



Published in final edited form as:

Infect Control Hosp Epidemiol. 2016 March ; 37(3): 281–288. doi:10.1017/ice.2015.298.

Hospital Readmissions in Patients with Carbapenem-Resistant *Klebsiella pneumoniae*

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Preliminary results from this study were presented at IDWeek; October 8-12, 2014, Philadelphia, Pennsylvania, USA.

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Conflict of Interest:

No potential conflicts: J.A.M, E.C., F.P., R.A.S., R.C.K., R.R.W., N.M.S., and S.E.

Potential conflicts of interest:

All other authors: no conflicts reported

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Abstract

Background—Various transmission routes contribute to spread of Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in hospitalized patients. Patients with readmissions during which CRKP is again isolated (“CRKP readmission”) potentially contribute to transmission of CRKP.

Objective—Evaluate CRKP readmissions in the Consortium on Resistance against Carbapenems in *K. pneumoniae* (CRaCKle).

Design—Cohort study from 12/24/2011 to 7/1/2013

Setting—CRaCKle is a multicenter consortium of acute care hospitals in the Great Lakes region.

Patients—All patients who were discharged alive during the study period were included. Each patient was included only once at the time of the first CRKP positive culture.

Methods—All readmissions within 90 days of discharge from the index hospitalization during which CRKP was again found were analyzed. Risk factors for CRKP readmission were evaluated in multivariable models.

Results—Twenty percent of patients who were discharged alive (56/287) had a CRKP readmission. A history of malignancy was associated with CRKP readmission (aOR 3.00, 95% CI 1.32-6.65, $p < 0.01$). During the index hospitalization, 160 (56%) patients received antibiotic treatment targeted against CRKP. The choice of antibiotic regimen was associated with CRKP readmission ($p = 0.02$). Receipt of tigecycline-based therapy (aOR 5.13, 95% CI 1.72-17.44, using aminoglycoside-based therapy as a reference in those treated with anti-CRKP antibiotics) was associated with CRKP readmission.

Conclusion—Hospitalized patients with CRKP – specifically those with a history of malignancy – are at high risk of readmission with recurrent CRKP infection or colonization, which may contribute to transmission of CRKP in healthcare systems. Treatment during the index hospitalization with a tigecycline-based regimen increases this risk.

Keywords

carbapenem resistant Enterobacteriaceae; *Klebsiella pneumoniae*; readmission; transmission; tigecycline

Introduction

In spite of aggressive treatment, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections remain associated with high morbidity and mortality.^{1,2} Posing a global threat, CRKP are now endemic in areas worldwide including in the United States, Asia, India, Europe and South America.³ *Klebsiella* spp. expressing *Klebsiella pneumoniae* carbapenemases (KPC) are the most common carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States and have increased rapidly in prevalence during the past two decades.^{4,5}

The rising prevalence of CRKP impacts infection control policies within healthcare settings. KPC β -lactamases encoded by *bla*_{KPC} may be acquired through both clonal and plasmid expansion, facilitating spread of carbapenem resistance among *Enterobacteriaceae*.⁶ Various routes of transmission were demonstrated in recent CRKP outbreaks.⁷⁻⁹ Patients residing in long-term care facilities (LTCF) who are subsequently admitted to acute care hospitals are thought to significantly contribute to the transmission of CRKP. A recent study confirms that patients who are admitted to acute care hospitals from high-acuity LTCF are more likely to be colonized with KPC-producing *Enterobacteriaceae*.¹⁰

As hospital readmissions of patients with persistent or recurrent CRKP may contribute to the accelerated spread of this pathogen, rates of and risk factors for readmission in patients with CRKP during which the organism is again isolated are important to delineate. In order to better understand the manner in which CRKP is disseminated in the Great Lakes region, we sought to determine how often patients infected or colonized with CRKP were readmitted with repeat positive cultures for CRKP and whether the choice of treatment regimen directed against CRKP influenced CRKP readmission rates.

