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Resistance in gram-negative bacilli in a cardiac intensive care unit in India: Risk factors and outcome

Mandakini Pawar, Yatin Mehta¹, Apoorva Purohit, Naresh Trehan¹, Rosenthal Victor Daniel²

Escorts Heart Institute and Research Centre, New Delhi, India, ¹Indraprastha Apollo Hospital, New Delhi, India, ²Medical College of Buenos Aires, Argentina

ABSTRACT

The objective of this study was to compare the risk factors and outcome of patients with preexisting resistant gram-negative bacilli (GNB) with those who develop sensitive GNB in the cardiac intensive care unit (ICU). Of the 3161 patients ($n = 3,161$) admitted to the ICU during the study period, 130 (4.11%) developed health care-associated infections (HAIs) with GNB and were included in the cohort study. *Pseudomonas aeruginosa* (37.8%) was the most common organism isolated followed by Klebsiella species (24.2%), *E. coli* (22.0%), Enterobacter species (6.1%), *Stenotrophomonas maltophilia* (5.7%), Acinetobacter species (1.3%), *Serratia marcescens* (0.8%), *Weeksella virosa* (0.4%) and *Burkholderia cepacia* (0.4%). Univariate analysis revealed that the following variables were significantly associated with the antibiotic-resistant GNB: females ($P = 0.018$), re-exploration ($P = 0.004$), valve surgery ($P = 0.003$), duration of central venous catheter ($P < 0.001$), duration of mechanical ventilation ($P < 0.001$), duration of intra-aortic balloon counter-pulsation ($P = 0.018$), duration of urinary catheter ($P < 0.001$), total number of antibiotic exposures prior to the development of resistance ($P < 0.001$), duration of antibiotic use prior to the development of resistance ($P = 0.014$), acute physiology and age chronic health evaluation score (APACHE II), receipt of anti-pseudomonal penicillins (piperacillin-tazobactam) ($P = 0.002$) and carbapenems ($P < 0.001$). On multivariate analysis, valve surgery (adjusted OR = 2.033; 95% CI = 1.052-3.928; $P = 0.035$), duration of mechanical ventilation (adjusted OR = 1.265; 95% CI = 1.055-1.517; $P = 0.011$) and total number of antibiotic exposure prior to the development of resistance (adjusted OR = 1.381; 95% CI = 1.030-1.853; $P = 0.031$) were identified as independent risk factors for HAIs in resistant GNB. The mortality rate in patients with resistant GNB was significantly higher than those with sensitive GNB (13.9% vs. 1.8%; $P = 0.03$). HAI with resistant GNB, in ICU following cardiac surgery, are independently associated with the following variables: valve surgeries, duration of mechanical ventilation and prior exposure to antibiotics. The mortality rate is significantly higher among patients with resistant GNB.

Key words: Cardiac surgery, gram-negative bacilli, intensive care unit, nosocomial infection, resistance

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INTRODUCTION

Antibiotic-resistant organisms are the common causative organisms of health care-associated infections (HAIs), particularly in the intensive care unit (ICU) setting.^[1] Over the past several decades, the frequency of antimicrobial resistance and its association with serious infectious diseases have increased at alarming rates.^[2] The increasing resistance rate among the nosocomial pathogens is particularly

disconcerting. This high rate of resistance increases the morbidity, mortality and the costs concerned with the HAIs.^[3,4]

Extensive antibiotic resistance has been observed in GNB, due to both innate resistance in some species and the fact that they are highly adept at acquiring antibiotic-resistant determinants from each other. Antibiotic resistance develops through different mechanisms, including the alteration

of the drug target, prevention of drug access to the target (including active elimination of the drug from the bacteria) and drug inactivation.^[5]

A study conducted in India has identified the risk factors associated with infection by antibiotic-resistant pathogens in the ICU;^[6] however, none has analyzed these factors in cardiac surgical ICU. We therefore conducted a prospective study to compare the risk factors and outcome between patients with resistant GNB and those who develop sensitive GNB in the cardiac surgical ICU.

MATERIALS AND METHODS

Between July 2004 and January 2005, 3161 patients were admitted to the cardiac surgical ICU. Patients who developed HAI with GNB within 48 h of admission to the ICU were enrolled in the study. This study was approved from the institutional review board, and informed consent obtained from the patients for this prospective study.

