Different induction effects of antibiotic on Klebsiella pneumoniae and Escherichia coli: a retrospective study from China

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Research

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Abstract

Background: One of the main factors leading to Carbapenem-resistant Enterobacteriaceae (CRE) is antibiotics usage. The main objective of this study was to assess the correlation between antibiotic use and carbapenem-resistant Klebsiella pneumoniae (CRKP) and carbapenem-resistant Escherichia coli (CREC) induction by antibiotics.

Methods: A retrospective study was conducted including patients with Klebsiella pneumoniae (KP) and Escherichia coli (EC) from January 2017 to December 2020. Kaplan-Meier analysis and Cox proportional hazard model were used to estimate the hazard of CRE, while restricted cubic spline regression was used to visualize the hazard of CRE by antibiotics at different doses.

Results: 2056 patients with KP and 3243 patients with EC were included. Survival analysis indicated that carbapenem, lactamase inhibitors and quinolones were associated with higher 30-day CRKP hazards than other antibiotics (χ^2=33.670, P<0.001). Further restricted cubic spline regression analysis found that the hazard of CRKP induction decreased with the increase dose of lactamase inhibitors, but there was no significant change in that with the increase dose of quinolones. Moreover, there was an obvious characteristic of "parabolic curve" for the hazard of CREC induction due to lactamase inhibitors, and the hazard value gradually increased with the dose, reached the maximum at 24g, and then gradually decreased from 26g.

Conclusions: Lactamase inhibitors had different drug resistance inducing effects on CRKP and CREC. Rational use of antibiotics should be implemented according to the characteristics of microorganism.

Introduction

Over recent years, antimicrobial resistance among Enterobacteriaceae has become a serious public health problem in the world. Antimicrobial resistance greatly limits therapeutic options, resulting in higher morbidity, mortality and huge economic burden [1].

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 multidrug-resistant Gram-negative Enterobacteriaceae infection [2, 3]. However, the incidence of carbapenem-resistant Enterobacteriaceae (CRE) has constantly increased over past years, posing a challenge for clinical antimicrobial chemotherapy and hospital infection control [4–6]. In China, *Klebsiella pneumoniae* and *Escherichia coli* were the most common Enterobacteriaceae according to CHINET surveillance in 2018 which could cause nosocomial infections, such as pneumonia, urinary tract infection and catheter-related bloodstream infection [7]. Previous studies had reported that CRE was associated with high mortality [8–10].

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, 12]. Numerous studies reported the significant relationship between antimicrobial consumption and CRE prevalence, but whether antibiotics at different doses contributes to CRE was not yet certain. It was necessary to understand the risk factors of CRE and evaluate the correlation between antibiotic dose and CRE, to provide evidence for developing a plan to reduce selective pressure imposed by antimicrobial agents in the future. Accordingly, we conducted this study to assess the correlation between antibiotic use and isolation of carbapenem-resistant *Escherichia coli* (CREC) and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in a large cohort.

Materials And Methods

Design and subjects

A retrospective analysis was performed in Sichuan Academy of Medical Sciences and Sichuan People's Hospital, a 3270-bed teaching hospital in Western China for the period January 2017 to December 2020. This study population comprised all patients with KP or E. coli cultured from any of the clinical specimens. This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan People's Hospital. The Review Board exempted requirement for informed consent because of the retrospective study and absence negative impact on the patients.

Microbiology

Drug sensitivity test and result interpretation referred to the guideline of the Clinical and Laboratory Standards Institute (CLSI) 2017. The drug susceptibility test methods were the disc-diffusion synergy test and the MIC method. The automated instrument used VITEK 2 (BioMerieux, France) Compact automatic microbial identification and drug sensitivity analysis system. The disc-diffusion synergy test was the Kirby-Bauer method, and the source of the drug sensitive paper was purchased from BBL and Oxoid.

Outcomes and definition

CRKP and CREC were the primary outcome of this study. Carbapenem resistance is defined as an MIC of ≥ 2ug/mL for ertapenem or MIC of ≥ 4ug/mL for meropenem or imipenem or dolipenem, according to the guideline of CLSI 2017.

Confounding factors

Potential confounders were selected based on previous literature [13–15], 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 now or in the past and infection status before CRE detection.

Statistical analysis

Statistical analysis of the data was performed using STATA version 20.0 (StataCorp. College Station, Texas, USA) and SPSS version 23.0 (IBM Corporation, Armonk, NY). 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 CRE. Restricted cubic spline regression was used to visualize the hazard of CRE by antibiotics at different doses.

