Prevalence of carbapenem resistant *Enterobacteriaceae* from a tertiary care hospital in Mumbai, India

Pravin K. Nair, Michelle S Vaz

*Holy Spirit Hospital, Department of Clinical Microbiology, Mumbai, India*

**ABSTRACT**

**Objective:** The emergence of Carbapenem Resistant *Enterobacteriaceae* (CRE) in recent times has become a serious threat to public health due to the high mortality, potential dissemination rates and limited treatment options associated with these organisms. Thus, the present study was conducted in our tertiary care hospital in Mumbai, to retrospectively analyze the prevalence of CRE in the hospital.

**Methods:** The study was carried out in the microbiology department of the tertiary care hospital over a period of 12 months. The samples tested were clinical samples from hospitalized and Out-Patient Department (OPD) patients sent to the department for microbiological testing. CRE isolates were identified using the Vitek 2-Compact system (BioMérieux, France).

**Results:** A CRE prevalence rate of 12.26% was obtained from the study, from which the majority of the isolates were detected in urine samples (46%). Although most of the CRE isolates were detected in patient samples from the wards (42%) and the ICU (26%), a significant number of isolates was also detected from the OPD patients (19%).

**Conclusion:** Thus, the study shows a significant rate of carbapenem resistance among *Enterobacteriaceae* isolated from hospitalized and OPD patients. This emphasizes the urgent need for CRE control at the hospital and community level, and to rationalize the use of antibiotics. *J Microbiol Infect Dis* 2013;3(4): 207-210

**Key words:** Carbapenem Resistant *Enterobacteriaceae*, Antimicrobial Stewardship

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**ÖZET**

**Amaç:** Karbapenem dirençli *Enterobacteriaceae* (CRE) enfeksiyonlarındaki artış halk sağlığı için önemli bir tehdit oluşturmaktadır çünkü bu bakterilerin enfeksiyonlarında kullanılabilecek sınırlı sayıda antibiyotik vardır ve mortalitesi yüksektir. Bu çalışma, Mumbai’de bulunan üçüncü basamak hizmet veren hastanenin CRE prevalansını belirlemek amacıyla retrospektif olarak yapıldı.

**Yöntemler:** Çalışma mikrobiyoloji bölümünde 12 aylık bir sürede yapıldı. Hem hastane kökenli hem de toplum kaynaklı örnekler çalışmaya dahil edildi. Örnekler Vitek 2-Compact System (BioMérieux, France) ile analiz edildi.

**Bulgular:** Çalışmamızda CRE sıfırda %12.26 olarak bulunmuş olup örneklerinizin büyük bir kısmı idrar (% 46) örneklerinden elde edildi. Ancak CRE izole edilen örneklerin önemli bir kısmı yara örneklerinden (% 42) idi. Örneklerin % 26’sı yoğun bakım hastalarından izole edilirken %19’u da toplum kaynaklı örneklerden izole edildi.

**Sonuç:** Çalışmamızda *Enterobacteriaceae* üvelerinin önemli bir kısmında karbapenem direnci olduğu gösterilmiştir. CRE örneklerinin toplumda ve hastanede kontrol edilmesini sağlayacak önlemlere ve akıcı antibiyotik kullanımı sağlayacak tedbirlerle ihtiyaç vardır.

**Anahtar kelimeler:** Karbapenem Dirençli *Enterobacteriaceae*, Antibiyotik yönetimi

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Correspondence: Pravin K. Nair, Consultant Microbiologist and Head of Infection Control, Holy Spirit Hospital, Mumbai, India Email: drpravinnair@gmail.com

Received: 25.03.2013, Accepted: 25.09.2013

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INTRODUCTION

Carbapenems are a group of β-lactam antimicrobial agents with an exceptionally broad spectrum of activity. They are used as a last resort against many multi drug resistant, gram negative bacteria, and in cases of infections due to Extended spectrum beta lactamase (ESBL) and Amp C enzyme producing Enterobacteriaceae. The emergence and dissemination of carbapenem resistant bacteria in recent times represents a serious threat to public health. Resistance has been observed in several Enterobacteriaceae, as well as in members of the Pseudomonas and Acinetobacter genera. These organisms are associated with high mortality rates and have the potential to spread widely.

