STUDY OF GRAM-NEGATIVE INFECTIONS AND PATTERN OF RESISTANCE TO CARBAPENEMS IN PATIENTS OF CHRONIC KIDNEY DISEASE

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ABSTRACT

BACKGROUND

Gram-negative infections are the most common cause of morbidity and mortality among critically-ill immunosuppressed patients especially in CKD. The increasing emergence of multidrug resistance among these patients is an important point of concern in today's practice. In recent times, there has been increasingly reported incidence of resistance to carbapenems also, which leave the intensivists with very few options of antibiotics. With no new antibiotics in pipeline, increasing incidence of resistance to carbapenems is an important threat to all.

The aim of the study is to study the pattern of gram-negative infections in patients of chronic kidney disease and pattern of carbapenem resistance among the isolated organisms with the impact of multidrug resistance on clinical outcome of patients.

MATERIALS AND METHODS

A total of 50 patients were included in study that were known case of chronic kidney disease presenting with evidence of infection. Urine culture, blood culture and sputum culture reports of these patients were included in the study. All the culture and sensitivity reports were obtained from Department of Microbiology of our institute.

Inclusion Criteria- Known case of chronic kidney disease with evidence of infection.

Exclusion Criteria- Patients with associated comorbidities leading to immune suppression like malignancy AIDS, etc. and culture-negative patients.

RESULTS

The commonest organism isolated in cultures was Klebsiella (40%). Acinetobacter was isolated in 24% cases. E. coli was isolated in another 24% cases. Proteus and pseudomonas was isolated in 6% patients each. No resistance to any carbapenems was found in 24% patients. 36% patients were found to be resistant to all carbapenems. Another major group of 40% patients were found sensitive to all carbapenems except meropenem. If meropenem is excluded, then sensitivity to carbapenems rise to 64%. The group resistant to all carbapenems have the highest mortality. Isolates resistant to meropenem are responsive to other carbapenems like imipenem.

CONCLUSION

Increasing incidence of gram-negative infections and increasing resistance to all the conventional antibiotics pose a major threat to all the healthcare providers. The multidrug-resistant organisms including those resistant to carbapenems have been found to have increased mortality despite appropriate antibiotic therapy. Resistance to meropenem is reportedly higher than all other carbapenems even in community-acquired infections. Rational use of antibiotics and targeted therapy is warranted.

KEYWORDS

Gram Negative, Infection, Multidrug-Resistance, Sensitivity, Prognosis.

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BACKGROUND

The nosocomial infections in critically-ill immunocompromised patients is the major cause of mortality. Klebsiella, Pseudomonas and Acinetobacter are the most commonly isolated gram-negative infections among these patients. The increasing incidence of high-grade antibiotics resistance including carbapenem resistance among these organisms is an escalating problem, which has substantially increased over all healthcare cost, hospital stay, morbidity and mortality. Gram-Negative Bacillus (GNB)

are a common cause of sepsis, pneumonia, urinary tract infections and postsurgical infections in patients in acute care hospitals.[1,2]Antimicrobial resistance among GNB is increasing worldwide.[3] This is a major public health problem and a cause for both substantial morbidity and mortality among hospitalised patients. A direct correlation has been shown between resistance of GNB and patient mortality, cost of patient care and length of stay in the hospital.[4,5,6,7] The problem of GNB resistance is of particular concern in the Intensive Care Unit (ICU) setting. The proportion of healthcare-associated infections caused by multidrug-resistant pathogens is increasing.[8] Compared with infections caused by susceptible strains of the same organism, infections caused by several antibiotic-resistant bacteria have been associated with worse outcomes including longer hospitalisations, higher mortality rates and greater healthcare expenditures.[9-14] These poor outcomes are likely multifactorial in aetiology including greater severity of underlying illness, delays in initiation of effective therapy, and in some cases a lack of effective antimicrobial therapy. Carbapenem-resistant Enterobacteriaceae were first described in the early 1990s[15] and the isolation of carbapenem-resistant K. pneumoniae strains occurred sporadically throughout that decade.[16,17] A surveillance study in Brooklyn, New York, demonstrated that over one-third of K. pneumoniae isolates collected in 2004 carried blaKPC, the gene encoding the carbapenem-hydrolysing enzyme KPC.[18] Approximately, one-quarter of these isolates demonstrated resistance to fluoroquinolones and aminoglycosides as well as to carbapenems and b-lactams. The limited number of antimicrobials available to treat carbapenem-resistant K. pneumoniae infection may adversely affect patient outcomes. A recent study from Israel demonstrated an independent association between the acquisition of carbapenem-resistant K. pneumoniae and in-hospital mortality even after adjustment for underlying severity of illness.[19]

Aims and Objectives

1. To study the pattern of gram-negative infections in patients of chronic kidney disease having evidence of gram-negative infection.
2. To study the pattern of carbapenem resistance among the isolated organisms.
3. To study the impact of multidrug resistance on clinical outcome of patients.