To assess the hazard of CRE induction by antibiotics, the data was gradually analyzed in 2 parts. First, in the COX proportional hazard model, we evaluated the CRE induction effect of various commonly used antibiotics on the basis of excluding other confounding factors, and we used the predictive survival probability diagram to test the Cox proportional hazard hypothesis. Second, in order to analyze the dose-response relationship between the antibiotics and the CRE induction effect, we fitted the curve of the specific antibiotics with the strongest CRE induction effect on the basis of excluding other confounding factors. P values below 0.05 were considered significant.

Data availability statement

All data generated and analyzed during this study are included in this article.

Results

Patient inclusion

From January 1, 2017 to December 31, 2020, a total of 6339 inpatients with Enterobacteriaceae cultured from any of the clinical specimens who had been admitted in the hospital, including 2056 patients with Klebsiella pneumoniae cultured and 3243 patients with Escherichia coli cultured, as Fig. 1 shows.

Clinical Characteristics

Among 2056 patients with Klebsiella pneumonia and 3243 patients with Escherichia coli, there were 308 (14.98%) CRKP and 183 (5.64%) CREC, respectively, whereas the remaining were cases with carbapenem-sensitivity Enterobacteriaceaes.

Univariate analysis (Table 1) showed the following factors to be associated with a higher risk of CRKP: gender, principal diagnosis, urinary cannula, vascular cannula, mechanical ventilation, tracheotomy, blood transfusion or use of blood products, respiratory failure, ICU admission now or in the past and infection status before CRE detection. Moreover, the following factors was showed to be associated with a higher risk of CREC: gender, principal diagnosis, urinary cannula, vascular cannula, mechanical ventilation, blood transfusion or use of blood products, respiratory failure, heart failure, ICU admission now or in the past and infection status before CRE detection.

Table 1
Base line characteristics

Variables	CSKP (n = 1748)	CRKP (n = 308)	Statistics	*P*	CS-E. coli (n = 3060)	CR-E. coli (n = 183)	Statistics	*P*
Gender	1142(65.33%)	232(75.32%)	11.796	0.001	1248(40.78%)	112(61.20%)	29.563	0.000
Urinary cannula	759(43.42%)	173(56.17%)	17.171	0.000	1084(35.42%)	92(50.27%)	16.471	0.000
Vascular cannula	550(31.46%)	122(39.61%)	7.897	0.005	717(23.43%)	78 (42.62%)	34.369	0.000
Mechanical ventilation	479(27.40%)	122(39.61%)	18.864	0.000	360(11.76%)	44 (24.04%)	23.873	0.000
Tracheotomy	157(8.98%)	44(14.3%)	8.352	0.004	79(2.58%)	8 (4.37%)	2.119*	0.145
ICU admission now or in the past	784(44.85%)	193(62.66%)	33.310	0.000	797(26.05%)	68(37.16%)	10.903	0.001
Hemodialysis*	15(0.86%)	2(0.65%)	0.001	0.975	10(0.33%)	1 (0.55%)	0.000	1.000
Blood transfusion or use of blood products	651(37.24%)	168(54.54%)	32.711	0.000	835(27.29%)	97(53.01%)	55.767	0.000
Hypertension	707(40.45%)	140(45.45%)	2.711	0.100	1101(35.98%)	75(40.98%)	1.870	0.171
Diabetes	484(27.69%)	86(27.92%)	0.007	0.933	806(26.34%)	48(26.23%)	0.001	0.974
Chronic obstructive pneumonia	192(10.98%)	36(11.69%)	0.132	0.717	173(5.65%)	14(7.65%)	1.267	0.260
Tumor	270(15.50%)	48(15.58%)	0.001	0.971	563(18.40%)	31(16.94%)	0.246	0.620
Liver failure	27(1.54%)	9(2.92%)	2.888	0.089	36(1.18%)	3(1.64%)	0.044*	0.835
Kidney failure	178(10.18%)	37(12.01%)	0.936	0.333	217(7.09%)	19(10.38%)	2.772	0.096
Heart failure	137(7.84%)	27(8.77%)	0.308	0.579	181(5.91%)	19(10.38%)	5.955	0.015
Respiratory failure	282(16.13%)	92(29.87%)	33.207	0.000	202(6.60%)	28(15.30%)	19.831	0.000
Surgery	1340(76.66%)	241(78.25%)	0.372	0.542	2195(71.73%)	137(74.86%)	0.838	0.360
infection status before CRE detection	451(25.80%)	104(33.77%)	8.430	0.004	679(22.19%)	52(28.42%)	3.833	0.050
Principal diagnosis(ICU-10 code)			68.783	0.000			38.511	0.005
Certain infectious diseases and parasites(A00-B99)	142(8.12%)	26(8.44%)			215(7.03%)	12(6.56%)		
Tumor(C00-D48)	206(10.99%)	30(9.74%)			442(14.44%)	38(20.77%)		
Blood and hematopoietic diseases and certain diseases involving immune mechanisms(D50-D89)	7(0.22%)	2(0.65%)			17(0.56%)	1(0.55%)		
Endocrine, nutritional and metabolic diseases(E00-E90)	45(2.57%)	1(0.32%)			122(3.99%)	6(3.28%)		