Patients and Methods

Design

A nested cohort study was conducted within the Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle) cohort, which was previously described¹¹. Briefly, CRaCKle is a multicenter, prospective, longitudinal, observational study of hospitalized patients with positive cultures for CRKP in the Great Lakes Region. The cohort consists of CRaCKle patients who survived their index hospitalization and whose index hospitalization started after 12/24/2011 and ended on or before July 1, 2013. Routine screening of asymptomatic patients for CRKP carriage was not performed at any of the study sites during the study period. The Institutional Review Boards of all sites involved approved the study.

Definitions

The primary outcome of this study was CRKP readmission, which was defined as a hospital readmission within 90 days of the index hospitalization during which CRKP was again cultured from the patient. The index hospitalization was defined as the first hospitalization within the study period during which CRKP was identified. Each patient was included only once at the time of the index hospitalization.

Standardized definitions of infection were used, as previously described.¹¹ Treatment regimens effective against CRKP were defined as follows: receipt of an aminoglycoside, colistin, tigecycline, trimethoprim-sulfamethoxazole (TMP-SMX), or fosfomycin unless *in vitro* resistance was documented to that antimicrobial in the patient's isolate. In all instances guidelines from the Clinical and Laboratory Standards Institute (aminoglycosides, TMP-SMX, and fosfomycin) and the European Committee on Antimicrobial Susceptibility Testing (colistin and tigecycline) were followed. For analysis purposes, the type of regimen was assigned as previously reported.¹² Briefly, any regimen which contained an aminoglycoside was deemed "aminoglycoside-based", then any regimen that contained colistin but not an aminoglycoside was designated "colistin-based", followed by any regimen that contained tigecycline but not colistin or aminoglycoside, was regarded as "tigecycline-based". All other regimens were classified as "other". Chronic kidney disease (CKD) was defined as a serum creatinine >2 mg/dL upon admission. Critical illness was designated using a Pitt bacteremia score greater or equal to 4 points on the day of the index culture.¹³ Charlson comorbidity index was calculated as described.¹⁴

Microbiology

In our study CRKP are *K. pneumoniae* isolates with non-susceptibility per CLSI guidelines to the following carbapenems: meropenem, imipenem, or ertapenem.¹⁵ Bacterial identification and routine antimicrobial susceptibility testing was performed with MicroScan (Siemens Healthcare Diagnostics) or Vitek2 (BioMerieux), supplemented by GN4F Sensititre tray (Thermo Fisher) or Etest (bioMerieux), as indicated. In more than 90% of tested isolates, carbapenem resistance was mediated through *bla*_{KPC-2} or *bla*_{KPC-3}, as previously described.¹¹

Statistical Analysis

Differences between groups were analyzed using Wilcoxon Rank Sum for continuous variables. Fisher's Exact, and Pearson testing were used for categorical variables where appropriate. All variables that were associated with CRKP readmission at the p<0.1 level were included in multivariable logistic models, and adjusted odds ratios (aOR) with associated confidence intervals (CI) were calculated. A Kaplan-Meier curve was constructed to compare time to readmission. A Cox proportional hazards model on time to 90-day readmission was used to calculate adjusted hazard ratios (aHR). All variables that were associated with CRKP readmission at the p<0.1 level were included in this model in addition to treatment variables. P values of <0.05 were considered statistically significant. JMP 10.0.1 software (SAS, Inc, Cary, NC) was used for all analyses.

Results

Patients

The demographic characteristics of the 287 patients who met inclusion criteria are summarized in Table 1. CRKP infection was present during index hospitalization in 109 (38%) patients, and the remaining 178 patients were classified as having CRKP colonization. During the index hospitalization, 192 (67%) patients had CRKP isolated from a urine sample, 32 (11%) patients had CRKP isolated from respiratory specimens, 30 (10%)

patients had CRKP isolated from wounds, 24 (8%) patients had CRKP isolated from blood, and 9 (3%) patients had CRKP isolated from “other” sites, which included abdominal sources such as bile, ascites, and abdominal abscess.