Resistance to carbapenems can be brought about by various mechanisms, the most common being the production of carbapenemases, a class of enzymes capable of hydrolyzing carbapenems and other β-lactams. Resistance to carbapenems can also be due to the poor binding of carbapenems to penicillin-binding proteins present in the bacteria, the over-expression of multidrug efflux pumps by the bacteria or lack of porins present in the bacterial cell membrane. However, for significant resistance to emerge, it is thought that a combination of resistance mechanisms is required.

Carbapenem Resistant Enterobacteriaceae (CRE) can be defined as Enterobacteriaceae that are resistant to one or all of the following carbapenems: ertapenem, meropenem, imipenem or doripenem; and resistant to all of the following third-generation cephalosporins: ceftriaxone, cefotaxime, and ceftazidime. Klebsiella species and Escherichia coli that meet the CRE definition are a priority for detection; however, other Enterobacteriaceae (e.g. Enterobacter species) are also of significant importance. CRE have been associated with high mortality and morbidity rates of up to 40-50% recorded in some studies. Also, CRE are found to carry genes that confer high levels of resistance to many other antimicrobials, often leaving very limited therapeutic options.

In 2007, the overall worldwide susceptibility to carbapenems was 98% among the Enterobacteriaceae. Presumably this is caused due to a number of factors, including antibiotic usage, dosing regimens, and local hospital practices concerning isolation of patients with multiresistant pathogens. With the increasing incidence of CRE in hospitals, a rapid and accurate routine protocol for CRE screening and detection is required. Appropriate detection of CRE is vital in patient care and infection control in order to institute correct, targeted treatment and to reduce the escalation of resistance.

The primary objective of this study was to evaluate the prevalence of CRE in a 330 bedded tertiary care hospital in Mumbai. This study is epidemiologically important since studies based on the emergence and spread of carbapenem resistance in India, are very limited, of which studies pertaining to CRE specifically are even fewer.

METHODS

The study was a retrospective study carried out in the Microbiology department of a tertiary care hospital, Mumbai, from January 2012 to December 2012. The clinical samples tested were those collected from patients hospitalized in the wards, the Intensive Care Unit (ICU), the Cardiac Care Unit (CCU), the Neonatal Intensive Care Unit (NICU), the Pediatric Intensive Care Unit (PICU), as well as from OPD patients coming to the hospital for treatment. These included blood, urine, stool, endotracheal secretions, sputum, pus, wound, and other samples. All samples were processed as per standard microbiology protocol. The identification and antibiotic susceptibility study of all clinical isolates was done using the Vitek 2 Compact System (Bio-Mérieux, France). Isolates that showed elevated MICs to one or all of the following carbapenems- meropenem, imipenem and ertapenem; as well as resistance to ceftriaxone, cefotaxime and ceftazidime were considered to be carbapenem resistant. The resistance breakpoints used for detecting carbapenem resistance among Enterobacteriaceae was ≥4µg/ml for imipenem and meropenem, and ≥2µg/ml for ertapenem. The resistance breakpoints used for ceftriaxone and cefotaxime was ≥64µg/ml and for ceftazidime was ≥32 µg/ml. All resistance breakpoints were according to CLSI guidelines (document M100-S22).

RESULTS

A total of 1282 bacterial isolates were obtained from the clinical samples tested over 12 months, of which 465 were Enterobacteriaceae. 57 isolates of the total 465 Enterobacteriaceae were found to be carbapenem resistant (12.26%).

The CRE isolates obtained are given in Table 1.

The area wise distribution of CRE identified from the samples in the hospital is given in Fig. 1, and the sample wise distribution is given in Fig. 2.

The prevalence of CRE in the hospital was found to be 12.26%. This is similar to the CRE prevalence rates obtained in similar studies from other parts of India. Datta et al. reported a CRE prevalence rate of 7.87% from a study conducted in a tertiary care hospital in North India while Gupta et al reported carbapenem resistance varying from 17 to 22% among Enterobacteriaceae strains. Wattal et al. reported a high CRE prevalence rate ranging from 13 to 51% in a tertiary care hospital in Delhi. Thus, the significant CRE prevalence rates recorded in different parts of India emphasize the need for controlling the further dissemination of CRE. Of the CRE identified in the hospital, maximum were from patient urine samples (46%). In addition, although most CRE isolates were obtained from patients admitted in the hospital wards (42%) and ICU (26%), a significant number of CRE isolates were also isolated from OPD patient samples (19%). This suggests that several CRE isolated in the study may have been community acquired.

