SEYBOLD Report
ISSN: 1533 - 9211
DOI: 10.5281/zenodo.7221731

CARBAPENEM RESISTANCE *KLEBSIELLA PNEUMONIAE* - A REVIEW

Vetriselvi Subramaniyan[1], Anitha Akilan[2], K. Revathi[2], Senthilkumari [3,] Jayanthi [4], Suresh Dhanaraj[*]

[1]Department of Microbiology, School of Life Sciences, Vels Institute of Science, Technology, and Advanced Studies (VISTAS), Pallavaram, Chennai, 600 117 Tamil Nadu, India.

[2] Professor and Former Director of Research, Meenakshi Academy of Higher Education and Research, Chennai – 600078, Tamil Nadu, India.

[2] Meenakshi Academy of Higher Education and Research, Chennai – 600078, Tamil Nadu, India.

[3] Assistant professor; Head of department of zoology, Chellammal College, Chennai.

[4] Department of zoology Arignar Anna govt.arts college for women walajapet - 632 513

Corresponding Author [*]Department of Microbiology, School of Life Sciences, Vels Institute of Science, Technology, and Advanced Studies (VISTAS), Pallavaram, Chennai, 600 117 Tamil Nadu, India.

Abstract:

As carbapenems is the last line of defense for the treatment of life-threatening infections by drug-resistant Enterobacteriaceae, there is a major public health risk in the formation and dissemination of carbapenem-resistant Enterobacteriaceae, in particular *Klebsiella pneumoniae*.The resistance to carbapenem in *Klebsiella pneumoniae* was first discovered a decade ago and has since spread to many countries. *Klebsiella pneumoniae* carbapenemase (KPC), a community of carbapenem-resistant *Klebsiella pneumoniae* strains conferred by plasmid-encoded carbapenem enzymes, is rapidly spreading worldwide. In addition to KPC-producing *Klebsiella pneumoniae* several different metallo-b-lactamase-producing *Klebsiella pneumoniae* strains have been reported. These enzymes include New Delhi metallo-b-lactamase, Verona integrin-encoded metallo-b-lactamase, and imipenemases metallo-b-lactamase. Finally, has carbapenemases of class D, including carbapenemases of the oxacillin form. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has been related to a high mortality rate and can cause pneumonia, bloodstream infections, meningitis, and urinary tract infections, among other infections. Hygienic handling, touch protocols, patients' and cohorting of staff must be part of a multifaceted approach to reducing CRKP nosocomial transmission, avoiding intrusive device use, encouraging antimicrobial stewardship, screening, aggressive monitoring and chlorhydrate bathing. In addition, immediate clinical infection notification after detection of CRKP in clinical specimens will allow control measures to be taken.

Keywords: Carbapenem**,** *Klebsiella pneumoniae* ,drug-resistant

Background:

Enterobaceriaceae as a gram-negative bacterium cause a number of infections, including blood stream, urinary tract, and breathing tract. Gram-negative bacteria were increasingly immune to

SEYBOLD Report
ISSN: 1533 - 9211
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a wide range of global antibiotics during the past two decades. Enteropacteriacea, in particular, is seriously endangered in public health due to the emergence and spread of carbepene resistance. The mortality rate of these species is high and it is capable to spread widely. The gram-negative, optional anaeropic, non-motile, and non-flagellated bacillus belonging to the Enterobacteriaceae family is *Klebsiella pneumoniae*. It lives in soil and surface water, on plants and as a commensal resident of the nasopharynx and gastrointestinal tract of the mammalians and is a commonly used residence. A number of infections, including urinary tract, blood streams and lower air tract infections, are caused by enterobacteriaceae **[1].** Infections caused by Enterobacteriaceae **[2]** are often used as a last-stage treatment with carbapenems. Resistence to carbapenems defines the ability of bacteria to thrive and grow at concentrations of carbapenem that are of clinical significance [**3].** The emergence and dissemination of carbapenem resistance has been more common worldwide and the use of carbepenems has been constrained **[4].**

