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Epidemiology, management, and outcome of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections in hospitals within the same endemic metropolitan area

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ABSTRACT

In the last decade, carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) has become endemic in several countries, including Italy. In the present study, we assessed the differences in epidemiology, management, and mortality of CR-Kp bloodstream infection (BSI) in the three main adult acute-care hospitals of the metropolitan area of Genoa, Italy.

From January 2013 to December 2014, all patients with CR-Kp BSI were identified through the computerized microbiology laboratory databases of the three hospitals. The primary endpoints of the study were incidence and characteristics of CR-Kp BSI in hospitals within the same endemic metropolitan area. Secondary endpoints were characteristics of CR-Kp BSI in hospitals with and without internal infectious diseases consultants (IDCs) and 15-day mortality.

During the study period, the incidence of healthcare-associated CR-Kp BSI in the entire study population was 1.35 episodes per 10,000 patient-days, with substantial differences between the three hospitals.

Abbreviations: CR-Kp, carbapenem-resistant *Klebsiella pneumoniae*; BSI, bloodstream infections; ID, infectious diseases; LHU, Local Health Unit; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; MICs, minimum inhibitory concentrations; EUCAST, European Committee on Antimicrobial Susceptibility Testing; 95% CI, 95% confidence intervals; IQR, interquartile range; ICU, intensive care unit; OR, odds ratio.

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Patients admitted to the two hospital with internal IDCs were more likely to receive post-susceptibility test combined therapy including carbapenems (77% vs. 26%, $p < 0.001$), adequate post-susceptibility test therapies (86% vs. 52%, $p < 0.001$), and post-susceptibility therapies prescribed by an infectious diseases specialist (84% vs. 14%, $p < 0.001$). Overall, the crude 15-days mortality was 26%. In the final multivariable model, only septic shock at BSI presentation was unfavorably and independently associated with 15-days mortality (odds ratio [OR] 6.7, 95% confidence intervals [CI] 2.6–17.6, $p < 0.001$), while a protective effect was observed for post-susceptibility test combined therapies including a carbapenem (OR 0.11, 95% CI 0.03–0.43, $p = 0.002$).
Mortality of CR-Kp remains high. Differences in the incidence of CR-Kp BSI were detected between acute-care centers within the same endemic metropolitan area. Efforts should be made to improve the collaboration and coordination between centers, to prevent further diffusion of CR-Kp.

Introduction

In the last decade, carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) has become endemic in several countries, including Italy, and outbreaks of bloodstream infections (BSI) caused by this pathogen continue to be increasingly reported worldwide [1–13].

CR-Kp BSI are associated with high mortality, mostly because of the paucity of antimicrobials active against CR-Kp and the frequent heavy burden of comorbidities in patients developing the disease [14–18]. However, most information regarding treatment strategies, outcomes, and characteristics of patients with CR-Kp BSI derives from multicentre observational studies conducted in large hospitals in different cities, while multicentre data from a same metropolitan area remain scant [10,17,18]. In this regard, possible differences in the characteristics, management, and outcomes of patients within neighboring centers might help identifying aspects to be specifically addressed for improving care locally.

In the present study, we assessed the differences in epidemiology, management, and mortality of CR-Kp BSI in three large hospitals in Genoa, Italy.

Material and methods

Study design and setting

A multicenter retrospective study was conducted in the three main adult acute-care public hospitals of the metropolitan area of Genoa, Northern Italy: IRCCS AOU San Martino – IST, a 1300-beds adult acute-care tertiary teaching hospital (hospital A); Galliera hospital, a 450-beds adult acute-care tertiary non-teaching hospital (hospital B); Local Health Unit (LHU) hospital, a 630-beds adult acute-care secondary non-teaching hospital (hospital C). The number of intensive care unit (ICU) beds in the three centers is as follows: 55 (hospital A); 10 (hospital B); 28 (hospital C). Of note, hospitals A and B have their own internal senior infectious diseases consultants (IDCs), while hospital C relies on external consultations. More specifically, external consultations are conducted at the bedside upon request, by senior infectious diseases specialists from hospital A.

