

A Retrospective Observational Study Comparing Clinical and Microbiological Parameters of Carbapenem Sensitive and Resistant *Enterobacteriaceae* Infections in a Tertiary Care Centre in Kerala

G. Manoj¹, Arya R. V², Sivaprasad P.S.³, Anitha A.⁴

¹Senior Consultant Physician, Department of General Medicine, General Hospital, Ernakulam, Kerala. ²Consultant Microbiologist, Department of Microbiology, General Hospital, Ernakulam, Kerala. ³Consultant Paediatrician, Nodal Officer, Sepsis Management Program, General Hospital, Ernakulam Kerala. ⁴Superintendent, Public Health Expert, General Hospital, Ernakulam, Kerala.

ABSTRACT

BACKGROUND

The alarming rise in carbapenem Resistance (CR) among *Enterobacteriaceae* is posing a great threat to the humanity, all over the world. This study is intended to evaluate the CR in a tertiary care centre in Kerala.

METHODS

It is a retrospective observational study of one year duration, analysing the culture and sensitivity reports of various body fluids from sick patients admitted in General Hospital, Ernakulam.

RESULTS

The study revealed 7.4% incidence of carbapenem resistance (CR) among the isolated *Enterobacteriaceae*. *Klebsiella* species showed more CR than *E. coli*. Uncontrolled diabetes mellitus is a major risk factor for the patients to contract entero infections. CKD and chemotherapy contribute significantly to higher mortality.

CONCLUSIONS

The incidence of CR in the study population is at par with the world statistics and good diabetic control along with combination therapy of colistin and meropenem, significantly reduces mortality in infections due to CR *Enterobacteriaceae*.

KEY WORDS

CR- Carbapenem Resistance, CRE- Carbapenem Resistant *Enterobacteriaceae*, CKD- Chronic Kidney Disease, CLSI- Clinical and Laboratory Standards Institute, COPD- Chronic Obstructive Pulmonary, LAMA- Left Against Medical Advice

Corresponding Author:

Dr. Arya R. V.,
Consultant Microbiologist,
General Hospital, Ernakulam,
Kerala.

E-mail: aaryarv@gmail.com

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BACKGROUND

Globally, the consumption of last resort antibiotics like carbapenems and Colistin has been increasing. This rise is consistent with a well-documented increase in the number of infections due to drug resistant bacteria.^{1,2} carbapenem resistance in *Enterobacteriaceae* is a growing global concern with highest rates reported from South Asia and Mediterranean countries (7-14%). carbapenem resistant *Enterobacteriaceae* (CRE) have emerged as one of the major multidrug resistant pathogens in recent times. carbapenem resistant (CR) *Klebsiella pneumoniae* constitute about 92% of carbapenem resistant *Enterobacteriaceae*. *Klebsiella pneumoniae* carbapenemase (KPC) is the predominant molecular mechanism of resistance in the west, while New Delhi Metallo-beta-lactamase (NDM) is the most common one in South Asia among *Klebsiella* isolates. Additional carbapenemases that have been associated with epidemics in *Enterobacteriaceae* include the Verona integron-encoded metallo-β-lactamase (VIM), Imipenemase (IMP) metallo-β-lactamase and Oxacillinase-48-type (OXA-48) enzymes. Though there are plenty of publications on the in vitro characteristics of carbapenem resistant bacteria, lack of published data on clinical profile including morbidity, mortality and treatment options from Indian subcontinent; is a serious impediment, forcing clinicians to infer available data from the west, while making therapeutic decisions.^{3,4,5} carbapenem-resistant *K. pneumoniae* (CrKP) was first reported in 1996, and is now found worldwide.^{6,7,8} Multi drug resistant (CR) *Klebsiella pneumoniae* which constitute a major portion of carbapenem resistant *Enterobacteriaceae* were observed to be associated with high mortality.^{9,10}

