Observational study of healthcare associated infections and mortality caused by carbapenem resistant Gram-negative bacteria in a Greek ICU

Maria Gamvrouli RN; BSN, MSc, Staff Nurse, General Hospital of Nikaias, Piraeus, Greece
Ioanna Pavlopoulou MD, PhD, Associate Professor of Paediatrics-Infection, P & A Kyriakou Children's Hospital; Department of Nursing, National and Kapodistrian University of Athens, Athens, Greece
Maria Kapritsou RN; BSN, MSc, PhD, Staff Nurse, Hellenic Anticancer Institute, Saint Savvas Hospital, Athens, Greece; Department of Nursing, National and Kapodistrian University of Athens, Greece
***Margarita Giannakopoulou RN, BSc, PhD,** Associate Professor, Department of Nursing, National and Kapodistrian University of Athens, Greece
Maria Kalafati RN; BSN, MSc, PhD, Laboratory Teaching Staff, Clinical Instructor, Department of Nursing, National and Kapodistrian University of Athens, Greece
Evangelos A Konstantinou RN; BSN, MSc, PhD, Associate Professor of Nursing Anesthesiology, Department of Nursing, National and Kapodistrian University of Athens, Greece
Eleni Apostolopoulou RN; BSc, PhD, Professor, Department of Nursing, National and Kapodistrian University of Athens, Greece

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***Email:** mgiannak@nurs.uoa.gr

SUMMARY

- Healthcare associated infections (HCAIs) are a growing problem worldwide and contribute significantly to morbidity and mortality.
- The aim of this study was to assess the incidence and associated costs of HCAIs caused by carbapenem resistant (CR) Gram-negative bacteria at a single hospital and to evaluate predictors of mortality in this group of patients.
- In this prospective cohort study, all adult patients hospitalized for more than 48 hours in two intensive care units at a general hospital, during a six-month period, were recruited. All patients were assessed clinically by severity scores (APACHE II and SOFA) on admission and daily thereafter during hospitalization. Patients' blood and urine culture findings were examined daily. Costs were calculated by considering current costs of hospitalization in euro.
- The overall incidence of healthcare-associated infections was estimated at 40.8 per 1000 days of hospitalization. Ventilator associated pneumonia (VAP), and bloodstream infection (BSI) by carbapenem resistant Gram-negative pathogens were observed in 57.1%, and 28.6% of cases, respectively. The incidence of VAP, BSI and UTI was calculated at 22.8/1000 days of mechanical ventilation and at 9.6/1000 patient- days. Cost per case of VAP was calculated at 35610,37 euro and per case of BSI at 16095 euro.
- It is concluded that among healthcare associated infections caused by CR Gram-negative bacteria, VAP and BSI, were identified among a great proportion of adult patients hospitalized in the ICU.

INTRODUCTION

Healthcare Associated Infections (HAIs) are a growing problem worldwide and contribute significantly to morbidity and mortality, as well as to prolonged hospitalization. They have been observed in 5%-10% of hospitalized patients, threatening patients' lives in intensive care units (ICUs) even in high income countries (Pittet et al., 2008).

The additional cost of HAIs creates a significant burden on resources for health care. It is estimated that the cost of HAIs for the National Health Care System in the United States of America is $1 billion annually (National Nosocomial Infections Surveillance System, 2002).

The European Centre for Disease Prevention and Control has reported an average prevalence of 7.1% in European countries and it is estimated that 4,131,000 patients are affected by approximately 4,544,100 HAIs episodes each year. This has resulted in, approximately, 16 million added hospital days per year, 37,000 attributable deaths and annual financial losses estimated at approximately 7 million per year, including only direct costs (National Nosocomial Infections Surveillance System, 2002).