Due to its transmittibility and limited treatment options, Centers for Disease Control and Prevention (CDC) are considered particularly dangerous **[5].** In a bacteriological laboratory both in the community and hospital environment, the enterobaceae family contains many species most often isolated among human pathogens. Many diseases are caused by these diseases, such as urinary, gastrointestinal, abdominal and septicemic infections **[6,7].**

Klebsiella pneumoniae is now regarded as one of the major opportunist pathogenes causing nosocomial and collectively acquired infections **[8].** It is in fact the fourth largest cause of pneumonia and the fifth most common cause of bacteremia in patients with intensive care **[9].** The main sources of nosocomial infection **[10]** are contaminated surgical supplies, hands of hospital staff and patients with gastrointestinal tracts.

Infections with *Klebsiella* are rare in healthy individuals. In health care environments among sick patients receiving treatment for other conditions *Klebsiella* infections, on the contrary are popular. In patients who have need of devices such as respirators or intravenous catheters, diabetics, alcoholics and those who take long courses of antibiotics, *Klebsiella* infections are most common. Intensive treatment centres, *Klebsiella spp* is one of the most common pathogen. All infections caused by the microorganism are: pneumonia, bloodstream infections, wounded infections or surging infection in the site, urinary tract and meningitis.

Antimicrobial resistance among gluten bacteria has become increasingly common in the Carbapenem antibiotic class in the last few years. Antimicrobial drug resistance is growing especially in the *Klebsiella pneumoniae* (CRKP) carbapenem resistant region, which has caused considerable increases in disease and death. CRKP-related infections have few treatment options for antimicrobials **[11].** In various studies, mortality rates associated with CRPK infections range between 20% and 30% **[12]** and in cases of bacteriaemia, 70% **[13].**

Enterobacteriaceae carbapenem-resistant:

In the 1950s and 1960s, Enterobacteriaceae developed a number of mechanisms to evade these medications since the introduction of broad-spectrum antibiotics for the treatment of Gramnegative infections. Beta-lactam (e.g., penicillins and Cephalosporins) antibiotics are particularly susceptible to beta-lactamase hydrolysis **[14].** The first hospital outbreak in France

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ISSN: 1533 - 9211
DOI: 10.5281/zenodo.7221731
[15], which quickly followed by major outbreaks in the United States, began in the middle of the 1980s for ESBL producers. ESBL producers are currently found all over the world with fluoroquimolones and amingoglycosides being frequently immune. The first clinical use of Carbapemes was made in 1985, a form of antibiotic b-lactamase **[14].**

Increasing use of cephalosporin **[16]** has coincided with the appearance of enterobacteriaceaes with extended-specific b-lactamases (ESBLs). Several types of thesis enzymes have been reported in developing countries, with the majority of the *Klebsiella spp*. These isolates are particularly troubling because they resist many antibiotics **[10].**

These drugs have been the choice of treatment for ESBL-causing strains infections because the majority of common b-Lactamases (including ESBLs) have excellent antibacterial properties. In the United States and elsewhere, carbapenems, such as imipenem or meropenem, are therefore widely used to treat multiple Gram-negative nosocomial pathogens **[17].** In reality they are often used to treat people with serious illness. Patients with severe infections. Ipenem has been in clinical use since 1986 and enterobacteiaceae resistance cases to carbapenem were highly uncommon in the 1990s, as were the cases involving the dehydropeptidase inhibitor cilastatin **[14].**

Because of its capacity to produce ESBL, *Klebsiella pneumoniae* , a member of the family Enterobacteriaceaes, has been widely concerned. Carbapenems have traditionally been treated for infection caused by ESBL-producing *Klebsiella pneumoniae* . Regrettably, over the last decade a major global health issue and clinical challenge has emerged for medical practitioner, as carbapenem is a last resort drug used in the treatment of drug-resistant Enterobacteriaceae infections [**19].**

Document on the Guidance for Control of Carbapenem-resistant Enterobacteriaceae(CRE) according to Centers of Disease Control and Prevention(CDC)' CRE is defined as the Enterobacteriaceae (http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf): Not subject to one of: doripenem, meropenem or imipenem and all of the cephalosporins of the next third generation reisitant: ceftriaxone,cephotaxime, and ceftazim. (Note: The Enterobacteriaceae members are advised to include all three of these antimicrobials in primary or secondary susceptible panels).

