Bloodstream infections among carriers of carbapenem-resistant *Klebsiella pneumoniae*: etiology, incidence and predictors

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Abstract

Carriers of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) are increasingly recognised through active surveillance in much of the world. We studied incidence, aetiology and predictors of bloodstream infections (BSI) among such carriers. Via a retrospective cohort study conducted in a tertiary care teaching hospital, we examined occurrence of BSI within 45 days of CRKP carrier detection. Three nested case-control studies were conducted to analyse parameters associated with all-cause (ALL), Gram-negative rod (GNR) and CRKP BSI. Cases and controls were compared with respect to demographics, clinical parameters and recent receipt of antibiotics. A total of 431 patients were identified as CRKP carriers (28% by clinical culture, 72% by rectal surveillance), mean age was 75.2 years. Twenty percent of the patients (n = 85) developed BSI, of them 80% (n = 68) with GNR. Of 83 GNR isolates, 58 (70%) were Enterobacteriaceae, of which 19 were CRKP and 20 were extended-spectrum β-lactamase (ESBL) producers (23% and 24% of total GNR, respectively); 29% of the GNR isolates were nonfermenters (14.5% *Pseudomonas aeruginosa*, 14.5% *Acinetobacter baumannii*). Mechanical ventilation predicted ALL BSI (p = 0.04), whereas *Clostridium difficile*–associated diarrhoea predicted GNR BSI (p = 0.04). Receipt of broad-spectrum antibiotics (piperacillin-tazobactam, amikacin, imipenem) was significantly associated with ALL BSI or GNR BSI. No exposure independently predicted CRKP BSI. We conclude that patients detected as CRKP carriers are at high risk for BSI within 45 days of detection, primarily with multidrug-resistant GNR. Lack of predictive factors differentiating between pathogens and associated high mortality raises once more the dilemma regarding the appropriate empiric therapy for CRKP carriers who develop severe sepsis.

Keywords: Bloodstream infections, carbapenem-resistant *Klebsiella pneumoniae*
Original Submission: 7 March 2014; **Revised Submission:** 14 July 2014; **Accepted:** 1 August 2014
Editor: M. Paul
Article published online: 12 October 2014

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Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a major public health threat, imposing considerable clinical and epidemiological challenges. These strains are usually extensively drug resistant, have very few available treatment options, and those are often of uncertain effectiveness and carry high toxicity [1-3]. Clinicians in various parts of the world are increasingly encountering patients who carry or are infected by CRKP strains. In the United States, 543 of 4577 (12%) *Klebsiella* spp. strains reported to the National Healthcare Safety Network in 2009–2010 as associated with nosocomial infections were resistant to carbapenems [4]. European authorities report local outbreaks in numerous countries across the continent, with a high proportion of CRKP in bloodstream isolates in Greece, Italy, and Cyprus (proportion of resistance 68%, 27% and 15%, respectively [5,6]). Multiple countries in the Middle East and southern Mediterranean basin, South America and Asia are affected. CRKP has become endemic in the Indian

http://dx.doi.org/10.1016/j.cmi.2014.08.001

subcontinent [7]. Similar to other multidrug-resistant (MDR) organisms, CRKP is usually acquired after prolonged hospital stay and tends to affect debilitated patients with poor functional status, who require intensive care and are heavily exposed to antibiotics [8–10]. CRKP bloodstream infections (BSI) are associated with an immense case fatality rate of 40% to 70% [11–13]. This increased mortality rate is partly related to the aforementioned host factors and partly to the infection with these extensively drug-resistant strains for which targeted treatment is almost always delayed, frequently of uncertain effectiveness, and occasionally nonexistent.

