Abstract

Background: Infection/colonization due to carbapenem-resistant enterobacteriaceae (CRE) are emerging as an important challenge, particularly in high risk patients due to widespread use of Carbapenems. Therefore, preventing both CRE infections and their transmission has become an important infection control objective. Aims and Objective: Determine the proportion of asymptomatic carriers of CRE among patients admitted to our critical care unit (CCU) from the community and other health care facilities. Enumerate risk factors and guide implementation of infection control interventions. Methods: This prospective surveillance study was done in a 24 bed CCU of a tertiary care hospital, at Chennai, India between August 2017 through December 2017. Patients were screened based on a composed questionnaire framed from Centers for Diseases Control and Prevention CRE tool-kit. Two rectal swabs were collected from each patient. They were processed in microbiology laboratory. Results: A total of 102 patients were included. CRE colonization were identified in 8 (7.8%) of the total samples. Among 8 CRE colonized patients 3 (37.5%) patients developed systemic infection. Patients who were exposed to high end antibiotic and past history of surgery had significant association with CRE colonization of \((P = 0.0029)\) and \((P = 0.0167)\) respectively. Conclusion: Overall CRE colonization rates among our CCU patients were found to be low. Risk factors associated with CRE colonization were high end antibiotic exposure and surgery in past 90 days. Hence rectal screening should be a risk factor–based active surveillance. Association of systemic infection among CRE colonizers was more significant. This study led us to modify our infection control practices in CCU.

Keywords: Carbapenem-resistant enterobacteriaceae, colonization, critical care unit, India, risk factors

Introduction

Infection/colonization due to carbapenem-resistant enterobacteriaceae (CRE) is emerging as an important challenge, particularly in high risk patients due to widespread use of Carbapenems. Centers for Diseases Control and Prevention (CDC) have responded to the rising peril by classifying CRE as an urgent threat to public health, its highest risk category.\(^1\) Therefore preventing both CRE infections and their transmission has become an important infection control objective.

The prevalence of CRE colonization in hospitalized patients ranges from 3 to 7%\(^2\) but can be higher in patients admitted to critical care units (CCUs).\(^3\) In one of the Indian study it was found that the prevalence of CRE in CCU ranges between 13% and 51%.\(^4\) A proactive approach by active surveillance and a strong compliance with infection control measures would be needed to prevent the spread of CRE transmission particularly in a CCU setup.

Aim

To minimize the risk of transmission in CCU by unknown CRE colonizers, we performed active surveillance using rectal swab for detection of CRE. The aim of this study was to

1. Determine the proportion of asymptomatic carriers of CRE among patients admitted to our CCU from the community and other health care facilities (HCF)
2. To enumerate risk factors associated with colonization
3. To guide implementation of interventions to prevent transmission of CRE.

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METHODS

This study was carried out to chart out a road map for infection control measures in our hospital.

This prospective surveillance study was done in a 24 bed CCU of a tertiary care hospital, at Chennai, India between August 2017 through December 2017. All patients more than 18 years of age admitted in CCU were included in the study. Patients transferred from different units within the hospital to CCU were excluded as these patients were not screened for CRE at the time of admission.

Two rectal swabs (for better yield) were collected simultaneously from patients getting admitted to the CCU.

Patients were also screened based on a predetermined/composite questionnaire which included duration of stay in the other hospital, exposure to high end antibiotics (carbapenem, colistin, tigecycline, polymyxin B, vancomycin, teicoplanin), devices inserted, surgery done in the past 90 days and past history of colonization and infection with CRE [Annexure].

A nylon flocked swab system was used for sample collection and this was immediately transferred to the laboratory, for processing. Swabs were vortexed for 10 s in peptone water, and 100 μl was plated on MacConkey agar with Meropenem at 1 μg/ml as well as on MacConkey agar plate without Meropenem for determination of viable colony counts. Plates were incubated overnight at 35°C in an incubator and then interpreted. Lactose fermenting colonies were identified as pink, mucoid or non-mucoid colonies on MacConkey agar plate and non-lactose fermenting colonies as colourless colonies. Suspected CRE colonies from MacConkey agar with Meropenem at 1 μg/ml were suspended in saline to the density of a 0.5 McFarland standard and antimicrobial susceptibility for Imipenem, Meropenem was determined in Muller-Hilton agar plate by Kirby Bauer method which was also confirmed by Vitek 2 system. Susceptibility was determined using 2017 breakpoint criteria of the Clinical and Laboratory Standards Institute. Pink lactose fermenting mucoid or non-mucoid colonies on MacConkey agar plate without Meropenem were identified and confirmed by MALDI-TOF. Isolates non-susceptible to either Imipenem or Meropenem were defined as CRE positive.

