

## Impact of therapy and strain type on outcomes in urinary tract infections caused by carbapenem-resistant *Klebsiella pneumoniae*

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**Objectives:** Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an important healthcare-associated pathogen. We evaluated the impact of CRKP strain type and treatment on outcomes of patients with CRKP bacteriuria.

**Patients and methods:** Physician-diagnosed CRKP urinary tract infection (UTI)—defined as those patients who received directed treatment for CRKP bacteriuria—was studied in the multicentre, prospective Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle) cohort. Strain typing by repetitive extragenic palindromic PCR (rep-PCR) was performed. Outcomes were classified as failure, indeterminate or success. Univariate and multivariate ordinal analyses to evaluate the associations between outcome, treatment and strain type were followed by binomial analyses.

**Results:** One-hundred-and-fifty-seven patients with physician-diagnosed CRKP UTI were included. After adjustment for CDC/National Healthcare Safety Network (NHSN)-defined UTI, critical illness and receipt of more than one active antibiotic, patients treated with aminoglycosides were less likely to fail therapy [adjusted OR (aOR) for failure 0.34, 95% CI 0.15–0.73,  $P=0.0049$ ]. In contrast, patients treated with tigecycline were more likely to fail therapy (aOR for failure 2.29, 95% CI 1.03–5.13,  $P=0.0425$ ). Strain type data were analysed for 55 patients. The predominant clades were ST258A ( $n=18$ , 33%) and ST258B ( $n=26$ , 47%). After adjustment for CDC/NHSN-defined UTI and use of tigecycline and aminoglycosides, infection with strain type ST258A was associated with clinical outcome in ordinal analysis ( $P=0.0343$ ). In multivariate binomial models, strain type ST258A was associated with clinical failure (aOR for failure 5.82, 95% CI 1.47–28.50,  $P=0.0113$ ).

**Conclusions:** In this nested cohort study of physician-diagnosed CRKP UTI, both choice of treatment and CRKP strain type appeared to impact on clinical outcomes.

**Keywords:** carbapenem-resistant Enterobacteriaceae, MDR, UTIs, aminoglycosides, tigecycline

### Introduction

Infections with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represent a growing threat to patients in the USA and worldwide.<sup>1</sup> The treatment of these infections is problematic, as few therapeutic options are available.<sup>2</sup> Antibiotics that may retain *in vitro* activity against CRKP include polymyxins such as colistin, tigecycline and aminoglycosides. Novel therapies that promise

to be effective against CRKP, such as ceftazidime/avibactam, plazomicin and BAL30072, are still far from the armamentarium of the physician.

Most CRKP in the USA produce carbapenemases of the *K. pneumoniae* carbapenemase (KPC) family. In addition, metallo- $\beta$ -lactamases such as New Delhi metallo- $\beta$ -lactamase (NDM-1) are prevalent causes of carbapenem resistance in Enterobacteriaceae in other parts of the world, and are beginning to be reported in the USA as

well.<sup>3,4</sup> The most common endemic strain of CRKP is ST258 by MLST, which can be further subdivided into clinically and microbiologically distinct clades by the use of high-resolution restriction mapping, repetitive extragenic palindromic PCR (rep-PCR) and whole-genome sequencing.<sup>3,5</sup> In most patients who have CRKP isolated during their hospitalization, CRKP is found in urine cultures.<sup>3</sup> About a third of patients with CRKP bacteriuria meet CDC/National Healthcare Safety Network (NHSN) criteria for urinary tract infection (UTI).<sup>3,6</sup> However, these criteria were primarily designed for surveillance purposes, and many patients with CRKP bacteriuria who do not meet these criteria are thought to have UTI by their providers and receive directed treatment. To address this point, we describe the impact of various treatment regimens on the outcomes of patients who were treated with antibiotics directed against CRKP—colistin, tigecycline, aminoglycosides, fosfomycin and trimethoprim/sulfamethoxazole—for CRKP bacteriuria, while adjusting for the presence of UTI as defined by CDC/NHSN. Our primary aims were to evaluate the impact of treatment and strain type on outcomes in physician-diagnosed CRKP UTI.

## Patients and methods

### Patients

The multicentre, prospective Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* (CRaCKle) study was described previously.<sup>3</sup> The current study represents a nested cohort within CRaCKle. All hospitalized patients who had a urine culture that grew CRKP and who received active treatment within 7 days of their first positive urine culture during their hospitalization were included if their index hospitalization began and ended in the study period, 24 December 2011 to 1 October 2013. Patients were included once at the time of their first episode of treated CRKP bacteriuria. The institutional review boards of all health systems involved approved the study.

