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An observational study on carbapenem-resistant Enterobacterales (CRE) colonisation and subsequent risk of infection in an adult intensive care unit (ICU) at a tertiary care hospital in India

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S U M M A R Y

Background: Carbapenem-resistant Enterobacterales (CRE) are a global health problem with a growing prevalence. India has a high prevalence of CRE. CRE infections are difficult to treat, and are associated with significant morbidity and mortality. Colonisation is generally a prerequisite for infection and the prevention of CRE colonisation is key to the prevention of CRE infection.

Objectives: To determine the prevalence of CRE colonisation and subsequent infections in an adult intensive care unit (ICU) in India.

Methods: We conducted a prospective observational study in which perirectal swabs were obtained along with relevant clinical details of consenting adult patients upon ICU admission between January 2019 and August 2020. Rectal screening was performed using MacConkey agar plates with ertapenem disks and further identification was performed using conventional microbiological techniques. Ertapenem minimum inhibitory concentration (MIC) was determined using an epsillometer (E) test. The modified carbapenem inactivation (mCIM) test and EDTA carbapenem inactivation test (eCIM) were performed to confirm carbapenem resistance using the Clinical Laboratory Standards Institute (CLSI) 2020 guidelines.

Results: 192 ICU patients were screened for CRE. 37 patients were found to be colonised with CRE. *Klebsiella pneumoniae* (N=25; 67.6%) was the most frequent CRE isolate, followed by *Escherichia coli* (N=11; 29.7%) and one *Enterobacter species* (N=1; 2.7%). 89.2% (33/37) patients developed CRE infection. Pneumonia was the most common CRE infection identified in 12/33 (36.4%) patients.during the hospital stay. The median duration of hospital stay was longer (17 days) for CRE colonised compared to CRE non-colonised patients (9 days) (P<0.001). Death occurred in 27 % (N=10/37) of CRE-colonised patients during the hospital admission.

Conclusion: CRE colonisation is associated with high risk of subsequent CRE infection and longer ICU and hospital admission.

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Introduction

Carbapenem-resistant Enterobacterales (CRE) have emerged as an urgent public health threat in the world including India. Intestinal colonisation with CRE is considered to be a risk factor for development of systemic CRE infection. Infections due to carbapenem-resistant organisms have become a major concern for the clinicians due to the limited therapeutic options. Infections with CRE disproportionately affect severely ill patients with multiple comorbidities. Patients admitted to the intensive care unit (ICU) have been found to have a particularly high burden of CRE infections as well as increased mortality. Immunocompromised patients including organ transplant recipients, patients with previous antibiotic exposure and medical devices such as central venous catheters are also at increased risk of developing a CRE infection [1].

Carbapenem resistance is mostly mediated by the production of carbapenemase enzymes that are present on the mobile genetic elements, as well as chromosomal-mediated porin loss and efflux pumps overexpression [2]. Carbapenemase-producing Enterobacterales (CPE) usually contribute the majority of CRE isolates from clinical sources, particularly in settings of high CRE prevalence. Carbapenemases are broadly of 2 types: Serine carbapenemases (Ambler class A or D) and Metallo-β-lactamases (Ambler class B) which can be phenotypically identified using mCIM (modified carbapenem inactivation method) and eCIM (EDTA-modified carbapenem inactivation method) done in parallel [3,4]. Knowing which carbapenemase is produced can help to guide the antimicrobial treatment of CRE infection. Ambler class B metallo-β-lactamases can destroy all beta-lactams except monobactams. It is important to recognise that not all CPE are CRE. CPE includes Enterobacterales with low carbapenem minimum inhibitory concentrations (MIC) which are carbapenem-susceptible phenotypically [3,4].

The majority of CRE infections worldwide are caused by *K. pneumoniae*. Other causative organisms may include *Escherichia coli*, *Klebsiella oxytoca*, and *Enterobacter cloacae* [5].

As part of a non-outbreak surveillance initiative at our institution, which is located in an area of high CRE endemicity (37% from a study done in Jodhpur, Rajasthan by Rajni *et al.* [6]), perirectal screening was performed in ICU patients to identify carriage with CRE. We examined the rates of colonisation with CRE at the time of ICU admission and determined the risk of any subsequent CRE infection during hospitalisation.