There are a number of factors that predisposes persons to infections by CRE. Exposure to these resistant organisms can cause serious infections in patients with the following reported risk factors: immune-suppression, advanced age, admission to intensive care unit (ICU), mechanical ventilation, previous exposure to antimicrobials, organ or stem-cell transplantation and prolonged hospital stay. Available data suggest high therapeutic failure and mortality rates upto at least 50%. Treatment options for multi- drug resistant *Enterobacteriaceae* typically include Colistin used alone or in combination with other agents like carbapenems and Rifampicin.^{11,12,13} The widely studied gene responsible for colistin resistance in bacteria as well as humans is known as 'mobilised colistin resistance' or MCR. But many Colistin resistant bacterial agents, particularly *Klebsiella* do not possess this gene. Instead they have an abnormality in another gene called mgrB. Colistin resistant *Klebsiella* with mgrB gene mutation can originate from food. mgrB gene is located in the chromosome of the bacteria. The presence of 'jumping genes' helps dissemination of mgrB gene mutation and colistin resistance from food bacteria to humans, creating bacteria resistant to the last line antibiotic-Colistin.

Objectives

- Study the incidence of carbapenem resistant *Enterobacteriaceae* in a tertiary care centre under the Kerala State Health Services.
- Comparison of clinical profile and outcome among carbapenem resistant infections.
- Analyse samples which screen carbapenem resistance and confirm with phenotypic tests.
- To study the efficiency of combination therapy in carbapenem resistant infections to reduce mortality in CRE infections.

METHODS

This is a retrospective observational study conducted in the Departments of General Medicine, General Surgery and Microbiology of General Hospital, Ernakulum from January 2018 to December 2018 (1 year) among 87 CRE isolates from various body fluids.

Inclusion Criteria

- Infection caused by an *Enterobacteriaceae*, as defined by at least one positive blood culture for organisms of this bacterial family for bacteraemia or respiratory, urinary specimen or pus culture growing any of these organisms.
- Hospitalised patients from 12-85 yrs. of either gender with blood stream infections, pneumonia, UTI or SSTI.
- Neutropenic patients on chemotherapy and CKD patients requiring Colistin were also included in the study.

Exclusion Criteria

The culture and sensitivity reports from the following group were excluded

1. Paediatric age group (<12 yrs.).
2. Pregnancy.
3. HIV infection.
4. Patients who received higher antibiotics from referring hospitals were also excluded.

Data Analysis

Institutional ethics committee's approval was first obtained. The data regarding all the patients satisfying the inclusion criteria was collected from the medical records library. The data was arranged in a tabular form, in the chronological order of the date of admission. The culture and sensitivity reports were cross verified from the regional diagnostic laboratory of our own hospital. The data was analysed for distribution of *Enterobacteriaceae* isolated, CR Status of each of them and age and major risk factors of patients who contracted CR *Enterobacteriaceae*. As per the direction of the Hospital Infection Control Committee, the antibiotic policy of a combination of meropenem and colistin had been administered to all patients who showed CR. The outcome of treatment was collected from the data and analysed to give final conclusion.

Methodology

All the *Enterobacteriaceae* isolated from patients satisfying inclusion criteria were screened for carbapenemase production by imipenem, meropenem, ertapenem, doripenem MIC. (CLSI guidelines). They underwent phenotypic tests including Modified Hodge Test. All isolates were confirmed as CRE by VITEK automated system, according to MIC for each carbapenem as per CLSI guidelines. All patients with carbapenem resistance were treated with a combination of Meropenem and Colistin and they were closely monitored for clinical outcome with all other necessary supports

