Risk factors correlated with antibiotic-induced carbapenem resistant in Gram-negative bacilli in China: a retrospective cohort study

Jing Chen
Sichuan Academy of Medical Sciences and Sichuan People's Hospital
Qian Xiang
Sichuan Academy of Medical Sciences and Sichuan Province People's Hospital
Jia-yu Wu
Sichuan Academy of Medical Science and Sichuan People's Hospital
Min-hong Cai
Sichuan Province People's Hospital
Chen Wang
Sichuan People's Hospital
Dao-qiong Wei
Sichuan Province People's Hosital
Hui Wang
Schuan Province People's Hospital
Yu Lv (29381636@qq.com)
https://orcid.org/0000-0002-8069-4801

Research

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Abstract

Background: Increasing resistance to carbapenem, particularly common in Gram-negative bacilli (GNB), has become a growing public health concern around the world. The objective of this study was to investigate risk factors associated with antibiotic-induced carbapenem resistant in Gram-negative bacilli (CR-GNB) among inpatients. Methods: A retrospective cohort study was conducted in one of the largest tertiary A-level hospitals including patients with GNB cultured from any of the clinical specimens who had been admitted for more than 2 calendar days from January 2017 to June 2019. Kaplan-Meier analysis and Cox proportional hazard model were used to estimate the hazard of CR-GNB induction by antibiotics. Results: 2490 patients including 7 cohorts were included. After cox proportional risk model analysis, carbapenems, β-lactamase inhibitors, and cephalosporins had significantly higher hazards than other types of antimicrobial (P<0.001). But even without using any antimicrobials, the hazard would increase with the length of hospital stay. On multivariate analysis, carbapenem was the most principal hazard factor for antibiotic-induced CR-GNB (hazard ratio [HR], 2.968; 95% confidence interval [CI], 1.706–5.162), followed by ICU admission (HR, 1.815; 95% CI, 1.507–2.186), cephalosporin (HR, 1.605; 95% CI, 1.288–1.999), tracheotomy (HR, 1.563; 95% CI, 1.251–1.952) and β-lactamase inhibitor (HR, 1.542; 95% CI, 1.237–1.921). However, quinolone effects on antibiotic-induced CR-GNB were not statistically significant. Conclusions: Prior carbapenem was a strong risk factor for antibiotic-induced CR-GNB, but quinolone was not associated with that. Rational use of carbapenems should be implemented and antimicrobial stewardship policies should be adjusted according to the characteristics of each hospital.

Background

Over recent years, antibiotic resistance has become an increasingly serious threat to public health. Multidrug resistance is especially common in Gram-negative bacilli (GNB), and the mortality, morbidity and cost burden are higher when infected with multidrug-resistant GNB [1-4].

Carbapenem is an atypical β - lactam antibiotic with wide antibacterial spectrum and strong antibacterial activity which is often used as a last resort in the treatment of drug-resistant GNB infection [5]. However, the incidence of carbapenem-resistant bacteria has constantly increased over past years, posing a challenge for clinical antimicrobial chemotherapy and hospital infection control [6, 7].

In China, the four major Gram-negative bacterial species were *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* according to CHINET surveillance in 2018 [8]. The resistance rate of *E. coli*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* fluctuated around 2.0%-2.1%, 25%-26.3%, 77.1%-78.1% and 25.8%-30.7%, respectively [8]. Previous studies had reported that carbapenem resistance may increase the mortality in patients with GNB infection [9-11].

Rational use of antibiotics can effectively treat bacterial infections and reduce the burden to patients. But unreasonable use of antibiotics will increase the selective pressure of antimicrobials commonly used, which is one of the important factors leading to antimicrobial resistance (AMR), and some evidence showed that increased use of antibiotics could lead to the emergence of AMR [11-17]. However, most

related studies reported the significant relationship between carbapenem consumption and carbapenem-resistant gram-negative bacilli (CR-GNB), and whether the use of other antibiotics contributes to CR-GNB is not yet certain. In addition, most of previous studies have focused on a certain type of CR-GNB, such as carbapenem-resistant P. aeruginosa (CRPA), while research on the whole CR-GNB is relatively insufficient. Accordingly, we conducted this study to assess the risk factors for isolation of antibiotic-induced CR-GNB in a large cohort.