Variables	CSKP (n = 1748)	CRKP (n = 308)	Statistics	*P*	CS-E. coli (n = 3060)	CR-E. coli (n = 183)	Statistics	*P*
Mental and behavioral disorders(F00-F99)	31(1.77%)	7(2.77%)			84(2.75%)	4(2.19%)		
Nervous system diseases(G00-G99)	69(3.95%)	17(5.52%)			122(3.99%)	6(3.28%)		
Eye and appendage diseases (H00-H59)	0(0.00%)	0(0.00%)			3(0.10%)	0(0.00%)		
Ear and mastoid diseases (H60-H95)	0(0.00%)	0(0.00%)			2(0.07%)	0(0.00%)		
Circulatory diseases(I00-I99)	299(17.11%)	42(13.64%)			276(9.02%)	16(8.74%)		
Respiratory diseases(J00-J99)	367(21.00%)	94(30.52%)			246(8.04%)	26(14.21%)		
Digestive diseases(K00-K93)	199(11.38%)	23(7.47%)			316(10.33%)	20(10.93%)		
Skin and subcutaneous tissue diseases(L00-L99)	22(1.26%)	3(0.97%)			51(1.67%)	2(1.09%)		
Musculoskeletal system and connective tissue diseases(M00-M99)	28(1.60%)	1(0.32%)			103(3.37%)	7(3.83%)		
Genitourinary diseases(N00-N99)	128(7.32%)	19(6.17%)			661(21.60%)	26(14.21%)		
Pregnancy, childbirth and puerperium(O00-O99)	3(0.17%)	0(0.00%)			74(2.42%)	0(0.00%)		
Diseases that originated in the perinatal period(P00-P96)	16(0.92%)	17(5.52%)			56(1.83%)	0(0.00%)		
Congenital malformations, deformation and chromosomal abnormalities(Q00-Q99)	5(0.29%)	1(0.32%)			15(0.49%)	0(0.00%)		
Abnormal symptoms, signs, clinical and laboratory results, and cannot be classified in other categories (R00-R99)	15(0.86%)	0(0.00%)			21(0.69%)	0(0.00%)		
Injury, poisoning and other external pathogenic factors (S00-T98)	130(7.44%)	24(7.79%)			139(4.54%)	12(6.56%)		

Variables	CSKP (n = 1748)	CRKP (n = 308)	Statistics	*P*	CS-E. coli (n = 3060)	CR-E. coli (n = 183)	Statistics	*P*
External causes of illness and death(V01-V98)	36(2.06%)	1(0.32%)			95(3.10%)	7(3.83%)		
Age(M ± SD)	66.51 ± 24.67	64.67 ± 26.26	1.194	0.233	62.08 ± 22.75	63.62 ± 23.05	-0.887	0.375

Antimicrobial therapy before CRE were detected

The antimicrobial therapy before bacteria were detected in the patient's clinical specimens was shown in Table 2. There was significant difference in antibacterial therapy between CSKP group and CRKP group (χ^2 = 90.667, P < 0.001), and the proportion of combination antibacterial therapy in patients with CRKP was relatively high (181/308, 58.77%). Moreover, there was also significant difference in mono-therapy between these two groups (χ^2 = 38.851, P < 0.001). Among CSKP and CRKP patients, the proportion of patients using lactamase inhibitors was relatively high, (252/575, 43.83%) and (50/74, 67.57%), respectively.