From January 2013 to December 2014, all patients with CR-Kp BSI were identified through the computerized microbiology laboratory databases of the three hospitals. Only health-care associated CR-Kp BSI were considered for the analysis, according to the definition of the European Center for Disease Control and prevention [19]. Briefly, CR-Kp BSI was defined as a positive blood culture collected at least 48 h after hospital admission, or within 48 h from hospital admission in those patients who had been discharged in the preceding two days. For patients with multiple episodes of CR-Kp BSI, a novel event was considered as independent if occurring at least 30 days after the last positive blood culture [19].

The primary endpoint of the study was incidence of CR-Kp BSI in the overall metropolitan area of Genoa. Secondary endpoints were characteristics of CR-Kp BSI in hospitals with and without internal IDCs and 15-day mortality. For transparency, information on the incidence of Cr-Kp BSI in the hospital A (but not the characteristics of the episodes) was already included in a previous study [4].

The study involved the analysis of existing anonymized clinical and laboratory data. An informed consent for the use of anonymized data for scientific purposes is signed by all patients admitted to the three adult acute-care hospitals and included in surveillance databases. The study was approved by the Regional Ethics Committee of Liguria Region.

Data collection

The following demographic and clinical data were collected: age, gender, Charlson score (i.e., a cumulative score summarizing different categories of comorbidity, with higher scores indicating a greater burden of baseline comorbid conditions [20]), chronic obstructive pulmonary disease (COPD), chronic renal failure, solid neoplasm, hematologic malignancy, diabetes mellitus, previous surgery, ward of stay at the time of CR-Kp BSI, time from hospital admission to CR-Kp BSI, presence of a central venous catheter (CVC), presence of mechanical ventilation, clinical presentation as septic shock (i.e., presence of organ dysfunction and persistent hypotension despite volume replacement [21]), type and adequateness of initial and post-susceptibility test antimicrobial therapy (an antimicrobial therapy was defined as adequate if including at least one drug showing in vitro activity against the CR-Kp isolate), post-susceptibility test therapy prescribed by IDCs (yes vs no), 15-day crude mortality.

Microbiology

The Vitek 2 system (bioMérieux, Marcy l'Etoile, France) was used for the identification of Kp and for antimicrobial susceptibility testing. Carbapenem minimum inhibitory concentrations (MICs) were classified as carbapenem-susceptible or resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (EUCAST breakpoint tables for interpretation of MICs and zone diameters, version 6.0, 2016; http://www.eucast.org). For the analysis, Kp isolates which were resistant to one or more carbapenems tested in our institutions (i.e., ertapenem, imipenem, or meropenem) were considered as carbapenem-resistant.

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Statistical analysis

The incidence of CR-Kp BSI with its 95% confidence intervals (95% CI) was calculated as the number of events per 10,000 patient-days.

Characteristics of patients are presented with absolute frequencies and percentages for categorical variables, and with median and interquartile range (IQR) for continue variables. Data were compared between hospital with and without IDCs, by means of the chi-square test, the Fisher exact test, or the Kruskal–Wallis test, as appropriate. All tests were two-sided, and a p value less than 0.05 was considered as statistically significant.

To identify risk factors associated with 15-day mortality in the entire study population, a univariable statistic was generated by using the same tests mentioned above, as appropriate. Then, all demographic and clinical covariates associated with 15-day mortality in univariable comparisons ($p < 0.10$) were included in a stepwise backward multivariable model. All statistical analyses were performed with STATA SE14 (StataCorp, Texas, USA).

Results

From January 2013 to December 2014, we observed 213 episodes of healthcare-associated CR-Kp BSI. Of them, 139 (65.3%) occurred at hospital A, 30 (14.1%) at hospital B, and 44 (20.6%) at hospital C. The incidence of healthcare-associated CR-Kp BSI in the entire study population was 1.35 episodes per 10,000 patient-days, divided in 1.5 episodes per 10,000 patient-days at hospital A, 1.0 per 10,000 patient-days at hospital B, and 1.2 episodes per 10,000 patient-days at hospital C. Substantial difference in the incidence of CR-Kp were observed between hospital A and the other two hospitals ($p = 0.02$).