Materials And Methods

Design and subjects

A retrospective cohort study was performed in one of the largest tertiary A-level hospitals in Sichuan Province, China from January 2017 through June 2019. The cohort study included all patients with gram negative bacilli (GNB) cultured from any of the clinical specimens who had been admitted for more than 2 calendar days. This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. The Review Board exempted requirement for informed consent because of the retrospective study and absence negative impact on the patients.

Cohorts

This study included 7 cohorts, including cohort-Carbapenems, cohort-β-lactamase inhibitor, cohort-Antifungal, cohort-Quinolones, cohort-Penicillins, cohort-Cephalosporins and cohort-Unused.

Cohort-Carbapenems: All patients with clinical samples positive for GNB who have only used carbapenem antibiotics before GNB was isolated.

Cohort-β-lactamase inhibitor: All patients with clinical samples positive for GNB who have only used β-lactamase inhibitor antibiotics before GNB was isolated.

Cohort-Antifungal: All patients with clinical samples positive for GNB who have only used antifungals before GNB was isolated.

Cohort-Quinolone: All patients with clinical samples positive for GNB who have only used quinolone antibiotics before GNB was isolated.

Cohort-Penicillin: All patients with clinical samples positive for GNB who have only used penicillins antibiotic before GNB was isolated.

Cohort-Cephalosporin: All patients with clinical samples positive for GNB who have only used cephalosporin antibiotics before GNB was isolated.

Cohort-Unused: All patients with clinical samples positive for GNB who have not used any antibiotic before GNB was isolated.

Outcomes and definition

Antibiotic-induced CR-GNB was the primary outcome of this study.

Carbapenem resistant Gram-Negative Bacilli (CR-GNB): Carbapenem-resistance in GNB was defined as being non susceptible to imipenem, meropenem, ertapenem or doripenem. Species identification and in vitro susceptibility to imipenem, meropenem, ertapenem and doripenem were determined using Vitek-2 (BioMerieux, France) following the breakpoints defined by the Clinical Laboratory Standards Institute [18].

Antibiotic-induced CR-GNB: CR-GNB isolated after 2 calendar days of antimicrobial use.

Confounding factors

Potential confounders were selected based on previous literature [19-21], and included age, gender, principal diagnosis, tumor, liver failure, kidney failure, heart failure, respiratory failure, diabetes, hypertension, chronic obstructive pulmonary disease, hemodialysis, venous catheterization, mechanical ventilation, urinary catheterization, tracheotomy, surgery, ICU admission during current or previous episodes.

Statistical analysis

Statistical analysis of the data was performed using STATA 12.0. Data were summarized using the mean and standard deviation (SD) for normally distributed variables. Categorical variables were expressed in absolute numbers and percentages.

We used both univariate and multivariate methods to analyze the data. Binary outcomes were tested using the $\chi 2$ test, and continuous data were compared using the T-test. Kaplan-Meier analysis and Cox proportional hazard model were used to estimate the hazard of CR-GNB induction by antibiotics. *P* values below 0.05 were considered significant.

Results

Patient inclusion

From January 1, 2017 to June 30, 2019, a total of 8748 inpatients with GNB isolated from any of the clinical specimens who were admitted, including 2587 patients with CRO isolated and 5417 patients with CSO isolated. After screening, 2490 patients including 7 cohorts were included in the final data set, as Fig. 1 shows.

Factors associated with antibiotic-induced CR-GNB in univariate analysis

Differences in antibiotic-induced CR-GNB effects between the 7 cohorts of antimicrobial drugs were statistically significant (, $P < 0.001$). In addition to antibacterial drugs, the effects of other factors on antibiotic-induced CR-GNB were also statistically significant, including gender, principal diagnosis, chronic

obstructive pulmonary disease, venous catheterization, mechanical ventilation, urinary catheterization, tracheotomy, blood transfusion or use of blood products, surgery, kidney failure, respiratory failure, ICU admission now or in the past and community infections. Table 1 shows these details.