Materials and methods

Study setting and design

A prospective observational study was done in patients of ≥ 18 years old admitted in adult intensive care unit (ICU). The patients comprised critically ill medical or post operative surgical patients of the All India Institute of Medical Sciences (AIIMS), Jodhpur. The Institute is a 960 bed tertiary care teaching hospital with about 35 different specialities including medical specialities such as gastroenterology, nephrology, cardiology, oncology and neurology as well as general medicine and surgical specialities in urology, gastro-intestinal surgery, neurosurgery as well as general surgery. Initially from January 2019 until March 2020, ICU had 7 beds then the ICU unit was 30 bedded from April 2020 onwards. There was no policy for routine CRE screening in the hospital. This study was completed as part of an MD thesis. Hand hygiene and bundle care approaches for central line insertion and management, ventilation and urinary catheterisation were the main infection prevention and control strategies in place in the ICU.

Sample collection

Perirectal swabs were obtained from all consenting patients within 48 hrs of admission to ICU and thereafter every alternate day until the 8th day of the ICU admission from January 2019 to August 2020. No further perirectal swabs were collected from the patients after 8 days of ICU admission because of logistic reasons.

Data collection

Relevant clinical details including, demographic details, any co-morbid conditions, antibiotic exposure, invasive device exposure along with subsequent culture results were collected from previous medical records and follow up was done for all patients until the patient was discharged or deceased. Antibiotic exposure history during the previous 3 months following the current admission was collected from the medical records and/or obtained by recall of the patient or their relative. Clinical details and laboratory results were recorded on a proforma.

Microbiology

Within 1 hour of perirectal swab collection from patient, swabs were cultured on MacConkey agar plate (HiMedia Laboratory Pvt Ltd. , Mumbai, India) with ertapenem (10 μg) disk (HiMedia Laboratory Pvt Ltd. , Mumbai, India) and immersed in trypticose soy broth (HiMedia Laboratory Pvt Ltd. , Mumbai, India) containing meropenem (10ug) disk (HiMedia Laboratory Pvt Ltd. , Mumbai, India) for identification of CRE isolates. There was no delay in the transport of samples to the microbiology laboratory. Identification of suspected CRE isolates was done using biochemical tests (nitrate reduction test, indole reaction, methyl red, Voges-Proskauer, mannitol motility agar, Christensen's urease gar, Simmons citrate agar, phenylalanine deaminase test) (reagents supplied by HiMedia Laboratory Pvt Ltd. , Mumbai, India) using standard microbiological techniques after overnight incubation. All organisms identified as Enterobacterales were screened for carbapenem resistance using the 2020 Clinical Laboratory

Standards Institute (CLSI) guidelines for antimicrobial susceptibility testing [4]. Susceptibility testing for carbapenems by disk diffusion was only done for the clinical isolates. Resistance to carbapenems and the production of carbapenemase enzyme detection were performed using ertapenem Etest® strip for MIC determination to confirm carbapenem resistance) and mCIM (modified Carbapenem Inactivation Method) eCIM (EDTA-modified carbapenem inactivation method) tests were also performed as per CLSI guidelines 2020 [4]. No molecular test was done to identify the gene involved for carbapenem resistance development.

Statistical analysis

Data were entered and analysed using Statistical Package for the Social Sciences (SPSS) version 23. Categorical data were described using frequency and percentages and analysed using Chi square test or Fischer's exact test as applicable. Continuous variables such as age, duration of hospitalisation and ICU stay were found to be non-parametric by Shapiro Wilk test. They were described using median (IQR) and analysed using the Mann Whitney *U* test. A *P*-value of < 0.05 was considered statistically significant.

Ethical approval

The study was approved by the institutional ethics committee dated 22 December 2018 (reference number: AIIMS/IEC/2018/791) at the All India Institute of Medical Sciences, Jodhpur, Rajasthan, India. Written informed consent was taken from all the participating patients or from relatives of the patients.

Results

During the study period from January, 2019 to August 2020, a total of 1113 patients were admitted to ICU. Most of these patients were transferred within a few hours to a ward or consent for CRE screening could not be obtained or they died. Perirectal swabs for CRE screening were collected from 192 patients. Because of the COVID-19 pandemic, certain restrictions were put in place from March 2020 during which time samples could not be collected.