### Definitions

The index hospitalization was designated as the first hospital stay within the study period during which CRKP was isolated from the urine followed by active treatment within 7 days. Active treatment was defined as receipt of an aminoglycoside, colistin, tigecycline, trimethoprim/sulfamethoxazole or fosfomycin, unless *in vitro* resistance was documented to that antimicrobial in the patient's isolate, following CLSI (aminoglycosides, trimethoprim/sulfamethoxazole and fosfomycin) and EUCAST (colistin and tigecycline) guidelines. The base of the regimen was assigned as follows: any regimen that contained an aminoglycoside was deemed aminoglycoside-based; any regimen that contained colistin, but not an aminoglycoside, was deemed colistin-based; and any regimen that contained tigecycline, but not colistin or an aminoglycoside, was deemed tigecycline-based. All other regimens were classified as 'other'.

Criteria as outlined by CDC/NHSN were used to define UTI and asymptomatic bacteraemic UTI (ABUTI); these two categories were grouped together as CDC/NHSN-defined UTI for analysis purposes.<sup>6</sup> Non-physiological urinary drainage was defined as the presence of an indwelling urinary catheter, permanent urinary diversion or intermittent urinary catheterization. All other patients were considered to have physiological urinary drainage.

Critical illness was defined as a Pitt bacteraemia score  $\geq 4$  points on the day of the index urine culture.<sup>7</sup> Treatment failure was defined as patients who had recurrent CRKP isolated from the urine at least 7 days after their index culture. In addition, those who did not survive their index hospitalization (death or discharge to hospice) were considered treatment failures. Treatment success was defined as patients who had a negative urine culture documented after their index culture and who did not meet any of the

criteria for treatment failure. Treatment outcome was deemed indeterminate in those patients who did not meet criteria for success or failure.

### Microbiology

CRKP is defined as *K. pneumoniae* isolates with non-susceptibility to the following carbapenems as per CLSI guidelines: meropenem, imipenem or ertapenem.<sup>8</sup> Bacterial identification and routine antimicrobial susceptibility testing was performed with MicroScan (Siemens Healthcare Diagnostics) or Vitek 2 (bioMérieux), supplemented by a GN4F Sensititre tray (Thermo Fisher) to confirm carbapenem results and to test tigecycline susceptibility.

### Detection of carbapenemases in CRKP and strain typing

Detection of carbapenemase genes and rep-PCR strain typing was performed as previously described.<sup>3</sup> Briefly, PCR amplification of *bla*<sub>KPC</sub>, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>IMP</sub> and *bla*<sub>OXA-48</sub> genes was conducted using established primers and methods; amplicons were sequenced at a commercial sequencing facility (MCLAB, San Francisco, CA, USA) and analysed.<sup>9,10</sup> rep-PCR was performed using the DiversiLab strain typing system (Bacterial BarCodes, bioMérieux, Athens, GA, USA). Isolates with  $\geq 95\%$  similarity were considered to be of the same rep-PCR type. MLST was performed on CRKP isolates from the predominant rep-PCR types, as previously described.<sup>11</sup> Sequences of seven housekeeping genes (*rpoB*, *gapA*, *mdh*, *pgi*, *phoE*, *infB* and *tonB*) were compared with the MLST database (<http://www.pasteur.fr/recherche/genopole/PF8/mlst>).

### Analysis

The primary outcome was analysed as an ordinal variable in the following order: failure, indeterminate, success. Ordinal logistic regression was used to estimate associations between outcomes and microbiological and clinical variables. For all models, ordinal lack-of-fit testing was performed to rule out a poorly fitted model. In addition, for the purpose of sensitivity analysis, as well as to estimate effect sizes, all associations were evaluated in binomial logistic models either combining indeterminates with success (i.e. comparing patients with failure versus all others) or with failure (i.e. comparing patients with success versus all others). Barnard's exact test was used to compare proportions. The Brown–Mood median test was used to compare medians. All analyses were performed using JMP software (SAS Inc., Cary, NC, USA).