Fifty-six out of 287 (20%) patients had a readmission during which CRKP was again isolated (“CRKP readmission”) within 90 days. We evaluated 17 patients on whom we had paired isolates from index admission and readmission. In 16/17 (94%) of patients the same rep-PCR strain was identified upon readmission. During their readmission, 22 (39%) patients had CRKP infection while 34 (61%) patients had colonization of a site with CRKP (Table 1). In univariable analysis, CKD and history of malignancy were significantly associated with CRKP readmission within 90 days. Eighteen of 56 (32%) of patients with CRKP readmission had CKD as compared to 45/231 (19%) in patients without CRKP readmission ($p=0.048$). A history of malignancy was present in 12/56 (21%) of patients with CRKP readmission, as compared to 22/231 (10%) in others ($p=0.02$). In addition, a trend towards increased CRKP readmissions was seen in Black patients; thirty out of 56 patients with CRKP readmission (54%) were Black compared to 90/231 (39%) without CRKP readmission ($p=0.051$). In a multivariable model which included CKD, history of malignancy, and Black race, only a history of malignancy remained associated with CRKP readmission (OR 3.00, 95% CI 1.32-6.65, $p<0.01$). Gender, age, and CRKP colonization vs. infection status were not associated with CRKP readmission. In addition, a trend was seen towards more CRKP readmissions in patients with index isolates resistant to trimethoprim-sulfamethoxazole was observed ($p=0.07$). Other antimicrobial susceptibility testing results were also not significantly associated with CRKP readmission (Table 2).

Treatment

During the index hospitalization, 160 (56%) patients received antibiotics directed against CRKP within the first 7 days of the first positive culture for CRKP. Being treated with antibiotics with *in vitro* activity against CRKP was not associated with CRKP readmission; 30/56 (54%) of those with CRKP readmissions received some form of treatment, whereas 130/231 (56%) of those without CRKP readmissions were treated ($p=0.77$).

The impact of specific treatment choices on CRKP readmissions was then evaluated in patients who received antibiotics effective against CRKP during their index hospitalization (Table 3). In univariable analysis, patients who received >1 drug with *in vitro* activity against CRKP were more likely to have a CRKP readmission; 13/42 (31%) of patients treated with more than one drug were readmitted versus 17/118 (14%) of patients treated with a single agent (OR 2.66, 95% CI 1.16-6.12, $p=0.02$). Most patients were treated with either an aminoglycoside-based regimen ($n=70$, 44%) or a tigecycline-based regimen ($n=49$, 31%) during their index hospitalization. In patients with CRKP readmission, 14/30 (47%) were treated with a tigecycline-based regimen as compared to 35/130 (27%) in those without CRKP readmissions (OR 2.38, 95% CI 1.05- 5.37, $p=0.047$). When evaluating the receipt of tigecycline during the index hospitalization – regardless of other anti-CRKP antibiotics – a similar association between tigecycline use and CRKP readmission was observed (OR 2.64, 95% CI 1.15-6.09, $p=0.03$). Fosfomycin use during the index hospitalization occurred in a total of 17 patients (11%) and was also associated with CRKP readmission in univariable

analysis (OR 3.65, 95% CI 1.26-10.58, $p=0.02$). In multivariable analysis (Table 4), regimen base remained significantly associated with CRKP readmission ($p=0.02$). Using patients who received aminoglycoside-based therapy as a reference group, the adjusted OR (aOR) of tigecycline-based therapy was 5.13 (95% CI 1.72-17.44). In addition, receipt of more than one anti-CRKP antibiotic during index hospitalization was strongly associated with CRKP readmission (aOR 5.14, 95% CI 1.78-16.41, $p<0.01$). When comparing patients who received more than one to those who received only one anti-CRKP antibiotic, no significant differences were found in age, Charlson comorbidity index, or Pitt bacteremia score.