Out of 192 patients included in the study, 112 (58.3 %) were males and 80 (41.7 %) females.

CRE isolates, patient demographics and characteristics

37 patients (21 males and 16 females) were found to be colonised with CRE (Table I). The maximum CRE isolates (*N*=19) were recovered from perirectal swab collection within 48 hours of ICU admission. 13 CRE isolates were recovered on the 4th day, 3 on 6th day and 2 on 8th day of ICU admission. The majority of the CRE were *Klebsiella pneumoniae* (*N*=25, 67.6%) followed by *Escherichia coli* (*N*=11, 29.7%). One CRE isolate was *Enterobacter* species (*N*=1, 2.7%).

Risk factor analysis for developing CRE colonisation

The antibiotic treatment of CRE may depend on the mechanism of carbapenem resistance and which carbapenemase enzyme is likely to be present. In Indian healthcare settings this information is not readily available. Therefore, polymyxins in combination with an additional agent with a susceptible MIC

Table I
Clinical characteristics in patients with and without CRE colonisation

Characteristics	Total patients (*N*=192)	Patients with CRE colonisation (*N*=37)	Patients without CRE colonisation (*N*=155)	*P*- value
Age, years (median, IQR)	50	51 (26—62)	50 (32—63)	0.682[a]
Sex, (male/female)	112/80	21/16	91/64	0.829[b]
History of previous hospitalisation (%) in past 3 months	81/192 (42.18%)	16/37 (43.2%)	65/155 (41.9%)	0.885[b]
History of previous surgery (%) in past 90 days	70/192 (36.45%)	15/37 (40.5%)	55/155 (35.5%)	0.565
Duration of hospitalisation (median, IQR)	10	17 (11—26)	9 (6—16)	<0.001[a]
Duration of ICU stay	8	12 (8—22)	9 (6—16)	<0.001[a]
History of chronic disease				
Diabetes mellitus	36/192 (18.75%)	4/37 (10.8%)	32/155 (20.6%)	0.168[b]
Renal disease	21/192 (10.93%)	3/37 (8.1%)	18/155 (11.6%)	0.770[c]
Liver disease	6/192 (3.12%)	1/37 (2.7%)	5/155 (3.2%)	1.00[c]
Cardiac disease	38/192 (19.79%)	6/37 (16.2%)	32/155 (20.6%)	0.544[b]
Malignancy	19/192 (9.89%)	2/37 (5.4%)	17/155 (11.0%)	0.539[c]
Pulmonary disease	25/192 (13.02%)	3/37 (8.1%)	22/155 (14.2%)	0.422[c]
Died	41/192 (22.35%)	10/37 (27.0%)	31/155 (20.0%)	0.349[b]

P- value calculated using a: Mann Whitney U test; b: Chi square test; c: Fisher's Exact test.

Table II
Comparison of different antibiotic exposure in last 3 months[a] and during current hospital stay among CRE colonised and non-colonised patients

Antibiotic exposure		Total patients (*N*=192)	CRE colonised patients (*N*=37)	Non colonised patients (*N*=155)	*P* − value
β-lactam antibiotic ± β lactamase inhibitor	Last 3 months	15 (7.8%)	3 (8.1%)	12 (7.7%)	1.00[a]
	Current stay	109 (56.8%)	28 (75.7%)	81 (52.3%)	0.01[b]
3rd/4th generation Cephalosporin	Last 3 months	6 (3.1%)	1 (2.7%)	5 (3.2 %)	1.00[a]
	Current stay	109 (56.8%)	18 (48.6%)	91 (58.7 %)	0.267[b]
Fluoroquinolone	Last 3 months	2 (1.0%)	1 (2.7%)	1 (0.6%)	0.349[a]
	Current stay	12 (6.2%)	2 (5.4%)	10 (6.%)	1.00[a]
Macrolide	Last 3 months	8 (4.2%)	2 (5.4%)	6 (3.9%)	0.652[a]
	Current stay	27 (14.1%)	5 (13.5%)	22 (14.2%)	0.915[b]
Carbapenem	Last 3 months	11 (5.7%)	4 (10.8%)	7 (4.5%)	0.228[a]
	Current stay	67 (34.9%)	16 (43.2%)	51 (32.9%)	0.236[b]
Polymyxin	Last 3 months	2 (1.0%)	0 (0%)	2 (1.23%)	-
	Current stay	33 (17.2%)	12 (32.4%)	21 (13.5%)	0.006[b]
Vancomycin	Last 3 months	0 (0%)	0 (0%)	0 (0%)	-
	Current stay	10 (5.20%)	0 (0%)	10 (6.5%)	-
Aminoglycoside	Last 3 months	2 (1.0%)	0 (0%)	2 (1.3%)	-
	Current stay	8 (4.1%)	2 (5.4%)	6 (3.9%)	0.652[a]