The estimated incidence rate of HAIs in the United States was 4.5% in 2002, corresponding to 9.3 infections per 1000 days of hospitalization and 1.7 million affected patients. Specifically, there were 561,667 episodes of urine infections (36%), which resulted in 13,088 deaths. Also, 250,000 episodes of bacteremia (11%) resulted in 28,000 deaths, and 5.4 VAP/1000 day ventilation (11%) (Klevens et al., 2007). Moreover, In a report of the American System National Nosocomial Infections Surveillance-NNIS), 83% of the episodes of nosocomial pneumonia were associated with mechanical ventilation, 97% of the UTIs were detected in patients with urinary catheters and 87% of the primary bacteremia cases were associated with central venous catheter insertion (Stone et al., 2005). The mortality rate in the study of Klevens et al. (2007) was 3.6%, accounting for 99,000 deaths and the annual economic impact was more or less 4.5 billion dollar.

The prevention of healthcare associated infections seems to have significant direct benefits for both the patient and the health care system, as it is associated with decreased rates of mortality and length of stay. This is a pilot study which reports preliminary results of HAI incidence evaluation in two Greek ICUs located in the same hospital, before introducing an active surveillance training program, such as care bundles and Six Sigma process, to the ICU staff, in order to change health care professionals' attitude toward ICU procedures. The aim of this study was to explore a) the incidence of infections caused by carbapenem resistant Gram- negative bacteria, b) effectiveness of severity and comorbidity scores to predict mortality in this group of patients, and c) the cost associated with the administered antibiotics.

METHODS

This was a prospective cohort study conducted from April until September 2011 at two ICUs with 12 beds, of Piraeus General Hospital in Athens, Greece. The sample consisted of 50 consecutive ICU adult patients and inclusion criterion was the hospitalization for more than 48 hours. Patients were observed for a total of 833 days, from the day of admission until the day of discharge or death.

The primary researcher was an ICU nurse at the hospital where the study was conducted and was present throughout the length of the study. The data collection was performed via patients' medical records, by the primary researcher. Demographic and clinical data were collected and included patients' age, gender, diagnosis, length of stay, trauma, coma, outcome, all the invasive techniques performed, (tracheotomy, ventilation, insertion of central and urine catheters, hemodialysis, tracheal intubation, parenteral nutrition, placement of nasogastric catheter), antibiotics administered, as well as the antibiograms that defined the type of bacteria and their resistance to antibiotics. Monitoring of patients' blood and urine culture results were performed daily. Costs occurring were calculated by considering current hospitalization cost rates per case, in euro. Calculation of costs was based on the current report by the Department of Economic Affairs of the Greek Ministry of Health.

To assess critically ill patients' severity, and to classify and quantify the degree of organ failure, we collected daily data using APACHE II score (Knaus et al., 1985) and SOFA score (Vincent et al., 1996). As comorbidities are among many factors that contribute to the risk of infection due to antibiotic-resistant bacteria, we used two comorbidity scores: the Chronic Disease Score (CDS) (McGregor et al., 2005) and Charlson Comorbidity Index (CCI) (McGregor et al., 2005). The CCI predicts the one-year mortality for a patient who may have a range of comorbid conditions (a total of 19 conditions). Each condition is assigned a score of 1 to 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality (McGregor et al., 2005). The CDS is a prescription-based comorbidity index used as a predictor of physician-rated disease status, self-rated health status, hospitalization, and mortality. An integer weight is given to each comorbidity category represented by selected medication classes, and all weights are summed to obtain an overall score (McGregor et al., 2005)

The research protocol was approved by the Hospital's Scientific Committee. In order to participate in the study, a signed informed consent was obtained from each patient's legal representative. Data collection, processing and management procedures complied with the principles of privacy and confidentiality.

Data were analyzed using SPSS software version 17.0 (IMB SPSS Software, Chicago, Illinois). Descriptive statistics of continuous variables are presented as means and standard deviations, whereas categorical variables are presented as absolute or relative frequencies. Variable values were examined for normal distribution, and Student t test, or Mann-Whitney test were calculated. Comparisons between categorical variables were tested using the X^2 test. Finally, stepwise linear regression analysis procedures were conducted to identify the predictive validity of any demographic and clinical factor as well as severity scores on the outcome of patients with or without HAI. Reported p-values are based on two-sided tests and statistical significance level was set at $\alpha = 0.05$.