Time to CRKP readmission

Tigecycline-based treatment was associated with a decreased time to 90-day CRKP readmission ($p=0.04$ by log-rank, Figure 1.A). Similarly, receiving any tigecycline – regardless of receipt of other antibiotics with *in vitro* activity against CRKP – was associated with decreased time to 90-day CRKP readmission ($p=0.02$ by log-rank, Figure 1.B). In Cox proportional hazards analysis (Table 5), treatment regimen base remained significantly associated with time to 90-day CRKP readmission ($p=0.02$). Using the patients who received aminoglycoside-based therapy as a reference group, the aHR for tigecycline-based therapy was 4.33 (95% CI 1.67-11.60). Of note, when urinary source was forced into the model as a confounding variable, the association between treatment regimen and time to CRKP readmission remained significant (data not shown). In addition, receipt of >1 *in vitro* active antibiotic in the first 7 days after the first positive CRKP culture during the index hospitalization was also associated with time to 90-day CRKP readmission (aHR 4.46, 95% CI 1.77-11.36; $p<0.01$). To determine if the association between tigecycline-based therapy and time to 90-day CRKP readmission was dependent on infection status during index hospitalization, a stratified analysis was performed. In both the CRKP colonization group as well as the CRKP infection group, treatment base was associated with time to 90-day CRKP readmission in Cox proportional hazard analysis ($p=0.03$ and $p=0.04$, respectively). The hazard ratios of tigecycline-based therapy, when using aminoglycoside-based therapy as a reference, were 3.99 (95% CI 1.20-14.31) and 6.56 (95% CI 1.39-34.81) for colonization and infection, respectively.

Discussion

The present study evaluates readmission rates with CRKP and analysis of risk factors from a prospective multicenter cohort. We observed that it was common for hospitalized patients with CRKP infection or colonization to have a readmission during which CRKP was again isolated. Interestingly, this occurred in 20% of patients who survived their index hospitalization. This finding suggests that patients with CRKP – especially those patients treated with tigecycline and those with a history of malignancy – carry CRKP for prolonged periods of time and have frequent and recurrent healthcare exposures during which they are likely to interact with other vulnerable patients. In contrast, the presence of CRKP infection vs. CRKP colonization did not appear to have an impact on CRKP readmission rates.

The observation of CRKP readmission is an outcome that requires two related but distinct occurrences. Firstly, the patient needs to be readmitted, and secondly, during that

readmission, CRKP must be cultured from a clinically important site. Thus, in the current study, we evaluated the overlapping risk factors for hospital readmission and prolonged CRKP carriage.

Hospital readmission rates are the subject of multiple studies to identify risk factors for readmission.^{16,17} Hospital reimbursement is increasingly being linked to readmission rates. In a recent report of 90-day readmissions following hospitalization for severe sepsis, the investigators noted a 42.6% readmission rate with 41.6% of these readmissions being for potentially preventable conditions such as heart failure exacerbation, pneumonia, and urinary tract infection.¹⁸ Potentially preventable readmissions occurred significantly more frequently in patients with severe sepsis compared to matched controls with other acute care diagnoses.

During a 90-day time period, a high rate of finding CRKP again during readmission was consistent with findings from studies of duration of CRE carriage. In one study, among patients who have CRE isolated during their index hospitalization, 78% of patients still had CRE carriage at 3 months while 39% still had detectable CRE carriage at 1 year.¹⁹ Those patients who were readmitted and in whom CRE was isolated in a clinical culture as opposed to a surveillance culture had significantly longer CRE carriage (641 days vs. 387 days).¹⁹ Another study identified risk factors for recurrent positive CRE screens during hospital encounters including prior fluoroquinolone use, admission from another hospital or healthcare facility, and hospital readmission within 3 months of initial positive CRE screen.²⁰ In a case-control study of recurrence of CRE carriage from Israel, recurrence of CRE was common after presumed eradication at 6 months after last positive sample and associated with recurrent admissions after presumed eradication.²¹

The current study did not directly address the role of CRE decolonization as a means to reduce the risk of future infection and spread of CRE to other patients. Decolonization is another potential target for infection control measures in high risk patients. In experimental models, oral high-dose polymyxin therapy resulted in long-term elimination of CRE carriage.²² This principle was then evaluated in a pilot study of selective digestive decontamination for eradication of CRKP carriage. A double blind randomized control trial was conducted in 40 patients comparing oral gentamicin and polymyxin E versus placebo.²³ The investigators showed the CRKP isolation in rectal cultures was significantly reduced by 2 weeks, and this reduction was maintained through the 6 week time period of the study.

