



A study of risk factors for Carbapenem Resistant Gram negative bacterial infections in a South Indian Hospital

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Article History

Received: 09.06.2025

Accepted: 28.06.2025

Published: 19.07.2025

Abstract: -

Objective: The objective of this study was to identify the various risk factors for carbapenem resistant gram negative bacterial infections. **Materials and methods:** This was a retrospective study done in a multispecialty hospital in Chennai. Data was collected from the medical records of the patients in a data collection sheet. **Results:** The various risk factors/ comorbidities associated with carbapenem resistant infections were presence of indwelling devices, hospitalisation within previous 12 months, Diabetes mellitus, ICU admission, previous exposure to antibiotics, prolonged hospitalisation for >10 days and Chronic kidney disease (CKD). **Conclusion:** Identifying risk factors for Carbapenem-resistant infections enables early detection, prompt initiation of suitable antibiotics, and timely isolation precautions, thereby reducing the spread of Multidrug resistant Organisms (MDROs). This insight aids clinicians in selecting effective presumptive therapy, improving patient outcomes. Furthermore, publishing such data raises awareness about the critical need for robust infection control and antimicrobial stewardship practices to combat antimicrobial resistance.

Keywords: Carbapenem resistant, GNB, risk factors.



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Introduction:

Antibiotics are a cornerstone and pillar of modern medicine, enabling the success of medical and surgical treatments ranging from minor procedures to complex transplantations. However, the widespread use of antibiotics in human and veterinary medicine has led to the emergence of Antimicrobial Resistance (AMR) among bacteria, rendering many antibiotics ineffective. Carbapenem-resistant Gram-negative bacteria (GNB) pose a significant threat to healthcare, causing substantial morbidity and mortality due to limited treatment options. Research on risk factors for Carbapenem-resistant (CR) infections is limited, underscoring the need for studies like this one to identify predisposing factors and inform effective prevention and treatment strategies.

Materials and methods:

This was a retrospective study done in a multispecialty hospital in Chennai from January 2021 to December 2023.

The objective of this study was to analyse the incidence and risk factors for CR GNB infections. All adult patients who were aged 18 years and above with one episode of CR GNB infection in any body site were included in this study. Data was collected from the medical records of the patients in a data collection sheet.

Results and Discussion:

TABLE 1

AGE:

AGE	Number n=68	%
>65 years	43	63
18-65 years	25	37

TABLE 2

GENDER:

GENDER	Number N=68	%
Male	50	74
Female	18	26

Cite this article:

John, V. S., Babu, J. J., (2025). A study of risk factors for Carbapenem Resistant Gram negative bacterial infections in a South Indian Hospital. *ISAR Journal of Medical and Pharmaceutical Sciences*, 3(7), 13-18.

TABLE: 3

DEPARTMENTS:

DEPARTMENTS	Number n=68	%
MEDICINE	35	52
NEPHROLOGY	18	26
SURGERY	15	22

TABLE: 4

SPECIMENS:

SPECIMENS	Number n=74	%
URINE	49	66
PUS	8	11
BLOOD	7	9
SPUTUM	8	11
TISSUE	2	3

TABLE: 5

ORGANISM

ORGANISM	Number n=74	%
Klebsiella pneumoniae	36	49
Escherichia coli	22	30
Pseudomonas aeruginosa	15	20
Acinetobacter baumannii	1	1

TABLE: 6

RISK FACTORS:

RISK FACTORS	Number n=68	%
Presence of Indwelling Devices	54	79
Hospitalisation within previous 12 months	43	63
Diabetes mellitus	40	59
Admission in ICU	39	57
Previous exposure to Antibiotics	37	54
Prolonged hospital stay (>10 days)	29	43
Chronic kidney disease (CKD)	18	26

A total number of 68 patients were included in this study, out of which 43 (63%) were aged more than 65 and 25 (37%) were between 18- 65 years. Out of 68 patients, 50 (74%) were male and 18 (26%) were female. Patients from various departments like General medicine 35 (51%), Nephrology 18 (26%) and General surgery 15 (22%) were included in this study. From the 68 patients, a total number of 74 samples were collected. The main samples collected were Urine 49 (66%), Pus 8(11%), Sputum 8(11%), Blood 7(9%) and Tissue 2(3%). Among the 74 organisms which are identified as Carbapenem resistant, *Klebsiella pneumoniae* 36 (49%) is the number one isolate followed by *Escherichia coli* 22 (30%) and *Pseudomonas aeruginosa* 15 (20%). Only one isolate of *Acinetobacter baumannii* was found to be Carbapenem resistant in this study.

