Infection Prevention in Practice 1 (2019) 100020

Available online at www.sciencedirect.com

Infection Prevention in Practice

journal homepage: www.elsevier.com/locate/ipip

Impact of bloodstream infections caused by carbapenem-resistant Gram-negative pathogens on ICU costs, mortality and length of stay

E. Kousouli [a], O. Zarkotou [a,b], K. Polimeri [a], K. Themeli-Digalaki [a,b], S. Pournaras [c,*]

[a] Infection Control Committee, Tzaneio General Hospital, Piraeus, Greece
[b] Department of Clinical Microbiology, Tzaneio General Hospital, Piraeus, Greece
[c] Laboratory of Clinical Microbiology, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece

ARTICLE INFO

Article history:
Received 1 July 2019
Accepted 15 August 2019
Available online 23 August 2019

Keywords:
Hospital acquired infections
financial impact
clinical outcomes
Klebsiella pneumoniae
Acinetobacter baumannii
Pseudomonas aeruginosa

SUMMARY

Background: The aim of this study was to estimate the impact of bloodstream infections (BSIs) caused by carbapenem-resistant Gram-negative (CRGN) pathogens on hospital costs, mortality and length of stay (LOS).

Methods: All patients hospitalized for ≥3 days in the Intensive Care Unit (ICU) of a tertiary-care general hospital from 1/1/2015 to 31/12/2017 were included in the study. A retrospective case-control study was performed in order to examine the difference in medical, pharmaceutical and operating costs, LOS and in-hospital mortality between patients with BSI caused by CRGN/without BSI (cases/controls, respectively). The statistical analysis was performed using the SPSS software (v23.0).

Results: A total of 419 patients (67.5% males, median age 60.0 years) were included in the analysis (142 cases/277 controls); 10 patients with non-CRGN BSIs were excluded. Overall mortality was 33.7% (49.3/25.6% in cases/controls). The median LOS and total cost were 30.0 vs. 12.0 days and 20 359.1 vs. 8,509.3 €, respectively, between patients with/without CRGN BSIs. After adjusting for baseline demographics, underlying disease severity and patients' specialties, CRGN BSIs remained a significant factor in mortality (odds ratio 2.9; 95% confidence interval 1.8—4.8; p <0.001). Additionally, CRGN BSIs seem to result in significantly prolonged LOS and extra cost per infected patient (p <0.001).

Conclusions: ICU patients with CRGN BSI are at increased risk for mortality and prolonged hospitalization and incur higher costs, imposing a heavy burden on healthcare system. Infection control strategies, considering also the cost-efficacy of interventions, are crucial in order to control the expansion of CRGN infections.

* Corresponding author. Department of Microbiology, Medical School, University of Athens, Athens PC 11527, Greece.
E-mail address: spournaras@med.uoa.gr (S. Pournaras).

https://doi.org/10.1016/j.infpip.2019.100020

Introduction

Hospital acquired infections (HAIs) represent a major burden for healthcare facilities; their average prevalence in acute care European hospitals is 5.7%, while in Greece they are considerably more prevalent (9.1%) [1]. HAIs caused by antimicrobial resistant pathogens result in 25 000 deaths, 2.5 days extra length of stay (LOS) and 1.5 billion € per year in Europe [2]. Carbapenem-resistant Gram-negative (CRGN) bacteria were stratified in critical priority, in 2016 WHO priority ranking list of antibiotic-resistant bacteria; overall mortality and health-care burden were weighed among the most important criteria to assess priority [3].

According to recent resistance surveillance data, Greece reports the highest rate of carbapenem-resistant *Klebsiella pneumoniae* in Europe (CRKP, 64.7%), and high rates of carbapenem-resistant *Acinetobacter baumannii* (CRAB, 94.8%) and *Pseudomonas aeruginosa* (CRPA, 39.3%) [4], leading to limited treatment options. The financial impact of these infections is also very important, considering the reduced hospital budgets due to the economic downturn in recent years [5,6].

Several studies evaluated the burden of HAIs caused by antibiotic-resistant Gram-negative bacteria [7—9]. However, the financial along with the clinical impact of such infections has not been evaluated in Southern European countries, including Greece, despite their high prevalence. The aim of this study was to estimate the impact of bloodstream infections (BSIs) caused by CRGN pathogens on medical, pharmaceutical and operating costs, LOS and in-hospital mortality in the ICU of a tertiary general hospital.

Materials and methods

Setting

Our institution is a 426-bed tertiary hospital with a 12-bed medical/surgical ICU without geographic patients' separation. The study was approved by hospital's Institutional Review Board (process number, 35/14-03-2017).

Definitions and data collection

All ICU patients hospitalized for $\geq$3 days from 1/1/2015 to 31/12/2017 were included. BSI was defined as the first positive blood culture with at least one of CRKP/CRAB/CRPA and consistent clinical presentation.

Due to the very limited ICU patients with BSI caused by carbapenem-susceptible Gram-negatives or Gram-positives (only 10 patients during the study period, excluded from the analysis) comparisons were performed between patients with/without CRGN BSIs.