Definitions

HAIs (urinary tract infection, blood stream infection and surgical site infections) were defined according to the criteria established by the Centers for Disease Control and Prevention (CDC).^[7] HAIs were required to be established within 48 h after admission to the surgical ICU. The diagnostic criteria for ventilator-associated pneumonia (VAP) were modified from those established by the American College of Chest Physicians.^[8] VAP was prospectively defined as the occurrence of a new and persistent radiographic infiltrate in conjunction with one of the following: positive pleural/blood culture findings for the same organism as that recovered in the tracheal aspirate or sputum; radiographic cavitation; histopathological evidence of pneumonia; or any two from fever, leukocytosis and purulent tracheal aspirate or sputum.

Persistence of an infiltrate was defined as persistence of radiographic infiltrates for at least 72 h. Fever was defined as an increase in the core temperature of ≥ 1 °C and the core temperature was > 38.3 °C. Leukocytosis was defined as a 25% increase in the number of circulating leukocytes from the baseline and a value of $> 10 \times 10^9$ /litre. Tracheal aspirate was considered purulent if abundant neutrophils were present per high power field using Gram Stain (i.e., > 25 neutrophils per high power field). Tracheal aspiration and/or bronchoscopic or aspiration lavage cultures were

obtained at the time when the diagnosis of VAP was being considered.

APACHE II score was calculated on the basis of the clinical data available in the first 24 h in the ICU.^[10] Hospital mortality was defined as death occurring within 30 days of admission to the ICU. Prophylactic antimicrobial treatment was defined as any antibiotic administered parenterally in the perioperative period for the prevention of infection resulting from the surgical procedure. All other antimicrobial administrations in the ICU were classified as either empirical or infection-directed treatment. Previous antimicrobial use was defined as the intravenous antimicrobial administration for more than 24 h prior to the isolation of the resistant organism. Antibiotic resistance was defined as resistance to at least two of the following antibiotics: piperacillin-tazobactam, ceftazidime, amikacin and imipenem.

Study design and data collection

A prospective observational study was conducted, segregating the patients having HAIs with resistant and sensitive GNB (group 1 and group 2, respectively) 48 h after admission to the surgical ICU. The 30-day hospital mortality was evaluated and other secondary outcomes were also assessed, including the length of stay in the ICU and hospital, duration of mechanical ventilation (MV), intra-aortic balloon counterpulsation (IABC), urinary catheter and central venous catheters (CVC).

The following characteristics were prospectively recorded for all patients at the beginning of the study: age; sex; type of surgery (elective/emergency); reexploration; underlying comorbid conditions such as obesity (BMI > 30), diabetes, chronic obstructive pulmonary disease (COPD), bronchial asthma, duration of CVC, IABC, MV and urinary catheterization; total number and group of administration of antibiotics prior to the development of resistance that included the use of prophylactic antibiotics. The first and second lines of empirical antibiotics were used when infection was suspected as well as when the use of antibiotics was based on the confirmed patterns of culture and sensitivity. The duration of antibiotic use prior to the development of resistance, severity of illness based on acute physiology and chronic health evaluation (APACHE II) score, total length of stay in ICU and hospital, total length of stay in hospital before surgery and before the development of resistance.

Patients received intravenous antibiotic prophylaxis of cefazolin 1 g twice a day and amikacin 15 mg/kg once a day for 24 h.

One of the researchers made daily rounds on all study patients, recording relevant data from the medical records, bedside flow-sheets and the mainframe computer of the hospital for microbiological reports. The patients enrolled in the study were prospectively followed-up until discharged from the ICU/ward or died.

Appropriate culture samples were obtained as clinically indicated by the patients' primary care physician. Species identification and antimicrobial susceptibility testing were performed using the min-API system (Bio-Merieux, Lyon, France). The antibiotics tested were amoxicillin, amoxicillin-clavulanic acid, ticarcillin, ticarcillin-clavulanic acid, piperacillin, piperacillin-tazobactam, cefalotin, cefoxitin, cefotaxime, ceftazidime, cefpirome, cefepime, imipenem, aztreonam, tobramycin, amikacin, gentamicin, netilmycin, ciprofloxacin, cotrimoxazole, meropenem and cefoperazone-sulbactam.