Patients with malignancies were found to be at increased risk for CRKP readmission. This is likely secondary to an increased overall readmission risk in this cohort. In addition, cancer has been linked to microbiome changes²⁴. This may theoretically influence the duration of CRKP carriage.

The finding of an increased risk of CRKP readmission when patients are treated with tigecycline raises concern for a potential relationship between tigecycline use and risk for subsequent CRKP treatment failure whether demonstrated through recurrent infection or persistent colonization. A number of potential explanations for this observed association could be considered. As this is an observational study, our data may simply reflect

we found that a history of malignancy and choice of treatment impact this risk. Further studies in patients with CRE are needed to better characterize relationships between treatment, subsequent risk for readmission, duration of CRE carriage and risk for subsequent CRE infection. Moreover, identifying patients at risk for CRKP treatment failure and readmission and intervening through infection control measures and choice of treatment regimens based on mechanism of action should be important future directions arising from this study.

Acknowledgements

none

Funding:

This work was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number UMI1A1104681, and by funding to DVD and FP from the Clinical and Translational Science Collaborative of Cleveland, UL1TR000439 from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research. VGF was supported by Mid-Career Mentoring Award K24-AI093969 from NIH. In addition, this work was supported in part by the Veterans Affairs Merit Review Program (RAB), the National Institutes of Health (Grant AI072219-05 and AI063517-07 to RAB), and the Geriatric Research Education and Clinical Center VISN 10 (RAB), the Research Program Committees of the Cleveland Clinic (DVD), an unrestricted research grant from the STERIS Corporation (DVD). YD was supported by research awards R01AI104895 and R21AI107302 from the NIH. KSK is supported by the National Institute of Allergy and Infectious Diseases (Division of Microbiology and Infectious Diseases protocol 10-0065 and RO1 1R01AI119446-01)

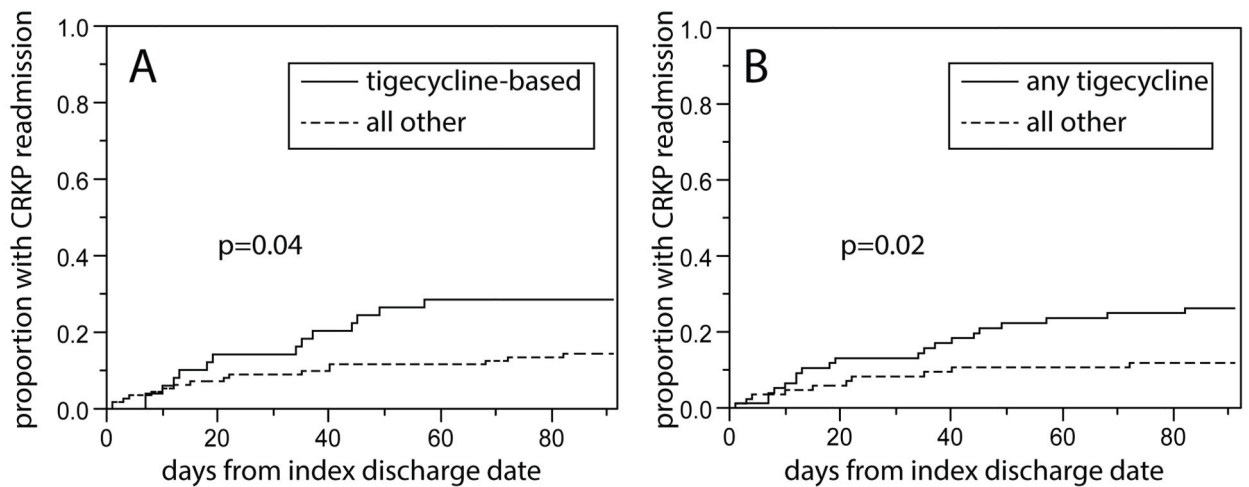
S.S.R.: Research support from bioMerieux, BD Diagnostics, BioFire, OpGen, Forest Laboratories, Achaogen, Nanosphere and Pocared. Honorarium from bioMerieux. **Y.D.:** Grant support: Merck, NIH. Consulting fee: Melinta. Advisory board: Shionogi. **K.K.:** Forest Laboratories, Inc., Consultant, Grant Investigator and Speaker's Bureau, Consulting fee, Grant recipient and Speaker honorarium. **R.A.B.:** AstraZeneca: Grant Investigator, Grant recipient, Merck: Grant Investigator, Grant recipient, Melinta: Grant Investigator, Grant recipient, Steris: Grant Investigator, Grant recipient, NIH: Grant Investigator, Grant recipient, VA Merit Review: Grant Investigator, Grant recipient. **V.G.F.:** Grant/ Research Support: Advanced Liquid Logic, Cubist, Cerexa, MedImmune, Merck, NIH, Novartis, Pfizer, Theravance. Paid Consultant: Affinium, Baxter, Cerexa, Cubist, Debiopharm, Durata, Merck, Novartis, NovaDigm, The Medicines Company, MedImmune, Pfizer, Theravance, Trius. Honoraria: Arpida, Astellas, Cubist, Inhibitex, Merck, Pfizer, Targanta, Theravance, Wyeth, Ortho-McNeil, Novartis, Vertex Pharmaceuticals. Membership: Merck Co-Chair V710 Vaccine. **D.v.D.:** Actavis, Tetrphase, Sanofi-Pasteur, Advisory Board. Steris Inc., Research funding. Scynexis Research funding