RESULTS

Patients' demographic and clinical data are presented in Table 1.

A total of 21 (42%) hospitalized ICU patients had active infection; 16 (32%) had a nosocomial one, and 5 (10%) a community-acquired one. During the day of admission, 8 patients suffered from pneumonia, 3 from septic shock, 2 from peritonitis, 2 from bloodstream infection (BSI), 1 from Fournier's disease, 1 from infection of central nervous system, 2 from pneumonia and BSI, and 1 from leptospirosis. Central venous and urine catheters were inserted to all patients, immediately after their admission to the ICU. All patients were intubated, 3 (6%) had a chest tube and 32 (64%) remained on mechanical ventilation for less than 15 days. Data on administration of medications show that 6 (12%) patients received cortisone, 26 (52%) antibiotics, 7 (14%) vasopressors, 49 (98%) heparin of low molecular weight, 2 (4%) inotropes, 13 (26%) corticosteroids and 27 (54%) parenteral nutrition.

Frequency of healthcare associated infection (HAI)

A total of 23 (46%) patients developed at least one HAI in the ICU. These 23 patients developed 34 HAIs, in total. The incidence density of HAIs was 40.8 per 1000 days of hospitalization. Furthermore, 16 (47%) patients developed ventilator associated pneumonia (VAP). The incidence of late-onset VAP was found to be 20.5%, while the early-onset type was 26.5%. Also, 15 (44.1%) participants developed a bloodstream infection (BSI). More specifically, 11 (32.4%) of them developed primary bacteremia of unknown origin, 2 (5.9%) developed a catheter-related one (the same serotype was isolated both in blood culture and catheter edge) and 2 (5.9%) developed a secondary BSI associated with VAP. Finally, a catheter-related urinary tract infection (CAUTI) was detected in 3 (8.8%) patients.

A total number of 28 CR Gram-negative pathogen (CR-GNP) infections was detected in 22 (44%) patients. More specifically, 15 CR-GNP BSI infections were developed in 12 (42.8%) of the participants; 8 (28.6%) were of unknown cause, 2 (7.1%) were catheter-related and 2 (7.1%) were secondary associated with another infection.

CR-GNP VAP was recorded in 16 (57.1%) participants; in 7 (25%) of them was lately developed and in 9 (32.1%) has already been developed. UTIs were not caused by Gram-negative pathogens, therefore they were not included. Generally, data collected from the

Table 1. Patients' demographic and clinical data

Description		n (%)
Gender	Male	35 (70)
	Female	15 (30)
Trauma	Head	39 (78)
	Thorax	10 (20)
	Multi	5 (10)
Other	Coma	21 (42)
	ARDS	4 (8)
	Septic shock	12 (24)
	End of life care	15 (30)
	Disease with good prognosis	35 (70)
Description		**Mean (SD, median, range)**
Age (years)		58.04 (20.20, 61.5, 16-88)
Length of stay in ICU (days)		16.66 (14.94, 12, 3-80)
Chronic disease score on admission		3.86 (3.07, 4, 0-9)
Charlson comorbity index score on admission		1.98 (1.76, 2, 0-6)
APACHE II score on admission		13 (6.02, 13, 3-29)
SOFA score on admission		3.88 (2.89, 3.5, 0-18)
Tracheal intubation (days)		16.66 (14.94, 12, 3-80)
Tracheotomy (days)		8.58 (14.98, 0, 0-80)
Mechanical ventilation (days)		14.02 (13.00, 10, 3-59)
Without mechanical ventilation (days)		2.64 (3.70, 2, 0-21)
Thorax intubation (days)		0.54 (2.57, 0, 0-17)
Central venous catheter (days)		16.66 (14.94, 12, 3-80)
Nasogastric tube (days)		16.08 (15.13, 10.5, 3-80)
Parental nutrition (days)		3.7 (4.79, 2.5, 0-21)
Intestinal nutrition (days)		12.74 (15.47, 8, 0-80)
Number of administrated antibiotics		4.78 (2.89, 4, 1-12)

22 patients who developed CR-GNP infection have shown that the most common type of infection was CR-GNP VAP (57.1%), followed by CR-GNP BSI of unknown cause (28.6%).