The complete demographic and clinical characteristics of the entire study population are summarized in Table 1, while Table 2 shows the data in hospitals with and without internal IDCs (the characteristics of patients with CR-Kp BSI in the different hospitals are detailed in Table S1). As shown in Table 2, a higher rate of patients with hematological malignancies was observed in the hospitals with internal IDCs (hospitals A and B) rather than in hospital C (11% vs. 0%, $p = 0.03$), while patients admitted at hospital C had a higher median Charlson score (3 vs. 2, $p = 0.03$). Patients admitted to the two hospitals with internal IDCs were also more likely to have a CVC at the time of infection (80% vs. 43%, $p < 0.001$), and septic shock at BSI presentation (22% vs. 9%, $p = 0.032$). In contrast, higher rates of CR-Kp BSI occurring in the intensive care unit (ICU) ward (64% vs. 43%, $p = 0.002$) and of patients receiving mechanical ventilation (50% vs. 33%, $p = 0.036$) were observed in hospital C. With regard to antimicrobial therapy, patients admitted to the two hospital with internal IDCs were more likely to receive post-susceptibility test combined therapies (82% vs. 38%, $p < 0.001$), post-susceptibility test combined therapy including carbapenems (77% vs. 26%, $p < 0.001$), adequate post-susceptibility test therapies (88% vs. 52%, $p < 0.001$), and post-susceptibility therapies prescribed by an infectious diseases specialist (84% vs. 14%, $p < 0.001$). Of note, 86.7% of post-susceptibility test therapy prescribed by IDCs were combined regimens including at least one carbapenem. Interestingly, also the antimicrobial pattern of isolates was very different. CR-Kp in hospital C was indeed less likely to be colistin-resistant (25% vs. 42%, $p = 0.033$), gentamicin-resistant (32% vs. 62%, $p < 0.001$), and tigecycline-resistant (29% vs. 13%, $p = 0.04$) than those in hospitals A and B.

Overall, the crude 15-days mortality was 26%. Univariable and multivariable analyses of risk factors associated with mortality are shown in Table 3. In univariable analysis, non-survivors were more likely to have solid malignancy, be exposed to mechanical ventilation, have a septic shock at clinical presentation, and receive post-susceptibility test therapy without carbapenems. In contrast, mortality was lower in patients with adequate initial therapy and patients with post-susceptibility test combined therapy including a carbapenem. In the final multivariable model, only septic shock at BSI presentation remained unfavorably and independently associated with 15-days mortality (odds ratio [OR] 6.7, 95% CI 2.6–17.6, $p < 0.001$), while a protective effect was observed for post-susceptibility test combined therapies including a carbapenem (OR 0.11, 95% CI 0.03–0.43, $p = 0.002$).

Table 1
Demographic and clinical characteristics of study population ($N = 213$).

Patient features	n	%
Healthcare organization of admission		
Hospital A	139	65.26
Hospital B	30	14.08
Hospital C	44	20.66
Age (years); median (IQR)	72 (61–78)	
Gender		
Male	139	65.26
Female	74	34.74
Comorbidities		
Charlson index score; median (IQR)	2 (1–3)	
Solid malignancy	31	14.55
Chronic renal failure	21	9.86
Diabetes	19	8.92
Hematologic malignancy	18	8.45
Solid organ transplantation	7	3.29
Length of hospital stay before onset of BSI (days); median (IQR)	22 (11–37)	
Ward of onset of BSI		
Intensive Care Units	100	46.95
Medical wards	73	34.27
Surgical wards	27	12.68
Rehabilitation wards	13	6.10
Healthcare interventions before onset of BSI		
Indwelling central venous catheter	155	72.77
Surgical intervention	101	47.42
Mechanical ventilation	77	36.15
Septic shock at presentation of BSI	42	19.72
Antimicrobial resistance pattern of isolated CR-Kp[a]		
Colistin resistant	83	38.97
Gentamicin resistant	119	55.87
Tigecycline resistant	55	25.82
Initial antibiotic treatment		
Adequate initial antibiotic therapy	43	20.19
Post-susceptibility test therapies[b]		
Monotherapy	13	6.91
Combined therapy	135	71.81
Combined therapy including a carbapenem	123	65.43
Combined therapy including two carbapenem	13	6.91
Combined therapy without carbapenems	12	6.38
Combined therapy including colistin and rifampin	4	2.13
Adequate	148	78.72
Post-susceptibility therapy prescribed by the infectious diseases specialist	128	60.09
Outcomes		
15-Days mortality	56	26.29

[a] For the analysis, strains with intermediate susceptibility to gentamicin and tygecicline were considered as resistant.
[b] Calculated only for survivors at the time of post-susceptibility test results.