MATERIALS AND METHODS

A total of hundred patients of chronic kidney disease admitted in Rama Medical College and Hospital during a period of last two years were included in the study. Patients had varied presentations including urinary tract infections, catheter-associated infections, blood stream infections caused by central venous cannulas, respiratory tract infections and hospital-acquired infections. Samples were sent for culture sensitivity in Department of Microbiology of this institute. Samples included urine cultures, blood cultures, sputum cultures and endotracheal tube tip cultures. Culture and sensitivity was performed by Kirby-Bauer methods. Patients were classified according to age, sex, sensitivity pattern and clinical outcome. Sensitivity among carbapenems was done from meropenem, imipenem and aztreonam. Sensitivity to carbapenems was classified into three classes. First group was sensitive to all carbapenems, second was resistant to all carbapenems and third group was sensitive to all carbapenems except meropenem. Group resistant to all carbapenems was found resistant to all other conventional antibiotics except colistin, polymyxin B and tigecycline. Data was entered on an excel spreadsheet and statistical analysis was done by Microsoft excel.

Inclusion Criteria

Known case of chronic kidney disease with evidence of infection.

Exclusion Criteria

Patients with associated comorbidities leading to immunosuppression-like malignancies, AIDS and others.

Patients in whom causative organism could not be isolated in cultures.

Patients with other nosocomial infections caused by gram positive or atypical organisms.

OBSERVATIONS

Age	Number of Patients
20-40 years	16
41-60 years	22
61-80 years	9

Table 1. Age Distribution of Total Number of Cases

Sex	Number of Patients
Female	26
Male	24

Table 2. Sex Distribution of Total Number of Cases

Category of Patients	Number of Patients
Critically ill (ICU)	20
Stable general ward	30

Table 3. Distribution of Cases According to Severity of Illness

Organism Isolated	Number of Patients
Acinetobacter	12
E. coli	12
Klebsiella	20
Proteus	3
Pseudomonas	3

Table 4. Distribution of Cases According to Isolated Organism

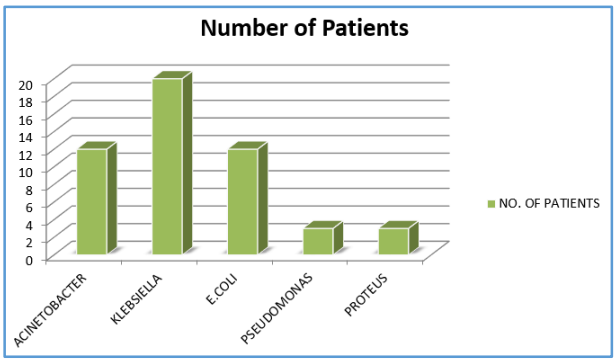

Figure 1. Number of Patients

Class of Patients	Number of Patients
On haemodialysis	16
Not on haemodialysis	34
Table 5. Distribution of Patients According to Need of Haemodialysis	

Pattern of Sensitivity	Number of Patients
Sensitive to all carbapenems	12
Resistant to all carbapenems	18
Resistant to meropenem only (sensitive to imipenem)	20
Table 6. Distribution of Patients According to Sensitivity Patterns	

Pattern of Sensitivity	Number of Patients
Acinetobacter	12
Resistant to carbapenems	7
Sensitive to carbapenems	4
Resistant to meropenem only	1
Table 7. Sensitivity Pattern of Acinetobacter	