While analysing the various risk factors/ comorbidities associated with carbapenem resistant, we found the following results in decreasing order of frequency: presence of indwelling devices in 54 (79%) patients, hospitalisation within previous 12 months in 43 (63%) patients, Diabetes mellitus in 40 (59%) patients, ICU admission in 39 (57%) patients, previous exposure to antibiotics in 37 (54%) patients, prolonged hospitalisation for >10 days in 29 (43%) patients and Chronic kidney disease (CKD) in 18 (26%) patients.

Ever since the discovery of Penicillin in 1928 by Alexander Fleming, antibiotics remains the cornerstone of modern medicine. Now, AMR has emerged as the greatest threat to human health. This is mainly due to unregulated and unnecessary usage of Antimicrobials both in human and animal health and the problem is further worsened by globalisation and medical tourism which led to resistant strains spreading worldwide.

GNb with their wide array of Resistance mechanisms and ability to rapid transfer of such mechanisms to other groups of bacteria are becoming greatest threat with regard to AMR emergence and spread. Both in hospitals and in community all over the world.

Quantifying and identifying the risk factors for CRE is need of the hour to early recognition and treatment of patients who are at increased risk of infections like CRE. Few articles have been published related to this topic [6]

Carbapenems belong to the beta lactam group of antibiotics and have a broad spectrum of activity against many bacterial species. They are less likely to be destroyed by enzymes like beta lactamases including Amp C and ESBL enzymes. These qualities make them the most sought after antibiotics for bacterial infections. Since polymyxins are much toxic, Carbapenems are preferred more often due to their lower adverse effects. Due to this CR has emerged as a global health crisis. Bacteria develop resistant to carbapenems through various mechanisms like production Carbapenamase enzymes, efflux pumps which expel the carbapenems out of periplasmic space and by decreasing the outer membrane permeability by limiting expression of outer membrane porin. In CRE, treatment options are very limited and mortality is also high for such infections. [10]

The risk factors which are most commonly associated with CR infections can be used for targeted interventions which will help in reducing the possibility of an outbreak.

In this study, 43 (63%) patients were aged more than 65. In a study from Saudi [4] MDR infections were highest in age group of 70 to

79 years, while in another study by Swati et al,[6] MDR GNB infections were more common in <65 years of age.

There was a male preponderance of 74% in the current study which correlates with another study [6] on risk factors for MDR GNB bacteremia where 57% of patients were male. In a study by Aisha et al, [4] MDR infections were noted more often in female patients. In an Indian study from ICU [16], the mean age of patients with CRE is around 52 years and there was a male dominance of 64%. In a study from Saudi ([3] also, MDR GNB infections were common in male gender (61%). Urine was the most common sample in this study. In another study [4] also, urine was the most common sample which shows that MDR infections were common in UTIs.

In this study *Klebsiella pneumoniae* was the most common CRE followed by *Escherichia coli*. Similar finding is noted in a study from India [16] whereas in another study [4] *Escherichia coli* was the predominant bacteria causing MDR infections.

While analysing the various risk factors/ comorbidities associated with carbapenem resistant, we found the following results in decreasing order of frequency: presence of indwelling devices in 54 (79%) patients, hospitalisation within previous 12 months in 43 (63%) patients, Diabetes mellitus in 40 (59%) patients, ICU admission in 39 (57%) patients, previous exposure to antibiotics in 37 (54%) patients, prolonged hospitalisation for >10 days in 29 (43%) patients and Chronic kidney disease (CKD) in 18 (26%) patients.

Swati et al have identified the following risk factors in MDR patients: presence of comorbidities like CKD (6%), Diabetes mellitus (29%), Previous antibiotic administration, Indwelling devices like Urinary catheter and CVC, longer duration of hospitalisation.[6]

In a recent study the prevailing risk factor linked with CR infection is prior use of Antimicrobials which correlates well with the selective pressure exerted by antibiotics in selecting drug resistant bacterial population.

