Interactive CardioVascular and Thoracic Surgery 23 (2016) 762–769
doi:10.1093/icvts/ivw228 Advance Access publication 1 July 2016

Cite this article as: Salsano A, Giacobbe DR, Sportelli E, Olivieri GM, Brega C, Di Biase C *et al*. Risk factors for infections due to carbapenem-resistant *Klebsiella pneumoniae* after open heart surgery. Interact CardioVasc Thorac Surg 2016;23:762–9.

Risk factors for infections due to carbapenem-resistant *Klebsiella pneumoniae* after open heart surgery

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Received 25 January 2016; received in revised form 17 May 2016; accepted 2 June 2016

Abstract

OBJECTIVES: Patients undergoing major surgery are at increased risk of developing infections due to resistant organisms, including carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp). In this study, we assessed risk factors for CR-Kp infections after open heart surgery in a teaching hospital in northern Italy.

METHODS: A retrospective study was conducted from January to December 2014. The primary outcome measure was postoperative CR-Kp infection, defined as a time-to-event end-point. The effect of potentially related variables was assessed by univariable and multivariable analyses. Secondary end-points were in-hospital mortality and 180-day postoperative mortality.

RESULTS: Among 553 patients undergoing open heart surgery, 32 developed CR-Kp infections (6%). In the final multivariable model, CR-Kp colonization [hazard ratio (HR) 227.45, 95% confidence intervals (CI) 67.13–1225.20, $P < 0.001$], cardiopulmonary bypass time in minutes (HR 1.01, 95% CI 1.01–1.02, $P < 0.001$), chronic obstructive pulmonary disease (HR 3.99, 95% CI 1.61–9.45, $P = 0.004$), SOFA score (HR 1.29, 95% CI 1.08–1.53, $P = 0.007$), preoperative mechanical ventilation (HR 8.10, 95% CI 1.31–48.57, $P = 0.026$), prolonged mechanical ventilation (HR 2.48, 95% CI 1.08–6.15, $P = 0.032$) and female sex (HR 2.08, 95% CI 1.00–4.36, $P = 0.049$) were associated with the development of CR-Kp infection. Increased in-hospital mortality and 180-day mortality were observed in patients who developed CR-Kp infections in comparison with those who did not.

CONCLUSIONS: In our cohort, CR-Kp colonization was an important predictor of CR-Kp infection after open heart surgery. CR-Kp infection after surgery significantly affected survival. Preventing colonization is conceivably the most effective current strategy to reduce the impact of CR-Kp.

Keywords: *Klebsiella* • KPC • Carbapenemases • Postoperative infections • Cardiac surgery

INTRODUCTION

The number of hospital outbreaks caused by carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) has rapidly increased in recent years, and CR-Kp is now considered endemic in several countries, including Italy [1]. The global spread of this pathogen is a matter of concern because of the shortage of therapeutic options and the impressive mortality associated with CR-Kp infections, which has been reported to be as high as 40–60% [2, 3]. From a pathogenic standpoint, CR-Kp infections are mostly preceded by colonization of the bowel flora, although they may also follow colonization or contamination of different body surfaces and devices [4].

Patients undergoing major surgery are at increased risk of developing CR-Kp infections in comparison with other patient populations [4–6]. In this regard, identifying risk factors for CR-Kp infection might be crucial to prevent the disease and reduce morbidity and mortality in the postoperative period. However, while the pivotal role of underlying diseases and former healthcare contacts in influencing the risk of CR-Kp infection has been extensively recognized [4, 5], few data exist on unique risk factors for postoperative CR-Kp infection by surgical specialty [6, 7].

The aim of the present study was to assess risk factors for CR-Kp infections after cardiac surgery in a large teaching hospital in northern Italy, as well as to describe the related postoperative mortality.

MATERIAL AND METHODS

A single-centre retrospective study was conducted at the IRCCS AOU San Martino-IST teaching Hospital, University of Genoa,

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Genoa, Italy. From January 2014 to December 2014, all patients who underwent open heart surgery were included in the study. The primary outcome measure was postoperative CR-Kp infection, defined as a time-to-event end-point (with origin set at the time of surgery). Secondary end-points were (i) crude in-hospital mortality and (ii) 180-day postoperative mortality.

