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Carbapenem Consumption and Rate of carbapenem-resistant gram-negative bacteria: results from the Sicilian Surveillance System

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Parole chiave: Esistenza ai carbapenemi, Salute Pubblica, tassi di resistenza, sorveglianza, consumo di antibiotici carbapenemici

Abstract

Background. *In the last decades, multidrug-resistant gram-negative bacteria have been increasing and they are involved in severe healthcare associated infections. In treating drug-resistant gram-negative bacterial infections, carbapenems are generally administered as a last choice. However, the rate of carbapenem-resistant bacteria is constantly increasing the last years. The aim of the present study is to describe the relationship between the rate of carbapenem-resistant gram-negative bacteria and antibiotic consumption intensity.*

Study design. *In 2017, the Sicilian Region implemented a regional surveillance system to describe and analyze consumption of antibiotics in hospital settings, as well as prevalence of antibiotic resistant microorganisms.*

Methods. *Resistance data were retrospectively collected from routinary clinical antimicrobial susceptibility tests. Resistance rates (RRs) of carbapenems were calculated and Spearman's correlation analysis was performed to investigate the relationship between annual antibiotic consumption and rate of carbapenem resistance.*

Results. *In 2015, the overall prevalence of carbapenem-resistant Klebsiella pneumoniae isolates was 43.9 %, and was positively correlated with beta-lactam consumption ($R=0.529$, $p<0.01$), and with carbapenem consumption ($R=0.364$, $p<0.05$). In 2016, the overall prevalence of carbapenem-resistant Klebsiella pneumoniae isolates was 53.8 %, and was positively correlated with carbapenem antibiotic consumption ($R=0.364$, $p<0.05$). In 2017, the overall prevalence of carbapenem-resistant Klebsiella pneumoniae isolates was 58.7 %, and was significantly positively correlated with carbapenem antibiotic consumption ($R=0.427$, $p<0.05$). In 2015, the overall prevalence of carbapenem-resistant Escherichia coli isolates was 6.5 %, and was significantly positively correlated with antibiotic consumption for the ATC class J01 (i.e., antibacterial for systemic use) ($R=0.402$, $p<0.05$).*

Conclusion. *The results of the present study highlight the need for comprehensive strategies targeting the appropriate use of antibiotics and infection control measures.*

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Introduction

Infections due to resistant gram-negative bacteria are becoming growingly prevalent and constitute an important threat to public health worldwide because are associated with high morbidity and mortality rates. Furthermore, antimicrobial resistance (AMR) is associated with a considerable economic and clinical burden, causing increasing antibiotic costs, longer stays in hospitals, and higher mortality, especially in intensive care units (1-7). In the last decades, multidrug-resistant (MDR) gram-negative bacteria have been increasing (8) and pathogens, such as *Acinetobacter baumannii*, *Klebsiella pneumoniae* and other *Enterobacteriaceae* that produce extended-spectrum beta-lactamases (ESBL), are involved in severe healthcare associated infections (HAIs) and are commonly involved in outbreaks, especially in intensive care units (4, 9-12). Moreover, most of carbapenem-resistant gram-negative bacteria are resistant to other antibiotics, such as aminoglycosides and fluoroquinolones and represent a global concern around the world (13). Increasing evidence indicates that the inappropriate and the large use of broad-spectrum antimicrobial agents, both in the community and in health care settings, is one of the biggest causes of the emergence and spread of AMR (4, 14) and can increase selective pressure of bacterial resistance (15-18), together with poor adherence to infection prevention and control strategies (19). Carbapenems are a beta-lactam antibiotic agent with a wide antimicrobial spectrum and effective antibacterial activity. Few effective therapeutic choices are available to treat infections caused by carbapenem-resistant microorganisms (20). In treating drug-resistant gram-negative bacterial infections, carbapenems are generally administered as a last choice. However, the rate of carbapenem-resistant bacteria is constantly increasing the last years (21, 22). AMR needs immediate strategies to monitor and fight the inappropriate use of antibiotics agents at the local, national and international level as it represents a severe public health threat (23). In Italy, in 2017, the National Action Plan on Antimicrobial Resistance (Piano Nazionale per il Contrasto dell'Antimicrobico-Resistenza, PNCAR 2017–2020) was adopted (24) and, in the same year, in the framework of a Regional Action Plan on HAIs and AMR prevention, the Sicilian Health Authority, Sicilian Region (Southern Italy), a surveillance system of antibiotic consumption in the hospital wards as well as at a community level was implemented together with the monitoring of antibiotic resistance in hospitals (23, 25, 26).