Discussion

CR-Kp has been increasingly reported in Italy during the last two decades, and unfortunately remain endemic [4,5,8,9]. The incidence of 1.35 CR-Kp BSI episodes per 10,000 patient-days reported in the present study is indeed in line both with our previous experience

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Table 2
Demographic and clinical characteristics of the patients admitted in hospitals with and without internal infectious diseases consultants.

Variables	Hospitals with internal infectious diseases consultant *n*/*N* (%)	Hospital without internal infectious diseases consultant *n*/*N* (%)	*p*-Value
Age (years); median (IQR)	72 (61–78)	69.5 (55–79.5)	0.59
Gender			
Male	115/169 (68.05)	24/44 (54.55)	0.63
Female	54/169 (31.95)	20/44 (45.45)	
Comorbidities			
Charlson index score; median (IQR)	2 (1–3)	3 (1–3)	0.03
Solid malignancy	26/169 (15.38)	5/44 (11.36)	0.50
Chronic renal failure	18/169 (10.65)	3/44 (6.82)	0.45
Diabetes	18/169 (10.65)	1/44 (2.27)	0.13
Hematological malignancy	18/169 (10.65)	0/44 (0)	0.03
Solid organ transplantation	5/169 (2.96)	2/44 (4.55)	0.64
Length of hospital stay before onset of BSI (days); median (IQR)	23 (12–38)	17 (9.5–32)	0.11
Ward of onset of BSI			0.002
Intensive Care Units	72/169 (42.60)	28/44 (63.64)	
Medical wards	61/169 (36.09)	12/44 (27.27)	
Surgical wards	27/169 (15.98)	0 (0)	
Rehabilitation wards	9/169 (5.33)	4/44 (9.09)	
Healthcare interventions before onset of BSI			
Indwelling central venous catheter	136/169 (80.47)	19/44 (43.18)	<0.001
Surgical intervention	78/169 (46.15)	23/44 (52.27)	0.50
Mechanical ventilation	55/169 (32.54)	22/44 (50.00)	0.036
Septic shock at presentation of BSI	38/169 (22.49)	4/44 (9.09)	0.032
Antimicrobial resistance pattern of CR-Kp isolates[a]			
Colistin resistant	72/169 (42.60)	11/44 (25.00)	0.033
Gentamicin resistant	105/169 (62.13)	14/44 (31.82)	<0.001
Tigecycline resistant	49/169 (28.99)	6/44 (13.64)	0.04
Initial antibiotic treatment			
Adequate initial antibiotic therapy	32/169 (18.93)	11/44 (25.00)	0.37
Post-susceptibility test therapy[b]			
Monotherapy	7/146 (4.79)	6/42 (14.29)	0.08
Combined therapy	119/146 (81.51)	16/42 (38.10)	<0.001
Combined therapy including a carbapenem	112/146 (76.71)	11/42 (26.19)	<0.001
Combined therapy including two carbapenem	11/146 (7.53)	2/42 (4.76)	0.53
Combined therapy without carbapenems	7/146 (4.79)	5/42 (11.90)	0.14
Combined therapy including colistin and rifampin	3/146 (2.05)	1/42 (2.38)	0.89
Adequate post-susceptibility test therapy	128/146 (87.67)	22/42 (52.38)	<0.001
Post-susceptibility test therapy prescribed by ID consultants	122/146 (83.56)	6/42 (14.29)	<0.001
Outcome			
15-Days mortality	49/169 (28.99)	7/44 (15.91)	0.08

[a] For the analysis, strains with intermediate susceptibility to gentamicin and tigecycline were considered as resistant.
[b] Calculated only for survivors at the time of post-susceptibility test results. All post-susceptibility tests were based on susceptibility test results and were adequate according to study definitions.

in hospital A and with other surveys in our country [4,22,23]. However, we also detected some differences between centers, with a significantly higher incidence being observed in the largest (hospital A). Although such differences are possibly related to the higher number of ICU-beds in hospital A (critically-ill patients in ICU are at increased risk of developing CRKP BSI [24]), we think our analysis highlight a possible heterogeneity of CR-Kp diffusion not only between countries and regions [25,26], but also within the same endemic metropolitan area. In turn, this stresses the need of a strict coordination between neighboring facilities (e.g., providing complete information on proven/possible colonization of transferred patient, sharing mutually recognized contention protocols), to avoid the unwilled introduction of undetected carriers in those centers still partially spared from an extensive CR-Kp diffusion.