Kaplan-Meier analysis

Comparison of 7 cohorts showed that carbapenem, β-lactamase inhibitor, and cephalosporin had significantly higher hazards than any other type of antimicrobials. Even without the use of any antimicrobials, the hazard would increase with the length of hospital stay. Figure 2 shows these details. Log-rank test results showed that the differences were statistically significant (chi-square = 76.190, $P < 0.001$).

Multivariate analysis

The results of the COX proportional hazard model showed that carbapenem use was the principal hazard factor for antibiotic-induced CR-GNB (hazard ratio, 2.968; 95% confidence interval, 1.706–5.162), followed by ICU admission now or in the past (hazard ratio, 1.815; 95% confidence interval, 1.507–2.186), cephalosporin (hazard ratio, 1.605; 95% confidence interval, 1.288–1.999), tracheotomy (hazard ratio, 1.563; 95% confidence interval, 1.251–1.952) and β-lactamase inhibitor (hazard ratio, 1.542; 95% confidence interval, 1.237–1.921). In addition, the hazard factors affecting antibiotic-induced CR-GNB included kidney failure, blood transfusion or use of blood products, gender, chronic obstructive pneumonia and principal diagnosis. But antifungal, quinolone, and penicillin effects on antibiotic-induced CR-GNB were not statistically significant. The details are shown in Table 2.

Discussion

Carbapenems are the most effective drugs for the treatment of severe infections with gram-negative bacteria due to their broad antimicrobial spectrum and high stability for hydrolysis by most β-lactamases, including extended-spectrum β-lactamases (ESBLs) and AmpC cephalosporinases [22]. But unreasonable use of antibiotics leads to the emergence of CR-GNB, which is becoming more and more serious, and the treatment of some drug-resistant infections is extremely limited [8, 23, 24]. Therefore, understanding the hazard factors for antibiotic-induced CR-GNB is very important in the early selection of empirical antibiotic program. We demonstrated that previous carbapenem exposure was the major risk factor for antibiotic-induced CR-GNB in our study population.

During the period, cephalosporins were the most commonly used antibiotics, followed by β-lactamase inhibitors and penicillins. Unlike this, physicians in Europe preferred to prescribe more penicillins than cephalosporins [25]. The difference might be explained by that most antibiotics were used for inpatient treatment in China while outpatient institutions accounted for the majority of antibiotic consumption in foreign countries [26-28]. The clinical application of carbapenem, as a special class antibiotic, is limited and requires pre-authorization during the using period in our country.

In this study, carbapenem, β-lactamase inhibitor, and cephalosporin had significantly higher hazards than other types of antimicrobials. Our finding that carbapenem use was the most principal hazard factor associated with antibiotic-induced CR-GNB was in accordance with some previous studies [5, 29-35]. The use of carbapenem may promote the production of carbapenemase, such as *K pneumoniae* carbapenemase and metallo-β-lactamases, which could increase *carbapenem-resistant Escherichia coli* (CRE) [36]. Other mechanisms of carbapenem resistance include outer membrane porin expression loss combined with extended-spectrum β-lactamase (ESBL) and AmpC enzyme, change of antimicrobial target and high expression of efflux pump [37-39]. This suggested that controlling the use of carbapenems could slow down the production of CR-GNB. However, unlike some studies, we did not find that previous use of quinolones was significantly correlated with antibiotic-induced CR-GNB [29, 34, 35, 40-45]. It was speculated that quinolones might induce the high expression of efflux pump and lead to the multidrug-resistant phenotype, probably CR-GNB [46-48]. The reason for this difference might be that our design or study population was different from previous studies. Another large-scale research in China showed that fluoroquinolone consumption was not associated with CR-GNB [5]. In one way, this may be a feature of our country, and could provide basis for our choice of anti-infective therapy. Although using antibiotic was an important risk factor for drug resistance, even without the use of any antimicrobials the hazard would increase with the length of hospital stay after cox model analysis. The result might be explained by that these patients with longer hospital stay had prolonged exposure to invasive devices or use of antibiotics.

