ORIGINAL ARTICLE

Clinical Characteristics and Risk Factors of Carbapenem-Resistant *Enterobacteriaceae*: A Case-Control Study in a Tertiary Hospital in Malaysia

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ABSTRACT

Introduction: Carbapenem-resistant *Enterobacteriaceae* (CRE) is increasingly reported worldwide causing serious threats to healthcare. This study aimed to identify the common organisms associated with CRE, the clinical characteristics and risk factors for acquiring CRE infection and colonisation among hospitalised patients. **Methods:** This is a matched, case-control study. Patients aged 18 years and above whom were hospitalised from January 2019 to December 2019 and had CRE isolated from clinical specimens were matched with carbapenem-susceptible controls (CSE), based on gender and age. Univariate and multivariate statistical analysis was performed. **Results:** Among 184 patients, *Klebsiella pneumoniae* was the most common organism causing CRE infection and colonisation. Chronic kidney disease (p=0.025, OR:3.12, 95% CI:1.15-8.41), urinary catheterisation (p=0.005, OR:3.67, 95% CI:1.49-9.00), prior use of cephalosporin (p<0.001, OR:4.69, 95% CI:1.96–11.22) and beta-lactam combination agent (p<0.001, OR:7.18, 95% CI:2.98-17.26) were identified as the independent risk factors. **Conclusion:** Chronic kidney disease, urinary catheterisation, prior use of cephalosporin and beta-lactam combination agents were independently associated with CRE infection and colonisation. These findings enable targeting potential CRE cohorts, hence, necessitate early undertaking of prevention measures to delay the onset of CRE. A rigorous effort by antibiotic stewardship an infection control team are pivotal.

Keywords: Risk factors, Carbapenem-resistant *Enterobacteriaceae*, Antibiotics

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INTRODUCTION

Since the discovery of *Klebsiella pneumoniae* carbapenamase (KPC) in 1996, there have been other types of carbapenemases including New Delhi metallo-β-lactamase-1 (NDM-1), Verona integron-encoded metallo-β-lactamase (VIM), oxacillinase-48-type (OXA-48), and imipenemase-1 (IMP-1) reported worldwide (1,2). Apart from carbapenamase production, resistance to carbapenems may involve other mechanisms which include alteration or loss of porin channels, extrusion of antibiotics by efflux pumps and alteration of binding site. In Malaysia, the first reported case of carbapenem-resistant *Enterobacteriaceae* (CRE) was an imipenem-resistant *Enterobacteriaceae* bacteraemia of a patient with acute myeloid leukaemia (3).

The emergence of CRE has caused serious threats to healthcare and is associated with a high mortality rate (4,5). Furthermore, antibiotic treatment options for these multidrug-resistant infections are limited (6). As with other multi-drug resistant organism, infections caused by CRE were associated with prolonged duration of hospitalisation which will further increase the cost and burden of healthcare (5,7).

Understanding the local epidemiology and identification of risk factors had helped to refine the criteria used for target active surveillance screening for CRE amongst hospitalised patients (8). While the incidence of CRE is increasing every year, the epidemiology and risk

factors involved in CRE have not been well-described in Malaysia. In light of these challenges, we conducted a case-control study to determine the common organisms associated with CRE as well as to investigate the clinical characteristics and risk factors in acquiring CRE infection and colonisation.

MATERIALS AND METHODS

Study design and population

This is a matched case-control study to identify the clinical characteristics of patients with CRE infection and colonisation along with its associated risk factors amongst hospitalised patients. We analysed patients admitted at Kuala Lumpur Hospital, a 2300-bed, tertiary government hospital from January 2019 until December 2019. Patients included in this study were those aged 18 years and above, had CRE isolate from clinical specimens of sterile and non-sterile source. Patients with CSE isolate were conveniently selected as control, matched with gender and age (±2 years) at 1:1 ratio. Repetitive CRE isolates from same patients were not counted and clinical variables from the first event was collected as a case. Patients were classified as having CRE nosocomial infection if they were symptomatic and CRE-positive specimen was obtained 48 hours after hospitalisation or CRE colonisation if the CRE does not cause any symptoms or disease to the patient.