In this study, we also explored the characteristics and the outcome of CR-Kp BSI in the different hospitals within the metropolitan area of Genoa. Several multicenter observational studies have already investigated these issues in patients with CR-Kp BSI [8,10–14,18]. In endemic areas such as Italy and Greece, CR-Kp BSI mostly occur among patients with multiple comorbidities, neutropenia, indwelling devices, recent surgery, and previous hospitalizations [10,17]. As regards antimicrobial therapy, an increased survival has been reported in patients treated with combined therapies paradoxically including carbapenems, although randomized clinical trials definitely assessing the validity of this approach have still to be completed [17,18,27,28]. Keeping in mind this important lack of high-level evidence, it is nonetheless worth noting that PK/PD studies have suggested that high-dose meropenem might retain bactericidal serum concentrations against some CR-Kp strains, as a possible explanation for the survival benefit reported in observational studies [12,29]. Against this complex background, the role of the IDCs might be critical. Indeed, expertise with dedicated and constant update is needed to balance benefits (administration of an active therapy on the basis of patients' isolates and local antimicrobial epidemiology, appropriate dosages, escalation and de-escalation approaches) and costs (toxicities, selection of resistant strains) of the different therapeutic approaches in every single case, and to identify as soon as possible the most appropriate therapy to be administered [30–32].

In this study, a significantly higher rate of adequate post susceptibility test therapies was observed in the two hospitals with internal IDCs than in that without (86% vs. 52%), with an even higher difference being observed in the overall amount of therapies prescribed by IDCs (86% vs. 14%). This result is in line with the increase in appropriateness of prescriptions following ICs already reported by different studies [33–36]. Consistently, most of IDCs prescriptions in our study were combined therapy including carbapenems, which in turn were associated with increased survival.

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Table 3
Association between 15-days mortality and potential independent variables: results of univariate and multivariate logistic regression.

Variables	Univariate analysis			Multivariate analysis[c]	
	Survivors *n*/*N* (%)	Non-survivors *n*/*N* (%)	*p*-Value	Odds ratio (CI 95%)	*p*-Value
Age (years); medians (IQR)	71 (59–78)	72 (62–80)	0.25		
Gender					
Male	102/157 (64.97)	37/56 (66.07)	0.88		
Female	55/158 (34.8)	19/56 (33.9)			
Comorbidities					
Charlson index score; median	2 (1–3)	2 (1–3.5)	0.13		
Solid malignancy	18/157 (11.46)	13/56 (23.21)	0.046		
Chronic renal failure	16/157 (10.19)	5/56 (8.93)	0.79		
Diabetes	16/157 (10.19)	3/56 (5.36)	0.41		
Hematologic malignancy	11/157 (7.01)	7/56 (12.50)	0.26		
Solid organ transplantation	7/157 (4.46)	0/56 (0)	0.19		
Length of hospital stay before onset of BSI (days); median (IQR)	20 (10–36)	24.5 (15–37.5)	0.25		
Ward of onset of BSI			0.67		
Intensive Care Units	76/157 (48.41)	24/56 (42.86)			
Medical wards	50/157 (31.85)	23/56 (41.07)			
Surgical wards	21/157 (13.38)	6/56 (10.71)			
Rehabilitation wards	10/157 (6.37)	3/56 (5.36)			
Healthcare interventions before onset of BSI					
Indwelling central venous catheter	114/157 (72.61)	41/56 (73.21)	0.93		
Surgical intervention	78/157 (49.68)	23/56 (41.07)	0.28		
Mechanical ventilation	50/157 (31.85)	27/56 (48.21)	0.03		
Septic shock at presentation of BSI	19/157 (12.10)	23/56 (41.07)	<0.001	6.70 (2.55–17.59)	<0.001
Antimicrobial resistance pattern of isolated CR-Kp[a]					
Colistin resistant	65/157 (41.40)	18/56 (32.14)	0.26		
Gentamicin intermediate or resistant	88/157 (56.05)	31/56 (55.36)	0.96		
Tigecycline intermediate or resistant	42/157 (26.75)	13/56 (23.21)	0.69		
Initial antibiotic treatment					
Adequate initial antibiotic therapy	38/157 (24.20)	5/56 (8.93)	0.02		
Post-susceptibility test therapies[b]					
Monotherapy	10/157 (6.37)	3/31 (9.68)	0.51		
Combined therapy	113/157 (71.97)	22/31 (70.97)	0.091		
Combined therapy including a carbapenem	107/157 (68.15)	16/31 (51.61)	0.08	0.11 (0.03–0.43)	0.002
Combined therapy including two carbapenem	10/157 (6.37)	3/31 (9.68)	0.45		
Combined therapy without carbapenems	6/157 (3.82)	6/31 (19.35)	0.001		
Combined therapy including colistin and rifampin	2/157 (1.27)	2/31 (6.45)	0.13		
Adequate post-susceptibility test therapy	123/157 (78.34)	25/31 (80.65)	0.77		
Post-susceptibility test therapy prescribed by ID consultants	110/157 (70.06)	18/31 (58.06)	0.21		
Hospitals with internal ID consultations	120/157 (71.01)	49/56 (28.99)	0.08		