Three known mechanisms can mediate the resistance to the most commonly used carbapenems **[14,17**]: High development of AmpC cephalosporinsis, combined with a reduction in the permeability of the outer membrane due to the loss or modification of porins, may be responsible for carbapenem resistance. Carbapenems This was demonstrated by the inactivation in various enterobacteriaceas of genes coding for external membrane proteins. (The K. pneumoniae OmpK35 and Ompk36) Changes in carbapenem affinity of target enzymes, the carbohydrates-binding proteins.B-lactamases development Crabapenem-hydrolysis (carbapenemases). Carbapenemases have been formed and distributed throughout the enterobacteriaceaes, enzymes which hydrolyze most b-lactams including carbapenemes.

The Ambler rating is most commonly used in carbapenemases, but the classification of Bush Jacob is also used. B-lactamases are divided into four groups, A-D, based on their molecular structure, while the three most epidemiologically significant carbapenemases form three: Class

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A carbapenemases (b-lactamases containing serine at the site in which they are active); Class B carbapenemases (MBLs) and Class D carbapenemases(oxacillinases that include oxa-llinin(OXA) type carbapenemases) **[10]** are zinc-dependent at their operational locations. Carbapenem resistance was first identified a decade ago in *Klebsiella pneumoniae* and has spread to many countries since then. *Klebsiella pneumoniae* carbapenemase (KPC), a group of carbapenemase enzymes encoded in a transmissible plasmid, confers *K.pneumoniae* resistance **[20]** and spreads rapidly worldwide. KPC is a carbapenemase of Ambler class A to mediate both carbapenem resistance and extended-spectrum cephalosporinds **[21,22].**

As KPC strains often be multi or extremely pharmaceutical resistant, treatment choices are limited **[23],** with the only options being tigecycline and polymyxins. However, the clinical use of these antimicrobials was limited due to their pharmacokinetic properties and toxicity. In addition, no new antibiotics are currently in clinical trails for the multidrug-resistant species(MDROs). KPC is the most common type A carbapenemase in the blaKPC gene.I n addition to its KPC-2 to KPC-13 variants, they vary only from Aminopathic Acid mutations across the world. The blaKPC gene is mediated by plasmid and is carried by Tn4401, a Tn3 transposon which can be transmitted easily between bacteria. In addition in other *Enterobacteria* and *Pseudomonas aeruginosa*, the blaKpc genes have been most common in *Klebsiella pneumoniae* **[24].** In 2001, the first cases were identified in the United States of blaKPC-positive *Klebsiella pneumoniae* [**17].** In *Klebsiella pneumoniae* , both KPC-2 and KPC-3, the regional distribution of these enzymes was limited until 2005**[25],** in the eastern United States. As a result of travelling patients, blaKPC was efficiently distributed across international frontiers **[19, 26].**

A sinle, a large KPC-production clone *Klebsiella pneumoniae* (ST) [ST] 258) has recently been suggested spread throughout East America **[25,27].** It has been mentioned. This was an epidemic in the USA and spread mainly through contacts with patients to other countries. [ST] 258 appeared first on Isreal in 2006, a national outbreak sparking. As many reports from different parts of the world show, the strain spread to other nations. *Klebsiella pneumoniae* [ST] 258 has a high morbicidity and mortality rate **[28]** and is immune to nearly every antibiotic.

The species of KPC produced have now been identified in 27 US staes, including China, Brazil, Isreal, France, Greece, Ireland (where HCP-related infections are mostly the result of hyper-ecpidemic clones) and more recently in Italy **[29].** CPC-created species have been reported in 27 other countries worldwide. In France, the first KPC-producing case, KPC-2(*Klebsiella pneumoniae* (KPC-2), was discovered **[30].** Isreal was the first country outside the United States to experience an epidemic **[18,31].** In Europe, there have been several cases of KPC-producing *Klebsiella pneumoniae* , but outbraeks occurred in Greece**[32].** Germany**[33]** confirms that a *Klebsiella pneumoniae* isolate containing blaKPC -2 was responsible for nine-patient outbreaks. Apart from KPC-producing Enterobacteae, a number of different strains producing metallo-b-lactamase have been reported in the United States since 2009. New Delhi Metallo-b-lactamase(NDM), Verona Integrated Metallo-b-lactamase(VIM) and Metallo-b-lactamase(IMP) **[21].**

The bulk of the MBL farmers in hospitals are multidrug resistant *Klebsiella pneumoniae* .

