic shock	57 (25.3)	43 (9.9)	<0.001	3.10 (1.96–4.91)
APACHE III score ≥15 at onset	208 (92.4)	273 (62.6)	<0.001	7.30 (4.24–13.23)
colistin resistance of the isolate	62 (27.6)	70 (16.1)	<0.001	1.99 (1.32–2.98)

Continued

Table 4. *Continued*

Variable	Non-survivors, $n=225$ (34.1%)	Survivors, $n=436$ (65.9%)	*P* value	OR (95% CI)
Treatment variables				
inadequate empirical antimicrobial treatment	144 (64.0)	221 (50.7)	0.001	1.73 (1.23–2.44)
post-antibiogram monotherapy	118 (52.4)	189 (43.3)	0.03	1.44 (1.03–2.02)
tigecycline	45 (20.0)	71 (16.3)	0.23	1.28 (0.83–1.97)
colistin	45 (20.0)	76 (17.4)	0.41	1.18 (0.77–1.81)
gentamicin	28 (12.4)	42 (9.6)	0.26	1.33 (0.77–2.27)
post-antibiogram combination therapy	107 (47.6)	247 (56.6)	0.03	0.69 (0.49–0.97)
two-drug combination	38 (16.8)	96 (22.2)	0.21	0.71 (0.46–1.10)
three-drug combination	67 (29.7)	150 (34.4)	0.23	0.81 (0.56–1.15)
combination including a carbapenem[d]	54 (24.0)	151 (34.6)	0.005	0.59 (0.41–0.87)
double-carbapenem combination	3 (1.3)	5 (1.1)	0.83	1.16 (0.18–6.05)
combination plus rifampicin	6 (2.7)	6 (1.4)	0.24	1.96 (0.52–7.43)

Data are expressed as *n* (%), unless otherwise stated.
[a]During the 12 months preceding infection onset.
[b]During the 30 days preceding infection onset.
[c]During the 72 h preceding infection onset.
[d]All carbapenem-containing regimens included meropenem; double-carbapenem regimens included meropenem and ertapenem.

Table 5. Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

used to treat these infections, can significantly reduce viable counts of KPC-Kp, including isolates that are carbapenem resistant.[30,31] Data from time–kill studies have also indicated that carbapenems (as well as several other antibiotics) exert synergistic effects with colistin against KPC-Kp.[32,33]

A problem of considerable importance is the increasing rate of colistin resistance among Kp isolates. *In vitro* resistance to this drug was an independent predictor of 14 day mortality in our cohort and similar findings have been reported by others in patients with carbapenem-resistant Kp infections.[34] It is worth noting that during the 4 year period covered by our study, the percentage of KPC-Kp isolates displaying colistin resistance almost tripled.

The presence of chronic renal failure also emerged as an important predictor of 14 day mortality, probably because it reduced the therapeutic options. Drugs with potential renal toxicity (colistin or gentamicin, especially when combined with other agents) would have to be avoided and less toxic—and also less effective—single-drug regimens prescribed. This finding is consistent with recently reported data on patients with carbapenem-resistant Kp infections treated with polymyxin B monotherapy: in this population, baseline renal insufficiency was associated with a 6.0-fold increase in clinical failure after adjustment for the presence of septic shock.[35]

Our study has certain limitations that must be acknowledged. Firstly, the nature of our analysis was retrospective. Secondly, our study was performed in a country with a high prevalence of KPC-Kp, therefore the results may not be necessarily applicable to other settings different from ours. Thirdly, it is possible that there may have been some degree of misclassification as infection (instead of colonization) cases among non-bacteraemic patients. Fourthly, but not less importantly, despite the large population sample included, the present is an observational study and not a clinical trial; therefore, of course, our data and conclusions cannot represent therapeutic recommendations for clinicians.

In conclusion, this large multicentre cohort study shows that infections caused by Kp strains expressing KPC-2 or KPC-3 enzymes are associated with a high mortality rate. Our findings confirm the survival benefits of non-empirical regimens that include two or three active drugs (as compared with active monotherapy) and indicate that the most significant reduction in mortality is seen in patients with more severely compromised clinical conditions. Combination regimens that include meropenem can provide appreciable therapeutic benefits if the meropenem MIC for the KPC-Kp isolate is $\leq$8 mg/L, but no benefits are likely when the meropenem MIC exceeds 32 mg/L. Further study is needed to define the potential value of carbapenem-containing combinations for isolates with intermediate meropenem MICs, including those as high as 16 mg/L.

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Transparency declarations

None to declare.

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