ICU stay and tracheotomy were also important hazard factors associated with antibiotic-induced CR-GNB. ICU is considered as the main source of development of multidrug-resistant bacteria and transmission due to the extremely critically ill patients, the use of invasive devices and higher intensity of selection pressure by broad-spectrum antibiotics. When patients receive tracheotomy and ventilation, the normal upper respiratory barrier will be destroyed and the pipe will be gradually polluted by bacteria which will increase chance of bacterial invasion. Our results showed that the risk of antibiotic-induced CR-GNB isolation was 1.563 times higher in patients receiving tracheotomy than in patients without tracheotomy. This indicated that some preventive and control measures related to the use of tracheotomy, such as understanding the indication of tracheotomy, operation procedure and hand hygiene, could effectively reduce the CR-GNB in our hospital.

In our hospital, infection control measures against resistant bacteria are relatively comprehensive, including training for prevention and control methods for bacteria, active surveillance of the most common multidrug resistant bacteria (MDRO), computer system alerts for MDRO species, active screening for high risk inpatients, supervision of adherence to precaution measures and so on, to reduce the spread of MDROs in hospital.

There are several potential limitations in our study. Firstly, this study was a retrospective design conducted in a large tertiary A-level hospital, not a multicenter research. Secondly, we did not take into account the dose of the antibiotic and antibiotic combinations. Thirdly, the generation of CR-GNB could be varied by the practice of infection control and other risk factors, but we did not take the former into

account. Despite these limitations, we believe that the main advantage of our research is its large cohort. Therefore, our research can at least provide reference value for the use of antibacterial drugs.

Conclusion

In conclusion, the use of carbapenem was strongly associated with antibiotic-induced CR-GNB in our study. Other antibiotics including cephalosporin and β-lactamase inhibitor were also related with CR-GNB. However, we did not find significant correlation between quinolones and antibiotic-induced CR-GNB. The findings will be useful for directing antimicrobial stewardship policies. Rational use of antibiotics and infection control measures are urgently needed to reduce the selective pressure of antibiotics, delay the occurrence of CR-GNB and control its cross transmission.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. The Review Board exempted requirement for informed consent because of the retrospective study and no any negative impact on the patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

YL and JW designed the study. MC, HW, DW and CW collected the data. YL and QX performed the data analysis. JC and YL wrote the manuscript. All authors have read and critically revised the manuscript.

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Tables

Table 1. Baseline characteristics

Variables	CSO (n=1838)	CRO (n=652)	Statistics	*P*
Antibacterial drugs			80.051	0.000
Unused	998(54.30%)	257(39.42%)		
Carbapenem	8(0.44%)	14(2.15%)		
β-lactamase inhibitor	216(11.75%)	144(22.09%)		
Antifungal	34(1.85%)	14(2.15%)		
Quinolone	74(4.03%)	26(3.99%)		
Penicillin	188(10.23%)	54(8.28%)		
Cephalosporin	320(17.41%)	143(21.93%)		
Gender	1061(57.73%)	480(73.62%)	51.544	0.000
Urinary cannula	717(39.01%)	331(50.77%)	27.294	0.000
Vascular cannula	303(16.49%)	176(26.99%)	34.208	0.000
Mechanical Ventilation	230(12.51%)	189(28.99%)	93.326	0.000
Tracheotomy	114(6.20%)	112(17.18%)	70.252	0.000
ICU admission now or in the past	388(21.11%)	253(38.80%)	78.820	0.000
Hemodialysis	5(0.27%)	6(0.92%)	3.242	0.072
Blood transfusion or use of blood products	382(20.78%)	235(36.04%)	60.124	0.000
Hypertension	873(47.50%)	333(51.07%)	2.465	0.116
Diabetes	454(24.70%)	157(24.08%)	0.100	0.752
Chronic obstructive pneumonia	203(11.04%)	111(17.02%)	15.617	0.000
Tumor	269(14.64%)	84(12.88%)	1.214	0.270
Liver failure	12(0.65%)	9(1.38%)	3.046	0.081
Kidney failure	138(7.51%)	77(11.81%)	11.289	0.001