Medical charts and laboratory databases were reviewed to collect demographic, clinical and microbiological data. Survivors were followed for at least 180 days after surgery, including daily assistance in intensive care unit (ICU), surgical wards and rehabilitation wards, and scheduled out-patient visits every 3 months after discharge.

Definitions

CR-Kp infection was defined and classified according to the Centers for Disease Control and Prevention (CDC) criteria [8]. For the purpose of this study, only the first CR-Kp infection episode after cardiac surgery was considered for the analysis. Identification of CR-Kp from rectal swab in the absence of signs and symptoms of infection was defined as CR-Kp colonization [7].

For all the patients, routine surveillance rectal swabbing was performed at standard points in time: (i) before surgery and (ii) the first day after surgery and every 7 days thereafter until discharge. According to the time of the first positive culture, isolation of CR-Kp from rectal swab was categorized as pre-surgery (i) or post-surgery (ii) CR-Kp colonization.

Data collected for the analysis

The following variables were evaluated as potential risk factors for CR-Kp infection after cardiac surgery: age; gender; body surface area (BSA); preoperative length of stay in days; preoperative New York Hearth Association (NYHA) class; hypertension; diabetes mellitus (defined as oral antihyperglycaemic therapy or insulin intake); obesity [defined as body mass index (BMI) $\geq$30 kg/m^2]; smoking (defined as current smoking); dyslipidaemia [defined as one or more of the following: triglyceride (TG) $\geq$200 mg/dl, high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, total cholesterol (TC)/HDL-C ratio $\geq$4, TG/HDL-C ratio $\geq$3.8, low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio $\geq$2.5]; chronic kidney disease (defined as baseline serum creatinine >200 µmol/l); chronic obstructive pulmonary disease (COPD, defined as long-term use of bronchodilators or steroids for lung disease); extracardiac arteriopathy (defined as one or more of the following: claudication; carotid occlusion or >50% stenosis; amputation for arterial disease; previous or planned intervention on the abdominal aorta, limb arteries or carotids); history of cerebrovascular accident; previous myocardial infarction; Charlson comorbidity index [9]; baseline left ventricular ejection fraction (LVEF); requirement of preoperative mechanical ventilation; history of immunosuppression [defined as one or more of the following: HIV infection; solid organ transplantation; malignancy; neutropenia (absolute neutrophil count <1000 cells/mm^3); therapy with at least 10 mg of prednisone or its equivalent per day for >14 days prior to surgery; chemotherapy within 45 days before surgery]; European System for Cardiac Operative Risk Evaluation II (EuroSCORE II); full sternotomy; type of surgery [categorized as isolated coronary artery bypass surgery, isolated valvular surgery, surgery of thoracic aorta and other procedures (including combined procedures, pericardiectomy and surgery for cardiac tumours)]; surgical priority (urgency/emergency versus scheduled); cardiopulmonary bypass (CPB) time in minutes; aortic cross-clamp time in minutes; need for intraoperative blood transfusion; Sequential Organ Failure Assessment (SOFA) score immediate after surgery; prolonged mechanical ventilation (defined as postoperative mechanical ventilation >48 h); CR-Kp colonization. The following descriptive data were also recorded: postoperative stroke (defined as cerebrovascular accident with symptoms lasting more than 24 h with or without residual disability, confirmed at computed tomography or magnetic resonance imaging; in the case of no evidence of stroke at neuro-imaging, the diagnosis of stroke was made by consultant neurologists); pacemaker implantation; reoperation for bleeding; length of postoperative ICU stay in days; length of postoperative hospital stay in days.

Microbiology

The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for the identification of Kp isolates and for antimicrobial susceptibility testing. The interpretative breakpoints for carbapenem resistance were based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (EUCAST breakpoint tables for the interpretation of MICs and zone diameters, version 5.0, 2015; http://www.eucast.org). For the analysis, Kp isolates resistant to one or more carbapenems tested in our institution (i.e. ertapenem, meropenem and imipenem) were classified as CR-Kp. For blood CR-Kp isolates, identification of carbapenemase-encoding genes (bla_{VIM-}, bla_{IMP-}, bla_{NDM-}, bla_{KPC-}) and their variants was also performed by means of PCR as previously described [10].