Statistical analysis

All comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were compared using the 'student's *t* test' for normally distributed variables and the Wilcoxon rank sum test for non-normally distributed variables. The Chi square or Fisher's Exact test was used to compare categorical variables. The primary data analysis was used to compare patients who acquired resistant GNB HAI and those who developed sensitive GNB HAI. Multiple logistic regression analysis was used to identify the independent risk factors for resistant GNB HAI.

A stepwise approach was used to introduce new terms into the logistic regression models where 0.05 was set as the limit for the acceptance or removal of new terms. Model overfitting was examined by evaluating the ratio of outcome events to the total number of independent variables in the final models. The interactions between the independent variables were included in the analyses.^[9] Results of the logistic regression analyses were reported as adjusted odds ratios (AOR) with 95% confidence intervals (CIs). Relative risk and their 95% CIs were calculated using the standard methods. Values are expressed as mean \pm SD (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All *P* values were two-tailed; *P* values of ≤ 0.05 were considered

statistically significant. Statistical analysis was carried out by using SPSS version 13.0.

RESULTS

Of the 3,161 patients admitted to the ICU during the study period, 130 (4.11%) developed HAI with GNB and were included in the study cohort. The mean age of the patient was 58.08 ± 11.67 years (range, 12-88 years) and the mean APACHE II score of the study cohort was 9.71 ± 3.38 (range, 3-20). Of the 130 patients, 32 (24%) were females [Table 1].

During the study period, 227 clinically significant GNB isolates were collected from 130 patients. Overall VAP (72.7%) was the most common infection followed by urinary tract infection (15.2%), blood stream infection (5.2%), surgical site infection (1.6%) and other infections (5.2%). There were no significant differences in the distribution sites between resistant and sensitive GNB.

Pseudomonas aeruginosa (37.8%) was the most common organism isolated followed by *Klebsiella* species (24.2%), *E. coli* (22.0%), *Enterobacter* species (6.1%), *Stenotrophomonas maltophilia* (5.7%), *Acinetobacter* species (1.3%), *Serratia marcescens* (0.8%), *Weeksella virosa* (0.4%) and *Burkholderia cepacia* (0.4%). Imipenem (95.76%), meropenem (82.56%) and amikacin (71.6%) showed best activity against

Table 1: Baseline characteristics of the study cohort for the comparison of the resistant and sensitive gram-negative bacilli intensive care unit nosocomial infections (univariate analysis)

Characteristics	Resistant (n = 73)	Sensitive (n = 57)	P value
Age	59.28 \pm 11.02	56.56 \pm 12.38	0.190
Gender, number %			
Male	49 (68.1)	49 (86)	0.018
Female	23 (31.9)	8 (14)	
Emergency surgery, number %	1 (1.4)		0.558
Previous surgery, number %	11 (15.3)	6 (10.5)	0.428
Redo surgery, number %	6 (8.3)	4 (7.0)	0.526
Surgical procedure, number %			
Coronary artery bypass graft	30 (41.7)	41 (71.9)	
Valve	34 (47.2)	12 (21.1)	0.003
Others	8 (11.1)	4 (7.0)	
Underlying illness, number %			
Obesity	-	1 (1.8)	0.442
Asthma	4 (5.6)	-	0.093
Diabetes mellitus	31 (43.1)	24 (42.1)	0.914
Hypertension	35 (48.6)	30 (52.6)	0.650
Others	10 (13.9)	6 (10.5)	0.565
APACHE II score	10.35 \pm 3.25	8.93 \pm 3.43	0.018
Mortality, number %	10 (13.9)	1 (1.8)	0.013

Data are presented as number % or mean \pm SD, APACHE: acute physiology and age chronic health evaluation score

E. coli, *Klebsiella* species, *Enterobacter* species and *S. marcescens*. Of these isolates, 65% were susceptible to piperacillin-tazobactam. *P. aeruginosa* were less susceptible to imipenem (40%), piperacillin-tazobactam (40.2%), meropenem (39.5%) and amikacin (22.3%). *S. maltophilia* was resistant to imipenem, meropenem, amikacin and piperacillin-tazobactam and showed poor susceptibility to ceftazidime (46%), ciprofloxacin (46.1%), cefoperazone-sulbactam (30.7%) and ticarcillin-clavulanic acid (30.7%). *Acinetobacter* species showed 100% susceptibility to amikacin and 80% susceptibility to imipenem, piperacillin-tazobactam, meropenem, cefoperazone-sulbactam, piperacillin, ceftazidime, cefepime and ciprofloxacin [Table 2].