Data collection

Data were retrieved from medical records. Among the variables analysed were demographics (age, race, gender, admission unit), underlying diseases, prior admission within three months, prior corticosteroid use within one month, prior antibiotic use within three months and recent events (urinary catheterisation, central venous catheterisation, mechanical ventilation, stenting, nephrostomy, chemotherapy port insertion) within one month.

Microbiological methods and definition of CRE

Clinical isolates were identified by using conventional biochemical tests with Vitek® 2 (bioMérieux, France) or API® 20E (bioMérieux, France). Antibiotic susceptibility testings for selected penicillin, cephalosporin, carbapenem, aminoglycoside and flouroquinolone were done by Kirby-Bauer disk diffusion method. The carbapenem minimum inhibitory concentration (MIC) of CRE isolates were determined by ETEST® (bioMérieux, France) gradient strip. All results were interpreted according to M100 Performance Standards for Antimicrobial Susceptibility Testing, Clinical Laboratory Standards Institute (9). Modified carbapenem inactivation method (mCIM) and EDTA modified carbapenem inactivation method (eCIM) were done for all CRE isolates to identify carbapenemase-producing CRE (9). Escherichia coli ATCC® 25922 and Pseudomonas aeruginosa ATCC® 27853 were used as control strains.

Data analysis

Univariate analyses were performed for the clinical characteristics and risk factors. The CRE and CSE groups were analysed using Chi-square or Fisher's exact test (if the minimum expected count was less than five) for categorical variables. For continuous variables, the independent t-test was used to analyse normally distributed variables; the Mann–Whitney test was used for non-normally distributed variables. Variables with $p<0.05$ on univariate analysis were further analysed as potential covariates in multivariate logistic regression model and $p<0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Chicago, Illinois, USA).

Ethical approval

Ethical approval for this study were obtained from Research Ethics Committee of National University of Malaysia (UKM) and Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia. This study was registered under National Medical Research Registration (NMRR-18-2948-44535) and UKM Research University Information System (FF-2019-066).

RESULTS

Demographic data

A total of 92 CRE-positive and 92 CSE-positive control patients were included in this study. The distribution of CRE and CSE cases is shown in Fig. 1. The demography characteristics, underlying diseases, healthcare associated factors, recent procedures and culture-positive specimens were summarized in Table I. In descending order, the CRE cases were from medical ward (n=30; 32.6%), intensive care unit (n=25; 27.2%) and urology ward (n=10; 10.9%). The overall mean ± SD age of these patients was 58.0 ± 15.6 years, and 61 patients (66.3%) were men. Compared with CSE cases, the median hospital length of stay was significantly longer in CRE cases, 13.5 days (IQR 5-25, $p<0.001$).

Specimen and bacterial isolates

As shown in Table I, CRE isolates were mostly isolated from urine (n=40; 43.5%), blood (n=29; 31.5%) and