Heart failure	142(7.73%)	48(7.36%)	0.090	0.764
Respiratory failure	127(6.91%)	118(18.10%)	67.913	0.000
Surgery	1071(58.27%)	455(69.79%)	26.898	0.000
Community infections	327(17.79%)	147(22.55%)	7.060	0.008
Principal diagnosis(ICU-10 code)			105.165	0.000
Certain infectious diseases and parasites(A00-B99)	52(2.83%)	20(3.07%)		
Tumor(C00-D48)	202(10.99%)	60(9.20%)		
Blood and hematopoietic diseases and certain diseases involving immune mechanisms(D50-D89)	4(0.22%)	4(0.61%)		
Endocrine, nutritional and metabolic diseases(E00-E90)	56(3.05%)	4(0.61%)		
Mental and behavioral disorders(F00-F99)	63(3.43%)	15(2.30%)		
Nervous system diseases(G00-G99)	149(8.11%)	71(10.89%)		
Eye and appendage diseases(H00-H59)	2(0.11%)	0(0.00%)		
Ear and mastoid diseases(H60-H95)	3(0.16%)	2(0.31%)		
Circulatory diseases(I00-I99)	434(23.61%)	171(26.23%)		
Respiratory diseases(J00-J99)	270(14.69%)	152(23.47%)		
Digestive diseases(K00-K93)	101(5.5%)	19(2.91%)		
Skin and subcutaneous tissue diseases(L00-L99)	38(2.07%)	9(1.38%)		
Musculoskeletal system and connective tissue diseases(M00-M99)	76(4.13%)	6(0.92%)		
Genitourinary diseases(N00-N99)	153(8.32%)	28(4.29%)		
Pregnancy, childbirth and puerperium(O00-O99)	12(0.65%)	0(0.00%)		
Diseases that originated in the perinatal period(P00-P96)	5(0.27%)	12(1.84%)		
Congenital malformations, deformation and chromosomal abnormalities(Q00-Q99)	9(0.49%)	3(0.46%)		
Abnormal symptoms, signs, clinical and laboratory results, and cannot be classified in other categories (R00-R99)	15(0.82%)	6(0.92%)		

Injury, poisoning and other external pathogenic factors (S00-T98)	148(8.05%)	60(9.20%)		
External causes of illness and death(V01-V98)	46(2.50%)	9(1.38%)		
AGE(M±SD)	68.27±20.53	69.65±20.98	-1.473	0.141

Table 2. Equation parameters of Cox proportional hazard model

Covariate	HR	95% *CI.*	
		Lower	Upper
Antibacterial drugs			
Carbapenem	2.968	1.706	5.162
β-lactamase inhibitor	1.542	1.237	1.921
Antifungal	1.107	.627	1.956
Quinolone	1.300	.865	1.953
Penicillin	1.139	.842	1.541
Cephalosporin	1.605	1.288	1.999
Kidney failure	1.360	1.059	1.746
ICU admission now or in the past	1.815	1.507	2.186
Blood transfusion or use of blood products	1.288	1.078	1.539
Tracheotomy	1.563	1.251	1.952
Gender	1.531	1.278	1.834
Chronic obstructive pneumonia	1.273	1.007	1.610
Principal diagnosis(ICU-10 code)			
Tumor(C00-D48)	.541	.321	.912
Blood and hematopoietic diseases and certain diseases involving immune mechanisms(D50-D89)	2.478	.827	7.428
Endocrine, nutritional and metabolic diseases(E00-E90)	.435	.147	1.284
Mental and behavioral disorders(F00-F99)	.703	.355	1.395
Nervous system diseases(G00-G99)	1.050	.628	1.757
Eye and appendage diseases(H00-H59)	/	/	/
Ear and mastoid diseases(H60-H95)	4.807	1.108	20.850
Circulatory diseases(I00-I99)	.793	.490	1.283