Patients' data were extracted from medical charts and laboratory records. Data on medical/pharmaceutical/operating costs were obtained from IT and accounting department using the bottom-up costing methodology that is deemed to be more informative in terms of type, quantity and unit costs and allows estimation of individual patient costs.

Medical costs included all consumables and equipment (arterial/central venous/urinary catheters, endotracheal tubes, transducers, manometers, drainage devices etc.) and pharmaceutical costs included all drugs per patient during ICU hospitalization. Operating cost was calculated by the daily ICU cost as determined by the current national legislation (700€ for the three first days, 500€ from 4th-15th day, 350€ from 16th day); personnel costs, imaging and medical laboratory tests, cleaning products, disinfectants and PPE are all included in operating cost. The outcome was documented until the patients' discharge or death.

The severity of underlying medical conditions was evaluated by using the McCabe score [non-fatal (NF); expected survival at least five years; ultimately fatal (UF); expected survival between 1-5 years; rapidly fatal (RF); expected death within one year]. McCabe score was determined at the time of admission. Patient specialty (Medical/Surgical) was defined according to the diagnosis at ICU admission.

Bacterial identification and antimicrobial susceptibility testing

Identification to species level was performed by Vitek2 Compact (bioMerieux, Marcy l' Etoile, France); antimicrobial susceptibilities and MIC values were determined by Vitek2 and Etest (bioMerieux).

Statistical analysis

A retrospective case-control study was performed in order to examine differences in medical and pharmaceutical costs, LOS and in-hospital mortality between cases and controls. A non parametric Mann-Whitney test for two Independent Samples was used to detect possible differentiations in hospital costs and LOS. In order to examine possible differentiations in mortality rates, a Chi-Square Test for Independence was used. Multivariable regression models were constructed to determine whether CRGN BSIs are significantly associated with in-hospital mortality (logistic regression) and increased LOS and costs (linear regression) after adjusting for other potential risk factors. All continuous variables (LOS and costs) were logarithmised (using the natural logarithm) in the linear regression model to adjust for non-normality. For all tests, the level of significance was set to 5%. The statistical analysis was performed using the SPSS statistical software, version 23.0 (IBM SPSS Statistics 23).

Results

The study included 419 patients (67.5% males, median age 60.0 years); 142 patients were classified as cases (33.9%) and 277 as controls (66.1%). All ICU patients had central venous and urine catheters and prolonged mechanical ventilation. Of the 142 BSIs, 26.1% were caused by CRKP, 35.2% by CRAB, 8.4% by CRPA, 25.3% by CRKP plus CRAB, 0.7% by CRKP plus CRAB plus CRPA, 1.4% by CRKP plus CRPA and 2.8% by CRAB plus CRPA. Although molecular epidemiological analysis was not performed for all the study isolates, typing of selected isolates showed that the CRKP belonged to at least four ST types, CRAB were mostly clonal and CRPA belonged to several unrelated clones.

Median time from ICU admission to BSI onset was 14.0 days.

A Mann-Whitney test for two Independent Samples revealed a significant difference in LOS and costs between cases/

Table I
Baseline characteristics comparing patients with/without CRGN BSI (n=419)

	Patients with CRGN BSI (n=142)[a]	Patients without CRGN BSI (n=277)[a]	p-value[b]
Age	62.0 ± 21.0	58.0 ± 30.0	0.026
Gender			
Male	98 (69.0%)	185 (66.8%)	0.645
Death			
Yes	70 (49.3%)	71 (25.6%)	<0.001
Severity of underlying disease (McCabe classification)			
Rapidly fatal	24 (16.9%)	41 (14.8%)	0.030
Ultimately fatal	52 (36.6%)	71 (25.6%)	
Non fatal	66 (46.5%)	165 (59.6%)	
Specialties			
Surgical	75 (52.8%)	162 (58.5%)	0.268
Medical	67 (47.2%)	115 (41.5%)	
LOS	30.0 ± 30.0	12.0 ± 13.0	<0.001
Hospital costs			
Medical cost/Day	15.1 ± 29.5	7.5 ± 14.6	<0.001
Pharmaceutical cost/Day	205.4 ± 213.8	102.3 ± 80.0	<0.001
Operating cost	13 350.0 ± 10 500.0	6,600.0 ± 5,600.0	<0.001
Total cost	20 359.1 ± 16 339.7	8,509.3 ± 8,317.0	<0.001

[a] Median ± IQR or n (%).
[b] Chi-squared test was used for Gender, Death, McCabe and Specialties. Mann-Whitney test was used for Age, LOS and Hospital costs.

controls leading to a median extra LOS of 18.0 days ($p<0.001$) and median extra total cost of 11 849.8€/patient ($p<0.001$) for cases. No significant differentiation was observed in costs, LOS and mortality rates when analysis was performed separately for each pathogen. In-hospital crude mortality rates were also significantly higher in case patients (49.3% vs 25.6%; $p<0.001$) (Table I).