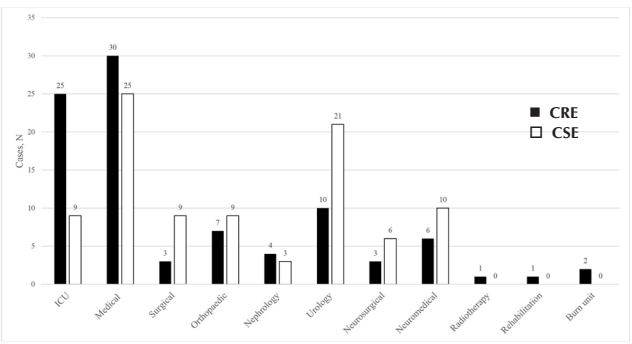

Figure 1: Distribution of CRE & CSE cases

Table I: Comparison of patients' clinical characteristics and risk factors

Parameters	Group		p-value*
	CRE (N=92) n (%)	CSE(N=92) n (%)	
Part 1: Demography characteristics			
Age in years, mean (SD)	58.0 (15.6)	58.0 (15.5)	0.989
Male sex	61 (66.3)	61 (66.3)	1.000
Race:			
Malay	48 (52.2)	53 (57.6)	0.846#
Chinese	21 (22.8)	20 (21.7)	
Indian	20 (21.7)	17 (18.5)	
Others	3 (3.3)	2 (2.2)	
Admission to intensive care unit	25 (27.2)	9 (9.8)	0.002
Admission to medical unit	30 (32.6)	25 (27.2)	0.421
Length of stay (days), median (Q1-Q3)	13.5 (5 - 25)	2.5 (1-13)	< 0.001
Part 2: Underlying diseases/comorbidity			
No comorbidity	22 (23.9)	29 (31.5)	0.249
Diabetes mellitus	50 (54.3)	37 (40.2)	0.055
Hypertension	54 (58.7)	44 (47.8)	0.140
Chronic kidney disease	22 (23.9)	11 (12.0)	0.035
Cardiovascular disease	20 (21.7)	16 (17.4)	0.457
Dyslipidaemia	10 (10.9)	13 (14.1)	0.504
Benign prostate hyperplasia	7 (7.6)	8 (8.7)	0.788
Obstructive uropathy	9 (9.8)	6 (6.5)	0.419
Part 3: Healthcare associated factors			
Prior admission within 3 months	32 (34.8)	24 (26.1)	0.200
Prior corticosteroid use within 1 month	18 (19.6)	7 (7.6)	0.018
Overall antibiotic use within 3 months	76 (82.6)	34 (37.0)	NA
Penicillin	12 (13.0)	5 (5.4)	0.075
Carbapenem	22 (23.9)	5 (5.4)	< 0.001
Fluoroquinolone	7 (7.6)	2 (2.2)	0.169#
Cephalosporin	40 (43.5)	14 (15.2)	< 0.001
Cotrimoxazole	3 (3.3)	0 (0.0)	0.246#
Beta-lactam combination agents	47 (51.1)	15 (16.3)	< 0.001
Part 4: Recent events			
Urinary catheterisation	75 (81.5)	49 (53.3)	< 0.001
Central venous catheterisation	44 (47.8)	26 (28.3)	0.006
Mechanical ventilation	39 (42.4)	19 (20.7)	0.002
Stenting	2 (2.2)	0 (0.0)	0.497#
Nephrostomy	2 (2.2)	0 (0.0)	0.497#
Part 5: Types of specimen			
Blood	29 (31.5)	35 (38.0)	0.353
Urine	40 (43.5)	53 (57.6)	0.055
Tracheal aspirate	13 (14.1)	0 (0.0)	< 0.001#
Tissue	2 (2.2)	3 (3.3)	1.000#
Bone	1 (1.1)	0 (0.0)	1.000#
CSF	1 (1.1)	0 (0.0)	1.000#
Pus	3 (3.3)	0 (0.0)	0.246#
Sputum	1 (1.1)	1 (1.1)	1.000#
Swab	1 (1.1)	0 (0.0)	1.000#
Blood & tracheal aspirate	1 (1.1)	0 (0.0)	1.000#

Independent t-test to compare mean whereas Mann-Whitney test to compare median.
*Chi-Squared test to compare categorical variables.
#Fisher Exact test

tracheal aspirate (n=13; 14.1%). *Klebsiella pneumoniae* was the most common organism causing CRE infection and colonisation (n=55; 59.8%), followed by *Escherichia coli* (n=18; 19.6%) and *Enterobacter cloacae* (n=10; 10.9%). Other CRE organisms were *Proteus mirabilis, Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Morganella morganii* and *Providencia rettgeri*.