RESULTS

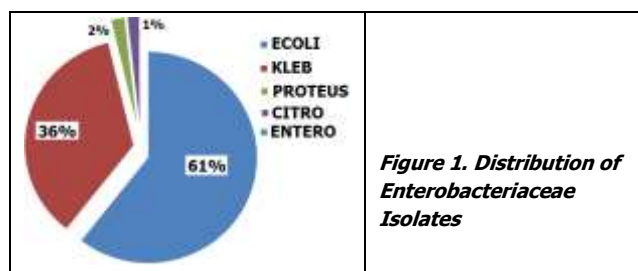


Figure 1. Distribution of Enterobacteriaceae Isolates

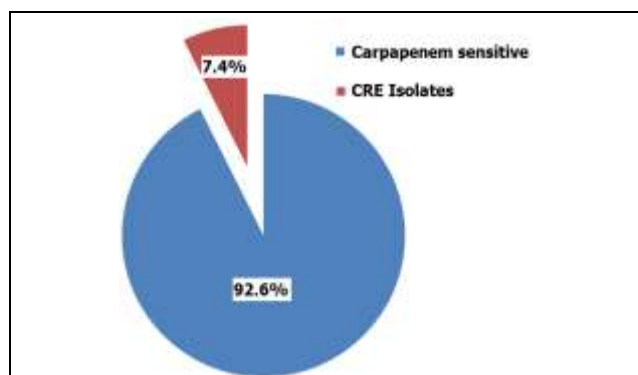


Figure 2. Enterobacteriaceae Isolated

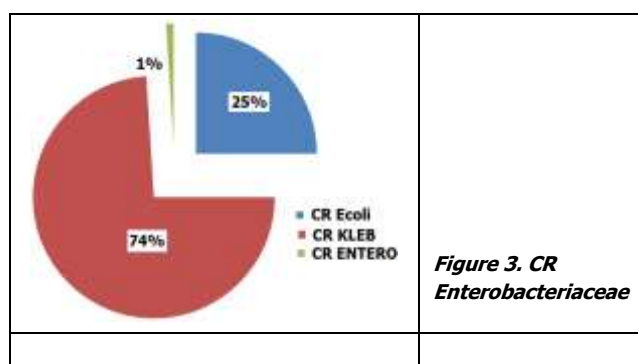


Figure 3. CR Enterobacteriaceae

CR <i>E. coli</i>	22 out of 710
CR <i>Klebsiella</i> Pneumoniae	64 out of 418
CR <i>Enterobacter</i>	1 out of 1

Table 1. carbapenem Resistance

Age Group	No. of CR Isolates	Mortality
<50 yrs.	10	1 (10%)
51-60 yrs.	20	6 (30%)
61-70 yrs.	28	7 (25%)
>71 yrs.	29	4 (14%)

Table 2. Age Wise Distribution and Percentage of Mortality of Patients in Whom CR Enterobacteriaceae was Detected