Incidence-density rates

The incidence-density rate of VAP was 22.8/1000 days of mechanical ventilation. Similarly, the incidence-density rate of early-onset VAP was 9.98/1000 days of mechanical ventilation and late-onset VAP was 12.8/1000 days of mechanical ventilation.

The incidence density rate of primary-CR-GNP BSI of unknown cause was 9.6/1000 days of hospitalization, the CR-GNP BSI by central catheters was 2.4/1000 days and the secondary CR-GNR BSI was 2.4/1000 days of hospitalization.

The crude mortality rate of the studied population was 0.24% (12/50). The attributable mortality of CR-GNP infection was 0.36% (8/22) in the ICU. Twelve patients (24%) of the studied population had died. In 8 (16%) cases the cause of death was CR-GNP infection whereas 4 (8%) of them died from other causes. Mortality rate was significantly different ($p < 0.001$) between patients with and without CR-GNP Infection. See Table 2.

Prediction of mortality

A multiple logistic regression analysis showed that only the APACHE II score, that took into account the daily occurrence of infection, adequately predicted for patients with CR-GNP infection [Adjusted odds ratio (AOR) = 1.601, 95% CI 1.017-2.522, $p = 0.042$]. The predicted mortality calculation using the APACHE II and SOFA scores, on the day of ICU admission and day 0 of CR-GNP infection appearance, is shown in Table 3.

Table 2. Mortality rate with and without CR-GNP infection and mortality rate in days from the day of CR-GNP infection diagnosis (n = 50)

CR-GNP infection	Overall mortality (n, %)	≤ 14 day mortality (n, %)	15-28 day mortality (n, %)	≥ 28 day mortality (n, %)
Primary CR-GNP infection (n = 22, 44%)	8, 36.4	3, 37.5	2, 25.0	3, 37.5
Non CR-GNP infection (n = 28, 56%)	4, 14.3	0, 0	0,0	0, 0

Table 3. Predicted mortality using the APACHE II and SOFA scores, on the day of ICU admission and the day 0 of CR-GNP infection appearance

Measures	Survival mean (SD, median, range)	Death (SD, median, range)	Significance *p*
APACHE II score (admission)	12.1 (4.5, 11, 5-21)	18.1 (5.9, 17, 10-29)	0.022
SOFA score (admission)	4.8 (4.2, 4,1-18)	4.2 (2.25, 4.5, 1-8)	0.809
APACHE II score (infection)	14.8 (3.7, 16, 8-20)	20.6 (4.8, 20, 15-30)	0.011
SOFA score (infection)	3.7 (2.4, 3.5, 1-8)	4.25 (2.37, 4, 1-9)	0.628

Table 4. Antibiotic cost for CR-GNP infection resistant to carbapenems

CR-GNP Infections	Cost (%)	% of total cost
CR-GNP BSI	€ 16095 (27.38)	18.10
CR-GNP BSI with catheter	€ 2244 (3.82)	2.53
Secondary CR-GNP BSI	€ 4832 (8.22)	5.44
CR-GNP VAP	€ 35610 (60.58)	40
TOTAL	€ 58782 (100)	66.07

Pathogens-antibiotics

Of the 16 patients with CR-GNP VAP, 37.5% had polymicrobial infection. The most common pathogen isolated from CR-GNP VAP patients was Acinetobacter Baumannii (75%). The percentages of Pseudomonada Aeroginosa and Klebsiella Pneumoniae were the same (37.5%). Furthermore, the 8.3% of CR-GNP BSI participants had polymicrobial infection. The most common pathogens isolated from CR-GNP BSI participants were Klebsiella Pneumoniae (66.6%), Acinetobacter Baumannii (33.3%) and Pseudomonada Aeruginosa (8.3%).