Risk factor analysis

The variables of CRE and CSE control patients were compared to determine the risk factors for CRE infection and colonisation. The results of univariate analysis are as shown in Table I. In multivariate analyses, prior use of cephalosporin (OR 4.69; 95% CI: 1.96-11.22, p<0.001) or beta-lactam combination agents (OR 7.18; 95% CI: 2.98-17.26, p<0.001) were significant risk factors for CRE infection and colonisation. Other variables non-related to antibiotic exposure that were identified as independent risk factors for CRE infection and colonisation were chronic kidney disease (OR 3.12; 95% CI: 1.15-8.41, p=0.025) and urinary catheterisation (OR 3.67; 95% CI: 1.49-9.00, p=0.005), as shown in Table II. The cephalosporin and beta-lactam combination agents that were frequently used within three months prior to CRE infection and colonisation are detailed in Table III and IV. Cefuroxime (n=16; 40%), ceftriaxone (n=11; 27.5%), piperacillin-tazobactam (n=16; 34%) and amoxicillin-clavulanate (n=14; 29.8%) were the most commonly prescribed antibiotics.

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DISCUSSION

This case-control study analysed the common organisms associated with CRE, its clinical characteristics and risk factors in acquiring CRE infection and colonisation compared with CSE cases. Among the *Enterobacteriaceae* causing CRE infection and colonisation in our study, *Klebsiella pneumoniae* accounted for the highest number of organism isolated. This is in accordance with previous studies which showed similar finding (10,11). CRE outbreak due to *Klebsiella pneumoniae* in hospital setting have been reported in many studies (12,13).

Klebsiella pneumoniae is frequently associated with hospitalised patients especially among patients in intensive care unit (14). This organism typically infects patients with indwelling medical devices. Biofilm formation on these devices is important in the pathogenesis of CRE infections. The fimbriae possessed by *Klebsiella pneumoniae* type 3 have been identified as appendages which mediated the formation of biofilms, resulting in colonisation and growth on indwelling devices (15).

In our study, chronic kidney disease is considered as an independent risk factor associated with acquisition of CRE, consistent with a study done by Kofteridis et al (14). Alterations in primary host defence mechanism, use of

Table II: Univariate & multivariate analysis of risk factors associated with CRE

Parameters	Group		Univariate		Multivariate	
	CRE (N = 92)	CSE (N = 92)	Crude OR with 95% CI	p-value	Adjusted OR with 95% CI	p-value
Part 1: Demography characteristics						
Admission to intensive care unit	25 (27.2)	9 (9.8)	3.44 (1.51 - 7.87)	0.003	2.82 (0.85 - 9.43)	0.092
Length of stay (days), median (Q1 - Q3)	13.5 (5 - 25)	2.5 (0 - 13)	1.03 (1.01 - 1.05)	0.004	1.00 (0.98 - 1.02)	0.982
Part 2: Underlying diseases/co-morbid						
Chronic kidney disease	22 (23.9)	11 (12.0)	2.31 (1.05 - 5.11)	0.038	3.12 (1.15 - 8.41)	0.025
Part 3: Healthcare associated factors						
Prior corticosteroid use within 1 month	18 (19.6)	7 (7.6)	2.95 (1.17 - 7.46)	0.022	2.18 (0.67 - 7.14)	0.198
Prior antibiotic use within 3 months						
Carbapenem	22 (23.9)	5 (5.4)	5.47 (1.97 - 15.18)	0.001	3.10 (0.90 - 10.66)	0.072
Cephalosporin	40 (43.5)	14 (15.2)	4.29 (2.12 - 8.65)	< 0.001	4.69 (1.96 - 11.22)	< 0.001
Beta-lactam combination agents	47 (51.1)	15 (16.3)	5.36 (2.70 - 10.67)	< 0.001	7.18 (2.98 - 17.26)	< 0.001
Part 4: Recent events						
Urinary catheterisation	75 (81.5)	49 (53.3)	3.87 (1.99 - 7.54)	< 0.001	3.67 (1.49 - 9.00)	0.005
Central venous catheterisation	44 (47.8)	26 (28.3)	2.33 (1.26 - 4.29)	0.007	0.48 (0.18 - 1.32)	0.155
Mechanical ventilation	39 (42.4)	19 (20.7)	2.83 (1.47 - 5.43)	0.002	0.66 (0.22 - 2.01)	0.463
Part 5: Type of specimen						
Tracheal aspirate^	13 (14.1)	0 (0.0)	NA	NA	NA	NA

Odd ratio based on CRE group (CRE/CSE).
^This group is not included in the analysis due to small number.