The reservoir of patients carrying CRKP is increasing, and these patients are more often recognised because recommendations to control the spread of CRKP include active surveillance of high-risk patients [14–18]. Thus, physicians are encountering more often the clinical scenario of a recognised CRKP carrier who develops signs of infection. Currently, little is known regarding incidence, predictors and outcome of infections, BSI specifically, among CRKP carriers. The clinician thus faces an intricate decision-making process when empirically treating a patient with a history of CRKP colonisation or infection, due to patient selection (i.e. mostly elderly, often frail patients with several comorbidities), infection-related morbidity and mortality and a limited antibiotic arsenal. Data regarding infections among CRKP carriers are therefore of paramount importance to assist decision making. The aim of this study was twofold: to assess the rates and characterise all BSI, Gram-negative rod BSI (GNR BSI) and CRKP BSI among a cohort of CRKP carriers; and to identify demographic and clinical predictors of CRKP BSI within this group.

Methods

Study setting and patient population

The Tel-Aviv Medical Centre is a 1500-bed, tertiary-care teaching hospital. An active surveillance policy for CRKP carriage among high-risk patients has been implemented in the hospital since 2007. Those arriving from long-term care facilities, another acute care facility or abroad are screened for CRKP upon admission. Over 1000 patients are screened monthly, and carriage rate is roughly 0.5% with a great majority of the isolates belonging to the ST-258 subtype [18]. Electronic databases were searched to identify all CRKP-positive patients, whether discovered by active surveillance or a clinical culture between January 2008 and April 2010. The study was approved by the local ethics committee.

Study design

We conducted a series of retrospective, nested case-control studies within a cohort of CRKP carriers, each followed up for a period of 45 days since the first isolation of CRKP. BSI was defined using CDC criteria (http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf). The case groups were defined as follows: 1) ALL BSI, which included all patients with BSI within the CRKP cohort; 2) GNR BSI; 3) CRKP BSI. In each of these case-control studies, the different-group CRKP carriers with BSI were compared with control CRKP-carrier cohort patients. Study entry day was defined as the first CRKP isolation date; exit day was defined as BSI, death, or the passage of 45 days since first CRKP isolation. Because we aimed at assessing BSI rate among known CRKP carriers, patients from whom the first isolation site of CRKP was the blood were excluded, i.e. we excluded every patient with CRKP BSI within 2 days of study entry.

Data abstraction

Data were extracted from hospital electronic medical records according to a preprepared questionnaire. Cases and controls were compared regarding demographics (age and sex, admission from home vs. an institution), functional status (poor was defined as a score of 14 or less in the Norton pressure ulcers risk scale), comorbid conditions (diabetes mellitus, cardiovascular disease, pulmonary disease, liver disease, malignancy), surgery and/or mechanical ventilation before BSI, the presence of *Clostridium difficile*, the source of the CRKP-positive culture, recent receipt of antibiotics and the classes of antibiotics received before a positive culture was obtained (Table 1).

Statistical analysis

Statistical analysis was performed using SPSS version 18. We used Cox regression for univariate survival analysis to compare the different groups of bacteraemic patients within the CRKP-carrier cohort. Covariates that were statistically significant ($p < 0.05$) were selected for Cox regression multivariate model. Comparison of exposure to antibiotics (defined daily dose) by days was performed using a time-dependent covariate (i.e. accumulative exposure to antibiotics); $p < 0.05$ was considered to be statistically significant.

Results

Between January 2008 and April 2010, 431 patients were identified as carriers of CRKP either from clinical samples (28%, n = 121) or from a rectal swab as part of active surveillance (72%, n = 310). As previously published [11–13], CRKP carriers often were old, with poor functional status and comorbidities (Table 1). Within 45 days of initial CRKP detection, 85 patients (19.7%) developed BSI (ALL BSI group), of whom 68 (80%) had

TABLE 1. Clinical and demographic characteristics of CRKP-carrier cohort vs. ALL BSI and GNR BSI groups

