ORIGINAL ARTICLE

# Risk factors for carbapenem resistant bacteraemia and mortality due to gram negative bacteraemia in a developing country

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## Abstract

**Objective:** To identify the risk factors for carbapenem resistant bacteraemia and mortality due to gram negative bacteraemia in a developing country.

**Methods:** A prospective cohort study was conducted at the Sindh Institute of Urology and Transplantation (SIUT) from June to October 2012. Hospitalized patients > 15 years of age with gram negative bacteraemia were included and followed for a period of 2 weeks for in hospital mortality. Data was collected and analyzed for 243 subjects.

Multivariate analysis was used to determine the risk factors for carbapenem resistant bacteraemia and mortality due to gram negative bacteraemia. Crude and adjusted odds ratio and 95% CI are reported.

**Results:** A total of 729 out of 1535 (47.5%) cultures were positive for gram negative isolates. Out of 243 subjects, 117 (48%) had an MDR isolate. Having an MDR isolate on culture (AOR, 2.33;95% CI, 1.35 -4.0), having multiple positive cultures (AOR, 1.8; 95% CI, 0.94 -3.4) and stay in ICU >48 hours (AOR, 2.0 ; 95% CI, 1.12 -3.78) were identified as significant risk factors for mortality due to gram negative organisms.

Risk factors for carbapenem resistant bacteraemia were age >50 years (AOR, 1.83; 95% CI, 1.0-3.5), septic shock on presentation (AOR 2.53; 95% CI, 1.03 -6.2) , ICU stay of >72 hours (AOR 2.40; 95% CI, 1.14-5.0) and receiving immunosuppressant medications (AOR 2.23; 95% CI, 0.74 - 6.7).

**Conclusion:** There is a high burden of MDR and carbapenem resistant gram negative bacteraemia, with a high mortality rate.

**Keywords:** Gram negative bacteraemia, Mortality, Developing country, Multidrug resistance, Carbapenemresistance. (JPMA 64: 530; 2014)

## Introduction

Bloodstream infection is a major cause of morbidity and mortality in hospitalized patients despite advances in antimicrobial therapy and in supportive care. The proportion of blood stream infection caused by gram-negative bacilli is increasing worldwide. Hospitals in the United States participating in the National Nosocomial Infections Surveillance (NNIS) System reported that by 2003 gram-negative bacilli were responsible for 24 percent of nosocomial bacteraemia cases in intensive care units.[1] In some areas of Europe and the Far East, the proportion of bacteraemia caused by gram-negative bacilli was greater than that identified in the United States.[2] This is of concern since gram-negative bacillary sepsis with shock has a mortality rate of 30 to 50 percent.[3,4]

Gram negative bacteraemia has become a serious therapeutic problem due to emergence of multidrug resistance (MDR), defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[5-7] In South East Asia, the emergence of the New Delhi metallo-β-lactamase-1 (NDM-1) in enterobacteraciae was reported in 2009.[8] Metallo-β-lactamases are enzymes that mediate resistance to various β-lactam agents, including carbapenems. Infection with MDR pathogens leads to increased mortality, length of hospital stay and cost, especially among the critically ill, immunocompromised and those exposed to invasive procedures.[9,10] The importance of appropriate and timely empirical antibiotic therapy for a favourable outcome in gram negative bacteraemia is well documented but therapeutic options are limited in infection with resistant strains.[11]

There are several reports on outcomes of gram negative bacteraemia but there are limited reports on risk factors for mortality due to gram negative bacteraemia and risk factors for carbapenemase resistant organisms, particularly from developing countries like Pakistan.[12] This study aims to describe the risk factors for mortality due to gram negative bacteraemia, and evaluate the risk factors for carbapenem resistant bacteraemia in adults at a tertiary care hospital in Pakistan.

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## Patients and Methods

This prospective cohort study was conducted at the Sindh Institute of Urology and Transplantation (SIUT) in Karachi, Pakistan from June 10th till October 10th 2012.

SIUT is a 500-bed urban tertiary care hospital. This institute caters mainly for nephrology and urology patients from all over the country and offers services to patients with acute and chronic renal failure, those on maintenance dialysis, urological malignancies and hepatic and gastrointestinal disorders. SIUT is the largest renal transplantation centre in the country.