Table III: Prior cephalosporin use within 3 months in CRE and CSE group

Types of Cephalosporin, N (%)	CRE (N = 40)	CSE (N = 14)	Total (N = 54)
Cefuroxime	16 (40.0)	4 (28.6)	20 (37.0)
Ceftazidime	4 (10.0)	1 (7.1)	5 (9.3)
Ceftriaxone	11 (27.5)	5 (35.7)	16 (29.6)
Cefoperazone	3 (7.5)	2 (14.3)	5 (9.3)
Cefepime	2 (5.0)	2 (14.3)	4 (7.4)
Ceftazidime & cefepime	1 (2.5)	0 (0.0)	1 (1.9)
Cefuroxime & ceftriaxone	1 (2.5)	0 (0.0)	1 (1.9)
Ceftriaxone & ceftazidime	1 (2.5)	0 (0.0)	1 (1.9)
Cefuroxime & cefepime	1 (2.5)	0 (0.0)	1 (1.9)

Table IV: Prior beta-lactam combination agents use within 3 months in CRE and CSE groups

Types of beta-lactam combination agents N (%)	CRE (N = 47)	CSE (N = 15)	Total (N = 62)
Amoxicillin-clavulanate	14 (29.8)	7 (46.7)	21 (33.9)
Ampicillin-sulbactam	8 (17.0)	1 (6.7)	9 (14.5)
Piperacillin-tazobactam	16 (34.0)	5 (33.3)	21 (33.9)
Piperacillin-tazobactam & ampicillin-sulbactam	5 (10.6)	2 (13.3)	7 (11.3)
Piperacillin-tazobactam & amoxicillin-clavulanate	4 (8.5)	0 (0.0)	4 (6.5)

immunosuppressive drugs, nutritional deficient state and disruption of cutaneous and mucosal barriers amongst patients with chronic kidney disease may increase the risk of bacterial infection (16,17). Saminathan et al. showed an increased prevalence of chronic kidney disease (18). Having CKD as an independent risk factor for CRE acquisition, we expect a substantial increase in CRE-positive cases in the near future if no preventive measure is taken. Most of sepsis complications among CKD patients occurred as a result of dialysis catheter use. Among the fundamental principles of infection prevention include diligent hand hygiene practice during haemodialysis care. Gloves are recommended to be worn upon touching patient's intact skin or patient's equipment at the haemodialysis station and it should be removed and followed by hand hygiene between patients. Equipment cleaning and disinfection are equally important to reduce cross-contamination. Ideally, non-disposable items that cannot be comprehensively cleaned and disinfected should be dedicated for use on a single patient (19). Most importantly, training and assessment on infection prevention and control should be provided to all health-care workers at a regular basis. Patients and caregivers should also be educated on proper vascular access care. Furthermore, surveillance which involved process measures (adherence to protocol) and outcome (infection) should be done to evaluate the effectiveness of infection control and preventive strategies (20).

Previous studies have reported prior antibiotic exposure, central line device insertion, urethral catheterisation, prolonged hospitalisation, ICU admission and invasive procedures as risk factors in acquiring CRE infection (5,8,21,22). Based on the findings of our study, urinary catheterisation, was regarded as one of the independent risk factors in acquiring CRE infection and colonisation. A study done by Guh et al. has similar findings with our study in which most CRE patients had indwelling urinary catheter inserted prior to acquiring CRE and most of the isolates were from urine specimen (23). This is in line with previous studies which described urinary catheterisation as a significant risk factor for CRE infection (22). Appropriate indications for urinary catheterisation, aseptic insertion, proper maintenance and timely removal of urinary catheter are among the

recommendations to be reinforced for the prevention of catheter-associated urinary tract infection (24).