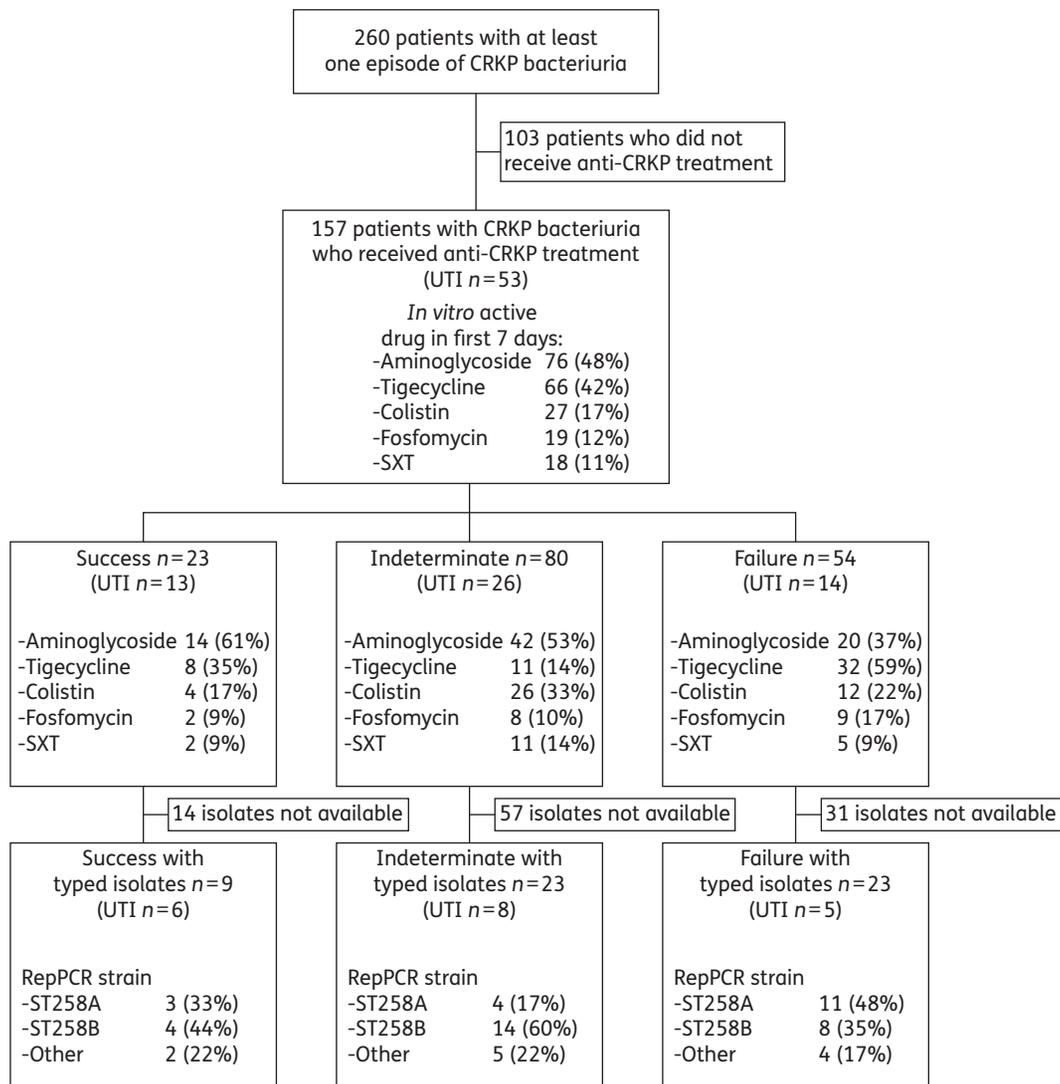
## Results

### Patients

During the 21 month study period, 157 unique patients with physician-diagnosed CRKP UTI were included in the study (Figure 1). Their clinical characteristics are outlined in Table 1. Median follow-up time from date of discharge of the index hospitalization to the end of the study period was 306 days (IQR 193–487 days). Antimicrobial susceptibility testing was performed as clinically indicated (Figure 2). Colistin and amikacin demonstrated the most reliable *in vitro* activity, with susceptibility rates of 91% and 83% in tested isolates, respectively. Only five isolates were tested against fosfomycin; four of these were resistant.

### UTI as defined by NHSN

Within this cohort of 157 patients with physician-diagnosed CRKP UTI, 53 (34%) met CDC/NHSN criteria for UTI. Of these 53 patients, 10 (19%) had CRKP bacteraemia. In addition, 2 (4%) and 2 (4%)



**Figure 1.** Flow diagram showing the treatment of patients in various outcome categories. UTI was as defined in CDC/NHSN criteria. SXT, trimethoprim/sulfamethoxazole.

patients had CRKP isolated from wounds and respiratory tract, respectively. Of the 104 patients who did not meet criteria for infection, 14 (13%) had CRKP isolated from non-urinary sources, 8 (8%) from wounds and 3 (3%) from respiratory sources, and 3 (3%) had CRKP bacteraemia >24 h after their urine culture.

**Outcomes**

In 23 (15%) of 157 patients with physician-diagnosed UTI, treatment success was documented, whereas 54 patients (34%) were deemed treatment failures. The remaining 80 patients (51%) had an indeterminate outcome. Of the 54 patients with treatment failure, 16 (30%) died and 1 (2%) was discharged to a hospice. The remaining 37 (69%) patients had recurrent CRKP bacteriuria. In univariate ordinal regression, CDC/NHSN-defined UTI, location at the time of culture and critical illness were associated with outcome. In a multivariable ordinal model including these variables and urinary drainage, only the association with CDC/NHSN-defined UTI

remained significant ( $P=0.0289$ ). To determine the direction and magnitude of these associations, we used multivariable binomial models to compare patients with failure versus all others and patients with success versus all others. In the multivariable binomial model comparing patients with failure versus all others, critical illness was associated with failure [adjusted OR (aOR) for failure 2.66, 95% CI 1.09–6.53,  $P=0.0313$ ]. None of the other variables was associated with failure. In comparing success versus all others, both CDC/NHSN-defined UTI (aOR for success 2.93, 95% CI 1.13–7.85,  $P=0.0273$ ) and critical illness (aOR for success 3.62, 95% CI 1.08–11.98,  $P=0.0376$ ) were associated with success. None of the other variables was associated with success.