P- value calculated using a: Fisher's Exact test; b: Chi square test.
[a] Information was collected based on past medical records obtained from the patient or based on recall by the patient or relative.

such as tigecycline, aminoglycosides, fosfomycin are commonly used for treatment of CRE infections [7]. In the study, 12 out of 33 patients on polymyxin treatment during the current hospital admission (*N*=12/37; 32.4%) were CRE colonised which was statistically significant (*P*=0.006). This reflects that polymyxins along with other antibiotics are frequently used in ICU as a 'last resort' therapy for treatment of CRE and other serious multi-drug resistant Gram negative infections (Table II).

It was observed that 28 (75.7%) patients who were treated with beta-lactam antibiotic therapy during the current admission developed CRE which was statistically significant (*P*=0.01) (Table II).

In the present study, it was observed that if patient had prior history of being exposed to urinary catheterisation (*N*=11 out of 37 CRE colonised, 29.7%), there is an increased likelihood of developing CRE infection (Table III). Patients who had been exposed to central line (*N*=34; 91.9%) during ICU stay had been shown to develop CRE colonisation more as compared to non-colonised (*N*=115; 74.2%) which was statistically significant (*P*=0.02) (Table III). It was also observed that the longer a patient was exposed to any medical device, the more likely they were to get CRE infection (*P*=0.002) (Table IV).

Median duration of stay in hospital was 17 days in CRE colonised patients compared with 9 days for non-colonised patients (*P*<0.001) (Table I).

It was observed that if a patient became colonised with CRE, the duration of hospital stay increased for the patient (median of 12 days) as compared to non-colonised patients (median of 9 days) (*P*<0.01) (Table I).

Resistance pattern of CRE isolates

Metallo-beta-lactamase was detected in 10 *Klebsiella pneumoniae* isolates and 3 *Escherichia coli* isolates. Serine carbapenemases were detected in 12 *Klebsiella pneumoniae* isolates and 6 isolates of *Escherichia coli*. In 6 CRE isolates (including 3 isolates of *Klebsiella pneumoniae*; 2 isolates of *Escherichia coli* and 1 isolate of *Enterobacter* species), carbapenemase enzyme was not detected (Figure 1).

CRE infections developed in 33 (89.2%) out of 37 colonised patients during hospital stay. Pneumonia was the most common infection occurring during hospital stay (*N*=12, 36.4%), followed by surgical site infection (*N*=7, 21.2%). One patient had developed bloodstream infection (3.0%) and four had urinary

Table III
Comparison of different device exposures in last 3 months among CRE colonised and non-colonised patients

Device exposure		Total patients (*N*=192)	CRE colonised patients (*N*=37)	Non colonised patients (*N*=155)	*P*- value
Ventilator support	Last 3 months	9 (4.7%)	2 (5.4%)	7 (4.5%)	0.685[a]
	Current stay	165 (85.3%)	35 (94.6%)	130 (83.8%)	0.092[b]
Central line	Last 3 months	20 (10.4%)	7 (18.9%)	13 (8.4%)	0.073[a]
	Current stay	149 (77.6%)	34 (91.9%)	115 (74.2%)	0.020[b]
Urinary catheterisation	Last 3 months	25 (13.0%)	11 (29.7%)	14 (9.0%)	0.002[a]
	Current stay	187 (97.4%)	36 (97.3%)	151 (97.4%)	1.00[a]

P value calculated using a: Fisher's exact test; b: Chi-square test.