	Entire cohort *n* (%)	ALL BSI *n* (%)	GNR BSI *n* (%)
Number	431	85	68
Female sex	226 (52)	48 (56.5)	(54.4)37
Mean age (y, SD)	75.2 (±17.2)	73.9 (±16.3)	75.3 (±17.4)
Resident of long-term care facilities	157 (36.4)	29 (34.1)	22 (32.4)
Norton score (mean, SD)	11.3 (±4.2)	11.4 (±4.6)	11.4 (±4.7)
Diabetes	139 (32.3)	34 (40)	26 (38.2)
Cardiovascular disease	103 (23.9)	22 (26)	20 (29.4)
Respiratory disease	63 (14.6)	17 (20)	13 (19.1)
Malignancy	63 (14.6)	15 (17.6)	13 (19.1)
Any comorbidity	255 (59.2)	55 (64.7)	45 (66.2)
CRKP by screen	310 (72)	59 (69.4)	45 (65.2)
Surgery	47 (11)	10 (12)	10 (15)
Mechanical ventilation	44 (10.2)	10 (11.8)*	8 (11.8)
Clostridium difficile–associated diarrhoea	37 (8.6)	6 (7.1)	6 (8.8)*
Antibiotic exposure			
Levofloxacin	8 (1.9)	4 (4.7)	2 (2.9)
Ceftazidime	26 (6.0)	9 (10.6)*	4 (5.9)
Piperacillin-tazobactam	43 (10.0)	15 (17.6)*	13 (19.1)*
Amikacin	21 (4.9)	8 (9.4)*	6 (8.8)
Ertapenem	24 (5.6)	8 (9.4)	7 (10.3)
Imipenem	20 (4.6)	8 (9.4)*	7 (10.3)*
Meropenem	16 (3.7)	5 (5.9)	4 (5.9)
Colistin	62 (14.4)	19 (22.4)*	15 (22.1)*

CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ALL, all patients; BSI, bloodstream infections; GNR, Gram-negative rod.
*Significant predictor vs. cohort in univariate analysis, p <0.05.

at least one GNR isolated (GNR BSI group). There were 19 CRKP BSI (22.4% of ALL BSI, 4.5% of the entire cohort). High rates of extended-spectrum β-lactamase (ESBL) producers and MDR nonfermenters were noted as well (Fig. 1); 66% of GNR isolates were resistant to ceftazidime, 68% to ciprofloxacin, 53% to gentamicin and 41% to piperacillin-tazobactam. To identify predictors of BSI within the cohort of CRKP carriers, we compared demographic and clinical characteristics of the various BSI groups with those of the CRKP-positive cohort population (Table 1). Surprisingly, the various BSI groups had very similar characteristics to the general cohort and very few predictors were found. Being mechanically ventilated predicted being in the ALL BSI group (p = 0.04) and having *Clostridium difficile*–associated diarrhoea (CDAD) predicted belonging to the GNR BSI group (p = 0.04). The CRKP BSI group showed a trend toward having one or more comorbid conditions (p = 0.06), but otherwise shared similar characteristics with the rest of the cohort (not shown). We also examined previous exposure to antibiotic agents among the groups; the use of several broad-spectrum antibiotics (e.g. carbapenems, piperacillin-tazobactam) was significantly associated with having any BSI (ALL BSI group), as well as GNR BSI. However, there was not a single antibiotic to which exposure predicted CRKP BSI. In multivariable analysis, carbapenems, amikacin and colistin predicted being in the ALL BSI group. Multivariable models for the GNR BSI group identified CDAD and broad-spectrum antibiotics as predictors. A multivariable model for predictive factors for CRKP bacteraemia could not be established. The 7-day case fatality rate was 24.4% for patients with GNR BSI excluding CRKP, and 38.9% for patients with CRKP bacteraemia (p = 0.26).