**Treatment**

The majority of patients (110/157, 70%) received only one active agent (Table 2). In patients who received a single active agent, aminoglycosides (gentamicin or amikacin) or tigecycline were

**Table 1.** Clinical characteristics and outcomes

	All	Success	Indeterminate	Failure	<i>p</i> <sup>a</sup>	<i>p</i> <sup>b</sup>
<i>n</i>	157	23	80	54		
Female	93 (59)	11 (48)	55 (69)	27 (50)	0.4260	
Age (years), median (IQR)	72 (61–82)	73 (58–84)	74 (63–82)	71 (59–81)	0.4231	
Race/ethnicity					0.9433	
white	88 (56)	14 (61)	44 (55)	30 (56)		
black	63 (40)	8 (35)	33 (41)	22 (41)		
Hispanic	4 (3)	1 (4)	2 (3)	1 (2)		
other	2 (1)	0	1 (1)	1 (2)		
Charlson comorbidity index, median (IQR)	3 (2–5)	2 (1–4)	4 (2–5)	3.5 (2–6)	0.1653	
Renal failure upon admission <sup>c</sup>	34 (22)	3 (13)	18 (23)	13 (24)	0.3771	
UTI <sup>d</sup>	53 (34)	13 (57)	26 (33)	14 (26)	0.0210	0.0289
Urinary drainage					0.0783	0.3898
physiological	48 (30)	8 (35)	26 (33)	14 (26)		
Foley catheter	82 (52)	9 (39)	39 (49)	34 (63)		
other	27 (17)	8 (35)	15 (19)	6 (11)		
Location at time of culture					0.0159	0.1974
ward	62 (39)	10 (43)	33 (41)	19 (35)		
emergency department	61 (39)	10 (43)	35 (44)	16 (30)		
ICU	34 (22)	3 (13)	12 (15)	19 (34)		
LOS (days), median (IQR)	11 (7–17)	13 (10–17)	10 (6–16)	9 (6–21)	0.1393	
Critical illness <sup>e</sup>	39 (25)	8 (35)	9 (11)	22 (41)	0.0295	0.3792
Origin					0.4438	
skilled nursing facility	86 (55)	13 (57)	47 (59)	26 (48)		
home	44 (28)	4 (17)	22 (28)	18 (33)		
hospital transfer	17 (11)	3 (13)	7 (9)	7 (13)		
long-term acute care	10 (6)	3 (13)	4 (5)	3 (6)		
Disposition					— <sup>f</sup>	
skilled nursing facility	78 (50)	12 (52)	45 (56)	21 (39)		
home	33 (21)	5 (22)	20 (25)	8 (15)		
long-term acute care	29 (18)	6 (26)	15 (19)	8 (15)		
death	16 (10)	—	—	16 (30)		
hospice	1 (1)	—	—	1 (2)		

LOS, length of stay.

All data are expressed as *n* (%) unless otherwise indicated.

<sup>a</sup>*P* value indicating the univariate relationship between the variable of interest and the ordinal outcome (success, indeterminate, failure).

<sup>b</sup>Multivariable model including UTI, location, critical illness and urinary drainage.

<sup>c</sup>Renal failure defined as creatinine >2 mg/dL upon admission.

<sup>d</sup>UTI as defined by CDC/NHSN.

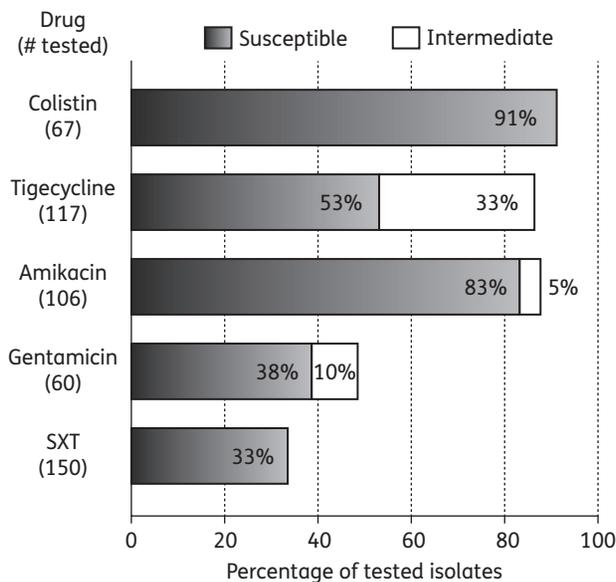
<sup>e</sup>Critical illness defined as Pitt bacteraemia score ≥4.