Enterobacteriaceae majorly contribute to the intrinsic human gut flora. They are also capable of colonizing the gut of patients and spreading through the community via the faeco-oral route. Thus the spread of CRE is deeply disconcerting in a country such as India with a reservoir of more than 1.4 billion people. The first step in dealing with the problem of CRE is the identification of infected patients. Appropriate detection of CRE is vital in patient care and infection control in order to institute correct, targeted treatment and to reduce the escalation of resistance. Although molecular techniques are regarded as the gold standard for detection of carbapenem resistance, it becomes impractical in a routine diagnostic laboratory setup due to cost factors. Thus, the need of the hour is the rapid, practical and cost effective phenotypic detection of CRE.

CRE infected patients serve as reservoirs for spreading infection and contaminating the environment. Thus, identified CRE infected/ colonised patients must be contact isolated. Antimicrobial stewardship may be the most effective in the control of CRE through targeted specific antimicrobial usage. Limited use of invasive procedures is also an

**Table 1.** Strain and sample distribution of Carbapenem Resistant Enterobacteriaceae isolates

<table>
<thead>
<tr>
<th>Sample</th>
<th>E. coli</th>
<th>Klebsiella sp.</th>
<th>Enterobacter sp.</th>
<th>E. coli</th>
<th>Klebsiella sp.</th>
<th>Enterobacter sp.</th>
<th>E. coli</th>
<th>Klebsiella sp.</th>
<th>Enterobacter sp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU/CCU</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Ward</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCU</td>
<td>7</td>
<td>-</td>
<td>8</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>NICU/PICU</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>-</td>
</tr>
<tr>
<td>Blood</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sputum</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine</td>
<td>7</td>
<td>-</td>
<td>8</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>7</td>
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<td>Stool</td>
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<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pus/Abcess ET secretion</td>
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<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Wound</td>
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<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
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<td>-</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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</table>

**DISCUSSION**

The prevalence of CRE in the hospital was found to be 12.26%. This is similar to the CRE prevalence rates obtained in similar studies from other parts of India. Datta et al. reported a CRE prevalence rate of 7.87% from a study conducted in a tertiary care hospital in North India while Gupta et al reported carbapenem resistance varying from 17 to 22% among Enterobacteriaceae strains. Wattal et al. reported a high CRE prevalence rate ranging from 13 to 51% in a tertiary care hospital in Delhi. Thus, the significant CRE prevalence rates recorded in different parts of India emphasize the need for controlling the further dissemination of CRE. Of the CRE identified in the hospital, maximum were from patient urine samples (46%). In addition, although most CRE isolates were obtained from patients admitted in the hospital wards (42%) and ICU (26%), a significant number of CRE isolates were also isolated from OPD patient samples (19%). This suggests that several CRE isolated in the study may have been community acquired.
important intervention in CRE prevention in hospital settings.\textsuperscript{12}

The major limitation of our study was the lack of a confirmatory test for the carbapenem resistant \textit{Enterobacteriaceae} identified by the Vitek 2 system. However, since this was a retrospective study of a routine diagnostic lab, the ability of the Vitek 2 system to identify >90\% of \textit{Enterobacteriaceae} that are resistant to or that have reduced susceptibility to one or more carbapenems was considered sufficient.\textsuperscript{13}

In conclusion, this study shows a significant rate of carbapenem resistance among \textit{Enterobacteriaceae} isolated from hospitalized and OPD patients as reported in similar studies from other parts of India. It provides a clearer picture of the current CRE scenario in the hospital setup of the country and thus further emphasizes the need for control of CRE dissemination within the community. The need of the hour would be to have a strong antimicrobial stewardship program, which is followed by all concerned Doctors, with further emphasis on better cost effective, logical infection control measures to prevent the dissemination of such multidrug resistant bacteria. Would Antibiotic holiday, i.e. stopping the use of certain carbapenems, bring back organism sensitivity is another approach to be looked into.

REFERENCES

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