Indeed, after adjusting for age, gender, McCabe score and specialties in the logistic model, the relative risk of mortality was 2.9 for patients with BSI ($p<0.001$). From the linear regression analysis, logarithmised LOS was significantly prolonged in case patients ($p<0.001$) and logarithmised total hospital cost was higher ($p<0.001$) among case patients (Table II).

Table II
Regression models for the association between mortality, LOS* and total costs* with other examined factors

Examined factors	Mortality		LOS*		Total_cost*	
	OR (95% CI)	p-value	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value
CRGN BSI	2.9 (1.8, 4.8)	<0.001	0.8 (0.6, 0.9)	<0.001	0.8 (0.7, 1.0)	<0.001
Group age (15−34)	*		*		*	
Group age (35−54)	1.2 (0.5, 2.8)	0.729	-.25 (-.5, -.0)	0.040	-.20 (-.4, 0.0)	0.058
Group age (55−74)	1.2 (0.5, 2.7)	0.711	-.2 (-.5, -.0)	0.036	-.2 (-.4, -.0)	0.023
Group age (75+)	3.5 (1.4, 8.9)	0.007	-.3 (-.5, -.0)	0.038	-.3 (-.5, -.0)	0.021
Gender (Female)	*	*	*		*	
Gender (Male)	0.8 (0.5, 1.4)	0.494	0.1 (-.0, 0.3)	0.138	0.1 (-.1, 0.2)	0.303
McCabe (NF)	*	*	*		*	
McCabe (UF)	3.3 (1.9, 5.7)	<0.001	-.1 (-.2, 0.1)	0.450	-.0 (-.2, 0.1)	0.886
McCabe (RF)	13.7 (6.9, 27.4)	<0.001	-.3 (-.5, -.1)	0.005	-.1 (-.3, 0.0)	0.10
Specialties (Medical)	*	*	*		*	
Specialties (Surgical)	0.8 (0.5, 1.3)	0.407	0.2 (0.0, 0.3)	0.023	0.1 (0.0, 0.3)	0.016
Constant	0.1	<0.001	2.7 (2.4, 2.9)	<0.001	9.2 (8.9, 9.4)	<0.001

OR, odds ratio for logistic models; Coef, regression coefficient for linear models; CI, confidence interval.
* The natunal logarithm values were used for continuous variables (LOS and costs) to adjust for non-normality.

Discussion

Multidrug-resistant (MDR) infections have major clinical and economic consequences; particularly, CRGN infections accounted for an estimated 8,636 attributable deaths per 100 000 population in EU and EEA countries in 2015 with the highest burden on Italy and Greece [10].

Overall LOS and hospital costs are typically higher in ICUs than wards. Also, BSIs by MDR Gram-negatives lead to higher costs [7–9,11]. In our institution, the majority of BSIs caused by CRGN (79.7%) occurs in the ICU. Intensive infection control (IC) interventions are applied to limit their occurrence, including in brief (i) promotion of hand hygiene, (ii) regular rectal screening in all ICU patients, (iii) promotion of contact precautions, (iv) immediate notification of ICU staff for every patient with CRGN, (v) educational reinforcement (6). In the present study we analyzed the impact of CRGN BSIs on hospital costs, mortality and LOS in our hospital's ICU.

After adjusting for severity of illness and other confounders, mortality rates, excess LOS and additional total cost were significantly higher among case patients. It has been reported that the average cost was 1.6 and 4 times higher for patients with MDR BSIs compared with non-MDR BSIs [8] and without BSIs [12], respectively, while in the present study the median total cost of hospitalization was more than double (20 359.1€, vs 8,509.3€).

In a relevant international study of the prevalence and outcomes of ICU infections (62% due to MDR Gram-negatives), mortality rates for infected patients were more than twice that of non-infected ones (25% vs. 11%) [13], similarly with our study (49.3% vs. 25.6%).

Lastly, the additional LOS was previously reported to be significantly higher among patients infected by resistant vs. susceptible pathogens [9]. In the present study comparing bacteremic with non-bacteremic patients, the median extra LOS was 18.0 days.

Our study has several notable strengths. It is the first study to examine the economic and clinical impacts of CRGN BSIs in Southern Europe, where CRGN are particularly prevalent [4]. In addition, we separately collected the direct medical, pharmaceutical and operating costs for each ICU patient. Furthermore, our cohort included large numbers of CRGN BSIs.

Some limitations also exist. Our study was conducted in a single ICU; therefore, the results may not be representative of all Greek hospitals. Due to the very limited number of BSIs caused by carbapenem-susceptible GN, comparisons were performed between patients with/without CRGN BSIs. Also, indirect costs possibly associated with hospital HAIs are not included in the present study, as the cost analysis was based on the direct medical, pharmaceutical and operating cost.

In conclusion, our results highlight that CRGN BSIs have significant impact on mortality, LOS and costs. Considering the preventability of many HAIs [14,15], a better understanding of the impact of CRGN infections on clinical and economic outcomes in endemic settings would validate the need for appropriate infection control strategies to minimize their burden.

Financial support

None reported.

Potential conflicts of interest

All authors report no conflicts of interest relevant to this article.

All authors will complete and upload the ICMJE Disclosure Form when and if they are asked to submit a revision of their manuscript.

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