The aim of the present study is to describe the relationship between the rate of carbapenem-resistant gram-negative bacteria and antibiotic consumption intensity and to report the results of the four-year monitoring period data, from 2015 to 2018, collected by the regional surveillance system.

Methods

Setting and definitions

In 2017, the Sicilian Region implemented a regional surveillance system to describe and analyze consumption of antibiotics in hospital settings, as well as prevalence of antibiotic resistant microorganisms. Thus, data were retrospectively collected in order to test and validate a shared and standardized system of indicators, useful for tracking and monitoring AMR in Sicily. Methods are previously described (23). Briefly, all public and private healthcare facilities were requested to provide antibiotic consumption and antibiotic resistance data for the years 2015, 2016, 2017 and 2018 through an online regional surveillance and participation was on a voluntary basis (23). Data on antibiotic use were obtained retrospectively from the pharmacies of the participating healthcare facilities and expressed, for each relevant antibiotic agent and class, as defined daily dose (DDD) - the average maintenance dose per day for a drug used for its main indication in adults. Resistance data on isolates from blood and cerebrospinal fluid (not repeated within 28 days), were retrospectively collected using routine clinical antimicrobial susceptibility data provided by microbiological laboratories of participating hospitals. The isolates were classified as resistant to an antibiotic class when they showed non-susceptibility to at least one of the antibiotics belonging to a specific class. With respect to carbapenems, resistance was defined as a strain resistant to imipenem and/or meropenem. Resistance rates (RRs) were calculated as the number of carbapenem-resistant isolates divided by the total number of isolates of the same species tested, multiplied by 100.

Statistical analysis

Spearman's rank correlation coefficient (R) was used to investigate the relationship between annual antibiotic consumption and rate of carbapenem resistance in 2015, 2016, 2017 and 2018, collected by the regional surveillance system. Specifically, the relationship between the rate of carbapenem resistance and the consumption intensity of overall antibiotic, beta-lactam antibiotics and carbapenems were analyzed individually. Trends from 2015 to 2018 were evaluated by the Chi-Square test. Statistical test with $p < 0.05$ were considered to significant, and all analyses were conducted using SPSS software (IBM SPSS Statistics for Windows, version 25.0).

Results

Antibiotic consumption

During the four-year period under investigation, data on antibiotic consumption was respectively collected from 91 (in 2015), 92 (in 2016), 83 (in 2017), and 107 (in 2018) private and public healthcare facilities.

Antibiotic consumption for the ATC class J01 (i.e., antibacterial for systemic use), was 74.2 DDD per 100 patient-days in 2015, 100.7 DDD per 100 patient-days in 2016, 92.3 DDD per 100 patient-days in 2017 (23) and 71.7 DDD per 100 patient-days in 2018. In particular, antibiotic consumption for the ATC class J01DH (i.e., carbapenems), was 5 DDD per 100 patient-days in 2015, 7.8 DDD per 100 patient-days in 2016, 4.4 DDD per 100 patient-days in 2017 (23), and 3.6 DDD per 100 patient-days in 2018. Considering only the 62 healthcare facilities that provided data for all four years of surveillance, antibiotic consumption for the ATC class J01DH (i.e., carbapenems), was 4.7 DDD per 100 patient-days in 2015, 4.2 DDD per 100 patient-days in 2016, 3.5 DDD per 100 patient-days in 2017, and 4.7 DDD per 100 patient-days in 2018.

Resistance rates and correlation with carbapenem consumption

In the last edition of the surveillance (i.e. 2018), we found that the overall prevalence of carbapenem-resistant strains was 81.8% for *A. baumannii*, 44.4% for *K. pneumoniae*, 44.3% for *P. aeruginosa* and 8.2% for *E. coli*. Next, we considered data from 62 healthcare facilities participating in all four years of surveillance to test trends of resistance rates. Notably, we noted that the proportion of carbapenem-resistant strains greatly varied across years and microorganisms (Table 1). Specifically, prevalence of carbapenem-resistant *E. coli* (CREC), decreased from 2015 to 2017, followed by a peak in 2018 ($p<0.001$). Prevalence of carbapenem-resistant *P. aeruginosa* (CRPA) decreased from 2015 to 2016 and then increased ($p=0.003$). Prevalence of carbapenem-resistant *A. baumannii* (CRAB) generally decreased from 2015 to 2018, with a peak in 2017 ($p<0.001$). No significant trend was demonstrated for carbapenem-resistant *K. pneumoniae* (CRKP). Similar results were obtained considering all the healthcare facilities independent of their year of participation, with slight differences across microorganisms (data not shown).