[a] For the analysis, strains with intermediate susceptibility to gentamicin and tigecycline were considered as resistant.
[b] Calculated only for survivors at the time of post-susceptibility test results. All post-susceptibility tests were based on susceptibility test results and were adequate according to study definitions.
[c] Only variables selected through stepwise approach and included in the final multivariate model are presented.

However, consultations themselves were apparently not associated with increased survival. These conflicting results could be explained by the fact that we were able to retrieve only IDCs prescriptions following susceptibility test results, while the overall effect of carbapenem-based regimens on the outcome was conceivably also related to those adequate therapies administered empirically, pending blood cultures results. In this regard, it should be noted that rates of adequate initial therapy were worryingly low in the entire study population, irrespective of the presence of internal IDCs. In our opinion, this result highlights the necessity of improving collaboration between ward physicians and IDCs. Indeed, consultations should be requested as soon as CR-Kp colonized patients develop signs and symptoms of infection and not after susceptibility test results, in view of the well-known favorable effect on survival of an adequate empiric therapy [30,31,37]. In this light, major efforts have been recently made to implement dedicated antimicrobial stewardship programs in our hospitals, with also the aim of increasing the number of early IDCs.

Finally, the present study confirmed the already well-known association between septic shock and mortality of CR-Kp BSI [17,18]. Of note, the percentage of patients presenting with septic shock was very low in hospital C, possibly explaining why mortality was not different from that of the other hospitals despite lower rates of IDCs and adequate therapies.

This study has some important drawbacks. First, it was retrospective, and under-reporting might have occurred in some cases. Second, as reported above, we were not able to collect data about IDCs for prescribing empirical therapies, since we did not have complete information regarding early telephone consultations. In view of their possible favorable impact on the outcome of CR-Kp BSI, we think they role deserves further dedicated investigation. Another limitation is the lack of information on possible concomitant infections due to other organisms, that might have also influenced the outcomes in some cases. Finally, from an epidemiological standpoint, an important limitation is the lack of more detailed microbiological data, which prevented us from assessing

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possible differences in the clonal types of CR-Kp and their mechanisms of resistance to carbapenems in the different centers.

In conclusion, mortality of CR-Kp remains high. Differences in the incidence of CR-Kp BSI were detected between acute-care centers within the same endemic metropolitan area. Efforts should be made to improve the collaboration and coordination between centers, to prevent further diffusion of CR-Kp.

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Competing interests

None declared.

Ethics approval

The study involved the analysis of existing anonymized clinical and laboratory data. An informed consent for the use of anonymized data for scientific purposes is signed by all patients admitted to the three adult acute-care hospitals and included in surveillance databases. The study was approved by the Regional Ethics Committee of Liguria Region.

Authors' contribution

MLC, CA, DRG conceived and designed the research, collected data, cleaned and analyzed the data, and drafted and revised the paper. MS conceived and designed the research, cleaned and analyzed the data, and revised the paper. VF collected data, drafted and revised the paper. AMS, VD, GC, AMD, MPC, GO and ES collected data and revised the paper. GP and LCB revised the paper. CV, AO and GI conceived and designed the research and revised the paper.

All authors read and approved the final manuscript.

Availability of data and materials

The datasets used in the current study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jiph.2017.06.003.

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