For the present study all hospitalized patients >15 years of age, admitted under the nephrology, urology, gastroenterology, oncology and intensive care services found to have laboratory confirmed blood stream infection with gram negative bacteria, whether in monomicrobial or polymicrobial cultures, either on admission or at any time during the course of their hospital stay were included. Patients receiving haemodialysis on out-patient basis and renal transplant récipients were excluded. Those with Salmonella typhi or paratyphi bacteraemia were also excluded.

Patients that met the eligibility criteria but died or were transferred or discharged prior to a positive culture report, and were no longer inpatients, were excluded from the study.

The patients were followed for a period of 2 weeks after the positive culture for in hospital mortality.

A data collection sheet was filled for patients fulfilling the eligibility criteria. Data was collected for demographics, recent hospitalization, co-morbidities, clinical features and any complications of bacteraemia. The presence of a central line, peripheral vascular catheter, urethral catheter, nephrostomy tubes, drains, endotracheal intubation, any recent surgical procedure and haemodialysis was noted. The most likely portal of entry and source of bacteraemia was determined on the basis of clinical and laboratory evaluation. Microbiological data regarding organism/s identified in blood cultures and their antimicrobial sensitivity was recorded.

The patients were then followed for the duration of their hospitalization up to a maximum of 2 weeks after the initial visit. Any mortality that occurred during hospitalization within the 2 week period after initial culture positivity was recorded.

In cases where multiple cultures were positive for an episode of gram negative bacteraemia, only the first positive blood culture was included. Each patient was counted only once. Patients were later stratified according to whether they had multidrug resistant or sensitive isolates.

Complete data was collected and analyzed for 243 subjects with gram negative bacteraemia.

Species identification and drug susceptibility testing of isolates were performed by disc diffusion method and according to standard Clinical and Laboratory Standards Institute (CLSI) guidelines 2011.[13] Multidrug resistant organisms with resistance to imipenem, were tested for sensitivity to polymyxin B.

The following terms were defined prior to data analysis:

Blood stream infection was defined as lab-confirmed infection with gram negative bacilli

Multidrug resistance was defined as resistance to 3 or more antimicrobial groups against which it has been tested, except for stenotrophomonas and burkholderia cepaciae where resistance to 2 or more antibiotic groups constituted resistance.[7]

Nosocomial bacteraemia was defined as bacteraemia that developed 48 hours after admission and/or occurred in a patient that had any history of hospitalization, surgical procedure, haemodialysis or central line placement within 1 month prior to bacteraemia.

The study was approved by the Ethical Review Committee of the SIUT.

Statistical Analysis: SPSS, version 19.0, was used for data entry and analysis. Frequencies are reported for categorical variables and mean and standard deviation for continuous variables. The frequency of gram negative bacteraemia was calculated by dividing the number of cultures positive for a gram negative isolate by the total number of cultures sent during the study period and is reported as a percentage. Multivariate analysis was used to determine the independent risk factors for carbapenem resistant gram negative bacteraemia and risk factors for mortality due to MDR gram negative blood stream infection. For all tests, P value $\leq$0.25 was considered significant at univariate level. All variables found significant at univariate level were entered in the multivariable model using the stepwise approach. Crude and adjusted odds ratio and 95% CI are reported.

## Results

A total of 5678 blood cultures were sent during the study period, out of which 1535 (27%) were positive for any microbial growth. Of 1535 positive cultures, the proportion of gram negative bacteraemia was 729

**Table-1:** Demographic and clinical characteristics in 243 hospitalized patients with MDR and non-MDR gram negative bacteraemia.

| Demographic and Clinical Characteristics | Non- MDR (n=126) n (%) | MDR (n=117) n (%) |
|---|---|---|
| Age (Years) | 42.7 (±15.5) | 42.5 (±18.8) |
| Males | 72 (57) | 77 (66) |
| Rural residence | 65 (51.6) | 56 (48) |
| Prior hospitalization[a] | 80 (63.5) | 73 (62.4) |
| Fever | 115 (91) | 107 (92.2) |
| Septic shock | 22 (17.5) | 17 (14.5) |
| Disseminated Intravascular Coagulation | 7 (5.6) | 5 (4.3) |
| Altered mental status | 34 (27) | 38 (32.5) |
| Rash | 12 (9.5) | 6 (5.1) |
| Neutropenia | 3 (2.4) | 7 (6.0) |
| Complications[b] | 6 (4.8) | 5 (4.3) |
| Immunosuppressant medications[c] | 8 (6.3) | 7 (6.0) |
| Associated Co-morbidities[d] | 119 (94.4) | 114 (97.4) |
| Central line >48 hours | 77 (65.3) | 74 (65.5) |
| **Source of bacteraemia** | | |
| Central line | 68 (54) | 58 (49.5) |
| Urinary tract | 26 (20.6) | 42 (36) |
| Surgical site | 8 (6.3) | 3 (2.6) |
| Skin and soft tissue | 2 (1.6) | 3 (2.6) |
| No source identified | 11(8.7) | 3 (2.6) |
| Others | 11 (8.7) | 8 (6.8) |
| Stay in ICU (>48 hours) | 36 (28.6) | 32 (27.4) |
| Mechanical ventilation | 11 (8.7) | 11 (9.5) |
| Surgeries | 19 (15.7) | 24 (20.7) |
| Died | 34(27.0) | 54(46.2) |