We also tested the correlations between antibiotic use – considering antibacterial for systemic use (J01), other beta-lactam antibacterials class (J01D), and specifically carbapenems (J01DH) – and rate of CREC, CRKP, CRPA and CRAB. Interestingly, we found several significant correlations, as summarized by the correlation matrix reported in Figure 1.

In 2015, a total of 91 hospitals were studied to determine the relationship between carbapenem consumption intensity and CRKP. The overall prevalence of CRKP isolates was 43.9%, and was significantly positively correlated with beta-lactam consumption (R=0.529, p<0.01), and with carbapenem consumption (R=0.364, p<0.05).

		K. pneumoniae	E. coli	P. aeruginosa	A. baumannii
2015	J01	0.21	**0.40**	0.09	0.02
	J01D	**0.53**	0.21	0.16	0.29
	J01DH	**0.36**	0.19	0.21	0.12
2016	J01	0.13	0.14	-0.31	-0.19
	J01D	0.03	0.13	0.12	-0.36
	J01DH	**0.36**	0.00	0.03	-0.27
2017	J01	-0.03	0.01	-0.02	0.07
	J01D	0.00	-0.18	0.15	-0.02
	J01DH	**0.43**	-0.02	-0.08	0.09
2018	J01	0.24	-0.05	-0.21	-0.06
	J01D	0.16	-0.23	0.06	0.21
	J01DH	0.21	-0.11	0.06	-0.06

Figure 1 - Correlation between antibiotic consumption intensity and antimicrobial resistant gram-negative bacteria during the four- year period (2015-2018)
Results are reported as Spearman's rank correlation coefficients and correlations with p<0.05 are indicated in bold font. Abbreviations: J01, antibacterial for systemic use; J01D, other beta-lactam antibacterials; J01DH, carbapenems.

In 2016, a total of 92 hospitals were studied to determine the relationship between carbapenem consumption intensity and CRKP. The overall prevalence of CRKP isolates was 53.8%, and was significantly positively correlated with carbapenem antibiotic consumption (R=0.364, p<0.05).

In 2017, a total of 83 hospitals were studied to determine the relationship between carbapenem consumption intensity and CRKP. The overall prevalence of CRKP isolates was 58.7%, and was significantly positively correlated with carbapenem antibiotic consumption (R=0.427, p<0.05).

In 2015, the overall prevalence of CREC isolates was 6.5 %, and was significantly positively correlated with antibiotic consumption for the ATC class J01 (i.e., antibacterial for systemic use) (r=0.402, p<0.05), as exhibited in Figure 1.

Discussion and Conclusions

The onset and the rapid spread of MDR bacteria in hospitals is a global health challenge (27, 28). The reason for this problem is multifactorial and the inappropriate use of antibiotics accelerates the emergence and spread of resistance (29). Increasing resistance may drive the increased consumption of several so-called "last-line" antibiotics, such as carbapenem consumption. It happens mainly among gram-negative bacteria such as *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*, which cause the life-threatening HAIs among critically ill and immunocompromised individuals (21). The World Health Organization considers these microorganisms as critical-priority bacteria, as they increase clinical and economic burden (30). In fact, it was demonstrated that patients with CRKP, CRPA, and CRAB infections were associated with longer hospital stay, higher mortality, and higher hospital costs compared with carbapenem susceptible cases (31-34). An appropriate use of carbapenem would result in cost savings and could be to reduce the development and spread of carbapenem resistance in hospital settings (35).

European Antimicrobial Resistance Surveillance Network (EARS-Net) data show wide variations depending on bacterial species, antimicrobial group, and geographical region with generally higher resistance prevalence reported from the southern and eastern parts of Europe than from Northern Europe. Different countries showed carbapenem resistance prevalence above 10% for *K. pneumoniae* and higher prevalence in *P. aeruginosa*, while carbapenem resistance remained a rare event for *E. coli* (36).