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No. at risk:									
tigecycline	49	42	35	35	76	67	59	57	
all other	111	101	99	95	84	78	76	75	

Figure 1. Time-to-90-day CRKP readmission for patients who received anti-CRKP antibiotics (n=160) during their index hospitalization. Panel A: comparing patients who received tigecycline-based treatment during index hospitalization (n=49) vs. all others (n=111). Panel B: comparing patients who received any tigecycline during index hospitalization (n=76) vs. all others (n=84).

Table 1
Clinical Characteristics

	All	CRKP readmission	No CRKP readmission	p*	p [†]
N	287	56 (20)	231 (80)		
Age, median (IQR)	70 (58-81)	69 (56-83)	70 (59-81)	0.73	
Female	167 (58)	28 (50)	139 (60)	0.18	
Race/Ethnicity					
White	150 (52)	26 (46)	124 (54)	0.37	
Black	120 (42)	30 (54)	90 (39)	0.051	0.06
Hispanic	8 (3)	0	8 (3)	0.36	
Other	9 (3)	0	9 (4)	0.21	
Charlson comorbidity index, median (IQR)	3 (2-5)	3 (2-6)	3 (2-5)	0.40	
Diabetes mellitus	153 (53)	28 (50)	125 (54)	0.65	
Renal failure[‡]	63 (22)	18 (32)	45 (19)	0.048	0.0922
Heart disease	160 (56)	28 (50)	132 (57)	0.37	
COPD	77 (27)	15 (27)	62 (27)	1.00	
Malignancy	23 (12)	12 (21)	22 (10)	0.02	<0.01
Origin					
Skilled nursing facility	159 (55)	30 (53)	129 (56)	0.49	
Home	84 (29)	20 (36)	64 (28)		
Hospital transfer	28 (10)	3 (5)	25 (11)		
Long term acute care	16 (6)	3 (5)	13 (6)		
Length of stay, days, median (IQR)	9 (6-16)	8 (6-16)	10 (6-16)	0.35	
Critical illness[§]	70 (24)	13 (23)	57 (25)	0.86	
Infection	109 (38)	22 (39)	87 (38)	0.88	
Source					
Urine	192 (67)	41 (73)	151 (65)	0.46	
Respiratory	32 (11)	4 (7)	28 (12)		
Wound	30 (10)	7 (13)	23 (10)		
Blood	24 (8)	2 (4)	22 (10)		
Other	9 (3)	2 (4)	7 (3)		
Any treatment	160 (56)	30 (54)	130 (56)	0.77	
Disposition					
Skilled nursing facility	157 (55)	28 (50)	129 (56)	0.51	
Home	58 (20)	14 (25)	44 (19)		
Hospital transfer	9 (3)	3 (5)	6 (3)		
Long term acute care	63 (22)	11 (20)	52 (23)		

All data expressed as n (%), unless otherwise indicated. IQR, interquartile range; LOS, length of stay.