Other risk factors identified in this systematic review were mechanical ventilation, previous stay in ICU, Presence of indwelling devices like catheter, length of hospital stay and patients with other comorbid conditions like Diabetes mellitus and Hypertension. [5]

In a systematic review of risk factors for CR in *Klebsiella pneumoniae*, Wei min Zhu et al have done a meta analysis from studies indexed in various journals. The risk factors identified in this analysis were as follows: admission in ICU, presence of various indwelling devices like urinary catheter and CVC, prior exposure to antibiotics particularly Carbapenems, Aminoglycosides, Vancomycin and Fluoroquinolones, prior hospitalisation, longer duration of hospital stay and CKD. All the above risk factors are commonly seen in critically ill patients whose immunity is compromised and therefore prone to more severe infections. Such group of patients are exposed to more antimicrobial selection pressure which ultimately results in infections with MDR pathogens.

Fluoroquinilone (FQ) exposure causes upregulation of Mex EF-OprN which is a multidrug efflux pump and also downregulation of porin OprD, causing resistance to both FQ and Carbapenems.

Vancomycin which is a glycopeptide if given for prolonged periods of time also causes disruption of microflora thus promoting the mutation and spread of Carbapenases which further augments risk of Carbapenem resistance. Use of FQ and Glycopeptides should be restricted to lower risk of transmission of MDR bacteria. [7]

A retrospective study by Sumanth et al reports that Bacteria which are multidrug resistant (MDR) pose a higher risk of morbidity and mortality in patients. In this study, the mortality rate of patients admitted with MDR pathogens was 13%. Results were obtained after data was compared between mortality rate of patients infected with drug susceptible bacteria vs MDR bacteria. MDR Gram negative bacteria (GNB) are a grave threat to public and also present considerable therapeutic challenge to clinicians as the treatment options are very limited. [15]

Various studies report CRE prevalence as 12% to 15%. In one study done in an Indian ICU, Diabetes mellitus (DM) and chronic kidney disease (CKD) were the most common comorbid conditions identified in 30% and 22% of patients respectively. In this research, 96% of patients had previous exposure to antibiotics. In ICU settings patients who are admitted for long duration are usually severely ill and they may be treated with various indwelling devices like central lines, urinary catheters and also ventilators which increase their chances of HAIs by MDR bacteria.

Almost all the patients have exposure to various antibiotics which is also a significant risk factor for such infections. [16] Evaluating the different risk factors for infections by MDR bacteria would be very helpful for the clinicians in selecting the antibiotic for presumptive therapy and also it will definitely help in improving the clinical outcome of the patient.

In a study published from Saudi, previous exposure to antibiotics like Imipenem, Amikacin and Cotrimoxazole was associated with Multidrug resistant organisms (MDRO) infections in a significant way. The most common comorbid conditions were DM and Hypertension. Another risk factor is the use of Antibiotics even before hospitalisation.

Other risk factors identified in this study were: ICU stay, use of indwelling devices, length of hospital stay and previous hospital admission in past 3 months. Such studies helps to identify patients with risk factors for infection with MDRO at the earliest, so that prompt and suitable antibiotics can be started and also isolation precautions can be initiated early to avoid spread of MDROs in the hospital. [3]

Presence of indwelling devices

Central line:

Central line denotes an intravascular access device which ends at or close to heart or in a major blood vessel. About 50% of patients in ICU are inserted CVC for various reasons. As they have direct contact with blood, patients with CVC have increased risk of septicemia. Any irregularities in catheter, fibrin sheath formation and thrombogenic tendency allow pathogens to adhere to CVC leading to formation of biofilm.[11]

Urinary catheter:

UTIs are more common in patients with indwelling urinary catheter. Patients who are in urinary catheter for >30 days are

colonised with two to three types of microbes. Treatment with frequent antibiotics also act as risk factor for emergence of antibiotic resistance. Patients on immunosuppression and catheter in upper urinary tract are prone for infections with MDR bacteria. Biofilms form on the surface of catheter due to colonisation by microorganisms. To tackle CAUTI, reduce unwanted catheters and remove catheters as early as possible. Also, in patients with asymptomatic bacteriuria, initial treatment is removal of catheter without starting the patient on antibiotics.[11]