Univariate analysis showed that female gender ($P = 0.018$), re-exploration ($P = 0.004$), valve surgery ($P = 0.003$), duration of CVC ($P < 0.001$), MV ($P < 0.001$), IABC ($P = 0.018$) and presence of urinary catheter ($P < 0.001$), the number of antibiotics administered prior to the development of resistance ($P < 0.001$),

duration of antibiotic exposure prior to the development of resistance ($P = 0.014$), receipt of antipseudomonal penicillins (piperacillin-tazobactam) ($P = 0.002$) and carbapenems ($P < 0.001$). APACHE II scores were significantly associated with group 1 (resistant GNB). Length of stay in hospital prior to surgery ($P = 0.044$), total length of stay in the ICU ($P < 0.001$), total length of stay in the hospital prior to the development of resistance ($P = 0.004$) and total stay in the hospital ($P \leq 0.001$) were significantly higher in group 1 than in group 2. Mortality rate was significantly higher in group 1 as compared with group 2 (13.9% vs. 1.8%; $P = 0.013$) [Table 3].

Multivariate analysis showed that valve surgery AOR = 2.033; 95%CI = 1.052-3.928; $p = 0.035$; duration of MV (AOR = 1.265; 95%CI = 1.055-1.517; $p = 0.011$) and receipt of total number of antibiotics before the development of resistance (AOR = 1.381; 95% CI = 1.030-1.853; $p = 0.031$) were independent risk factors in the development of resistant GNB HAI (group 1).

Table 2: Gram-negative bacilli associated with intensive care unit nosocomial infections

Gram-negative bacteria	Resistant $n = 162$ (%)	Sensitive $n = 65$ (%)	Total $n = 227$ (%)
<i>Pseudomonas aeruginosa</i>	72 (44.44)	14 (21.53)	86 (37.88)
<i>Klebsiella</i> species	41 (25.30)	16 (24.61)	57 (25.11)
<i>Escherichia coli</i>	28 (17.28)	22 (33.84)	50 (22.02)
<i>Enterobacter</i> species	5 (3.08)	9 (13.84)	14 (6.16)
<i>Stenotrophomonas maltophilia</i>	13 (8.02)	-	13 (5.7)
<i>Acinetobacter</i> species	1 (0.61)	2 (3.07)	3 (1.3)
<i>Serratia marcescens</i>	-	2 (3.07)	2 (0.88)
<i>Weeksella virosa</i>	1 (0.61)	-	1 (0.4)
<i>Burkholderia cepacia</i>	1 (0.61)	-	1 (0.4)

Data are presented as number %

Table 3: Process of care variables. Comparison of resistant and sensitive gram-negative bacilli intensive care unit nosocomial infections (univariate analysis)