Table 2
Basic situation of antimicrobial therapy

Variables	CSKP	CRKP	Statistics	*P*	CS-E. coli	CR-E. coli	Statistics	*P*
Antibacterial therapy			90.667	0.000			33.021	0.000
Monotherapy	575(32.89%)	74(24.03%)			718(23.46%)	38(20.77%)		
Combination therapy	545(31.18%)	181(58.77%)			693(22.65%)	75(40.98%)		
Unused	628(35.93%)	53(17.21%)			1649(53.88%)	70(38.25%)		
Monotherapy			38.851	0.000			26.824	0.000
Lactamase inhibitors	252(43.83%)	50(67.57%)			190(26.46%)	21(55.26%)		
Carbapenem	8(1.39%)	4(5.41%)			5(0.70%)	0(0.00%)		
1st -Cephalosporins	125(21.74%)	5(6.76%)			119(16.57%)	0(0.00%)		
2nd -Cephalosporins	40(6.96%)	2(2.70%)			93(12.95%)	4(10.53%)		
3rd -Cephalosporins	31(5.39%)	1(1.35%)			81(11.28%)	7(18.42%)		
Quinolone	40(6.96%)	10(13.51%)			176(24.51%)	5(13.16%)		
Penicillin	65(11.30%)	2(2.70%)			49(6.82%)	1(2.63%)		
Others	14(2.43%)	0(0.00%)			5(0.70%)	0(0.00%)		

There was significant difference in antibacterial therapy between CSEC group and CREC group (, P < 0.001), and the proportion of combination antibacterial therapy in patients with CREC was relatively high (75/183, 40.98%). Moreover, there was also significant difference in mono-therapy between these two groups (, P < 0.001), Among CSEC and CREC patients, the proportion of patients using lactamase inhibitors was relatively high, (190/718,26.46%) and (21/38, 55.26%), respectively.

30-day Hazard of CRE induction by antibiotics

The results of the predicted survival probability diagram indicate that the Cox proportional hazard hypothesis was valid (Supplementary Figure S1).

In the COX proportional hazard model (Table 3), CRKP patients showed association with antibacterial mono-therapy, gender (hazard ratio, 1.886; 95% confidence interval, 1.059–3.360), blood transfusion or use of blood products (hazard ratio, 1.535; 95% confidence

interval, 0.938–2.513) and ICU admission now or in the past (hazard ratio, 1.803; 95% confidence interval, 1.117–2.910). CREC patients showed only association with antibacterial mono-therapy.

Table 3
Equation parameters of Cox proportional hazard model

Covariate	KP		E. coli	
	HR	95% CI.	HR	95% CI.
Antibacterial Monotherapy (Control = Lactamase inhibitors)				
Carbapenem	3.252	1.159–9.124	0.995	/
1st -Cephalosporins	0.219	0.085–0.564	0.964	/
2nd -Cephalosporins	0.383	0.092–1.594	0.099	0.138–1.187
3rd -Cephalosporins	0.247	0.034–1.797	0.571	0.331–1.838
Quinolone	1.196	0.601–2.382	0.030	0.128–0.903
Penicillin	0.191	0.046–0.787	0.195	0.035–1.978
Others	0.000	/	0.991	/
Gender (Control = Female)	1.886	1.059–3.360		
Blood transfusion or use of blood products	1.535	0.938–2.513		
ICU admission now or in the past	1.803	1.117–2.910		

Survival analysis (Fig. 2) indicated that carbapenem, lactamase inhibitors and quinolones were associated with higher 30-day CRKP hazards than other antibiotics. Log-rank test results showed that the differences were statistically significant (, $P < 0.001$) (Fig. 2A). Moreover, the 30-day CREC hazards were significantly higher in patients with lactamase inhibitor and 3rd-cephalosporins than other antibiotics (, $P = 0.003$) (Fig. 2B).

Dose-response relationship between the hazard of CRE induction and antibiotics

In restricted cubic spline regression analysis (Fig. 3 and Fig. 4), the fitted curve showed that the hazard of CRKP induction decreased with the increase dose of lactamase inhibitors, but there was no significant change in the hazard ratio of CRKP induction with the increase dose of quinolones (Fig. 3).

Moreover, there was an obvious characteristic of "parabolic curve" for the hazard of CREC induction due to lactamase inhibitors, and the hazard value gradually increased with the dose, reached the maximum at 24g, and then gradually decreased from 26g. However, there was no significant change in the hazard ratio of CREC induction with the increase dose of 3rd-cephalosporins (Fig. 4).