Mechanical ventilation:

Patients who require ventilatory support are often in critical condition and intubation which is an invasive procedure further increases the risk of colonization by bacteria. The risk factors for Ventilator associated pneumonia (VAP) are multifactorial and include oropharyngeal colonisation, any thermal injuries, emergency intubation, reintubation, procedures like tracheostomy and bronchoscopy, nasogastric tube insertion, use of sedatives, immunosuppressants and antimicrobials. The various bacteria associated with VAP include *Pseudomonas aeruginosa*, *Enterobacteriales*, *Acinetobacter baumannii* and MRSA. The above bacteria have the ability to form biofilm and often cause MDR infections in this vulnerable population.

To avoid VAP, ventilator usage should be limited to critically ill and if possible weaned from ventilator at the earliest.[11]

Implant infections:

During surgery if a device is implanted there is higher chance of infections of the implant.

Diabetic patients are at higher risk of infections after surgery and emergency surgery is also associated with increased risk compared to elective surgery.[11]

The formation of biofilms on the surface of indwelling devices play a significant role in development of infections with resistant bacteria. The bacteria are protected by the biofilms against antibiotics and they multiply inside biofilm and also spread the resistant mechanisms to other bacteria. Thus, biofilms lead to formation of recalcitrant bacteria which are encased in a protective matrix and prevents antibiotics from reaching the bacterial cell which contributes to emergence of MDR bacteria. [27]

In a meta analysis, invasive procedures like insertion of central line, mechanical ventilation and parenteral nutrition increased risk of infection. Procedures like intubation destroys the normal defense barrier facilitating contact between interior surfaces and external environment which enhances opportunistic organisms to invade and get attached to the indwelling devices leading to biofilm formation and further infection.[24]

Diabetes mellitus

Diabetic patients are at increased risk of infection due to hyperglycemia and immunocompromised state of such patients. Increased occurrence of infections results in repeated hospitalisation which further increases their exposure to different antibiotics which in turn is a risk factor for occurrence of MDR infections.[26]

The association between type 2 DM and infections notably with drug resistant bacteria have gained importance. A recent meta analysis reveals that T2 DM patients are at increased risk of

acquiring infections in urinary and respiratory tracts.

Empirical treatment of patients in T2DM may not be the same as for general population and treatment should be initiated and guided by Antibigram to avoid failure of therapy and also emergence of MDR bacteria. [8]

In a study done in patients with DM, CRE infection was associated with rise in mortality. The interaction between elevated blood glucose and infection is well known. The factors which explain the reason for such predisposition includes various mechanisms like disorder in both humoral and cellular immunity, impaired cytokine secretion, disparity in response of oxidant/antioxidant, enhanced apoptosis of cells, elevated glucose levels enhancing growth of bacteria, diabetic neuropathy and vasculopathy. Along with control of blood sugar level, prompt and appropriate initiation of antibiotic therapy is crucial in decreasing morbidity and mortality in Diabetic patients. Clinical examination should be combined with biomarkers like C Reactive protein (CRP) and Procalcitonin (PCT) to recognize patients at risk of infection. [9]

ICU admission

In one meta analysis, ICU admission is closely associated with development of CRKP infections. Patients treated in ICU are severely ill with long hospital stay, on higher antibiotics and requiring various invasive procedures as part of treatment. Also, carbapenems are used in ICU patients to a larger degree which further acts as a risk factor for CR infection.[24] Patients who are in ICU are often critically ill with various organ dysfunction and immune system dysfunction. Indwelling devices and various invasive procedures often lead to injury to normal physiological barriers leading to increased infection risk in such patients. This problem is further aggravated by use of multiple antibiotics for longer periods of time which results in emergence of multidrug resistant pathogens. [13]

Previous exposure to antibiotics

The major driver for AMR is use of antimicrobials. According to study in 2010, India stands out first in the world as the largest user of antibiotics especially in human health. The major reasons for this are easy access to antibiotics, rising per capita incomes, under developed infrastructure in public health sector and huge disease burden. Also, the sale of antibiotics is unregulated which further fuels the reason for MDR infections. Among GNB, there is alarming rise in CR. Over the counter sale of carbapenems is highest in India which contributes to CR.