Statistical analysis

Categorical data are presented as percentages and continuous data as median and interquartile range. For descriptive purposes, demographic and clinical characteristics were compared between patients who developed postoperative CRKP infection and those who did not. Categorical variables were compared with the χ^2 test, whereas continuous variables were compared with the Mann–Whitney *U*-test.

The primary study analysis was the identification of variables associated with the development of postoperative CR-Kp infection. To this aim, the effect of the aforementioned potential risk factors was evaluated by means of univariable Cox regression models, after having verified proportional hazards using the test based on Schoenfeld residuals implemented in R survival library. For the purpose of the study, prolonged mechanical ventilation and CR-Kp colonization were considered as time-dependent variables, according to the persistence of mechanical ventilation beyond 48 h after surgery and the time of the first positive rectal swab, respectively. Because of the exploratory nature of the analyses, no correction for multiple testing was used, and the significance level was set to $P < 0.05$. To assess the independent role of variables, a multivariable Cox regression was carried out using a stepwise backward procedure employing the R algorithm based on the Akaike information criterion (estimation) at each step. All time-independent and time-varying variables associated with CR-Kp infection in univariable analyses ($P < 0.10$) were included in the model.

Crude in-hospital mortality was compared between patients who developed CR-Kp infection and those who did not develop CR-Kp infection by means of the χ^2 test. To describe postoperative

180-day mortality according to the development of CR-Kp infection, a Cox's proportional hazards model was carried out considering CR-Kp infection as a time-varying covariate, and the related survival curve was plotted [11].

The Firth's correction for monotone likelihood was applied to all Cox regression models in the present study [12]. All the analyses were performed using the R Statistical Software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 553 patients underwent open heart surgery at our hospital. Their median age was 71 years [interquartile range (IQR) 64–77] and they were mostly males (379/553, 69%). Thirty-two (6%) developed a postoperative CR-Kp infection, which occurred at a median time of 22 days after surgery (IQR 13–34). Observed types of CR-Kp infections are reported in detail in Table 1. Pneumonia and bloodstream infections (BSIs) accounted for the majority of events, occurring in as much as 59 and 34% of the cases, respectively. Among blood CR-Kp isolates, carbapenem resistance was conferred by the production of KPC-2 and KPC-3 in 2/11 (18%) and 9/11 (82%) cases, respectively.

Table 2 reports the demographic and clinical characteristics of patients with and without CR-Kp infections. As given in the table, 66 patients (12%) were found to be colonized by CR-Kp. Only five of them (8%) were already colonized before surgery (in 4 cases colonization was known at hospital admission), whereas most of colonized patients acquired CR-Kp in the postoperative period (61/66, 92%), at a median time of 17 days after surgery (IQR 9–30 days). Of note, preoperative CR-Kp colonization was not considered a contraindication to surgery. Overall, as many as 31/66 colonized patients (47%) developed a postoperative CR-Kp infection. Table 3 shows the results of univariable and multivariable Cox regressions of factors associated with postoperative CR-Kp infection. In univariable analyses, female sex, preoperative length of stay, NYHA class, chronic kidney disease, COPD, preoperative mechanical ventilation, Charlson comorbidity index, EuroSCORE2, type of surgery, CPB time, aortic cross-clamp time, need for intraoperative blood transfusion, SOFA score, prolonged mechanical ventilation and CR-Kp colonization were significantly associated with the development of CR-Kp infection. The final multivariable model confirmed the following variables as factors associated with the development of CR-Kp infection: CR-Kp colonization [hazard ratio (HR) 227.45, 95% confidence intervals (CI) 67.13–1225.20, $P < 0.001$], CPB time in minutes (HR 1.01, 95% CI 1.01–1.02, $P < 0.001$), COPD (HR 3.99, 95% CI 1.61–9.45, $P = 0.004$), SOFA score (HR 1.29, 95% CI 1.08–1.53, $P = 0.007$), preoperative mechanical ventilation (HR 8.10, 95% CI 1.31–48.57, $P = 0.026$), prolonged mechanical ventilation (HR 2.48, 95% CI 1.08–6.15, $P = 0.032$) and female sex (HR 2.08, 95% CI 1.00–4.36, $P = 0.049$).