Table IV
Comparison of duration of device exposure between CRE colonised and non-colonised patients

Device exposure duration	Non- colonised patients	CRE colonised patients	*P*-value
	Median (IQR)	Median (IQR)	
Duration of ventilator exposure (in days)	4 (1—6)	7 (3—10)	0.002
Duration of central line exposure (in days)	4 (1—7)	6 (4—15)	0.002
Duration of urinary catheterisation (in days)	6 (3—10)	10 (5—19)	0.002

tract infections (12.1%). There were 9 patients with multiple site infections (27.3%) (Table V). The other 4 patients who were CRE colonised did not develop any subsequent infection during hospitalisation.

Among these 37 patients, 8 (21.6%) patients already had past history of CRE infection before CRE colonisation status could be obtained during this admission. This is likely to indicated that they were already colonised when they were screened for CRE colonisation. On readmission, CRE colonisation was detected the first day of sample collection from all of these 8 patients.

All-cause mortality in CRE patients after perirectal swab collection

The mortality rate was found to be higher in CRE colonised patients (*N*=10/37; 27.0%) compared with non-colonised patients (*N*=31/155; 20.0%), but the difference was not statistically significant (*P*>0.05).

Of the 37 CRE colonised patients, 10 patients died during the hospital stay. Out of these 10 deceased patients, 5 had developed CRE infection at multiple sites (includes 2 patients with combination of surgical site infection and pneumonia; 1 patient with urinary tract infection and pneumonia; 1 with blood stream infection and pneumonia; and 1 with bloodstream infection and surgical site infection). 3 patients died following the development of pneumonia caused by CRE and one following surgical site infection caused by CRE. One patient who died was CRE colonised only and no CRE organism was isolated from any subsequent clinical samples sent to the microbiology laboratory (Table VI).

Discussion

The emergence and spread of CRE has become a challenge for healthcare providers globally. CRE infection can result in significant morbidity and mortality and the treatment of CRE infection is difficult and can be costly. In February 2017, WHO published its first ever list of antibiotic-resistant "priority pathogens" — a catalogue of 12 families of bacteria that pose the greatest threat to human health in which CRE was included in the critical priority category [8]. Therefore, identification of healthcare-associated and patient-associated risk factors related to CRE acquisition may guide preventive and control measures, particularly in hospitals with limited resources.

Worldwide, CRE colonisation prevalence rate among different countries varies ranging from 0.22% reported in Japan [9] to 52% in Vietnam [10]. In India, CRE prevalence rates reported in studies from different cities has ranged from 1.6% in Pune [11] to 38.4% in the Postgraduate Institute of Medical Education & Research (PGIMER) Chandigarh [12]. Our study showed a CRE prevalence rate of 19.9% which is much lower compared with PGIMER, Chandigarh [12] and more comparable with a study done by Dutta *et al.* (12%) [13]. Our hospital is one

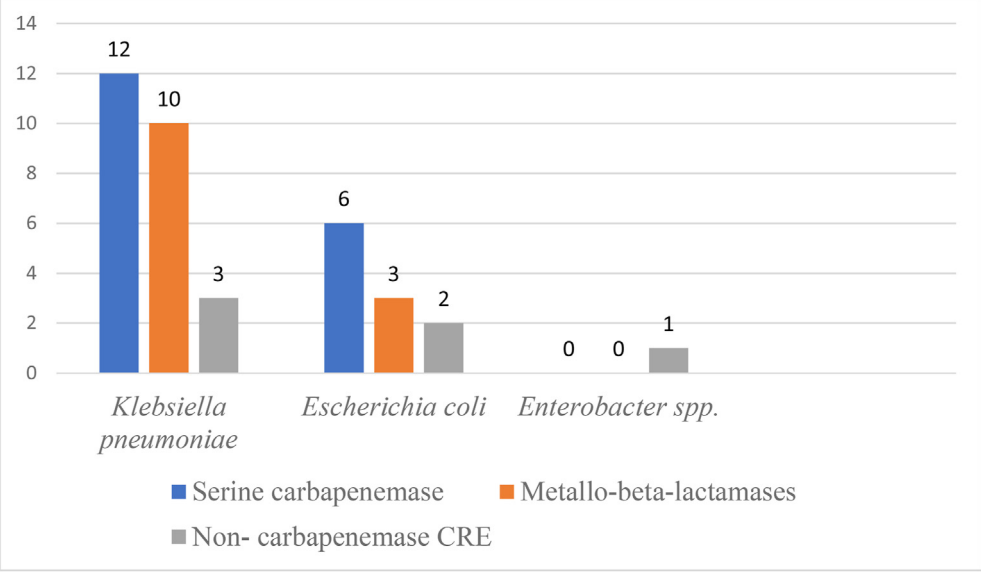

Figure 1. Carbapenemase enzymes detected in CRE isolates (*N*=37). *No genetic study on CRE isolates was done, so we could not determine if any of the CRE isolates had more than one carbapenemase gene present.