One hundred per cent (100%) of the Acinetobacter Baumannii bronchial secretions' isolates were sensitive to polymyxin E and 58.3% to minocycline. Also, Pseudomonad aeruginosa isolates were 66.7% sensitive to polymyxin E, whereas 100% of the Klebsiella pneumonia isolates were sensitive to polymyxin E and 66.7% to tigecycline and gentamicin. Additionally, 66.7% of the Klebsiella Pneumoniae blood culture isolates were sensitive to tigecycline, 55.6% to gentamicin, 44.4% to tetracycline, 44.4% to polymyxin E and 22.2% to amikacin. Finally, Pseudomonas Aeruginosa isolates were 100% sensitive to vancomycin as well as to polymyxin E.

Cost of antibiotic usage

The total cost of antibiotic usage was 88741.34 euro. Antibiotic usage for the CR-GNP VAP treatment consumed 40% of the overall cost, followed by the CR-GNP BSI treatment cost (18.1%). See Table 4.

DISCUSSION

In the current study, the overall estimated incidence of healthcare-associated infections (HAIs) was 40.8 per 1000 days of hospitalization. According to previous studies conducted in the United States and Europe the incidence-density rate of HAIs, ranges from 13 to 20.3 episodes per 1000 days of hospitalization and the cumulative incidence rate was 17 episodes per 1000 days of hospitalization in adult patients at risk (Richards et al., 2010). In our study, the HAIs incidence -density rate was higher (40.8 /1,000 days hospitalization) and associated with the use of invasive devices, particularly, central venous and urine, catheters and ventilators. This finding can be attributed to the prolonged hospitalization and clinical severity of these ICU patients.

According to our results, ventilator associated pneumonia (VAP), bloodstream infection (BSI) and catheter-associated urinary tract infection (CA-UTI) by CR-GNP were detected in 57.1%, 28.6% and 0% of the overall estimated HAIs, respectively. The estimated incidence of VAP, BSI and UTI was 22.8/1000 days of mechanical ventilation and 9.6/1000 patient-days.

Many studies report that urinary tract infections are the most frequent (31%), followed by pneumonia (27%) and primary bloodstream infections (19%). Eighty-seven percent of primary bloodstream infections were associated with central lines, 86% of nosocomial pneumonia was associated with mechanical ventilation, and 95% of urinary tract infections were associated with urinary catheters. Also, the most frequent pathogens associated with pneumonia were Gram-negative aerobic organisms (64%). Pseudomonas aeruginosa (21%) was the most frequently isolated. There was no association between these device-associated infection rates and number of hospital beds, number of ICU beds, or length of stay (National Nosocomial Infections Surveillance System, 2002).

In another study, which included 1,589 patients (16,970 patient-days), the infection rate was 21.6%. The VAP rate was 9.6%, the central venous catheter-associated infection 3.5%, the central venous catheter-associated bacteraemia 4.8%, and catheter-associated urinary tract infection 7.8%. The incidence density rate of ICU-acquired infections was 20.3% patient-days. Also, the catheter-associated urinary tract infection rate was 8.5% urinary catheter-days. A total of 410 strains of micro-organisms were found, 16.8% of which were Staphylococcus aureus (Legras et al., 1998). During another study an ICU prevalence of 2.1%, primary BSI comprises 12.8% of all nosocomial infections observed in ICU patients. This study showed a 60.4% prevalence of CVC use in German ICUs. The rates of CVC-associated BSI on individual hospital wards were very variable (Gastmeier et al., 1999).

