Section: Miscellaneous

Original Research Article

INTESTINAL RESERVOIR OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE IN ICU PATIENTS AND ITS IMPACT ON CLINICAL OUTCOMES

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ABSTRACT

Background: Carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major threat in healthcare settings. These organisms reside mainly in the intestine and can act as a source of endogenous and cross infections. The aim of this study was to find the prevalence of fecal carriage of CRE in patients on admission to ICU and to identify assocated risk factors and clinical outcomes.
Materials and Methods: Rectal swabs were screened for the presence of CRE using chromogenic CarbaResist agar. Analysis for predisposing factors and clinical outcome were done for carbapenem resistant gram negative fecal carriers. For assessing the significance, the same factors were also studied in non-carriers.
Results: A total of 90 non-replicative rectal swabs were analyzed, of which 30% grew CRE. Selective pressure exerted by antibiotics given very recently (after hospital admission but before ICU admission) seemed to be the most important factor predisposing for gut colonization with CRE. In outcome analysis, the duration of hospital stay and the need to use high end antibiotics were found to be greater for patients who were CRE colonizers. The mortality rates due to infection by other resistant gram negative rods were also significantly higher in this group of patients.
Conclusion: Antibiotics given very recently rather than within three months was the most important risk factor to get CRE colonized. These individuals can act as a source of infection to other patients also. Hence, routine surveillance and strengthened antimicrobial stewardship are essential to limit the spread of CRE in critical care settings.
Keywords: Carbapenem-resistant Enterobacteriaceae (CRE), Intestinal carriage, Carbapenemase-producing organisms.

INTRODUCTION

Carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major threat to hospitalized patients, particularly those admitted to intensive care units (ICUs), where the burden of multidrug-resistant organisms is highest.[1]
The gastrointestinal tract serves as an important reservoir for these resistant organisms, facilitating their persistence and transmission. Intestinal carriage of carbapenemase-producing Enterobacteriaceae is of significant clinical concern, as it can lead to subsequent nosocomial infections and contributes to the dissemination of resistance within healthcare settings.[2] Patients colonized with CRE are at an increased risk of developing invasive infections caused by the same organisms.[3]
In India, there is limited data on the prevalence and risk factors associated with fecal carriage of CRE among ICU patients, especially from the southern region. Understanding the local epidemiology is essential for guiding infection control practices and antimicrobial stewardship strategies. Therefore, this study was undertaken to determine the prevalence of fecal carriage of CRE in patients admitted to the ICU and to identify the associated risk factors.

MATERIALS AND METHODS

The study was conducted as a prospective observational study at a tertiary care hospital, South Kerala. The study protocol was approved by the Institutional Ethics Committee (IRB/02/2019). The study was conducted over a year from January 2023. A minimum sample size of 57 was calculated from the data obtained from a previous study by Pantel A et al with a confidence interval of 95% and a precision of 4%4. Patients who were more than 18 years, admitted to the Medical Intensive Care Unit (MICU) were recruited for the study. Patients who had acute diarrheal illness within the past one week, active bleeding per rectum, prolapsed hemorrhoids were excluded from the study. Rectal swabs were collected after admission to MICU, in patients who provided informed consent to participate in the study. Rectal swabs were plated on commercially available chromogenic culture media (HiCrome CarbaResist agar). Plates were incubated at 37°C and examined for growth at 24 hrs and 48 hrs. In case of growth, organisms were chromogenically identified based on 'manufacturers recommendations'. All the pink purple colonies were presumptively identified as Escherichia coli and metallic blue mucoid colonies as Klebsiella pneumoniae. Growth on CarbaResist agar plates was rechecked for resistance to Imipenem and Ertapenem by modified Kirby–Bauer method. For suspected carbapenemase production, modified carbapenem inactivation method was done5. All the relevant clinical data including patient demographics, co-morbidities, risk factors, clinical presentation, and course during hospital stay were noted in a detailed proforma and the patients were followed up till hospital discharge.

All data were entered into Microsoft Excel and then analyzed with Statistical Package for Social Sciences (SPSS) version. Continuous variables were compiled as means (with standard deviations) and categorical variables as frequencies (with percentages). The differences in predisposing factors and outcomes between the two groups (carbapenem-resistant versus carbapenem-sensitive gram-negative fecal carriers) were assessed using tests of means and tests of proportions, wherever applicable. Non-parametric tests were used based on the distribution of the data. For all statistical analyses, p-value < 0.05 was taken as statistically significant.