Discussion

The emergence and spread of CRKP in many parts of the world, and recommendations for enhanced control measures including active screening of high risk populations [14–18], have resulted in recognition of a growing number of hospitalised patients as CRKP carriers. These patients are often old, with multiple comorbid conditions, and are heavily exposed to antibiotics [8–10]. When a CRKP carrier develops sepsis, the clinician faces a difficult decision regarding empiric therapy: which organisms should be covered? What is the expected resistance pattern? Here, within a large cohort of patients with CRKP, we attempted to define the occurrence of each group of pathogens and to identify predictors that may assist the clinician in

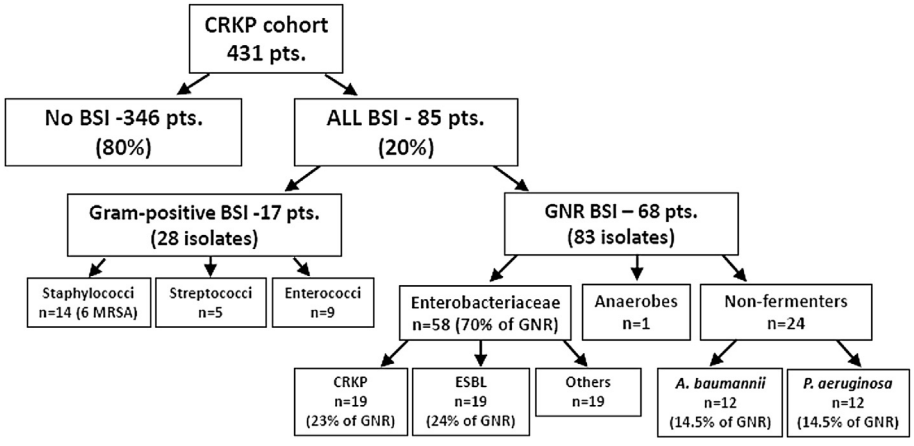

FIG. 1. Bloodstream infection (BSI) rates and causative pathogens within 45 days of entering a carbapenem-resistant *Klebsiella pneumoniae* (CRKP) cohort. GNR, Gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase.

decision making. We found that within the first 45 days of being identified as a CRKP carrier, nearly 20% of the patients developed BSI. The great majority (80%) of the BSI events in these patients were caused by GNR, of which nearly a quarter were caused by CRKP (n = 19, 4.5% of the entire cohort). Very few predictors of BSI in general, and predictors of BSI involving specific pathogens, were identified. Patients affected by any BSI as well as patients affected specifically by GNR BSI were sicker, as reflected by a higher proportion of mechanically ventilated patients, greater exposure to antibiotics and a higher proportion of patients with CDAD. Conversely, no specific predictor for CRKP bacteraemia was identified and mortality, although higher, did not significantly differ between this group and the GNR-excluding CRKP BSI group. This finding may be partly related to insufficient power of our study (the CRKP BSI group included only 19 patients) and partly to the homogeneity of the entire cohort, which included severely ill, aged patients [19,20]. Noteworthy, a similar study regarding *Staphylococcus aureus* BSI showed a rate of 7.7% among nasal carriers of this bacterium [21]. Similarly, there were very few demographic or clinical predictors for developing BSI within the *S. aureus* carrier group. Nevertheless, our finding of the high proportion of BSI caused by CRKP and other multidrug-resistant causative pathogens (including ESBL-producers, MDR *Acinetobacter baumannii* and methicillin-resistant *S. aureus*), refines the clinical dilemma. The currently available agents active against CRKP, namely, colistin, tigecycline and aminoglycosides, may be toxic and are of doubtful efficacy in certain clinical conditions. Likewise, they are believed to be less efficacious than β-lactam agents to treat other Gram-negative pathogens (which were more common than CRKP). Moreover, upon increased use of colistin, resistance among various Gram-negative bacteria should be anticipated and is of great concern, especially among carbapenem-resistant strains [22,23]. Thus, although a prudent use of antimicrobials is cardinal, especially in high-risk population, the epidemiology of BSI within the CRKP cohort suggests that combination chemotherapy may be advisable in cases of severe sepsis [24–26]. In conclusion, although this is a single-centre retrospective study, the data presented highlight the high likelihood of patients with CRKP to develop BSI, and the high proportion in which CRKP is the causative pathogen. Our findings illustrate the challenges in treating these patients and call for larger, prospective studies assessing infection risks among CRKP carriers and the efficacy of therapeutic interventions.

Transparency Declaration

The authors declare that they have no conflicts of interest.

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