<sup>f</sup>Not analysed as disposition was part of the outcome definition.

most commonly used. Forty-seven (30%) patients received more than one active agent, in a variety of combinations (Table 2). Presence of CDC/NHSN-defined UTI was not associated with the use of any specific antimicrobial. CDC/NHSN-defined UTI was also not associated with receipt of more than one active agent; 16/53 (30%) patients with CDC/NHSN-defined UTI received more than one agent compared with 31/104 (30%) patients without CDC/NHSN-defined UTI (not significant). The administration of fosfomycin was associated with absence of critical illness; none

of the 39 patients with critical illness received fosfomycin, compared with 19/118 (16%) patients without critical illness (*P*=0.004). Critical illness was not associated with receipt of more than one drug or any other treatment choice.

The association between the use of any single drug and outcomes was evaluated in a multivariable ordinal logistic model that included the drug in question, critical illness, the presence of CDC/NHSN-defined UTI and the use of more than one active antibiotic. In these models, use of aminoglycosides and tigecycline



**Figure 2.** Antimicrobial susceptibility patterns. SXT, trimethoprim/sulfamethoxazole.

was associated with outcomes. Multivariable binomial models indicated that patients treated with aminoglycosides were less likely to fail therapy (aOR for failure 0.34, 95% CI 0.15–0.73,  $P=0.0049$ ), whereas patients treated with tigecycline were more likely to fail therapy (aOR for failure 2.29, 95% CI 1.03–5.13,  $P=0.0425$ ). Neither the use of aminoglycosides (aOR for success 2.04, 95% CI 0.80–5.45,  $P=0.1362$ ) nor the use of tigecycline (aOR for success 0.59, 95% CI 0.19–1.65,  $P=0.3165$ ) was associated with treatment success. To determine whether these associations were influenced by the use of a composite definition for treatment failure, we repeated the models after excluding the 17 patients who did not survive their index hospitalization. The associations between treatment choice and treatment failure remained significant after excluding these patients (data not shown).

We then evaluated the associations between regimen base and outcomes. In multivariable ordinal regression adjusting for critical illness, CDC/NHSN-defined UTI and the use of more than one active antibiotic, regimen base was associated with outcome ( $P=0.0083$ ). Further evaluation of this effect with binomial analyses showed an association with failure ( $P=0.0065$ ), but not with success ( $P=0.4330$ ). Using the aminoglycoside-based regimen group as the reference group, the aORs for failure were 1.92 (95% CI 0.63–5.76) for colistin-based regimens, 5.19 (95% CI 2.03–14.13) for tigecycline-based regimens and 1.71 (95% CI 0.46–5.78) for other regimens.

A non-significant trend was seen towards association between outcome and receipt of more than one active antibiotic in multivariable ordinal regression ( $P=0.0575$ ). Patients who received more than one *in vitro* active agent were more likely to experience failure (aOR for failure 2.53, 95% CI 1.21–5.37,  $P=0.0141$ ).

### CRKP strains

The isolates of 55 patients were available for strain typing (Table 3). Significant differences were not seen between patients with available index isolates versus those whose isolates were

unavailable in demographics, treatment choices or outcomes (data not shown). The predominant strain types were rep-PCR A ( $n=18$ , 33%) and B ( $n=26$ , 47%), both part of the ST258 strain complex.<sup>3</sup> The remaining 11 patients had a variety of other strain types identified by rep-PCR. The majority of isolates expressed KPC; 24 (44%) carried *bla*<sub>KPC-2</sub> and 29 (53%) carried *bla*<sub>KPC-3</sub>. One isolate carried *bla*<sub>NDM-1</sub> and one was negative for all carbapenemases tested.

None of the clinical variables was significantly associated with ST258A, except for fosfomycin use, which was more common in patients with ST258A ( $P=0.0317$ ). On univariate ordinal regression, strain type was not associated with outcome. We then constructed a multivariable ordinal regression model (Table 4) that included strain type and the variables previously identified as related to outcome (CDC/NHSN-defined UTI, tigecycline use and aminoglycoside use). In this model, ST258A was associated with outcome ( $P=0.0343$ ). In binomial models, ST258A was associated with failure (aOR for failure 5.82, 95% CI 1.47–28.50,  $P=0.0113$ ), but not associated with success (aOR for success 0.73, 95% CI 0.12–3.74,  $P=0.7120$ ). We also constructed a model that included the base of the regimen used (Table 5). In this model a trend towards association was seen for ST258A and outcome ( $P=0.0598$ ). In the corresponding binomial models, ST258A was again associated with failure (aOR for failure 5.07, 95% CI 1.32–23.59,  $P=0.0176$ ), but not associated with success (aOR for success 0.89, 95% CI 0.14–4.62,  $P=0.8935$ ). To determine whether the increased failure rates of patients infected with ST258A were related to the increased use of fosfomycin, we repeated these models after exclusion of patients treated with fosfomycin. The association between strain type and treatment failure remained significant after excluding these patients (data not shown). Furthermore, we evaluated whether these results were influenced by the use of a composite outcome by repeating the analyses excluding those patients who did not survive their index hospitalization ( $n=7$ ). Excluding these patients also did not alter the association between strain type and treatment failure (data not shown).