The overall crude in-hospital mortality was 25% (8/32) and 6% (30/521) in patients with and without CR-Kp infection, respectively ($P < 0.001$), with most deaths in the infection group occurring within 30 days from the infectious event (6/8, 75%). The recorded causes of death in patients with CR-Kp infection were multiorgan failure and respiratory insufficiency in 75% (6/8) and 25% (2/8) of cases, respectively. After discharge, crude rates of 180-day mortality among survivors were 25% in patients with postoperative CR-Kp infection and 4% in those without (6/24 and 19/491, respectively).

In the Cox regression analysis for 180-day mortality, the development of CR-Kp infection was unfavourably associated with the outcome (HR 11.10, 95% CI 5.81–20.13, $P < 0.001$). The related survival curve stratified for CR-Kp infection as a time-varying factor is shown in Fig. 1.

Table 1: Observed types of postoperative carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections

Type of infection	Total, *n* (%) 32 (100)
Bloodstream infections	11 (34)
Isolated	6 (19)
With concomitant pneumonia[a]	5 (16)
Isolated pneumonia	14 (44)
Surgical wound infections	4 (13)
Urinary tract infection	3 (9)

[a]CR-Kp mediastinitis was also present in 1 case.

DISCUSSION

During the observed period, as much as 6% of the patients who underwent open heart surgery at our hospital developed a postoperative CR-Kp infection. This percentage dramatically increased to 47% among CR-Kp colonized patients, who generally acquired both colonization and subsequent infection in the early postoperative period. Life-threatening events such as pneumonia and BSIs accounted for the majority of CR-Kp infections.

A high incidence of postoperative CR-Kp infections was observed in our cohort, in line with the rates of CR-Kp infections reported after other major surgical procedures, such as solid organ transplantations and abdominal surgery in countries and hospitals where CR-Kp is endemic [6–9]. In the present study, CR-Kp colonization was an important risk factor for postoperative CR-Kp infection. This result *per se* is not surprising. Indeed, although intestinal colonization is not an absolute prerequisite for infection, the former precedes the latter in most cases [4, 5]. The major observation stemming from our study is that the rate of CR-Kp infections among colonized patients was very high, nearly 50%. This rate is far higher than the 8–9% reported among not homogeneous populations of colonized subjects, whereas it is similar to that observed by Giannella *et al*. in colonized patients after liver transplantation [4, 7, 13]. Although indirectly, these results strongly confirm the pivotal role of preventive efforts in reducing the incidence of postoperative CR-Kp infections. Indeed, CR-Kp colonization mostly occurs through interpatient cross-transmission, which could be dramatically decreased by the rigorous application of all in-hospital-based infection-control measures (e.g. systematic screening procedures, rapid patient isolation, mandatory use of disposable gowns and gloves, dedicated personnel and devices) [14].

Despite its pre-eminent role, CR-Kp colonization is not the only risk factor for CR-Kp infections in cardiac surgery. Indeed, we found that also increased CBP time, COPD, increased SOFA score at baseline, preoperative mechanical ventilation, prolonged mechanical ventilation and female sex were significant predictors of postoperative CR-Kp infection. The association between increased CPB time and CR-Kp infection might be of interest with

Table 2: Demographic and clinical characteristics of cardiac surgery patients with and without postoperative carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections

	CR-Kp infection (*n* = 32)	No CR-Kp infection (*n* = 521)	*P*-value
Demographic			
Age (years), median (IQR)	74 (67–77)	71 (63–77)	0.357
Female sex	15 (47)	159 (31)	0.053
BSA (m^2), median (IQR)	1.9 (1.7–2.0)	1.8 (1.7–2.0)	0.989
Preoperative and perioperative			
Length of preoperative hospital stay (days), median (IQR)	3 (1–6)	2 (1–4)	0.185
NYHA Class			0.132
I	3 (9)	81 (16)	
II	8 (25)	183 (35)	
III	14 (44)	204 (39)	
IV	7 (22)	53 (10)	
Hypertension	27 (84)	422 (81)	0.635
Diabetes	8 (25)	122 (23)	0.838
BMI ≥30 kg/m^2	7 (22)	72 (14)	0.206
Smoking	10 (31)	227 (44)	0.172
Dyslipidaemia	11 (34)	225 (43)	0.328
Chronic kidney disease	12 (38)	78 (15)	<0.001
COPD	10 (31)	62 (12)	0.002
History of immunosuppression	0 (0)	8 (2)	0.499
Extracardiac arteriopathy	11 (34)	91 (17)	0.017
History of cerebrovascular accident	4 (13)	24 (5)	0.048
Previous myocardial infarction	1 (3)	123 (24)	0.007
Charlson comorbidity index, median (IQR)	3 (1–4)	1 (1–2)	0.016
LVEF %, median (IQR)	55 (50–55)	55 (50–60)	0.288
EuroSCORE 2, median (IQR)	8 (4–27)	2 (1–5)	<0.001
Preoperative MV	3 (9)	15 (3)	0.044
Complete sternotomy	31 (97)	472 (91)	0.200
Type of surgery			<0.001
Isolated coronary artery bypass surgery	4 (13)	194 (37)	
Isolated valvular surgery	7 (22)	170 (33)	
Surgery of thoracic aorta	13 (41)	68 (13)	
Other[a]	8 (25)	89 (17)	
Urgency/emergency	16 (50)	194 (37)	0.150
CPB time (min), median (IQR)	168 (122–232)	102 (76–137)	<0.001
Aortic cross-clamp time (min), median (IQR)	100 (69–134)	63 (48–90)	<0.001
Need for intraoperative blood transfusion	21 (66)	205 (39)	0.003
SOFA score, median (IQR)	7 (4–9)	4 (3–6)	<0.001
Postoperative			
Prolonged MV	24 (75)	76 (15)	<0.001
Reoperation for bleeding	7 (22)	35 (7)	0.002
Pacemaker implantation	1 (3)	16 (3)	1.000
Postoperative stroke	5 (16)	7 (1)	<0.001
Length of postoperative ICU stay (days), median (IQR)	17 (5–23)	1 (1–2)	<0.001
Length of postoperative hospital stay (days), median (IQR)	33 (21–54)	8 (6–11)	<0.001
CR-Kp colonization			
Overall	31 (97)	35 (7)	<0.001
Before surgery	2 (6)	3 (1)	0.001
After surgery	29 (91)	32 (6)	<0.001

Results are presented as *n* (%) unless otherwise indicated.
IQR: interquartile range; BSA: body surface area; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; EuroSCORE: European System for Cardiac Operative Risk Evaluation; MV: mechanical ventilation; CPB: cardiopulmonary bypass; SOFA score: sequential organ failure assessment score; ICU: intensive care unit.
[a]Including combined procedures, pericardiectomy and surgery for cardiac tumours.

regard to colonized patients, since CPB-related intestinal ischaemia has been recognized to enhance intestinal permeability and thus bacterial translocation from the intestinal lumen to the bloodstream [15, 16]. Furthermore, a prolonged CPB time is also associated with both non-infectious postoperative complications and an increased utilization of ICU resources (e.g. mechanical ventilation), which increase *per se* the risk of infection [17]. An increased utilization of ICU resources predisposing to infections might also arise from the presence of a severe multiorgan dysfunction at baseline, as testified by the association between an increased SOFA score immediately after surgery and subsequent CR-Kp infection in our cohort. The unfavourable impact of comorbidities (COPD) and mechanical ventilation on the development of bacterial infections has already been described by other

Table 3: Univariable and multivariable analyses of risk factors for postoperative carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections in cardiac surgery patients