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ISSN: 1533 - 9211
DOI: 10.5281/zenodo.7221731
Carbapenem resistance varies from a manufacturer of MBL and mortality rates are 18 to 67 per cent for manufacturers of MBL **[34].** *Klebsiella pneumoniae* is a new form of NDM-1 that is highly resistant to the Indian subcontinent, spread globally **[35].** NDM-1 is encoded with a plasmid which the blaNDM-1 gene is readily transferable **[22].** Many antibiotic drugs, such as fluoroquinolones, aminoglycosides and b-lactams (in particular carbapenems), are resistant to NDM-producing bacteria **[36].** Many NDM-1, the producers of colistine and in lesser degree fossomycin remain susceptible to tigecycline**[34].** NDM-1 is mainly associated in the endemic trip to the Indian subcontinent.

Including China, Australia, the United States, Canada, and several parts of Europe, the latest being the Balkan region **[19,26].** Over the last decade, VIM-style MBLs spread to *Klebsiella pneumoniae* , with nd outbreaks of these strains. Forms of VIM have been found on all continents, but in southern Europe they are the most common **[37-40].** IMP metallo-b-lactamase is another metallo-b-lactamase which is often plasmid-mediated. When expressed effectively, the IMP-1 provides both carbapenem, penicillins and cephalosporins resistance, and no inhibitor of b-lactamase can conquer this resistance **[41].** IMP-1 and IMP-8 in Japan, Singapore and Taiwan were described in *Klebsiella pneumoniae* **[42,43].**

Most metallo-b-lactamases, especially NDM formations, are also ESBl-possessed and ampC genetically modified which make them immune to all antibiotics other than polymyxins (some aminoglycosides). Most NDM formats are NDM-sensitive. Finally, the carbapenemases of the OXA-type are class D carbapenemases, found mainly in *Acinetobacter spp*., while in Enterobacteriaceae OXA-48 is found. During a *Klebsiella pneumoniae* outbreak in Istanbul, Turkey, OXA-48 was discovered first. In the Middle East, India, Europe and North Africa by 2009, strains that contain the enzyme OXA-48 were found **[14].** OXA-48 gene codes for an enzyme called oxacillinase that reduces the susceptibility to penicillin resistance and carbapenem, not cephalosporin.

Monitoring and prevention measures:

Increased negative outcomes in several countries were associated with CRKP transmission and cross-infection, particularly in Greece **[44]** and Isreal **[45]** which pose a major threat to the health care system. In addition, an adequate and timely response is not evident.

Every day, hand washing is recommended for optimum transmission control after contact with patient surfaces or hospital equipment, as well as the use of surveillance crops and contact precautions **[46, 47].** A systematic intervention plan is crucial for effective monitoring of the spread of acute and long-term health care facilities CRKP I, as well as CR E in general, such as the eight core measures established by the CD Center in 2012.

Touch precautions hand hygiene There is an aggressive control and chlorhexidine baths between the patient and the staff who avoid the use of intrusive instruments to promote antimicrobial stewardship screening (listed below). Acute and long-term care prevention strategies (adapted from the Control Carbapenem Resistant Enterobacteriaceae (CRE) Directives,2012.htβ:/www.cdc.gov/hai/pdf/cre/CRE-guidance-508.pdf);;

Primary indicators of performance in both acute and long-term care:

Promoting manual track hygienics and ensuring the adherence of hand hygiene and access to

SEYBOLD Report
ISSN: 1533 - 9211
DOI: 10.5281/zenodo.7221731
stations of manual hygiene. Emergency care contact precautions. Put CRE on contact precautions in colonised or contaminated patients. Healthcare personnel should be educated on contact precautions. Monitor and provide input to follow up contact precautions. There is no recommendation that contact precautions be stopped. Develop lan procedures to notify the possible possibility of CRE to clinicians and infection control personnel. Contact precautions for long-term care.