Studies have shown that prior exposure to carbapenem, fluoroquinolone, glycopeptide, penicillin and macrolide were significantly associated with CRE infection (8,25,26). Apart from that, other studies have shown prior exposure to cephalosporin were associated with CRE infection which was consistent with our finding (27,28). In addition, exposure to beta-lactam combination agent was considered as an independent risk factor in acquiring CRE in our study which was in line with findings from Jiao et al (29). The use of beta-lactam combination agents has been reported with an outbreak of KPC-2 carbapenemase-producing *Klebsiella pneumoniae* strain in a tertiary hospital in Greece (30).

The mechanism responsible for carbapenem resistance is not only attributed to prior exposure to carbapenem antibiotics but to any class of antibiotics (25, 31). Among the substantial contributors of carbapenamase-producing bacteria were the intensity and the duration of antibiotic therapy, which resulted in the milieu in which carbapenemase-producing bacteria were selected (31). A study done by Hussein et al. has demonstrated exposure to any class of antibiotics for more than 14 days as a significant risk factor for CRE bacteremia (25). In addition, even a short exposure to imipenem was associated with a significant increase in carriage of imipenem-resistant gram-negative bacilli. The risk of acquisition was 5.9 times higher in patients who received 1 to 3 days of imipenem treatment as compared with controls and increased to 7.8 times higher in those who received longer treatments (32).

In addition to the selective pressure exerted on susceptible bacteria, resistance can result from modification of an antibiotic target as well as impermeability, efflux or enzymatic inactivation (33). Even though multi-drug resistant bacteria may exist as a colonizer, the resistance genes can be transferred to other bacteria through direct exchange of DNA either by conjugation or extrachromosomal plasmid leading to further spread of resistance (31).

Carbapenem-resistant *Enterobacteriaceae* have been reported worldwide as a consequence largely from acquisition of carbapenemase genes (34). A study done by Correa et al. has shown that the mechanism of carbapenem resistance in CRE isolates were contributed by the production of cephalosporinase namely $bla_{\text{CTX-M-2}}$ and $bla_{\text{GES-1}}$ which were associated with porin modifications encoded by ompK35 and ompK36 genes. However, no carbapenemase encoding genes including bla_{KPC} were identified (4). Thus, by focusing on appropriate antimicrobial use as a major preventive intervention in antimicrobial stewardship, the detrimental effect of antibiotic overuse and the spread of CRE are reduced (21).

Among the antimicrobial stewardship strategies incorporated to minimize the selective pressure of antimicrobial resistance is by de-escalation therapy, in which the spectrum of empirical antibiotics is narrowed when susceptibility result is available. A second strategy emphasized the importance of duration of treatment as a key to achieving optimal clinical outcomes (31). A recent study by Rooney et al. has highlighted the importance of appropriate antibiotic prescribing as a way to contain an outbreak of carbapenemase-producing *Enterobacteriaceae* as it minimizes antibiotic selective pressure within human gut, limiting clonal expansion and resistance gene transfer between species (35). Apart from that, targeted screening and cohorting of CRE carriers and infections, combined with appropriate antimicrobial stewardship measures have been proven to significantly decreased the institutional incidence of CRE infection and colonisation (36).

The limitation of this study was it only involved a single tertiary-care referral hospital. Though the number of patients included in the study was sufficient according to the calculated sample size, our findings may not be generalizable to other institutions with different population setting.

CONCLUSION

In this single-centre case-control study, we have identified chronic kidney disease, prior cephalosporin use, prior beta-lactam combination agent use and urinary catheterisation were independently associated with CRE infection and colonisation. These findings may assist clinicians to identify at-risk patients so that necessary actions measures can be implemented to prevent the onset of CRE. Antibiotic resistance continues to be a fundamentally important challenge which requires immediate attention. Therefore, a concerted effort involving antibiotic stewardship and strict infection control measures are pivotal in the prevention of CRE among hospitalised patients.

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