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age (years)	1.02 (0.99–1.06)	0.357		
Female sex	2.32 (1.19–4.53)	0.014	2.08 (1.00–4.36)	0.049
BSA (m^2)	1.62 (0.28–8.64)	0.585		
Length of preoperative hospital stay (days)	1.07 (1.01–1.12)	0.026		
NYHA class		0.005		
I	1 (Reference)			
II	1.24 (0.39–4.95)			
III	1.80 (0.63–6.88)			
IV	4.37 (1.35–17.72)			
Hypertension	1.26 (0.55–3.52)	0.605		
Diabetes	1.05 (0.46–2.18)	0.901		
BMI ≥30 kg/m^2	2.02 (0.88–4.19)	0.095		
Smoking	0.59 (0.16–1.57)	0.321		
Dyslipidaemia	0.63 (0.30–1.25)	0.207		
Chronic kidney disease	3.87 (1.91–7.56)	<0.001		
COPD	3.76 (1.79–7.45)	<0.001	3.99 (1.61–9.45)	0.004
History of immunosuppression	0.96 (0.01–1.45)	0.977		
Extracardiac arteriopathy	1.80 (0.81–3.67)	0.140		
History of cerebrovascular accident	2.51 (0.80–6.11)	0.104		
Previous myocardial infarction	0.78 (0.30–1.71)	0.553		
LVEF	0.98 (0.95–1.02)	0.388		
Preoperative MV	5.41 (1.46–14.31)	0.015	8.10 (1.31–48.57)	0.026
Charlson index	1.54 (1.23–1.92)	<0.001		
EuroSCORE 2	1.07 (1.05–1.09)	<0.001		
Complete sternotomy	2.76 (0.74–24.57)	0.152		
Type of surgery		<0.001		
Isolated coronary artery bypass surgery	1 (Reference)			
Isolated valvular surgery	2.17 (0.72–7.54)			
Surgery of thoracic aorta	9.09 (3.40–29.77)			
Other[a]	4.23 (1.40–14.66)			
Urgency/emergency	1.77 (0.91–3.45)	0.090		
CPB time (min)	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001
Aortic cross-clamp time (min)	1.02 (1.01–1.02)	<0.001		
Need for intraoperative blood transfusion	2.91 (1.48–5.98)	0.002		
SOFA score	1.28 (1.11–1.46)	<0.001	1.29 (1.08–1.53)	0.007
Prolonged MV[b]	11.33 (5.285–27.33)	<0.001	2.48 (1.08–6.15)	0.032
CR-Kp colonization[b]	447.30 (117.20–4007.39)	<0.001	227.45 (67.13–1225.20)	<0.001

Death was considered as a right-censoring event ($n = 49$).
BSA: body surface area; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; EuroSCORE: European System for Cardiac Operative Risk Evaluation; MV: mechanical ventilation; CPB: cardiopulmonary bypass; SOFA score: Sequential Organ Failure Assessment Score.
[a]Including combined procedures, pericardiectomy and surgery for cardiac tumours.
[b]Time-dependent variables.

authors [17–19]. Their results, as well as our findings, are in line with the well-recognized role of such factors in increasing length of stay and impairing the host immune and mechanical defences, thereby promoting the development of infection [17, 20]. Finally, while no differences between genders in the risk of developing CR-Kp infections have been reported so far in other patient populations, the intriguing association between female sex and CR-Kp infections in our cohort is consistent with the fact that women might be at an increased risk of developing bacterial infections after cardiac surgery, according to some literature data [21]. However, it should be noted that such a gender-related difference has not been observed in other studies, thus deserving further investigations [22].

With regard to postoperative outcomes, an in-hospital mortality as high as 25% was observed in patients who developed postoperative CR-Kp infections. This is consistent with the high short-term mortality reported after CR-Kp infections in other patient populations, conceivably related to the multidrug-resistant phenotype of CR-Kp [2, 3]. Indeed, it increases the risk of administering an inactive initial antimicrobial therapy pending strain identification, a factor that strongly and unfavourably influences survival [23]. Moreover, even when an active treatment is administered, and despite its overall benefits on the outcome, a residual impairment of survival might still result from antimicrobial toxicity in some cases, since two or three antimicrobials are often used together to increase the probability of CR-Kp coverage, and to take advantage of synergistic effects [2]. Postoperative CR-Kp infections also affected 180-day survival of our patients. In this regard, it is worth noting that a reduced mid- and long-term survival has been already reported in patients recovering from bacterial infections in comparison with