Patients were categorized into two groups based on rectal colonization as CRE-colonized or non-colonized. Intergroup analysis for categorical data was done using Chi-square test. \( P < 0.05 \) was considered statistically significant. Statistical analysis was done using IBM Statistical analysis was done using SPSS software (SPSS ver. 21, IBM, Chicago, USA).

The study was approved by the Institutional ethical committee.

RESULTS

Rectal swabs (204) were collected from 102 patients among whom 58 patients were transferred from other HCF and 44 patients admitted directly from the community. The results were extrapolated based on a single positive rectal swab from each patient. Distribution of individual risk factors across the two groups is summarized in Table 1.

The mean age of the study patients was 53.8 years and 74 (72.5%) were males and 28 (27.5%) were females. CRE colonization were identified in 8 (7.8%) of the total samples. Of the 58 patients from other HCF 5 (8.6%) patients with a minimum stay of 3 days elsewhere had rectal colonization with CRE. Of the 44 patients from community 3 (6.8%) had CRE colonization in their rectum.

In our study among 8 CRE colonized patients 3 (37.5%) patients developed systemic infection whereas only 2 (2.1%) among 94 patients who were non CRE colonizers developed systemic infection due to CRE. This emphasizes the statistical significance \( (P = 0.00001) \) of developing systemic infection among colonized patients as compared to non-colonized patients. Out of these 3 patients 2 of them developed bacteremia and 1 patient grew CRE *Klebsiella pneumoniae* in urine and all of these patients had history of hospitalization from other HCF [Figure 1].

None of the patients from community who were colonized developed any systemic infection.

The risk factors analyzed were high end antibiotic exposure (carbapenems, colistin, polymyxin B, vancomycin, tigecycline, polymyxin B, vancomycin, teicoplanin), other hospital, exposure to high end antibiotics (carbapenems, colistin, polymyxin B, vancomycin, teicoplanin), devices inserted, surgery done in the past 90 days and past history of colonization and infection with CRE [Annexure].

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None of the patients from community who were colonized developed any systemic infection.
Among the 8 isolates 6 (5.9%) isolates were K. pneumoniae and 2 (1.9%) were E. coli. The susceptibility reports done by MacConkey agar with Meropenem at 1 μg/ml correlated with Vitek-2 system and also to Kirby Bauer method.

**Discussion**

CRE often carry genes that confer high level resistance to almost all commonly used antibiotics, including Beta-lactams, fluoroquinolones, aminoglycosides and Beta-lactams beta lactamase inhibitors and Carbapenems,\(^{[5]}\) often leading to limited therapeutic options. The emergence and rapid dissemination of CRE worldwide is a cause for concern and is a global health crisis.\(^{[6]}\) So controlling their spread is of utmost importance.

Adler *et al.* proved in his study that agar dilution with 1 μg/ml of Carbapenem had a sensitivity of 84.9% and specificity of 94.3% and 92.1% accuracy of detection.\(^{[7]}\) Hence we used this methodology for the determination of CRE isolates.

In our study CRE colonization was detected in 7.8% patients during active surveillance by rectal swab. The CRE colonization rate in our study was very less as compared to study done by McConville *et al.* who detected colonization rate of 28%\(^{[8]}\) but almost similar to study done by Banach *et al.*\(^{[9]}\) Patients hospitalized from other health care facility were 8.6% and 6.8% of patients from community were CRE colonized. In a meta-analysis done in CCU it was observed, that the overall risk of systemic CRE infection varied widely between 26% and 73% among colonizers.\(^{[3,10]}\) In our study the systemic infection rate among colonizers was 37.5% which was statistically significant as compared to non-colonizers. Notably, among patients colonized with CRE who went on to develop a systemic CRE infection, the colonizing and infecting organism were the same species in all patients.