Respiratory diseases(J00-J99)	1.157	.713	1.878
Digestive diseases(K00-K93)	.508	.267	.967
Skin and subcutaneous tissue diseases(L00-L99)	.705	.317	1.568
Musculoskeletal system and connective tissue diseases(M00-M99)	.460	.183	1.156
Genitourinary diseases(N00-N99)	.691	.384	1.244
Pregnancy, childbirth and puerperium(O00-O99)	/	/	/
Diseases that originated in the perinatal period(P00-P96)	1.579	.749	3.329
Congenital malformations, deformation and chromosomal abnormalities(Q00-Q99)	.712	.210	2.417
Abnormal symptoms, signs, clinical and laboratory results, and cannot be classified in other categories (R00-R99)	1.576	.623	3.985
Injury, poisoning and other external pathogenic factors (S00-T98)	.638	.379	1.075
External causes of illness and death(V01-V98)	.559	.252	1.243

Figures

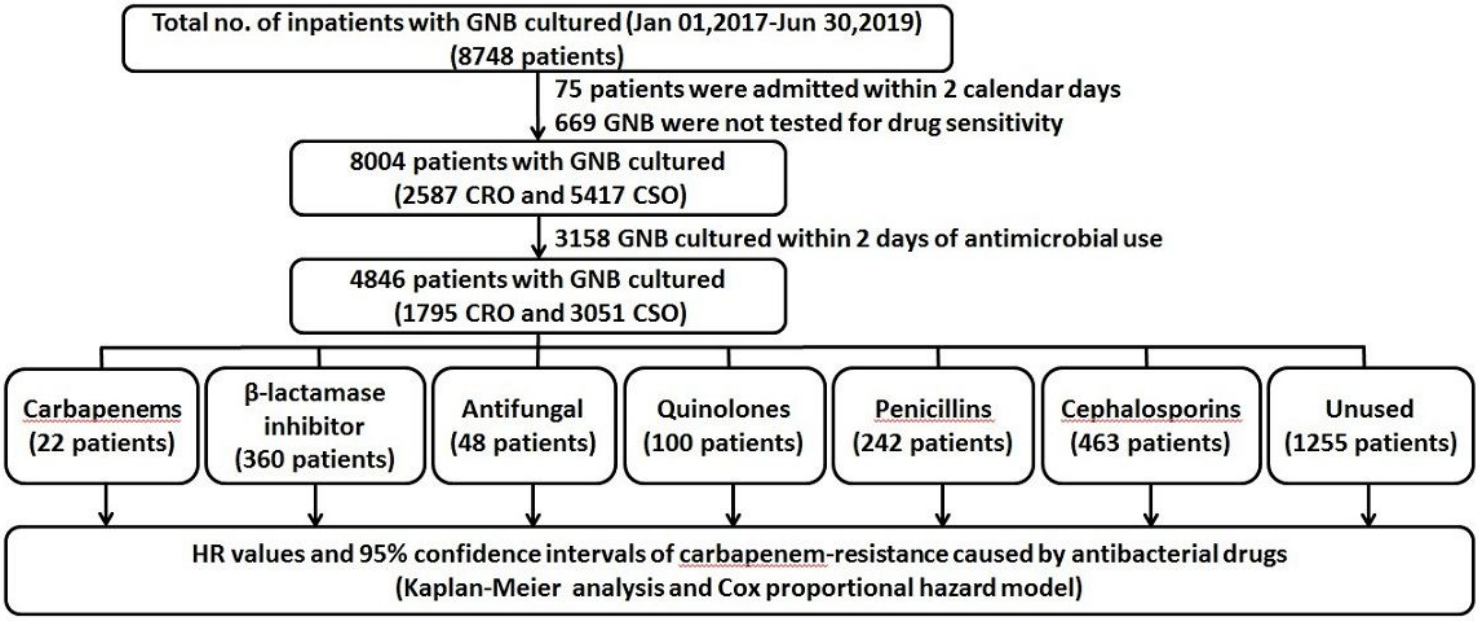

Figure 1

Flow chart of Patients inclusion

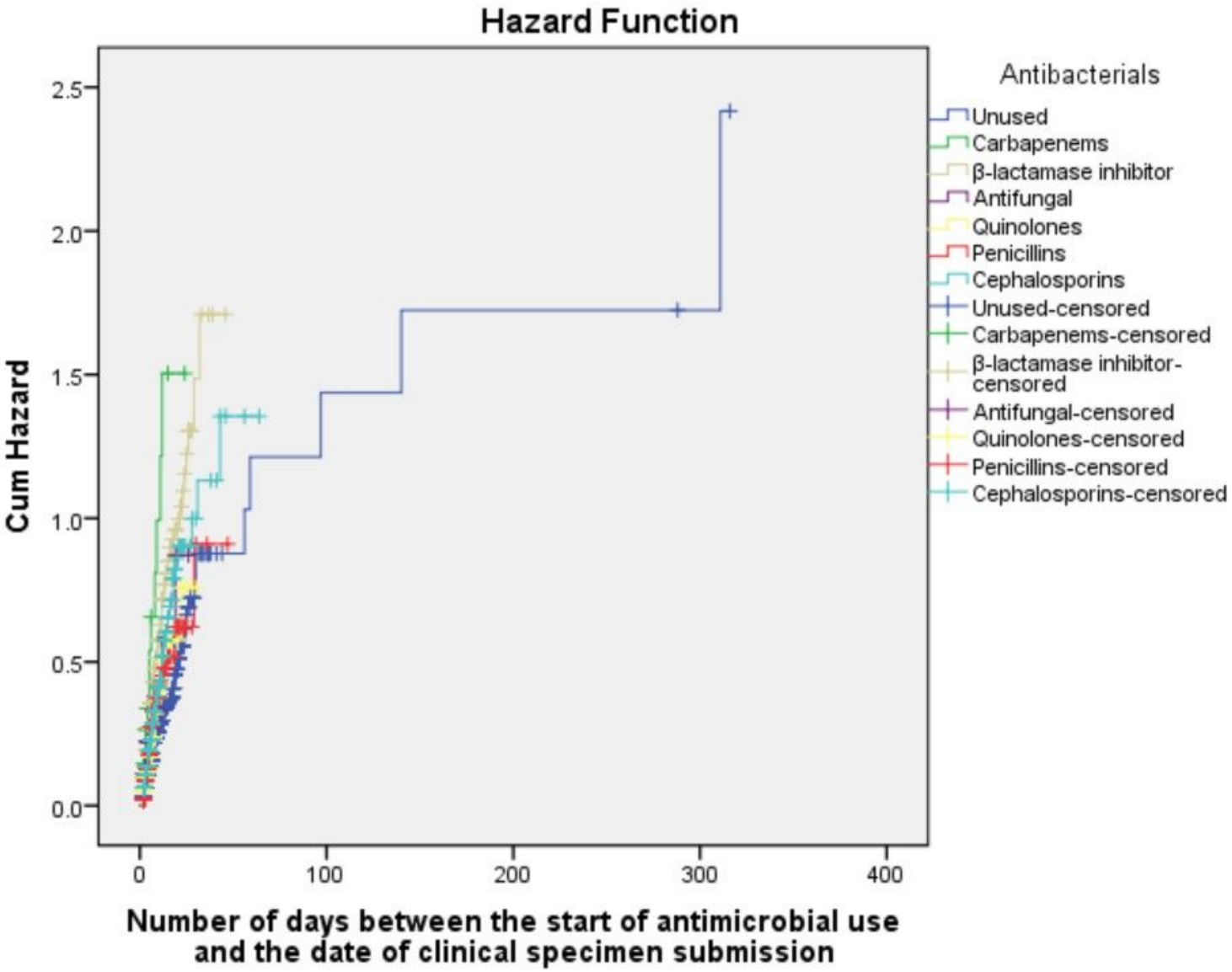

Figure 2

Results of Kaplan-Meier analysis