Another study was recorded that one hundred and sixty-nine ICU-acquired infections occurred in 74 (38.9%) of 190 patients during 2006 patient-days. The overall rate of ICU-acquired nosocomial infection was 88.9/100 patients and 84.2/1000 patient-days, as well as the overall mortality rate was 60%, mortality in patients with nosocomial infections was 69%. Logistic regression analysis showed nosocomial infection ($p < 0.05$), mechanical ventilation (P=0.009), the presence of two or more underlying diseases (P<0.05) and a low GCS score ($p = 0.0001$) to be risk factors for ICU mortality (Cevik et al., 2005).

In the current study, the calculated cost per case of VAP and BSI was 35610 and 16095 euro respectively. According to Gastmeier et al. (1999), a reduction in the number of infections would prevent 1000-1400 deaths due to CVC-associated BSI annually, as well 40,000 to 60,000 extra days of hospital stay and associated costs (Gastmeier et al., 1999). Moreover, in the study of Gikas et al. (2010), involving 2692 ICU patients, it was observed that mortality was higher in ICU patients with CR-BSI than in those without CR-BSI.

According to the aforementioned, it seems that there is a great variance of nosocomial infections rates across settings worldwide, that it could be attributed to different parameters such as surveillance levels, staff training, time period of recording and methods used for. Further study is needed to clarify and reconcile the observed heterogeneity.

In our study, the mean of APACHE II score both on patients' admission and on the day of CR-GNP infection diagnosis was greater than the corresponding mean value of survival patients. Of measurement systems of disease severity and predictive outcome of critically ill, only APACHE II Score accounted for the day of appearance of the CR-GNP infection and predicted patients' death. Our results were in agreement with a study, which showed that both SOFA and APACHE II scores were independent outcome predictors after adjustment for other parameters. Also, there was no significant difference in the predictions of the two scoring systems, and the scores were highly correlated ($p < 0.001$) (Chen et al., 2011).

According to Poses et al. (1996) in a sample of 201 patients in the ICU, the Charlson index Comorbidity Index compared with a part of the APACHE II system score, had substantial ability to discriminate between patients who survived and those who passed away, while the Chronic Health Points showed no ability of discrimination. Logistic regression analyses reported that the Charlson index could contribute significant prognostic information to that obtained from the components of APACHE II. The conclusion was that the use of detailed information about co-morbidity captured by the Charlson index could improve prognostic predictions even for critically ill patients (Poses et al., 1996).

Additionally, another study showed that between 10% and 20% of patients receiving greater than 48 hours of mechanical ventilation will develop VAP, patients who develop VAP appear to be twice as likely to die compared with similar patients without VAP, moreover patients with VAP have significantly longer ICU lengths of stay (mean = 6.10 days; 95% CI 5.32-6.87 days), concluding that patients who develop VAP incurring $10,019 in additional hospital costs (Safdar et al., 2005).

According to the results of this pilot study and taking into consideration results of other studies conducted worldwide, the development of training programs as well as the implementation of simple and cost-effective measures could be extremely beneficial. Healthcare professionals should follow training programs concerning care bundle elements and monitor compliance with bundle elements. Additionally, in order to estimate the results of training interventions, the rates of HAIs (outcome) prior the implementation of such programs should be assessed.

Study limitations

The limitations of this study include the multiple testing and comparisons in a small sample recruited only from two ICUs of one general hospital in Greece, the recruitment period limited to spring/summer months and the lack of electronic patient record that could lead to potential loss of information not recorded due to workload. Moreover, due to the single-center nature of this study generalizability is limited.

CONCLUSIONS

Among healthcare associated infections caused by CR Gram-negative bacteria, VAP and BSI, but not CR-UTI, were identified among a great proportion of adult patients hospitalized in the ICU of a single center, increasing accordingly the cost of hospitalization. Continuous education of healthcare staff and prudent antibiotic use could improve the quality of care and reduce workload of nursing staff.

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