a. Hospitalization within 4 weeks prior to current admission
b. Endocarditis, endophthalmitis, septic pulmonary emboli, stroke, osteomyelitis
c. Steroids or antineoplastic medications
d. Diabetes, neutropenia or malignancy.

**Table-2:** Crude and adjusted odds ratio and their 95% CI for factors associated with mortality in 243 hospitalized patients with gram negative bacteraemia.

| Mortality associated risk factors | P-value | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|
| Age >50 years | 0.57 | 1.72 (1-3.0) | - |
| Sex (male) | 0.40 | 1.3 (0.73-2.1) | - |
| Prior antibiotic therapy | 0.8 | 0.9 (0.53-1.6) | - |
| Prior hospitalization[a] | 0.57 | 1.28 (0.66-2.08) | - |
| On immunosuppressant medication[b] | 0.16 | 2.1 (0.7-6.0) | - |
| Immunocompromised[c] | 0.29 | 2.3 (0.5-11.3) | - |
| Renal failure | 0.45 | 1.5 (0.55-3.92) | - |
| Hepatic failure | 0.67 | 0.88 (0.35 - 2.3) | - |
| **Type of central line** | | | |
| Femoral | 0.15 | 1.8 (0.81-4.0) | |
| Internal jugular | 0.5 | 1.3 (0.6-2.7) | |
| Subclavian | 0.2 | 1.8 (0.8-4.1) | |
| Duration of central line (>48 hours) | 0.4 | 1.3 (0.73-2.3) | |
| Intubated | 0.15 | 2.0 (0.8-4.6) | - |
| Duration of mechanical ventilation >48 hours | 0.43 | 1.6 (0.50-4.8) | - |
| Stay in ICU >48 hours | 0.03 | 1.9 (1.06-3.3) | 2.0(1.12 -3.78) |
| **Source of infection** | | | |
| Line | 0.42 | 0.7 (0.3-1.8) | - |
| Other sources[d] | 0.95 | 1.08 (0.4 -2.3) | - |
| Received TPN[e] | 0.86 | 1.18 (0.20 -7.20) | - |
| Surgical procedure | 0.61 | 0.84 (0.42-1.7) | - |
| MDR gram negative isolate in culture | 0.002 | 2.32 (1.36-4.0) | 2.33(1.35 -4.0) |
| Carbapenem resistant pathogen | 0.2 | 1.3 (0.7-2.2) | - |
| Fluoroquinolone resistant pathogen | 0.09 | 0.61 (0.35-1.0) | - |
| Co-infection with candida species | 0.45 | 0.63 (0.20 – 2.26) | - |
| Co-infection with gram positive organisms | 0.52 | 0.75 (0.30-1.83) | - |
| More than one blood culture positive[f] | 0.062 | 1.8 (1.0-3.3) | 1.8(0.94 -3.4) |
| TLC >11,000 at admission | 0.35 | 1.32 (0.73-2.37) | - |
| Septic shock on presentation | 0.035 | 2.1 (1.05-4.20) | - |
| Developed secondary complications of infection[g] | 0.21 | 2.2 (0.7-7.4) | - |

a. Hospitalization within 4 weeks prior to current admission
b. Steroids or antineoplastic medications
c. Diabetes, neutropenia or malignancy
d. Urine, pneumonia, skin and soft tissue and surgical site infections
e. Total parenteral nutrition
f. With the same organism on two different occasions
g. Endocarditis, endophthalmitis, septic pulmonary emboli, stroke, osteomyelitis.

(47.5%) of which 552 (75.7%) were in monomicrobial, and 177 (24.3%) were in polymicrobial cultures. Of the total cultures sent, the proportion of gram negative bacteraemia was 12.8%.