### Discussion

This study shows that the outcomes of CRKP UTI are influenced by both the choice of antimicrobial treatment and the CRKP strain type. In this large prospective multicentre cohort, patients who were treated with aminoglycosides enjoyed better outcomes, whereas patients treated with tigecycline experienced worse outcomes. These associations remained significant after adjustment for relevant clinical co-variables. In addition, we report here the first evidence that patients infected with the CRKP strain ST258A are more likely to have treatment failure. The ST258 strain complex is the most common strain complex of CRKP globally, and was recently shown to consist of at least two clinically and molecularly distinct strain types.<sup>3,5,12,13</sup> The current finding that ST258A is associated with worse outcomes after treated CRKP bacteriuria adds to this growing knowledge base, and emphasizes the link between clinical and molecular findings. The molecular mechanisms causing these observed clinical differences between patients with different CRKP strains remain unclear. Different strains may carry different virulence factors encoded in chromosomal or plasmid DNA. In support of this, ST258 CRKP was shown

**Table 2.** Treatment

	All	Success	Indeterminate	Failure	<i>P</i> <sup>a</sup>	<i>P</i> <sup>b</sup>
<i>n</i>	157	23	80	54		
Any <i>in vitro</i> active drug in first 7 days						
aminoglycoside	76 (48)	14 (61)	42 (53)	20 (37)	0.0292	0.0041
colistin	27 (17)	4 (17)	11 (14)	12 (22)	0.3469	0.6531
tigecycline	66 (42)	8 (35)	26 (33)	32 (59)	0.0047	0.0365
SXT	18 (11)	2 (9)	11 (14)	5 (9)	0.7801	0.9633
fosfomycin	19 (12)	2 (9)	8 (10)	9 (17)	0.2168	0.2790
Base of regimen <sup>c</sup>					0.0269	0.0083
aminoglycoside	76 (48)	14 (61)	42 (53)	20 (37)		
colistin	23 (15)	3 (13)	10 (13)	10 (19)		
tigecycline	36 (23)	3 (13)	14 (18)	19 (35)		
other	22 (14)	3 (13)	14 (18)	5 (9)		
Single <i>in vitro</i> active drug in first 7 days <sup>d</sup>	110 (70)	16 (70)	63 (79)	31 (57)	0.0500	
aminoglycoside	47 (30)	8 (35)	28 (35)	11 (20)	0.2990	0.1004
colistin	11 (7)	2 (9)	8 (10)	1 (2)	0.2079	0.3182
tigecycline	30 (19)	3 (13)	13 (16)	14 (26)	0.0148	0.0102
SXT	14 (9)	2 (9)	9 (11)	3 (6)	0.6664	0.9531
fosfomycin	8 (5)	1 (4)	5 (6)	2 (4)	0.9444	0.9888
>1 <i>in vitro</i> active drug in first 7 days <sup>e</sup>	47 (30)	7 (30)	17 (21)	23 (43)	0.0500	0.0575
aminoglycoside + tigecycline	17 (11)	4 (17)	9 (11)	4 (7)	—	—
aminoglycoside + fosfomycin	7 (4)	1 (4)	3 (4)	3 (6)	—	—
aminoglycoside + colistin	2 (1)	1 (4)	0	1 (2)	—	—
aminoglycoside + colistin + tigecycline	2 (1)	0	1 (1)	1 (2)	—	—
aminoglycoside + SXT	1 (1)	0	1 (1)	0	—	—
colistin + tigecycline	11 (7)	1 (4)	2 (3)	8 (15)	—	—
colistin + fosfomycin	1 (1)	0	0	1 (2)	—	—
tigecycline + SXT	3 (2)	0	1 (1)	2 (4)	—	—
tigecycline + fosfomycin	3 (2)	0	0	3 (6)	—	—

SXT, trimethoprim/sulfamethoxazole.

All data are expressed as *n* (%), unless otherwise indicated.

<sup>a</sup>*P* value indicating the univariate relationship between the variable of interest and the ordinal outcome (success, indeterminate, failure).

<sup>b</sup>Adjusted for the presence of UTI, critical illness and for receipt of more than one anti-CRKP drug (except for single drug variables and single drug versus multiple drugs, which were adjusted for UTI only).

<sup>c</sup>Base of regimen was assigned as follows: any regimen that contained an aminoglycoside was deemed aminoglycoside-based; any regimen that contained colistin, but not an aminoglycoside, was deemed colistin-based; and any regimen that contained tigecycline, but not colistin or an aminoglycoside, was deemed tigecycline-based. All other regimens were classified as 'other'.

<sup>d</sup>Comparisons are made within the single drug group.