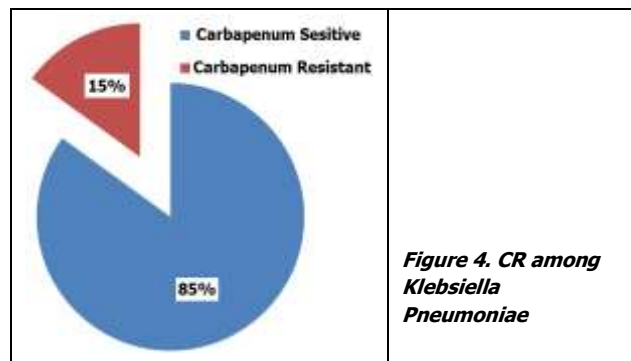


Figure 4. CR among Klebsiella Pneumoniae

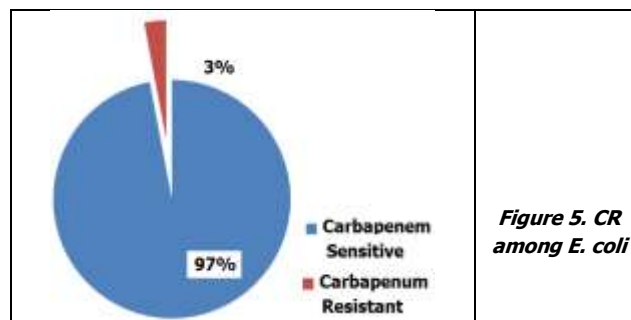


Figure 5. CR among E. coli

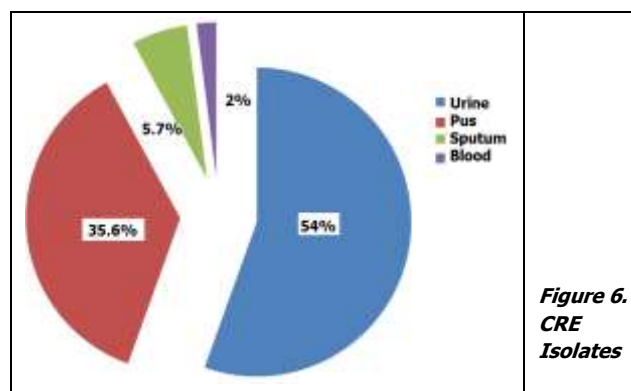


Figure 6. CRE Isolates

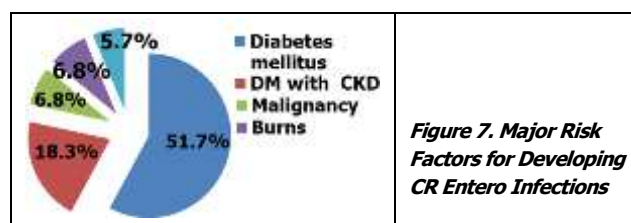


Figure 7. Major Risk Factors for Developing CR Entero Infections

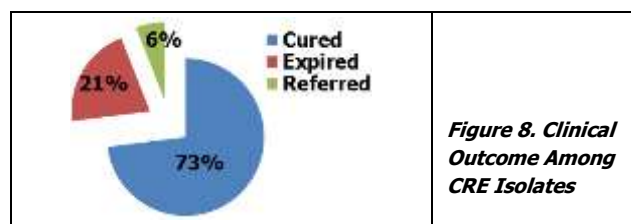


Figure 8. Clinical Outcome Among CRE Isolates

During the study period, *E. coli* was the most common isolated *Enterobacteriaceae* (60%), followed by *Klebsiella* (36%). Out of 1172 cases of *Enterobacteriaceae* isolated, 1085 (92.6%) were carbapenem sensitive and 87 (7.4%) were CRE isolates. CR amongst different *Enterobacteriaceae* showed CR *E. coli* with 25%, CR *KLEB* with 74% and CR *Enterobacter* with 1%. Even though *E. coli* was the most common *Enterobacteriaceae* isolated, carbapenem resistance was fivefold more among the *Klebsiella* species. CR was 3.09%

(22/710) among *E. coli* while CR was 15.3% (64/418) among the *Klebsiella* species. CR among *Klebsiella* Pneumoniae showed carbapenem sensitivity to 85% of incidences and carbapenem resistance to 15% of the incidence. CR among *E. coli* showed carbapenem sensitivity to 97% of incidences and carbapenem resistance to 3% of the incidence. The maximum number of CRE isolates was from the urine (47/87-54%), followed by Pus (31/87-35.6%) and sputum 5.7% and blood (2%). diabetes mellitus was the major risk factor for developing CR Enteroinfections (51.7%), followed by DM with CKD (18.3%), Malignancy 6.8%, Burns (6.8%) and COPD with mechanical ventilation (5.7%). Considering the outcome from the study, 73% of the CRE isolated patients were cured with colistin and imipenem therapy, 21% expired and 6% were referred or left against medical advice.

DISCUSSION

Carbapenem antibiotics (ertapenem, imipenem, meropenem, doripenem etc) are often used as last line of treatment for infections caused by resistant gram-negative bacilli. Over the past decade, members of *Enterobacteriaceae* family of bacteria have begun to develop resistance to carbapenems, by genetic mutations to produce carbapenemase enzymes. The alarming fact is that the CRE easily spread their antibiotic resistance to other kinds of germs, making those potentially untreatable. In this context there should be a co-ordinated effort from all stakeholders to recognise the epidemiological importance of CRE and to implement regional and facility-based interventions to hold the transmission of CRE.

We suggest the following core measures-

1. Hand hygiene
2. Contact precautions
3. Health care provider (HCP) education
4. Minimise device use
5. Patient and staff cohorting.
6. Laboratory notification
7. Anti-microbial stewardship

CONCLUSIONS

The present study confirms significant presence of carbapenem resistant *Enterobacteriaceae* (CRE) in the studied community. This is a warning against the irrational use of higher antibiotics by the clinicians. This fact should be read in the background that no new antibiotics could be marketed for therapeutic use for more than ten years. This real time study throws light to factors which predispose persons to serious and life-threatening infections due to CRE. In addition to advanced age, comorbidities like uncontrolled diabetes mellitus, chronic kidney disease, chemotherapy and mechanical ventilation contribute to higher mortality in CRE infections. In fact, these factors

accelerate mortality in younger age group (less than 60 years). The present study once again reaffirms the role of combination therapy of carbapenem & colistin together in CRE infections as in the previous studies. The combination therapy gives successful cure rate of 73% in this study.

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