According to antimicrobial surveillance network for the year 2017 by Indian Council of Medical Research *Enterobacteriaceae* isolates were 23%, 32%, 37% were resistant to Imipenem, Meropenem and Ertapenem respectively.\(^{[11]}\)

The risk factors analyzed were high end antibiotic exposure (Carbapenems, Colistin, Polymyxin B), devices *in situ* (Central line, endotracheal intubation, folesy's catheterization), surgery in the past 90 days and hospitalization in other health care facility. There was no statistical significance of association between CRE colonization among patients from community and from outside hospitalization provided patients from community (P = 0.737) do not have associated risk factors. Patients who were exposed to high end antibiotic had significant association with CRE colonization (P = 0.0029). Similarly patients who had undergone surgery in past 90 days had a statistical association with CRE colonization (P = 0.0167).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>CRE colonization (n=8)</th>
<th>No CRE colonization (n=94)</th>
<th>Total (n=102)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7</td>
<td>67</td>
<td>74</td>
<td>0.323</td>
</tr>
<tr>
<td>Age (mean±SD years)</td>
<td>55.85±15.6</td>
<td>53.5±16.03</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Patients received from other health care facility, n (%)</td>
<td>5 (8.6)</td>
<td>53</td>
<td>58</td>
<td>0.737</td>
</tr>
<tr>
<td>Patients received from community or not received from other health care facility, n (%)</td>
<td>3 (6.8)</td>
<td>41</td>
<td>44</td>
<td>0.737</td>
</tr>
<tr>
<td>High end antibiotic exposure, n</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>0.0029</td>
</tr>
<tr>
<td>History of surgery in past 90 days, n</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>0.0167</td>
</tr>
<tr>
<td>Endotracheal intubation, n</td>
<td>3</td>
<td>25</td>
<td>28</td>
<td>0.507</td>
</tr>
<tr>
<td>Central line <em>in situ</em>, n</td>
<td>1</td>
<td>8</td>
<td>9</td>
<td>0.702</td>
</tr>
<tr>
<td>Foley catheterization, n</td>
<td>4</td>
<td>32</td>
<td>36</td>
<td>0.822</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

SD: Standard deviation, CRE: Carbapenem-resistant *Enterobacteriaceae*
laboratory for processing but we thought it wouldn’t be a cost-effective measure at that point of time. But still there were no outbreaks during the study period.

The low prevalence of asymptomatic carrier rate among CCU patients and the strong association of the CRE colonizers with past history of surgery and high end antibiotic exposure guided us to propose risk factor based active surveillance. The low prevalence of CRE colonization in our study proves that screening all patients admitted in CCU either from other health care facility or from community is not cost effective. Hence risk factor based active surveillance in a high risk setting like CCU, transplant unit helps to detect asymptomatic CRE carriers who can serve as reservoirs for transmission during hospitalization. Based on these findings pre-emptive contact isolation of colonizers, proper staff allocation, dedicated equipment, environmental cleaning, and resource allocation to the correct patient was decided. So our current practices of routinely isolating patients only infected with CRE was modified based on risk factor based active surveillance.

Our study had few limitations, including short duration, CRE rectal screening was done only at the time of admission and was not repeated subsequently. We were unable to clarify the mechanism for resistance in the CRE and also no clonality was performed to determine that the bacteremia caused by CRE was only due to the colonization. However, phenotypic methods were employed for the detection of CRE. The patients were followed up for the current admission in CCU. So we were unable to assess the impact of CRE acquisition or loss of colonization during the CCU stay in the next visit if the same patient was readmitted to CCU from other units of hospital. Few drawbacks are turnaround time of laboratory for processing but we thought it wouldn’t be a cost-effective measure at that point of time. But still there were no outbreaks during the study period.

The benefits of active surveillance are it will protect vulnerable patients from the potentially devastating effect of CRE infection.

**CONCLUSION**

Overall CRE colonization rates among our CCU patients were found to be low. Hence rectal screening should be a risk factor–based active surveillance for proper utilization of resources. Risk factors associated with CRE colonization were high end antibiotic exposure and surgery in past 90 days. Association of systemic infection among CRE colonizers was more significant. Hence CRE rectal screening for detection of asymptomatic carriers should be carried out in high risk settings as these organisms can act as sources of endogenous infections. This study led us to modify our infection control practices to initiate empiric contact isolation precautions and active surveillance for the patients with risk factors in CCU. So our current practice of isolating patients infected with CRE alone was modified and bundled with proactive approach which was tailored to the available resources. This study guided us to revisit our contact isolation policy.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

Ramanathan, et al.: CRE screening in Indian CCU?

2012;31:1811-7.

Infect Control Hosp Epidemiol 2013;34:809-17.

ANNEXURE

Questionnaire

1. Previous admission in any health care facility for more than 48 h in past 90 days
   □ No □ Yes
2. Previous usage of broad spectrum antibiotics (imipenem, doripenem, meropenem, colistin, polymyxin B)
   □ No □ Yes
3. Device placed (central line, urinary catheter, endotracheal tube,)
   □ No □ Yes
4. Surgery done in past 90 days
   □ No □ Yes
5. Previous history of colonization/infection due to carbapenem resistant enterobacteriaceae
   □ No □ Yes