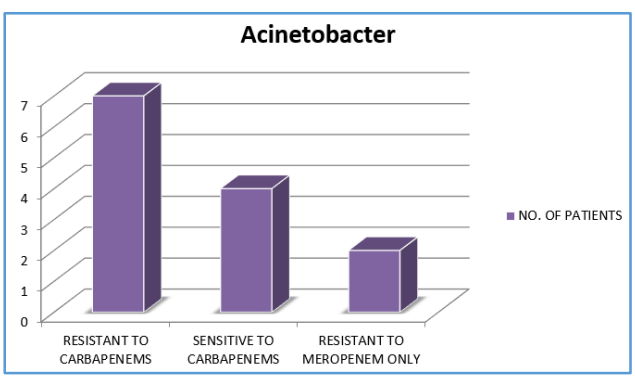

Figure 2. Acinetobacter

Sensitivity pattern of E. coli total	12
Resistant to carbapenems	1
Sensitive to carbapenems	2
Resistant to meropenem only	9
Table 8. Distribution of E. Coli Infections According to Sensitivity Pattern	

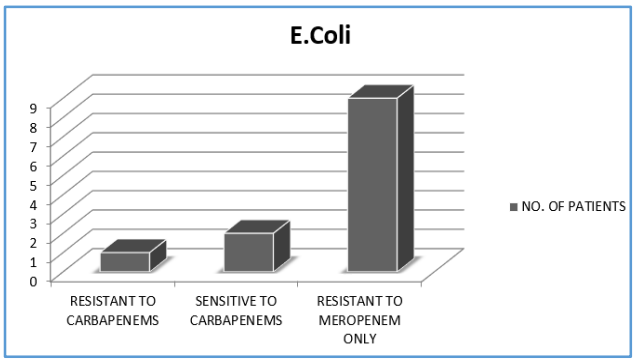

Figure 3. E. Coli

Klebsiella	20
Resistant to all carbapenems	10
Sensitive to all carbapenems	3
Resistant to meropenem only	7
Table 9. Sensitivity Pattern of Klebsiella	

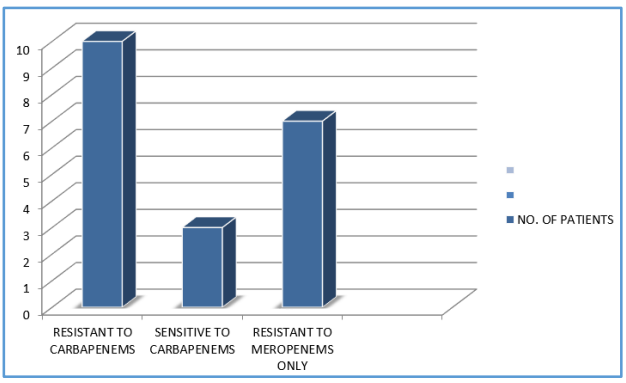

Figure 4. Graphical Distribution of Sensitivity Pattern in Klebsiella

Proteus	3
Resistant to carbapenems	0
Sensitive to carbapenems	3
Resistant to meropenem only	0
Table 10. Sensitivity Pattern of Proteus	

Pseudomonas	3
Resistant to carbapenems	0
Sensitive to carbapenems	1
Resistant to meropenem only	2
Table 11. Sensitivity Pattern of Pseudomonas	

Number of patients deteriorated/succumbed to infection	7
Number of male patients	3
Number of female patients	4
Table 12. Classification According to Clinical Outcome	

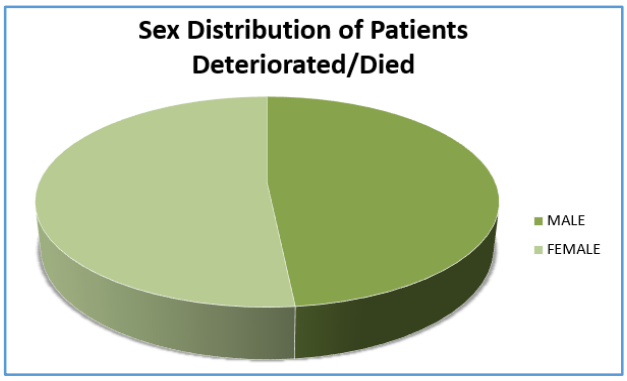

Figure 5. Sex Distribution of Patients Deteriorated/Died

Age	Number of Patients
20-40	0
41-60	3
61-80	4

Table 13. Number of Patients Deteriorated/Died According to Age

Acinetobacter	2
Klebsiella	4
E. coli	1
Pseudomonas	0
Proteus	0

Table 14. Distribution of Patients who Deteriorated/Died According to Organism Isolated

Number of patient died	7
Resistant to all carbapenems	6
Sensitive to all carbapenems	0
Resistant to meropenem only	1

Table 15. Distribution of Patients who Deteriorated/Died According to Sensitivity Patterns

Class of Patient	Number of Patients
Critically ill	7
Stable ward patient	0

Table 16. Classification of Mortality According to Severity of Illness

Severity of Renal Failure	No. of Patients
Mild CRF (S. creatinine - 1.4-2.5)	10
Moderate CRF (S. creatinine - 2.5-5.0)	28
Severe CRF (S. creatinine - >5.0)	12

Table 17. Classification of Patients According to Severity of CKD

Percentage of patients who died/deteriorated among critically ill - 35%.