RESULTS

A total of 90 patients were included in the study. Of these, 30% (27/90) were colonized with carbapenem resistant organisms. The distribution of carbapenem-resistant organisms is depicted in [Figure 1].

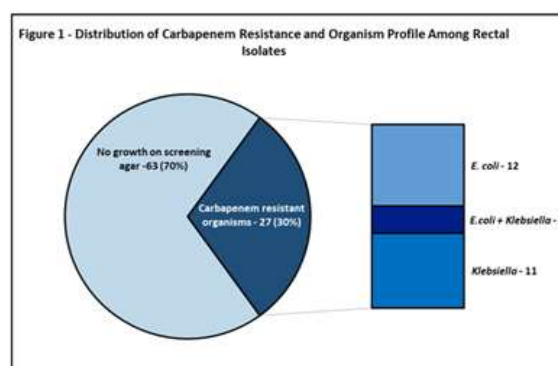

Figure 1: Distribution of carbapenem Resistance and Organism Profile Among Rectal Isolates

Escherichia coli accounted for 44.4% (12/27), Klebsiella pneumoniae for 40.7% (11/27), and both organisms for 14.8% (4/27). Among the carbapenem-resistant organisms, 55.6% (15/27) were carbapenemase producers, of which 93.3% (14/15) were Class B Metallo β-lactamase [Figure 2].

The clinical and demographic characteristics associated with rectal colonization of carbapenem-resistant organisms are given in [Table 1].

Table 1: Characteristics associated with rectal colonization with carbapenem resistant organisms

Characteristics	Carbapenem resistant carriers (%; n=27)	Negative for carbapenem resistant carriers (%; n=63)	P
Age	66.67 + 14.31	62.35 + 15.31	0.27#
Male	63 (17)	65.1 (41)	0.85*
Diabetes mellitus	55.6 (15)	54 (34)	0.89*
Hypertension	59.3 (16)	66.7 (42)	0.5*
Coronary artery disease	25.9 (7)	23.8 (15)	0.83*
Chronic obstructive pulmonary disease	18.5 (5)	6.4 (4)	0.07*
Chronic liver disease	11.1 (3)	19.1 (12)	0.35*
Chronic kidney disease	44.4 (12)	50.8 (32)	0.58*
Malignancy on chemotherapy	7.4 (2)	6.4 (4)	0.85*
Previous exposure to antibiotic (within 3 months of hospital admission	11.1 (3)	19.1 (12)	0.35*
Recent exposure to antibiotics (after hospital admission)	40.7 (11)	11.1 (7)	0.001*
Length of hospital stay before admission to intensive care unit	2.78 + 5.01	0.59 + 2.58	0.03#
* Chi-square test, # Mann-Whitney U-test			

Length of hospital stay before admission to ICU and exposure to antibiotics after hospital admission before shifting to ICU were significantly associated with colonization with carbapenem resistant organisms (p value 0.03 and 0.001 respectively). Among rectal colonizers with carbapenem-resistant

organisms, the most commonly used antibiotic for empirical therapy was Ceftriaxone (72.7%) followed by Amoxicillin-clavulanic acid (36.4%), whereas in those who were not colonized by these resistant organisms, the empiric antibiotic was mostly ceftriaxone (42.9%) or fluoroquinolones (42.9%).

The clinical course and outcome of patients who had rectal colonization with carbapenem-resistant organisms are presented in Table 2. Patients colonized with carbapenem-resistant organisms had a higher use of broad-spectrum antibiotics in the ICU (81.5% vs 58.7%, p=0.037), longer ICU stay (5.48 ± 3.72 vs 3.44 ± 3.22 days, p=0.005), and longer total hospital stay (13.48 ± 9.32 vs 8.49 ± 5.79 days, p=0.004). Mortality was significantly higher among colonized patients compared to non-colonized patients (14.8% vs 3.2%, p=0.042).