Of 243 subjects for whom data was collected, 233 (95.9%) had nosocomial gram negative bacteraemia. The most common source of bacteraemia was identified as the central line in 52% of subjects. Of 243, 117 (48%) had gram negative bacteraemia with an MDR isolate and 126 (51.8%) had non-MDR pathogens. The details of the clinical and demographic features of patients with MDR and non-MDR bacteraemia are shown in Table-1.

Overall mortality due to gram negative bacteraemia was 36%, and it was much higher (54%) in the group with an MDR isolate on culture. The crude and adjusted odds ratio and 95% CI for risk factors for mortality due to gram negative bacteraemia are shown in Table-2. Having an MDR isolate on culture, more than one culture positive with the same organism and stay in ICU >48 hours were identified as significant risk factors for mortality due to gram negative organisms.

## Antimicrobial Sensitivity Data of Gram Negative Isolates

In 243 patients, a total of 279 gram negative bacilli were isolated in either monomicrobial or polymicrobial cultures. Of these, klebsiella spp. was the most common isolate (n=78, 28%), followed by E. Coli (n=58, 20.8%), Pseudomonas aeruginosa (n=36, 12.9%), pseudomonas

**Table-3:** Crude and Adjusted odds ratio and 95% CI for risk factors for carbapenem resistant gram negative bacteraemia.

| Variable | P-value | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|
| Age >50 years | 0.091 | 0.6 (0.3-1.1) | 1.83(1.0-3.5) |
| Male | 0.89 | 1.04 (0.6-1.9) | - |
| Empiric antibiotic | 0.42 | 0.13 (0.34 -1.58) | - |
| Associated co-morbidities* | 0.8 | 1.05 (0.5-2.0) | - |
| Renal failure | 0.06 | 2.4 (0.97-6.0) | - |
| Dialysis | 0.24 | 1.5 (0.77-2.9) | - |
| Septic shock | 0.25 | 1.6 (0.7-4.0) | 2.53(1.03 -6.2) |
| ICU stay > 48 hours | 0.068 | 1.73 (0.96-3.1) | - |
| Complications of infection** | 0.23 | 3.53 (0.44-28) | - |
| Immune suppressant medications*** | 0.058 | 2.79 (0.96-8.04) | 2.23(0.74 - 6.7) |
| Prior hospitalization | 0.70 | 1.12 (0.61-2.03) | - |
| Urethral Catheterisation | 0.5 | 1.25 (0.67-2.3) | - |
| Intubated | 0.44 | 1.56 (0.5-4.8) | - |
| Mechanical ventilation >48 hours | 0.87 | 1.12 (0.3 -4.2) | - |
| Central line >72 hours | 0.89 | 1.04 (0.6 -1.82) | - |
| Stay in ICU (> 72 hours) | 0.056 | 1.93 (0.98 -3.7) | 2.40(1.14-5.0) |

*diabetes, hepatic failure, malignancy
**septic emboli or endocarditis
***steroids or antineoplastic mediaction.

spp.; (n=15, 5%), acinetobacter (n=30, 10.7%), aeromonas (n=15, 5%), stenotrophomonas (n=12, 4.3%), enterobacter (n=9 , 3%) and others (n=13, 4.6%) which included oochrobacter, citrobacter and brevendimonas vesicularis.

Resistance of 279 isolates to individual antimicrobials against which they were tested is shown in Figure, with 42% of isolates being resistant to imipenem.

Carbapenem resistance was highest amongst Acinetobacter (53.3%), followed by Pseudomonas aeruginosa (44.4%), Klebsiella spp. (37.2%) and E.coli (6.9%). All imipenem resistant isolates were tested for susceptibility to polymyxin, susceptibility to which was 100%.

Out of the 279 isolates 148 were carbapenem resistant. Table-3 shows the risk factors for having a carbapenem resistant gram negative isolate on culture. Four factors were identified on mutivariate analysis; age >50 years, septic shock on presentation, ICU stay of >72 hours and being on immunosuppressant medications. Amongst the patients having carbapenem resistant isolates, mortality