Mortality percentage of patients in Klebsiella with resistance to all carbapenems - 40%.

Mortality percentage of patients in Klebsiella with sensitivity to all carbapenems - 0%.

Mortality percentage of patients in Acinetobacter with sensitivity to all carbapenems - 0%.

Mortality percentage of patients in Acinetobacter with resistance to all carbapenems - 28.5%.

There was only one mortality in E. coli.

RESULTS

Fifty patients included in this study were known case of chronic kidney disease. Out of these 50, 10 patients had mild CRF, 28 had moderate CRF and 12 had severe CRF. 16 out of 50 patients were on haemodialysis support. Majority of the patients were from 40-60 yrs. age group (22 of 50). 26 patients were female while 24 were males. 20 patients were critically ill requiring inotropic/ventilatory support and ICU care. 30 patients were stable being treated in general wards. The commonest organism isolated in cultures was Klebsiella (40%). Acinetobacter was isolated in 24% cases. E. coli was isolated in another 24% cases. Proteus and pseudomonas was isolated in 6% patients each. No resistance to any carbapenems was found in 24% patients. 36% patients were found to be resistant to all carbapenems. Another major group of 40% patients were found sensitive to all carbapenems except meropenem. If meropenem is excluded, then sensitivity to carbapenems rises to 64%.

Proteus was one organism in which no resistance to carbapenem was seen with all cases found sensitive to all carbapenems. Highest incidence of resistance to all carbapenems was found in Klebsiella around 41.6%. 33.3% of patients with Acinetobacter were found resistant to all carbapenems. Only 8% of patients with E. coli were found resistant to all carbapenems. Resistance to all carbapenems was not found in any case of pseudomonas.

A significant subset of patients was found resistant to only meropenem while sensitive to other carbapenems like imipenem and aztreonam. 35% cases of Klebsiella were found resistant to meropenem only, but sensitive to others. 8.3% cases of Acinetobacter were found in the same group. Highest percentage in this group was found in patients with E. coli. 75% cases of E. coli were found resistant to meropenem only while being sensitive to other carbapenems. 66.6% patients of pseudomonas were found resistant to meropenem only while being sensitive to other carbapenems. No resistance to any carbapenem including meropenem was found in proteus.

Considering the clinical outcome of patients, 35% mortality was observed in critically-ill patients, while no mortality was observed in stable ward patients. 85.7% of those who died were from the group of patients who were found resistant to all carbapenems. While the rest, 14.3% were from those who were found to be resistant to meropenem only.

Among those who died, 28.5% were cases of Acinetobacter, 57.14% were of Klebsiella and 14.28% were cases of Pseudomonas. No mortality was observed in Proteus and Pseudomonas cases. Mortality percentage of patients in Klebsiella with resistance to all carbapenems was 40%. There was no mortality. Klebsiella with sensitivity to all carbapenems. There was also no mortality in patients of Acinetobacter with sensitivity to all carbapenems. Mortality percentage of patients in Acinetobacter with resistance to all carbapenems was 28.5%. There was only one mortality in E. coli and that patient was found to only meropenem while sensitive to other carbapenems.

57.14% mortality was among the patients on haemodialysis, while 42.86% among non-haemodialysis group.

DISCUSSION

Resistance to carbapenems is emerging as an important health concern. There is increased incidence of carbapenem resistance being reported among both community-acquired and hospital-acquired gram-negative infections. Klebsiella comes out to be the most commonly isolated organism in cultures followed by Acinetobacter and E. coli carbapenem-resistant K. pneumoniae is an emerging pathogen that is associated with several healthcare-associated risk factors, including recent solid-organ or stem cell transplantation, receipt of mechanical ventilation, prolonged hospitalisation and prior treatment with cephalosporins and/or carbapenems. The in-hospital mortality rate associated with carbapenem-resistant K. pneumoniae infection, even among case patients who received antibiotics demonstrating in vitro activity against the infecting organism was relatively high. These findings have important implications for the prevention, detection and treatment of carbapenem-resistant K. pneumoniae infection.