Table 2: Comparison of clinical course and outcome of patients with and without rectal colonization of carbapenem resistant organisms

Outcome	Carbapenem resistant carriers (%; n=27)	Negative for carbapenem resistant carriers (%; n=63)	P
APACHAE score	24.05 + 8.09	21.97 + 5.44	0.58#
Sepsis with elevated procalcitonin level	40.7 (11)	34.9 (22)	0.6*
Usage of antibiotics in intensive care unit	81.5 (22)	58.7 (37)	0.037*
Length of stay in intensive care unit	5.48 + 3.72	3.44 + 3.22	0.005#
Total length of hospital stay	13.48 + 9.32	8.49 + 5.79	0.004#
Mortality	14.8 (4)	3.2 (2)	0.042*
* Chi-square test, # Mann-Whitney U-test			

DISCUSSION

The prevalence of fecal carriage of CRE in India is highly varied throughout the country, with as high as 51.85% in Mumbai and 12% from a study conducted in Chandigarh.[6,7] In the present study, CRE colonizing gut is found to be 30%, of which more than 50% of the strains are carbapenemase producers (Metallo beta-lactamase). Not only are these statistics way higher in comparison to that in the west where the prevalence is less than 3%,[8,9] but they also differ in the predominant class of carbapenemase where most of their strains are Serino β-lactamases3 in contrast to Metallo beta-lactamases.

The mean age of patients with rectal colonization of carbapenem-resistant Enterobacteriales is found to be 66.67 years and that of the non-colonizers 62.35 years. Male patients have accounted for 63% among the colonized and 65.1% among the non-colonizers. As in previous studies, we have also found no difference in terms of age and gender between the colonizers and non-colonizers of carbapenem-resistant organisms.[10]

In our population, exposure to antibiotics during the present hospitalization has the greatest impact on colonization with carbapenem-resistant organisms. The odds that a person will be colonized with these resistant organisms were 5.5 times higher in those with very recent exposure to antibiotics with 95% confidence interval of 1.83 to 16.5. Though these findings are consistent with other studies, we have observed a strikingly contradictory finding with respect to the duration of antibiotics. In several studies, hospitalization and exposure to antibiotics within the previous three to six months are found to be strongly associated with colonization with carbapenem-resistant organisms.[11-13] But, in our study, it is not the antibiotic exposure within three months that is associated with rectal colonization with these resistant organisms. Rather, it is observed that the high selective pressure exerted by certain antibiotics like ceftriaxone and Amoxycillin-clavulanate given very recently (within three days) have resulted in significant colonization by carbapenem resistant organisms. The usage of ceftriaxone is observed to be 30% more among the carbapenem-resistant colonizers. Interestingly, patients who are not colonized with these resistant organisms are found to be not exposed to Amoxycillin-clavulanate. Treatment with β-lactam and its inhibitor combination can result in selective survival and multiplication of organisms resistant to these antibiotics.[13] Moreover, the genes encoding for resistance to these antibiotics are commonly found in mobile genetic elements which also carry genes encoding resistance for carbapenems.[12] Due to the overgrowth of these resistant organisms, the carrier rates for carbapenem-resistant organisms could be higher in these patients with recent exposure to antibiotics as it takes time for the restoration of normal colonic flora. Fluoroquinolones are another class of antibiotic that is identified as a predictive factor for carriage,[12,14] but in our study, none of the patients who have been treated with these agents are subsequently colonized with these resistant organisms.

People with liver diseases are prone to infections from bacteria translocating from their intestines. In our study, 20% (3/15) of people with chronic liver disease were carriers of carbapenem-resistant Enterobacteriales. Though this finding is not statistically significant, it is important to screen these group of individuals for fecal carriage of resistant organisms, as the risk of sepsis due to carbapenem-resistant organisms was nine times more in them.[15]

In a study conducted in cardiac care unit in Chennai, they found that patients who were exposed to high end antibiotics had significant association with CRE colonization.[16] This finding was in contrast to our study where patients who were exposed to rampantly used antibiotics like augmentin and cephalosporins were CRE colonized. Strikingly, it was post

colonization that the need to use high end antibiotics like piperacillin tazobactam and carbapenems were required in our set up.

In New York, 47% of CRE colonized patients developed CRE infection within a month and they found that CRE colonization was also associated with increased mortality (36%).[3] In Bangkok, 4.7% of CRE-colonized patients developed a CRE clinical infection, with 60% mortality.[17] Even though our mortality rates were not as high as in these studies, we also found a significant relationship between CRE colonization and mortality. These people developed infection by CRE and non-fermenters as well.

CONCLUSION

The high intestinal carriage rate (30%) observed in this study highlights the critical need for active surveillance and strengthened antimicrobial stewardship to limit the spread of CRE. The gut microflora can act as a reservoir for infection not only in the carrier, but can also be easily disseminated across other patients. Hence, it is important to routinely screen patients for colonization of these resistant bugs at hospital admission and during hospital stay so that these patients can be either isolated or cohorted and strict contact precautions can be implemented.

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