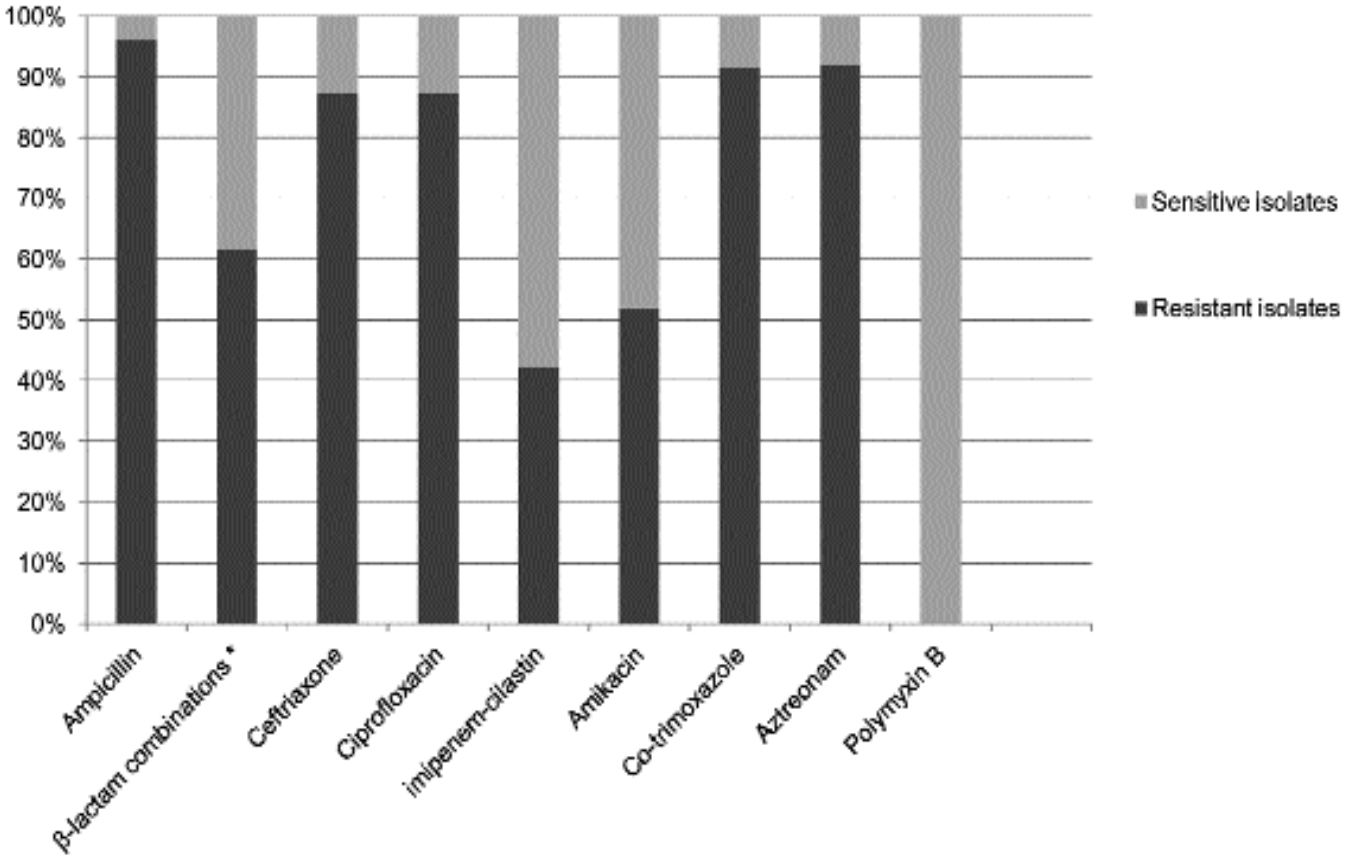


**Figure:** Resistance pattern of gram negatives isolates.

was high (n=53 65.4%).

## Discussion

We report a very high proportion of gram negative and MDR bacteraemia with a high mortality rate. Most subjects had nosocomially acquired gram negative bacteraemia. Furthermore, the high rates of carbapenem resistance are alarming. The EUROBACT international cohort study found high rates of resistance, particularly among gram negative pathogens, in hospital acquired blood stream infections in ICU patients.[14] Similar trends have been seen in developing countries.[15] In Lahore, Pakistan, a study of gram negative bacteraemia in cancer patients on chemotherapy found a high level of antimicrobial resistance.[12]