Among other isolated organisms, also the mortality was highest among the carbapenem resistant group even after being treated with colistin and increased doses of carbapenems in combination to get the synergistic effect of the combination of both. Proteus was the only organism with no identifiable resistance to carbapenems.

The most different and significant group, which comprised of 40% of patients were isolates resistant to meropenem only and sensitive to other carbapenems. This is underlining that the isolates resistant to meropenem were also resistant to all other group of antibiotics except colistin, polymyxin, tigecycline and other carbapenems like imipenem and aztreonam. The increasing prevalence of resistance for meropenem may be attributed to over and inadvertent use of this molecule in various ICUs in India. There was a significant subset of E. coli (75%) both hospital and community-acquired, which was found resistant to meropenem while being sensitive to other carbapenems. 8.3% Acinetobacter, 35% Klebsiella and 66% Pseudomonas cases fell in the same group. These observations may suggest that meropenem is no longer the carbapenem of choice in serious ICU infections in India.

Gram-negative bacilli are frequently associated with nosocomial infections in ICU patients particularly VAP and CA-UTI.[20] In a previous survey of the prevalence and antibiotic susceptibility pattern of consecutive gram-negative bacterial isolates in 2 ICUs in Saudi Arabia (Jeddah) and Kuwait, the most common bacterial isolates in the Kuwait ICU were P. aeruginosa (26%), Acinetobacter spp. (33%) Klebsiella pneumoniae (17%) and E. coli (3%) compared to 26, 9, 20 and 23% of the same organisms in Jeddah ICUs.[21] This however differs from findings of our study in which Klebsiella came out to be the most common organism isolated in 40% cases.

Most of the studies done in western countries show pseudomonas to be the most common organism isolated in nosocomial infections, but in our study, Klebsiella turned out to be the most common pathogen.

The crude mortality among our patients (35%) was higher than reported by Bueno-Cavanillas et al[22] (28%) and Ylipalosaari et al[23] (25.7%), but lower than that reported by Girou et al[24] (58.5%). The mortality was significantly higher in the patients who showed resistance to all carbapenems. In general, the differences reported between studies maybe related to some confusion between the associated and attributable parts. The impact of ICU infections on hospital mortality is controversial. However, recent reports support the conclusion that nosocomial infections increase the risk of death in critically-ill patients.[21,22] In our study, there was no difference in mortality between nosocomially infected and non-infected patients. There was also no significant difference in mortality based on severity of CRF. However, carbapenem-resistant Klebsiella infection seems to be associated with significantly high mortality independent of other factors like sex, age, severity of CRF and haemodialysis requirement. Similarly, high mortality was also observed among carbapenem-resistant Acinetobacter.

There were two patients in this study in whom there were two isolates in the same sample sent for culture. Both were combination of Acinetobacter and Klebsiella and both were hospital acquired. The sensitivity pattern of both the organisms was different, although being isolated from the same source. Because, no inferences can be drawn from just a couple of such cases, the statistical analysis has not been done and it is difficult to infer whether two isolates present simultaneously in the same patient contribute to increased mortality or not.

CONCLUSION

Carbapenem-resistant gram-negative infections pose a major health concern in ICUs, increasing resistance to all the conventional antibiotics and carbapenems leave us with very limited options of antibiotic selection. Increasing evidence of ESBL and carbapenemases in wide spread community-acquired E. coli infections are a threat and warrant immediate hard hitting to prevent progression of infection, regular hand washing, minimising the inadvertent usage in inappropriate dosage are a few measures to reduce the disease burden. Increasing resistance to meropenem in Indian ICUs should be taken into consideration in antibiotic selection. Klebsiella seems to be the most common isolate in CKD patients. A bigger group of isolates are being found to be resistant to only meropenem while being responsive to other carbapenems. Community-acquired E. coli infections are also showing high degree of antibiotic resistance including meropenem. Isolates found resistant to all carbapenems have higher mortality despite being treated with colistin and tigecycline. Considering the fact that no new antibiotics are in pipeline, appropriate antibiotic selection and targeted therapy is the mainstay of management of sepsis. Identifying the source of sepsis and identifying the organism with targeted antibiotic selection

may reduce the emerging resistance. Further studies are essential to identify the epidemiology of sensitivity patterns.

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