Variable	Nosocomial GNB infections		P value
	Resistant $N = 72$	Sensitive $N = 57$	
Reexploration, number (%)	9 (12.5)		0.004
IABC, number (%)	24 (33.3)	18 (31.6)	0.833
Duration of central vein catheterization (days)	14.04 ± 12.60	6.40 ± 4.86	<0.001
Duration of mechanical ventilation (days)	7.27 ± 10.80	2.02 ± 1.83	<0.001
Duration of urinary tract catheterization (days)	15.31 ± 13.45	7.23 ± 5.47	<0.001
Duration of intra-aortic balloon counterpulsation (days)	8.50 ± 5.31	5.11 ± 2.76	0.018
Number of days before surgery	6.22 ± 4.03	4.86 ± 3.27	0.044
Duration of stay before the development of resistance (days)	7.01 ± 7.25	4.04 ± 3.13	0.004
Length of ICU stay (days)	20.90 ± 17.39	11.56 ± 6.93	<0.001
Length of hospital stay (days)	30.07 ± 20.03	19.61 ± 9.68	<0.001
Total no. of antibiotic exposure prior to the development of resistance	3.49 ± 2.25	2.14 ± 1.22	<0.001
Total duration exposure to antibiotic prior to development of resistance- (days)	5.85 ± 2.64	4.71 ± 2.43	0.014
Number of times (%) of exposure to penicillin	17 (23.6)	16 (28.1)	0.564
Number of times (%) of exposure to aminoglycoside	33 (45.8)	25 (43.9)	0.823
Number of times (%) of exposure to the 1 st generation cephalosporins	58 (80.6)	39 (68.4)	0.113
Number of times (%) of exposure to the 3 rd generation cephalosporin	23 (31.9)	14 (24.6)	0.357
Number of times (%) of exposure to fluoroquinolones	14 (19.4)	5 (8.8)	0.089
Number of times (%) of exposure to carbapenem	21 (29.2)	3 (5.3)	0.001
Number of times (%) of exposure to aztreonam	2 (2.8)	-	0.310

Data are presented as number % or mean ± SD

DISCUSSION

Infections caused by multidrug-resistant bacteria constitute a serious problem in critically ill patients in the ICU all over the world.^[3,11,12] Resistance to antimicrobial agents is an increasing clinical complication and is recognized as a threat to public health in developed and developing countries.^[13-17] These resistant HAIs can have tremendous financial impact on a system with limited resources.^[18-20]

In this study, we found that mortality was significantly higher in patients with antibiotic-resistant GNB infections. Infections due to antibiotic-resistant bacterial strains are generally more severe in critically ill patients and a greater morbidity and mortality can be expected in them. Some antibiotic-resistant gram-negative bacteria are associated with more virulent factors than antibiotic-susceptible pathogens, which may also explain some of the excess attributable mortality rates observed in patients infected with these pathogens.^[21-25]

Some investigators have reported that in general, the prognosis from the infections caused by resistant organisms is poor. Worsened prognosis may relate to the severity of illness to the extent that inadequate therapy may be responsible for increased mortality. Resistance is probably a factor that directly contributes to a poor outcome through the mechanism of persistent and unresolving infectious insult.^[26]

In our study, prior administration of antibiotics such as piperacillin-tazobactam and carbapenems, (prior to the development of resistance) was observed to significantly increase the likelihood of the development of antibiotic resistance. Prior administration of antibiotic itself was an independent predictor of the occurrence of resistant GNB infection. Misuse of antibiotics (which are active against a wide spectrum of organisms) may be one of the reasons for the development of resistant varieties of microbial organisms. The use of such antibiotics also increases the overall cost of antimicrobial therapy.

Appropriate use of antibiotics is life saving in patients with severe HAIs; however, their inappropriate use must be restricted. Moreover, clinicians should balance the need to provide an adequate antimicrobial protection to infected patients while considering the risks of antibiotic misuse - predisposing to the subsequent emergence of antibiotic-resistant infections. A potential strategy for balancing these two competing issues would involve

early administration of broad-spectrum antimicrobial treatment to high risk patients with suspected HAIs. This should be followed by rapid de-escalation of the antimicrobial regimen or discontinuation of antimicrobial treatment on the basis of the culture results and the clinical course of the patient.^[27]

In patients with resistant infections, the duration of antibiotic administration is found to be significantly higher. Robert Muder *et al.*,^[28] have shown that the total number of days of exposure to antibiotics was correlated significantly with multiple resistance in *P. aeruginosa*. Prolonged exposure to these diverse antibiotics may have reduced the populations of endogenous flora in the patients facilitating the acquisition of the resistant *P. aeruginosa*.

P. aeruginosa is the leading cause of HAIs, which rank second among the gram-negative pathogens reported to the National Nosocomial Infection Surveillance system.^[29] There are limited numbers of antimicrobial agents with reliable activity against *P. aeruginosa*, including antipseudomonal penicillins and cephalosporins, carbapenems and fluoroquinolones, particularly ciprofloxacin. Aminoglycosides are frequently used as a part of combination regimens for the treatment of serious pseudomonal infections, but are generally not recommended as single-drug regimen.^[29] It is intrinsically resistant to various antibiotics at concentrations achievable in vivo. Under selective antibiotic pressure it has proven to be particularly capable of acquiring antibiotic resistance both by chromosomal-mediated and plasmid acquired mechanisms.