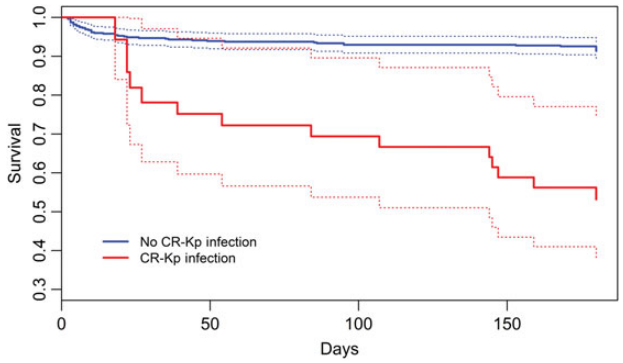

Figure 1: Postoperative 180-day survival in cardiac surgery patients with and without postoperative carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections (±95% confidence intervals). Curves were plotted on the basis of a Cox's proportional hazards model, considering CR-Kp infection as a time-varying variable according to the time of occurrence [11]. Origin was defined as the time of surgery.

those without postoperative infections [20]. The nature of this effect has still to be completely understood, but several potential and non-mutually exclusive mechanisms have been recognized, including interactions between infections and comorbidities, occurrence of infection-related complications, extent of organ damage after infection, prolonged length of hospital stay (which increase the risk of both other healthcare-associated infections and non-infectious complications) and persistent imbalances in the patient's humoural response [20]. Although dedicated studies and methods are needed to adequately weigh any possible additional unfavourable effect of CR-Kp infections on 180-day postoperative mortality in comparison with infections due to other bacteria, as well as the contribution of other important factors influencing mortality (e.g. type and appropriateness of antimicrobial therapy, antimicrobial toxicity, severity of the infection), in our opinion a cautious follow-up of this cohort particularly within the first 6 months after surgery should be recommended.

This study has some limitations. First, it was a single-centre experience and possible discrepancies between our hospital and other centres might result from different patient populations, type of procedures and screening policies. It should also be noted that the observed period was limited to 2014. However, no consistent variations in the referral and/or case-mix of patients occurred in our hospital over recent years, and the study sample could thus be assumed to be representative of the overall population undergoing cardiac surgery at our institution. Second, a major limitation of our study is related to the low number of events in our cohort, a factor possibly associated with biases in regression analyses [24]. Therefore, further study is needed to confirm our exploratory findings. Another limitation is that we could not evaluate the possible association between multisite colonization and infection, as specimens from non-sterile sites other than rectum were not routinely collected for screening purposes. Finally, the retrospective nature of the study prevented us from assessing the degree of adherence to infection–control measures and weighing its impact on the development of postoperative CR-Kp infections. In this regard, it should be reported that the rapid diffusion of CR-Kp in our region has prompted the continuous improvement of our infection–control measures both during and after the study period (e.g. adoption of laboratory-based computerized alert systems rapidly informing clinicians of any microbiological specimen positive for CR-Kp, institution of antimicrobial stewardship programmes, development of dedicated guidelines shared by all the hospitals in our region, routine audits to improve compliance), as an important concerted effort to ultimately reduce the important burden of morbidity and mortality related to CR-Kp [25].

In conclusion, in our cohort, CR-Kp colonization was an important predictor of CR-Kp infection after cardiac surgery, with most colonization and infections occurring in the early postoperative period. CR-Kp infection after cardiac surgery significantly affected survival. Because of the dramatic shortage of dependable therapeutic options, maximized preventive efforts might be the most effective strategy to reduce the unfavourable impact of CR-Kp on postoperative morbidity and mortality and to control dissemination.

Conflict of interest: none reported.