In our study, considering only hospitals that provided data for the entire study period, trends of carbapenem-resistant strains greatly varied across microorganisms and years. Particularly, prevalence of CREC decreased significantly from 2015 to 2017 followed by a peak in 2018. Prevalence of CRPA decreased significantly from 2015 to 2016 and then increased. Prevalence of CRAB significantly decreased from 2015 to 2018, with a peak in 2017. In any case, resistance rates of *A. baumannii* were very high for all the years included in the survey. We also tested, for the first time, the correlations between carbapenem-resistant gram-negative bacteria and antibiotic consumption in Sicily using data reported by voluntarily participating hospitals. Interestingly, carbapenem resistance moderately correlated with antibiotic use: specifically, resistance of *K. pneumoniae* correlated with the use of beta-lactam antibacterials and carbapenems while resistance of *E. coli* correlated with the use of antibacterial for systemic use in general. These results were consistent with those reported by previous studies in other countries (37-39). However, further research is needed to estimate the actual weight of the use of beta-lactam antibacterials and carbapenems on the growing impact of carbapenem-resistant bacteria. Surveillance of antibiotic consumption, in particular of carbapenems, can enable to find targets for interventions and improve antimicrobial usage patterns (28, 40). Furthermore, since these bacteria are often involved in outbreaks, the prompt identification of clusters, using molecular epidemiological typing methods are needed for effective control of antibiotic resistant bacteria (41, 42). Effective control of carbapenem resistance in *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* can improve clinical outcomes and reduce economic cost. Thus, results of the present study highlight the need for comprehensive strategies targeting the appropriate use of antibiotics and infection control measures.

One of the strengths of this study is that it was conducted in the framework of a regional surveillance system implemented in Sicily, which describes trends of antibiotic consumption and antibiotic resistance and help to identify targets for effective strategies against AMR. Despite its significant findings, one limitation of this study is the ecological study design that cannot fully prove a causative relationship between antibiotic consumption and resistance. Actually, other factors, including infection control practices and antimicrobial stewardship interventions implemented in participating hospitals, and the occurrence of outbreaks due to multidrug-resistant organism, should be considered to explain this complex issue in further research on this topic.

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Riassunto

Consumo di carbapenemi e prevalenza di batteri Gram-negativi resistenti ai carbapenemi: risultati del sistema di sorveglianza siciliano

Premessa. Negli ultimi decenni, vi è stato un aumento nella frequenza di batteri gram-negativi multiresistenti associati a infezioni correlate all'assistenza. Nel trattamento delle infezioni causate da batteri gram-negativi multiresistenti, i carbapenemi vengono generalmente somministrati come farmaci di ultima scelta. Tuttavia, negli ultimi anni il tasso di batteri resistenti ai carbapenemi è in costante aumento. Lo scopo del presente studio è descrivere la relazione tra il tasso di batteri gram-negativi resistenti ai carbapenemi e il consumo di antibiotici.

Disegno dello studio. La Regione Sicilia, nel 2017, ha implementato un sistema di sorveglianza regionale per descrivere e analizzare il consumo di antibiotici in ambito ospedaliero e la prevalenza di microrganismi resistenti agli antibiotici.

Metodi. I dati sulla resistenza sono stati raccolti retrospettivamente utilizzando dati clinici di *routine* sulla suscettibilità antimicrobica. Nel presente studio sono stati calcolati i tassi di resistenza ai carbapenemi ed è stata eseguita l'analisi di correlazione di Spearman per analizzare la relazione tra il consumo annuale di antibiotici e il tasso di resistenza ai carbapenemi.

Risultati. Nel 2015, la prevalenza complessiva di isolati di *Klebsiella pneumoniae* resistenti ai carbapenemi era del 43,9% ed era positivamente correlata con il consumo di antibiotici beta-lattamici (R= 0,529, p <0,01) e con il consumo di carbapenemi (R= 0,364, p <0,05). Nel 2016, la prevalenza complessiva di isolati di *Klebsiella pneumoniae* resistenti ai carbapenemi era del 53,8% ed era positivamente correlata al consumo di antibiotici carbapenemi (R= 0,364, p <0,05). Nel 2017, la prevalenza complessiva di isolati di *Klebsiella pneumoniae* resistenti ai carbapenemi era del 58,7% ed era positivamente correlata con il consumo di antibiotici carbapenemi (R= 0,427, p <0,05). Nel 2015, la prevalenza complessiva di isolati di *Escherichia coli* resistenti ai carbapenemi era del 6,5% ed era positivamente correlata con il consumo di antibatterici per uso sistemico (classe ATC J01) (R= 0,402, p <0,05).

Conclusione. I risultati del presente studio evidenziano la necessità di strategie globali mirate all'uso appropriato di antibiotici e misure di controllo delle infezioni.

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