Utilize CRE-colonized or infected residents at high risk of transmission with contact measures; in many cases, normal precautions are used for patients at lower risk of transmission. Patient and personnel cohorting. If available, even when patients are housed in single rooms, CRE cohort colonises patients or contaminates. Save for patients with the biggest risk of transmission if single patient rooms are scarce. Minimize the use of invasive devices.

Promoting and screening of antimicrobials. Conduct point prevalence surveys of CRE units containing unrecognised patients and epidermiologically-like, colonised or contaminated screen patients with unrecognised CRE. Additional interventions for CRE transmission medical facilities. Active monitoring and monitoring tests High-risk screen CRE patients may be used on admittance tests while preventative touch precautions are pending.

Consider screening patients who have moved from the premises which have reported CRE upon admission. Bathing with chlorhexidine. Bathe 2% chlorhexidine patients The screening goal is to find non-detected gluebs resistant to carbapenem or carbapenem. In other cases, infection-prevention measures should be substantially strengthened and surveillance culture should be repeated on an ongoing basis until no new cases have been discovered. In these cases, infection-prevention measures should be substantially increased. When CRKP is found in clinical specimens, rapid clinical infection notification allows for rapid control measures. The stool or rectal swab is the primary monitoring site, and the monitoring at these sites produces more efficiencies than at other body sites. (e.g., skin or narer) **[48].**

In patients with indoor devices, specimens from the site in question should also be screened. Some patient classes may also test for skin swabs, urine, and sputum, such as chronic wounds, urinary catheters and endotracheal tubes. As far as possible, their use should be restricted in terms of indoor appliances (e.g., central venous catheters, endotracheal tubes, urinary catheters, etc.) as their insertion constitutes a potential CRE infection. The use of equipment in acute and long-term care settings should be regularly checked to establish if it is still necessary and equipment should be retracted as soon as it is no longer needed. The timely implementation of multifactorial interventions seems to be key to the management of CRE spread. According to a report of CRKP outbreaks at Puerto Rican hospitals **[49]** patients with non-recognized colonisation of the CRKP had acted as transmission reservoirs.

In addition to a study of infection management procedures, active surveillance cultures have been performed in patients in the same units as those with a reported CRKP infection. After culture was performed in 30 patients with ICU who were not previously identified as having CRKP and not put in contact with touch precautions, two colonised patients were found. Failure to respect infection management practises and the control of the outbreak were hindered.

Health care personnel at the hospital followed only the gown use directives for 62 percent of

SEYBOLD Report
ISSN: 1533 - 9211
DOI: 10.5281/zenodo.7221731
cases and in only 48 percent of cases proper hand washing (i.e., hand washing or waterless alcohol-based hand rubbing prior to and after patient contact). Finally, the epidemic was controlled by Strengthening compliance with the control of infection, introducing patient cohorting and weekly perirectal crops for patients with outbreaks, until no new cases have been identified **[49].**

The early detection of CRKP can be monitored through targeted monitoring and strict infection control measures, including improved hygiene in hands and contact precautions, as evidenced by the Puerto Rican outbreak and other ecperiences **[10].** Schwaber et al**.[18]** described the containment, through concerted and closely monitored intervention, of a national outbreak of the virulent, rapidly spreading, K. pneuminiae strain of carbapenems, including a re emphasis on the infection control principles, physical divorce of carrier from carrier and the assijng of caregivers.

In addition, research emphasised that, even before emerging drug resistant bacteria in an area can be developed and implemented, it is important to develop and implement plans for early detection at national level, and rapid intervention plans for these bacteria if found. The efficacy of the national action depended on determination to fight the outbreak at the highest level of preparation of health policy **[18].** The effectiveness of a series of actions in order to curb the propagation of an outbreak caused by KPC-3 strain has been evaluated by Ciobotaro et el. **[50];** the result is a 16-fold decrease in the incidence of CRKP over 30 months.