* univariable relationship between variable of interest and CRKP readmission

[†] multivariable model including black race, renal failure and malignancy

[‡] renal failure defined as creatinine >2 mg/dL upon admission

[§] critical illness defined as Pitt bacteremia score ≥ 4 at the time of index culture

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Table 2

Antimicrobial susceptibilities

	All	CRKP readmission	No CRKP readmission
n	287	56 (20)	231 (80)
Amikacin*			
not tested	89	15 (17)	74 (83)
susceptible	151	31 (21)	120 (79)
intermediate	10	0	10 (100)
resistant	37	10 (27)	27 (73)
Gentamicin*			
not tested	2	0	2 (100)
susceptible	114	22 (19)	92 (81)
intermediate	25	6 (24)	19 (76)
resistant	146	28 (19)	118 (81)
Colistin [†]			
not tested	160	30 (19)	130 (81)
susceptible	117	25 (21)	92 (79)
resistant	10	1 (10)	9 (90)
Tigecycline [†]			
not tested	84	16 (19)	68 (81)
susceptible	107	25 (23)	82 (77)
intermediate	60	10 (17)	50 (83)
resistant	36	5 (14)	31 (86)
TMP/SMX*			
not tested	9	0	9 (100)
susceptible	82	11 (13)	71 (87)
resistant	196	45 (23)	151 (77)

* Based on Clinical and Laboratory Standards Institute guidelines

[†] Based on European Committee on Antimicrobial Susceptibility Testing

Table 3
Treatment characteristics

	All	CRKP readmission	No CRKP readmission	p
n	160	30 (19)	130 (81)	
Any <i>in vitro</i> active drug in first 7 days				
aminoglycoside	70 (44)	11 (37)	59 (45)	0.42
colistin	27 (17)	5 (17)	22 (17)	1.00
tigecycline	76 (48)	20 (67)	56 (43)	0.03
trimethoprim/sulfamethoxazole	14 (9)	1 (3)	13 (10)	0.47
fosfomycin	17 (11)	7 (23)	10 (8)	0.02
Base of regimen				
aminoglycoside	70 (44)	11 (37)	59 (45)	0.42
colistin	22 (14)	3 (10)	19 (15)	0.77
tigecycline	49 (31)	14 (47)	35 (27)	0.047
other	19 (12)	2 (7)	17 (13)	0.53
>1 <i>in vitro</i> active drug in first 7 days	42 (26)	13 (43)	29 (22)	0.02

Table 4
Multivariable logistic regression for CRKP readmission in treated patients (n=160)

	OR	95% CI	p
Black race	1.69	0.68-4.23	0.26
History of malignancy	4.07	1.14-14.45	0.03
Renal failure	1.10	0.37-3.05	0.86
Base of regimen			0.02
aminoglycoside (ref.)	-	-	
colistin	1.26	0.24-5.30	
tigecycline	5.13	1.72-17.44	
other	2.03	0.26-11.57	
>1 <i>in vitro</i> active drug in first 7 days	5.14	1.78-16.41	<0.01

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Table 5
Cox proportional hazards model on time to CRKP readmission within 90 days in treated patients (n=160)

	aHR	95% CI	p
Black race	1.93	0.85-4.30	0.12
Malignancy	3.17	1.12-7.83	0.03
Renal failure	1.06	0.41-2.46	0.88
Base of regimen			0.02
aminoglycoside (ref.)	-	-	
colistin	1.28	0.29-4.15	
tigecycline	4.33	1.67-11.60	
other	1.87	0.26-8.80	
>1 <i>in vitro</i> active drug in first 7 days	4.46	1.77-11.36	<0.01

aHR, adjusted hazard ratio; CI, confidence interval.

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