The significantly higher use of carbapenem and antipseudomonal antibiotics may explain the subsequent development of resistant *P. aeruginosa* in our study. Widespread use of carbapenem antibiotics has allowed the increase in other nosocomial pathogen such as *S. maltophilia*.^[30,31] Patients receiving carbapenems, particularly those on MV, are at an increased risk of colonization or infection with class B metallo-enzyme producers such as *S. maltophilia*.^[30] Indeed, with the increased use of carbapenems, more strains of *S. maltophilia* were isolated compared to the earlier study conducted at the same institution.^[32] The combination of high innate antibiotic resistance and selective antibiotic pressure has resulted in the emergence of pathogens such as *S. maltophilia* as important nosocomial pathogens.^[33,34] As studied by Gunten and colleagues, the most common gram-negative organisms identified in this study were *P. aeruginosa*, Klebsiella

species and *E. coli*.^[35] In this study, the incidence of urinary tract infection was significantly higher in the group that developed resistant GNB. Female gender was identified as an independent risk factor for infection with resistant GNB. Previous studies have shown that female gender, due to anatomical predisposition, may be associated with an increased incidence of wound and urinary tract infection.^[36,37]

The prolonged presence of invasive devices such as endotracheal tube, intravascular catheter and urinary catheter has been associated with the emergence of antibiotic resistance.^[13-17] These devices are frequently associated with the formation of biofilms on their surfaces. Antibiotic penetration into biofilms is usually diminished, allowing sequestered pathogens colonizing these devices within the biofilms to be exposed to subtherapeutic concentration of antimicrobial agents; further, the presence of such environment favours the emergence of antibiotic resistant microorganisms.^[38] This explains the significantly higher infection rates in patients in whom the invasive devices are retained for longer duration. The MV for ≥ 7 days was independently associated with the development of VAP due to antibiotic-resistant pathogens.^[39] In this study, multivariate logistic regression analysis duration of MV was an independent predictor of GNB-resistant infections.

Valve surgery was independently associated with antibiotic-resistant infections. We observed that the number of administrations of antibiotics prior to the development of resistance was significantly higher in the cohorts with resistant organisms. Compromised host resistance might be more significant in patients with valvular heart disease.^[40]

By univariate analysis, surgical reexploration was observed to be significantly higher in patients with resistant-GNB infections. This may be because a second surgery increases the risk by a longer surgical time, possible increased requirement of transfusion of blood and blood products, tissue trauma, inadvertent contamination during emergencies. Usually patients requiring reexploration are critically ill.^[41]

Antibiotic resistance is more common in patients who have a prolonged stay in ICU, but this is not the only cause of development of antibiotic resistance.^[42] In 1995, in Boston, the examination of cultures obtained from patients within 24 h of admission to the ICUs revealed that 18% of patients were colonized with ceftazidime-resistant GNB.^[42] These colonized patients were more

likely to have been admitted in a hospital in the previous 12 months and had longer hospitalisation prior to ICU admission. Extended stay in hospitals appears to predispose the patients to infection with antibiotic-resistant bacteria.^[39] This may be partly due to the greater likelihood of patients becoming colonized with such bacteria, from either horizontal nosocomial transmission or endogenous emergence of resistance, if the patient remains in hospital for prolonged duration.^[43] We found that the hospital stay before surgery, ICU stay before the development of resistance and total hospital stay were significantly higher in antibiotic-resistant population.

CONCLUSION

In conclusion, we found that the duration of MV, valve surgery and the total number of antibiotics received by the patient are significant predictors for the development of resistant GNB. Given the increasing rates of HAI due to antibiotic-resistant bacteria, clinicians should consider the risk factors for identifying the patients at risk, including prior antibiotic treatment, operative procedures and the duration of invasive devices. The previous use of carbopenems and antipseudomonal penicillins was associated with the development of resistant GNB HAIs; therefore, their use should be restricted.

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