Table V
CRE infection following CRE colonisation

CRE infection	*Klebsiella pneumoniae (%)*	*Escherichia coli (%)*	*Enterobacte spp. (%)*
Pneumonia (*N*=12)	83.3	8.3	8.3
Surgical site infection (*N*=7)	42.9	57.1	0
Bloodstream infection (*N*=1)	100	0	0
Urinary tract infection (*N*=4)	50	50	0
Multiple sites of infection[a] (*N*=9)	88.9	11.1	0

[a] Includes 6 patients who developed pneumonia and surgical site infection, 1 patient each developed bloodstream infection with pneumonia, bloodstream infection with surgical site infection and urinary tract infection with pneumonia.

of the referral centres of Rajasthan state, where the majority of the patients who come to the hospital already have a history of complex medical and surgical issues, prolonged exposure to healthcare settings and extensive exposure to broad-spectrum antibiotics. This may help explain the high CRE prevalence in our study.

A case-control study by Marchaim *et al*. emphasised the significant role of antimicrobial exposure in the prediction of CRE colonisation [14]. The majority of previous studies have shown that hospitalisation and cumulative antibiotic exposure history, especially previous use of beta-lactams and carbapenems, were considered as risk factors associated with CRE infection [5,10]. In our study, 12 patients out of total 33 patients treated with polymyxin during the current hospital stay (*N*=12/37; 32.4 %) were CRE colonised which was statistically significant ($P<0.05$). Among CRE colonised patients, the percentage of patients (10.8%) having prior history of carbapenem treatment was higher compared with non-CRE colonised patients (4.5%) but the difference was not found to be statistically significant ($P=0.228$). The comparison of prior history of β lactam treatment between the CRE colonised (*N*=3; 8.1%) and non-CRE colonised patients (*N*=12; 7.7%), did not identify a statistically significant difference ($P>0.05$). It was observed that 28 patients who were being treated with beta-lactam antibiotics during the current admission developed CRE which was statistically significant ($P<0.05$).

Invasive devices may act as a portal of entry for CRE which needs to be studied further [15]. In our study, we had observed that previous history of urinary catheterisation ($P<0.05$) predisposed patients to becoming colonised with CRE. The association between CRE colonisation and device use, including urethral catheterisation, central lines and ventilation, has been identified as risk factors for CRE colonisation in previous studies. [9,12].

The duration of hospital stay increased the risk of CRE colonisation. In our study, for CRE colonised patients, the median duration of stay in hospital was 17 days compared to 9 days for non-colonised patients. ($P<0.001$). This is consistent with previous studies done in India as well as internationally [9,12,16].

Rectal colonisation with CRE has already been identified as an important epidemiological risk factor for the development of subsequent CRE infection in previous studies [5,17]. In a study by McConville *et al*. [5], CRE-colonised patients had a 10.8-fold higher risk of CRE infection than in non-colonised patients. In our study also, 89.2% of CRE colonised patients developed CRE infection during the hospital stay. It was also observed that none of the CRE non-colonised patients had developed CRE infection supporting that CRE colonisation is a strong predictor of the development of CRE infection. We observed that among patients colonised with CRE who further developed infection, the colonising and infecting organism were of the same species as noted in previous studies [5,18]. This has important implications for good infection prevention and control practice and empiric antibiotic selection in CRE colonised patients. As pneumonia was the most common infection identified in our study, poor hand hygiene on the part of healthcare workers or aspiration of gastrointestinal contents may be a potential mechanism linking intestinal colonisation with the development of infection in the critically ill ICU

Table VI
Characteristics of CRE colonised patients who died during hospital stay (*N*=10)

Characteristic	Escherichia coli	Klebsiella pneumoniae	Enterobacter spp
Males	2	4	0
Females	0	4	0
Post-surgical patients	0	5	0
No CRE infection	1	0	0
CRE infection developed (*N*=9)			
Pneumonia	1	2	0
Surgical site infection	0	1	0
Pneumonia + surgical site infection	0	2	0
Pneumonia + urinary tract infection	0	1	0
Pneumonia + blood stream infection	0	1	0
Bloodstream infection + surgical site infection	0	1	0

patients [5]. Another study has hypothesised that CRE can stay for prolonged periods in the intestinal tract without causing any infections or they can also serve as a source of endogenous urinary tract infections, intra-abdominal infections or may translocate through the gut epithelium to cause bloodstream infection [19].