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eComment. Diagnostic intricacies and fortuitous treatment approaches for carbapenem-resistant *Klebsiella pneumoniae*

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doi: 10.1093/icvts/ivw266

We read with great interest the article by Salsano *et al.* on the risk factors for carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp) infections following open heart surgery [1]. Rapid dissemination of CR-Kp and other carbapenemase-producing Gram-negative bacteria inevitably confronts us with a panoply of controversial issues regarding the choice of detection methods and therapy in patients postoperatively. Therefore our aim was to emphasize the importance of meticulous laboratory work-up and to broaden the discussion by highlighting recently emerged treatment options.

In the methods section the authors state that the interpretative breakpoints for evaluating carbapenem resistance were based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, but it has to be emphasized that certain bacterial isolates that produce carbapenemases are categorized as susceptible by using these breakpoints and (as recommended by the EUCAST criteria) should be reported as tested [2]. Therefore the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility, and the EUCAST critera recommend further carbapenemase detection and characterization for public health and infection control purposes [2].

Still, the authors do not state whether they confirmed the carbapenemase detection by one of the commonly employed phenotypic screening methods, since polymerase chain reaction (PCR) was used only for blood CR-Kp isolates in this paper. The modified Hodge test would be the screening method of choice (although it is not without its sensitivity and specificity issues), while there are also several inhibitor based tests in various formats that can be employed (such as the combination disk test or imipenem (IPM)/imipenem-EDTA E-test strips) [3].

Considering a very high rate of CR-Kp infections among colonized patients in this study (almost 50%) and the ensuing life-threatening infectious events, it would be interesting to additionally investigate clonal relatedness of these bacterial isolates by using multilocus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE) analysis. The allelic variants that can be determined this way would help to understand the clonal relationship of CR-Kp strains, which is a pivotal step in epidemiological investigation and subsequent control of hospital-onset CR-Kp infections.

Treatment of patients infected with CR-Kp is always troublesome due to multidrug (and sometimes even pan-drug) resistance phenotype, thus the authors rightly state that two or three antimicrobials are often used concomitantly in order to increase the probability of adequate coverage and to take advantage of synergistic effects. One of such promising approaches is a combined therapy in which, rather surprisingly, one of the drugs is always a carbapenem (most appropriately meropenem) administered at high doses with an extended infusion to boost its pharmacokinetic and pharmacodynamic features [4].

Even a more counterintuitive (albeit clinically auspicious) approach is a double-carbapenem therapy that was effective in a dozen of patients with CR-Kp [4]. This type of treatment also shows promise in patients after heart surgery, as it resulted in a complete recovery of a patient from Italy who underwent aortic prosthesis replacement [5]. It is hypothesized that one of the carbapenem compounds can distract the carbapenemase enzyme by acting as a suicide inhibitor (akin to clavulanate in amoxicillin-clavulanate combination), hence preserving and allowing the activity of the other carbapenem drug.

Conflict of interest: none declared.

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eReply. Diagnostic intricacies and fortuitous treatment approaches for carbapenem-resistant *Klebsiella pneumoniae*

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Mestrovic and Bedenic provided some interesting comments on our article entitled "Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infections after open heart surgery" [1, 2]. Their points mainly concern diagnostic intricacies and antimicrobial therapy.

With regard to the formers, they emphasize the role of a meticulous diagnostic laboratory work-up, since minimum inhibitory concentrations (MICs) for carbapenems of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) might vary markedly across strains. Consequently, some of them remain susceptible to carbapenems [3], although this is the exception rather than the rule in our centre. With regard to our study, it should be stressed that it was conceived to investigate risk factors and prognosis of frank carbapenem resistance as defined by clinical breakpoints. On the other hand, from an epidemiologic standpoint, we agree that deeper investigations such as multilocus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE) might provide important insights on KPC-Kp diffusion. In our centre, more than 80% of the strains belong to the pandemic clone sequence type 258 (ST258), although other clones - mainly ST101 and ST307 - have also been detected in recent years (personal unpublished data).

The second part of Mestrovic and Bedenic comments deals with antimicrobial therapy of KPC-Kp infections. In this regard, although combination therapies showed a possible survival benefit over monotherapy in observational studies, it should be noted that no randomized clinical trials are currently available to reliably compare