The action plans which are urgently recommended are: regulatory body for antimicrobial sales, education and awareness to encourage behavior change among doctors and patients. [17] In one nested case control study in ICU patients, previous exposure to antibiotics like aminoglycosides, colistin, penicillin and linezolid increased the occurrence of subsequent MDR *klebsiella pneumoniae* infections. [30]

In one meta analysis, previous exposure to antibiotics like carbapenems, glycopeptides, quinolones and aminoglycosides was associated with greater chance of developing CRKP (*Carbapenem resistant Klebsiella pneumoniae*) infection. Combination of antibiotics used for longer duration and in large doses lead to increase in antibiotic selection pressure which leads to development of CR bacteremia [24] Another systematic review from USA found stronger association between exposure to

antibiotics which are in Watch and Reserve groups to development of infection by MDRO. Antibiotic use optimization is key to manage not only antibiotic resistance but also reduce the risk of toxicities and improved clinical outcomes.[31]

One recent study identified that there is more risk of sepsis within 90 days of discharge from hospital in patients who are exposed to antibiotics during hospitalisation. The antibiotics which are associated with this risk includes: Carbapenem, Vancomycin, Lincosamide, Fluoroquinolones, third, fourth generation Cephalosporins and BL/BLI combinations. Such antibiotics exposure causes disruption in microbiota of patient which increases risk of subsequent sepsis.

This gut microbiota disruption causes sepsis via one or combination of 3 mechanisms. The first one is loss of colonization resistance against pathogenic microbes. The next one is due to absence of immuno regulatory activity of gut microbiota which contributes to more strong septic response from another site of primary infection. The third pathway is loss of gut mucosal barrier integrity due to absence of healthy microbiota which produces short chain fatty acids and which in turn serves as the nutrient source for enterocytes in large intestine. [29]

It is being reported that around 30% to 60% of antibiotics used in ICUs are not necessary and often suboptimal. Such misuse contributes to development of AMR in bacterial population. Various Antimicrobial stewardship practices (AMS) recommended in ICU included rapid tests to identify bacterial infections, empirical therapy based on local antibiogram, using Pk-Pd characteristics to regulate dosage of antibiotics, appropriate de-escalation after culture reports and shortening duration of treatment. Implementing such structured AMS program using a multidisciplinary team is mandatory to prevent AMR crisis in ICU settings. [25]

Prolonged hospitalisation and Hospitalisation within previous 12 months

In a meta analysis, previous hospital admission and longer duration of hospital stay were also found to be significantly associated with CRKP infection. Both the above risk factors cause increased risk of infection due to antibiotic use and treatment with indwelling devices which themselves are independent risk factors for CR infection. [24] In a study from U.K, length of stay of patients increased due to HAIs and the average extended length of patients for all HAI types was 7.8 days. [28]

CKD (Chronic kidney disease)

In a study from China, impaired renal function was associated with increased prevalence of infections by MDROs. The factors which contribute to this were: frequent usage of Antimicrobials, higher risk of infections due to immune dysfunction and more recurrent hospitalisation which increases risk of HAIs. [32]

Conclusion:

Understanding the risk factors associated with Carbapenem-resistant infections is crucial for early identification of high-risk patients. This enables healthcare providers to initiate targeted antibiotic therapy promptly, reducing the risk of treatment delays and improving clinical outcomes. Moreover, early identification facilitates timely implementation of isolation precautions, thereby

minimizing the spread of multidrug-resistant organisms (MDROs) within healthcare settings. By presumptive therapy decisions, clinicians can optimize treatment strategies, ultimately enhancing patient care. Furthermore, disseminating such findings through publication promotes awareness among healthcare professionals about the importance of stringent infection control measures and antimicrobial stewardship programs. By emphasizing these practices, we can collectively mitigate the growing threat of antimicrobial resistance, ensuring better patient outcomes and public health protection.

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