<sup>e</sup>The group of patients who received more than one drug was compared with those who received a single drug. No analyses were performed on individual combination regimens secondary to small numbers.

to be more virulent compared with other CRKP strains in a *Caenorhabditis elegans* model, whereas *bla*<sub>KPC-2</sub> was not itself associated with virulence.<sup>14</sup> Candidates for virulence factors that may differ between various strains include changes in types of capsular polysaccharides (variations in the *cps* locus) or the mere overproduction of these polysaccharides, expression of iron chelators, mutations in porins such as OmpK35 and OmpK36 and other changes.<sup>15–17</sup>

The treatment of CRKP infections is challenging and, while new antibiotic options are on the horizon, unfortunately these will require time before they become widely available. In the meantime, most data on the treatment of CRKP infections have been

reported from patients with CRKP bloodstream infections, and only limited data exist for other CRKP infections.<sup>18–21</sup> Qureshi *et al.*<sup>22</sup> recently reported their retrospective experience in a cohort of 21 patients with UTI. Interestingly, use of doxycycline for these infections was common at their centre and resulted in clinical cure in all nine patients treated in this way. In our cohort, doxycycline was not a common treatment choice and was not included in analyses. We noted that treatment with aminoglycosides appeared to be associated with better outcomes. This is consistent with data from Satlin *et al.*,<sup>23</sup> who reported superior urinary clearance with aminoglycoside therapy. In another study that described a retrospective cohort that included seven patients

**Table 3.** Strain types

	All	ST258A	ST258B	Other	<i>P</i> <sup>a</sup>
<i>n</i>	55	18	26	11	
Female	27 (49)	11 (61)	12 (46)	4 (36)	0.1788
Age (years), median (IQR)	69 (59–80)	66 (51–73)	73 (61–83)	69 (60–85)	0.3801
Race/ethnicity					0.4595
white	35 (64)	11 (61)	16 (62)	8 (73)	
black	17 (31)	5 (28)	9 (35)	3 (27)	
Hispanic	2 (4)	1 (6)	1 (4)	0	
other	1 (2)	1 (6)	0	0	
Charlson comorbidity index, median (IQR)	3 (2–5)	3 (1–4)	4.5 (2–6)	3 (2–5)	0.1691
Renal failure upon admission <sup>b</sup>	15 (27)	4 (22)	7 (27)	4 (2–5)	0.3984
UTI <sup>c</sup>	19 (35)	6 (33)	8 (31)	5 (45)	0.4801
Urinary drainage					0.6588
physiological	16 (29)	4 (22)	9 (35)	3 (27)	
Foley catheter	32 (58)	12 (67)	15 (58)	5 (45)	
other	7 (13)	2 (11)	2 (8)	3 (27)	
Location at time of culture					0.7153
ward	26 (47)	9 (50)	10 (38)	7 (64)	
emergency department	16 (29)	4 (22)	11 (42)	1 (9)	
ICU	13 (24)	5 (28)	5 (19)	3 (27)	
LOS (days), median (IQR)	12 (8–22)	18 (8–41)	12 (8–20)	11 (9–28)	0.2093
Critical illness <sup>d</sup>	14 (25)	6 (33)	5 (19)	3 (27)	0.2253
Origin					0.2989
skilled nursing facility	21 (38)	7 (39)	12 (46)	2 (20)	
home	20 (36)	8 (44)	8 (31)	4 (36)	
hospital transfer	10 (18)	3 (17)	3 (12)	4 (36)	
long-term acute care	4 (7)	0	3 (12)	1 (9)	
Disposition					0.8829
skilled nursing facility	25 (45)	8 (44)	13 (50)	4 (36)	
home	15 (27)	4 (22)	8 (31)	3 (27)	
long-term acute care	8 (15)	3 (17)	2 (8)	3 (27)	
death	7 (13)	3 (17)	3 (11)	1 (9)	
Any <i>in vitro</i> active drug in first 7 days					
aminoglycoside	26 (47)	7 (39)	12 (46)	7 (64)	0.2435
colistin	10 (18)	5 (28)	5 (19)	0	0.1788
tigecycline	21 (38)	5 (28)	11 (42)	5 (45)	0.1789
SXT	7 (13)	1 (6)	4 (15)	2 (18)	0.1789
fosfomycin	7 (13)	5 (28)	1 (4)	1 (9)	0.020
>1 <i>in vitro</i> active drug in first 7 days	15 (27)	5 (28)	6 (23)	4 (36)	0.5049
Outcome					0.1073
success	9 (16)	3 (17)	4 (15)	2 (18)	
indeterminate	23 (42)	4 (22)	14 (54)	5 (45)	
failure	23 (42)	11 (61)	8 (31)	4 (36)	

LOS, length of stay; SXT, trimethoprim/sulfamethoxazole.

All data are expressed as *n* (%) unless otherwise indicated.

<sup>a</sup>Comparing rep-PCR A versus all others.

<sup>b</sup>Renal failure defined as creatinine >2 mg/dL upon admission.

<sup>c</sup>UTI as defined by CDC/NHSN.

<sup>d</sup>Critical illness defined as Pitt bacteraemia score  $\geq 4$ .