The multidisciplinary intervention included three core elements: protocol cohorting, cleaning & screening, education and training, automated guidance and CRKP notifications, In a long-term acute-care hospital study the effectiveness of a treatment package to prevent horizontal transmission of Gram-negative KPC-production Bacteria has been examined despite the continued admittance by patients who have colonised with KPC-producing bacteria. The results of the point prevalence monitoring carried out before and after implementation of the bundle showed a decrease in KPC-producing strains' rectal carrying rates. Four key componenets were present in the infection management package; the skin of the patient is decolonized.

Skin (by daily chlorhexidine baths), enhanced cleaning of environmental surfaces, identifying carriers of the strain producing KPC (by culture of admission and monitoring) and isolation (preemptive contact precautions and cohorting of high-risk patients on admission and on the basis of the results of clinical or surveillance cultures). The author proposes, in violations of insulation safeguards, minimising the bacterial load on the skin and surrounding surfaces of the patient, minimising possible contamination of the medical worker's hand, reducing even more horizontal transmission **[51].** Patients were purified every day with a 2 per cent solution of chlorhexidine soaked cotton washcloths up to their jaw kins, as prescribed by the CD.

By the 36th month of a multifaceted hospital-wide programme aimed at improving hand hygiene and practises in Australia, ESBL-producing klensiella clinical isolates decreased by more than 90% by 57% in Staphylococcus aureus (MRSA) resistant methicillin-bacteraemic episodes, with a significant decline in the number of MRSA clinical isolates **[52].**

The CDC stressed that policies that include hygiene of hands are not sufficient; adherence to them must be monitored and adherence rates should be provided directly to front line personnel.

DOI: 10.5281/zenodo.7221731

Workers who do not adhere to hand hygiene properly should be provided with immediate feedback. The facility should also provide access to the right hand hygiene stations (e.g. towels, soap, etc.) and remove any confusion, and ensure that they are well stocked. Patient cohorting has recently been demonstrated in settings with ongoing CRE outbreaks as an effective infection prevention measure for managing outbreaks of multiple MDROs in healthcare settings **[53, 54].**

Full separation is necessary in an ideal world: all carriers are included in the cohort and non-carriers are excluded **[55].** As a result, correctly estimating the CRE carriage status of past carriers is crucial in facilities that want to explicitly distinguish CRE carriers without overwhelming the cohort with non-carriers. Data on the length of CRE carriage is still scarce ten years after the disease's emergence.

A recent study **[54]** found that exposure to antimicrobials (especially fluoroquinolones), admission from another healthcare facility, and being less than 3 months after their first positive CRE test were all predictors of rectal CRE carriage at a future healthcare encounter. Healthcare facilities need to ensure that staff members are properly informed about why and the use of touch precautions and that staff caring for MDRO patients, including CRE patients, are properly implementing the right measures. This could include a regular monitoring of the use of contact precautions and an input on the outcome to frontline employees.

The preventive touch precautions often used in combination with surveillance crops can also be applied to patientes moving from high risk environments, pending the outcome of screening cultures. Residents in long-term care settings that have been infected or colonised with CRE can use contact controls, but these can be modified due to the inherent differences between acute and long-term care facilities. Residents with CRE that are at a higher risk of transmission, such as those who are entirely reliant on healthcare workers for their daily activities, are ventilator-dependent, have faecal incontinence, or have wounds with difficult-to-control drainage, should use touch steps.

Finally, antimicrobial stewardship is an essential aspect of MDRO administration. Antimicrobials from a variety of groups have been shown to increase CRE colonisation and infection risk. Antimicrobials should be used for the relevant conditions and durations, and the narrowest-spectrum antimicrobial appropriate for the particular clinical situation should be used as part of an antimicrobial stewardship programme intended to prevent MDRO transmission. Microbiological diagnosis could be sped up, allowing pathogens and their resistance to be detected in hours rather than days, with no need for culture. PCR or DNA arrays could be used to find species-specific and resistance-specific genes. Despite this, significant challenges remain, especially with non-sterile-site specimens containing pathogen and commensal DNA **[56].**

Acknowledgements :
Conflicts of interest - Nil

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