Klebsiella pneumoniae (*N*=25/37; 67.6%) was the most common CRE isolate recovered in our study followed by *Escherichia coli* (*N*=11/37; 29.7%) and 1 *Enterobacter spp.* (2.7%). Carbapenem resistance as a result of carbapenemase production is the most prevalent mechanism in CRE globally. Kang *et al.* [20] showed carbapenemase-producing CRE in 42.9% of total CRE isolates. In our study also, carbapenemase production was the most common resistance mechanism (83.8%). In only 6 out of 37 isolates, a carbapenemase enzyme was not detected and carbapenem resistance in such cases might be because of other mechanisms such as an efflux pump or porin mutation. For screening of carbapenemase producers, ertapenem and meropenem are proposed to be the most suitable antibiotics [21]. Ertapenem is preferred over meropenem for in vitro susceptibility testing due to its superior sensitivity (97% vs 71%) [22] and has been reported to detect most carbapenemase producers, as reported by Nordmann *et al.* and Gniadkowski *et al.* [13,23]. Out of members of Enterobacterales, the presence of carbapenemases was observed mainly in *Klebsiella pneumoniae* (59.5%) and *Escherichia coli* (24.3%) which is in agreement with a previous study by Xu *et al.* where *Klebsiella pneumoniae* (39.3%) and *Escherichia coli* (21.9%) were reported to have a high resistance to carbapenems [24]. By using mCIM and eCIM, the class of carbapenemase produced was identified. This can be important to guide antibiotic treatment. For example, isolates producing serine carbapenemases can be inhibited by ceftazidime-avibactam combination therapy.

Invasive infections caused by CRE have been shown to be associated with high mortality rates (about 40—50%) in various studies [5,25,26]. A study done by Kang *et al.* [20] showed 33% mortality in CRE colonised patients as compared to 9.9% mortality in non-colonised patients (*P*=0.004). In a study at PGIMER, Chandigarh by Mohan B *et al.* [12], there was no significant difference in the outcome of patients with or without CRE colonisation (*P*=0.245). In our study although the mortality rate was higher in CRE colonised patients (27.0%) as compared to non-CRE group of patients (21.3%), but it was not statistically significant (*P*=0.349).

Our study has a number of limitations. The number of patients in our study was small. Only 192 patients were included which yielded 37 CRE colonised positive cases, limiting our internal validity. There was also a risk of selection bias depending on the profile of the patient being admitted. There was a small number of follow up CRE screening samples as patients were only followed up for 8 days of ICU stay. We did not perform any molecular typing of the isolates or investigate bacterial virulence factors which may have contributed to transition from colonisation to infection. Patients were not matched, so the mortality comparison may be affected by unknown confounders. There is also risk of Berkson's bias as patients who were admitted during weekends, at night or died immediately after admission could not be recruited due to feasibility issues.

Conclusion

In conclusion, we found that in critically ill patients, CRE colonisation was associated with a high risk of subsequent CRE infection and longer ICU and hospital stay and increased mortality. CRE perirectal screening for detection of asymptomatic carriers should be carried out in high-risk settings as these organisms serve as source of endogenous infections and are a potential risk to other patients. The study also highlights the importance of infection prevention and control measures, including isolation and cohorting with barrier nursing of these patients to prevent further spread of CRE in hospital settings.

Disclaimer

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Potential conflicts of interest

All authors: No reported conflicts.

Credit author statements

Dr. Kirtika Sharma: Data acquisition, analysis and interpretation of data, writing original draft. **Dr. Vibhor Tak**: Concept and design of study, analysis and interpretation of data, review and editing and supervision. **Dr. Vijaya Lakshmi Nag, Dr. Pradeep Kumar Bhatia, Dr. Nikhil Kothari**: Conceptualization, review, editing and supervision.

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