**Table 4.** Strain type analysis adjusted for treatment regimen

	<i>p</i> <sup>a</sup>	aOR for success <sup>b</sup>	<i>p</i> <sup>b</sup>	aOR for failure <sup>c</sup>	<i>p</i> <sup>c</sup>
ST258A versus other	0.0343	0.73 (0.12–3.74)	0.7120	5.82 (1.47–28.50)	0.0113
UTI <sup>d</sup>	0.0575	4.32 (0.94–24.03)	0.0607	0.41 (0.10–1.50)	0.1807
Tigecycline	0.0094	0.15 (0.01–1.11)	0.0645	5.83 (1.46–28.52)	0.0116
Aminoglycoside	0.8147	0.54 (0.10–2.70)	0.4512	1.05 (0.29–4.05)	0.9413

The model includes the following variables: UTI, tigecycline, aminoglycoside and strain A versus all other.

<sup>a</sup>Ordinal logistic regression.

<sup>b</sup>Binomial logistic regression success versus all others.

<sup>c</sup>Binomial logistic regression failure versus all others.

<sup>d</sup>UTI as defined by CDC/NHSN.

**Table 5.** Strain type analysis adjusted for treatment regimen base

	<i>p</i> <sup>a</sup>	aOR for success <sup>b</sup>	<i>p</i> <sup>b</sup>	aOR for failure <sup>c</sup>	<i>p</i> <sup>c</sup>
ST258A versus other	0.0598	0.89 (0.14–4.62)	0.8935	5.07 (1.32–23.59)	0.0176
UTI <sup>d</sup>	0.0169	5.23 (1.17–28.59)	0.0302	0.28 (0.06–1.05)	0.0587
Regimen base	0.1495		0.7233		0.1052
aminoglycoside (reference)		—		—	
colistin		1.74 (0.19–13.35)		0.96 (0.16–5.31)	
tigecycline		0.47 (0.02–4.18)		5.08 (1.07–29.31)	
other		1.85 (0.20–14.14)		0.41 (0.04–2.84)	

The model includes the following variables: presence of UTI, regimen base and strain A versus all other.

<sup>a</sup>Ordinal logistic regression.

<sup>b</sup>Binomial logistic regression success versus all others.

<sup>c</sup>Binomial logistic regression failure versus all others.

<sup>d</sup>UTI as defined by CDC/NHSN.

who were treated with aminoglycosides, the same trend towards increased efficacy of aminoglycosides was observed.<sup>24</sup> In contrast, tigecycline—which is primarily excreted through faeces and does not achieve high urinary levels<sup>25</sup>—was associated with worse outcomes in our cohort. In addition to this link to poor clinical outcomes, we have recently reported that the use of tigecycline in these patients is associated with the subsequent rapid development of tigecycline resistance.<sup>26</sup>

Our study has several important limitations. First, the study of UTIs is problematic as a universally accepted gold standard does not exist. The distinction between colonization and infection is quite difficult, especially in older patients with urinary catheters. Therefore, we chose to study all patients in whom the treating clinician deemed directed therapy was necessary, rather than relying solely on criteria developed for the purpose of surveillance. As expected, only a subset of patients who were treated met criteria for UTI by CDC/NHSN guidelines. The disadvantage of this approach is that patients with urinary CRKP colonization may be included in whom antibiotic treatment was unlikely to be of any clinical benefit. In all analyses, we have adjusted for presence of UTI by CDC/NHSN criteria. A second limitation is that this was an observational study in which treating physicians were free to treat who they wanted and use whichever regimen they deemed appropriate. Confounding by indication will occur in this situation. As an example of this, we noted that receipt of

more than one active agent was associated with an increased likelihood of failure. Another consequence is that the treatment regimens were quite heterogeneous and difficult to analyse. Interventional studies will be needed to determine the best approach to CRKP UTI. A third limitation involves the difficulty of assigning a definitive outcome to all patients. For about half of the patients, the outcome was deemed indeterminate. To address this issue, we performed not only ordinal analyses, but also binomial analyses in both directions. In this way, we provided a sensitivity analysis by grouping the patients either with an indeterminate outcome with patients who failed, or with patients with a successful outcome. Furthermore, we repeated the models after exclusion of those patients who did not survive their index hospitalization and found very similar results.

In summary, we found, in concordance with previously published data, that aminoglycosides appear to be associated with the best clinical outcomes in patients treated for CRKP bacteriuria. This may inform the future design of the control arm in studies on treatment of CRKP UTI with newer agents with activity against carbapenem-resistant Enterobacteriaceae. In addition, we report preliminary data linking the molecularly and clinically distinct CRKP clade ST258A to worse clinical outcomes in CRKP bacteriuria. This finding will need to be validated in other independent studies to further our understanding of outcomes in *K. pneumoniae* strains.

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D. v. D. has received research funding from Steris Inc. and has served on the Speaker's Bureau for Astellas, on a drug safety monitoring board for Pfizer and on a consultancy board for Sanofi Pasteur. R. A. B. has received research funding from AstraZeneca, Merck and Checkpoints, and has served on a Tetrachase drug safety monitoring board. All other authors: none to declare.

## Disclaimer

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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