We identified 3 risk factors for mortality due to gram negative bacteraemia (infection with an MDR organism, prolonged ICU stay of >48 hours and more than one positive blood culture for that organism). Tam et al have reported a 30-day mortality that was significantly associated with multidrug resistance, immunosuppression and a high APACHE score of $\geq$22.[11] A study from Thailand from 2011 of Acinetobacter baumannii bacteraemia also reported a higher mortality in the MDR group as compared to the group with susceptible isolates.[16] A recent meta analysis has found increased rates of mortality in patients with gram negative bacteraemia caused by extended spectrum $\beta$-lactamase (ESBL) producing Enterobacteriaceae.[10] One of the probable reasons for increased mortality among these patients is delay in the initiation of appropriate treatment, which is an important factor for improved outcomes.[3,17]

The carbapenems have long been considered the last line of defence for the management of MDR gram negative infections. Rise of carbapenem resistance in Enterobacteriaceae is therefore of great concern.[10,18] We found a high proportion of carbapenem resistant gram negative bacteria amongst all gram negative isolates analyzed. Irfan et al, from Karachi, have documented a rising trend in carbapenem resistance in patients with febrile neutropenia and Acinetobacter bacteraemia.[19] Emerging resistance to carbapenems in the tertiary care setting has likewise been described in India.[20]

Our study found that age >50 years, septic shock, ICU stay of >72 hours and immunosuppressant medications are risk factors for carbapenem resistance. Out of these 3 factors, ICU stay of >72 hours is a potentially "partially" modifiable factor by reducing the ICU stay and implementing stringent infection control practices. However, ICU stay is also indirectly related to severity of illness at presentation and use of multiple antibiotics in a confined space and therefore this factor cannot be completely controlled.[21] Leanne B. Gasink, et al found that severe illness, prior fluoroquinolone and extended-spectrum cephalosporin use are risk factors for isolation of Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumonia and was independently associated with mortality.[22] We did not find any particular organism to be linked to mortality.

Therapeutic options for carbapenem resistant bacteria are limited to the polymyxins and tigecycline.[23] Polymyxin B and E (colistin) is increasingly being used for the treatment of resistant infections despite the safety profile and difficult dosing.[24,25] In a review by Hirsch and Tam, monotherapy with polymyxins was associated with a poor response whereas combination therapy was more effective.[26] A study of KPC producing klebsiella pneumoniae found a lower mortality with a combination of tigecycline, colistin and meropenem.[27] All of our imipenem resistant isolates were sensitive to polymyxin, except for those gram negatives that are known to be intrinsically resistant to polymyxin like burkholderia cepaciae. However, recent reports of resistance to colistin are emerging.[28] Tigecycline, a glycylcycline, is recommended for resistant skin, soft tissue and intra-abdominal infections and is not a good option for blood stream infections and urinary tract infections.[24] Anthony et al have reported poor clinical and/or microbiological outcomes with tigecycline.[29]

Central line was the major source of gram negative bacteraemia in our study in two-thirds of patients indicating breech of infection control practices in line insertion and care. Prevention of central line associated blood stream infection (CLABSI) can be achieved with adherence to hand hygiene, maximal barrier precautions, proper skin antisepsis, and daily review of line necessity with close observation for any signs of infection.[30] Compliance with these measures has brought CLABSI rates down significantly in some health care settings.[31] It is significant that in our study one-fourth of the blood cultures with gram negative bacteria were polymicrobial.

The clinical and economic impact of MDR gram negative bacilli has been reviewed and found to be substantial and worrisome.[10] Guidelines for standard precautions and contact isolation must be followed.[32,33] Strategic planning and intervention at a national level may be required to combat the spread of MDR bacteria.[34]

Although this is a prospective study with a good sample

size, it has some limitations. The major limitation is that this was an observational study and unknown risk factors for mortality might have been unequally distributed between the two groups, therefore, we cannot exclude the possibility of unmeasured confounding factors. Another limitation is that our institute caters for a high risk population and the results may not be generalizable to all tertiary care facilities. Multicentric studies with mixed categories of patients will allow better identification of risk factors for multidrug resistance. Since treatment decisions were made by the attending physician and not based on a controlled protocol, conclusions regarding outcome must be interpreted with caution. Further studies should incorporate molecular identification for metallo-β-lactamases in enterobacteraciae at our institution.

## Conclusion

The proportion of bacteraemia caused by gram-negative bacilli at our institution is very high. There was a high proportion of carbapenem resistance and MDR bacteraemia was associated with a high mortality. Polymyxins can be used in carbapenem resistant organisms. Infection Control policies must be strictly implemented for the prevention of nosocomial bacteraemia and to combat the spread of multidrug resistance.

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