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 [16]. But unreasonable use of antibiotics leads to the emergence of CRE, which is becoming more and more serious, and the treatment option is limited [7, 17, 18]. Therefore, understanding the hazard factors for antibiotic-induced CRE is very important in the early selection of empirical antibiotic program. In this study, we explored the relationship between the use of antibiotics and CRKP and CREC respectively. Compared with CSE, the risk factors of CRE in clinical samples were gender, principal diagnosis, urinary cannula, vascular cannula, mechanical ventilation, blood transfusion or use of blood products, respiratory failure, and ICU admission.

Previous studies comfirmed that antibiotic exposure was a risk factor for CRE infection [19, 20]. In our study, the first significant finding was that the difference in antibacterial therapy was significant between CSKP group and CRKP group, and the proportion of combined antibacterial therapy in CRKP group was higher. Increased exposure to one antibiotic increased the effect of exposure to

other antibiotics on the risk of CRKP infection [21]. Therefore, combined use of antibiotics would increase the selection pressure of antibiotics, allowing carbapenem-resistant bacteria to produce various carbapenem resistance mechanisms [22]. This result was consistent with that in CSEC group and CREC group. During the study, βlactamase inhibitors were the most commonly used antibiotics.

The second significant finding was that carbapenem, lactamase inhibitors and quinolones were associated with higher 30-day CRKP hazards than other antibiotics after survival analysis. Among the antibiotics, carbapenems the most principal hazard factor, which was consistent with previous studies [2, 23–29]. The use of carbapenem may promote the production of carbapenemase, such as *K pneumoniae* carbapenemase and metallo-β-lactamases, which could increase the production of CRE [30]. 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 [31–33]. The result suggested that restriction of carbapenems was associated with a significant reduction in the incidence of CRKP. However, for CREC, the 30-day hazards were significantly higher in patients with β-lactamase inhibitor and 3rd-cephalosporins than other antibiotics.

Last but not least, we found the hazard of CRKP induction decreased with the increase dose of lactamase inhibitors, but there was no significant change in the hazard ratio of CRKP induction with the increase dose of quinolones or carbapenems. The result indicated that the risk of CRKP was higher in low-dose lactamase inhibitor exposure. Therefore, we suggested that adequate dose of lactamase inhibitors should be used in the treatment of these patients. However, there was no relevant research, and further studies were necessary to explore the mechanism. We also found that increasing the use of carbapenem or quinolones did not lead to a significant increase in the resistance of carbapenem among Enterobacteriaceae which was similar to a few previous studies [34–36]. But some studies showed that carbapenem or fluoroquinolone use had a positive relationship with the incidence of CRE [35, 37]. The result was still controversial, which might be explained by the influence of multiple interactive factors that had an impact on induction of CRE. As a preceding result, hazard of CRKP induction decreased might be responsible for the increasing dose of β-lactamase inhibitors. Moreover, there was an obvious characteristic of "parabolic curve" for the hazard of CREC induction due to lactamase inhibitors, and the hazard value gradually increased with the dose, reached the maximum at 24g, and then gradually decreased from 26g. In other words, with the increasing use of lactamase inhibitors, the risk of CREC increased and reached the maximum when the dose of lactamase inhibitors reached 24g, but gradually decreased when the dose exceeded 26g. But no existing study reported this correlation. This result may explain why the incidence of CREC was low in CRE. Although antibiotic exposure may lead to all clinically significant antibiotic resistance, the effects are not consistent and vary with the organism and antibiotic resistance mechanism. Large sample studies were needed to further clarify the mechanism of the effect of β-lactamase inhibitor doses on CRE. In this study, lactamase inhibitors had different drug resistance inducing effects on CRKP and CREC, which suggested that the maximum dose should not be blindly pursued in clinical medication. We should choose the appropriate treatment plan according to the specific characteristics of microbial distribution, or adjust the antimicrobial treatment strategy in real time according to the characteristics of microbial distribution, which raised higher requirements for the rational use of antibiotics.

There were 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, Due to the low prevalence of CRE and the two types of CRE were analyzed according to the use of antibiotics, the sample size was not large enough. Thirdly, in our study, patients with CRKP were less likely to use carbapenems before detection of CRKP. So we found that there was no significant change in the hazard ratio of CRKP induction with the increase dose of carbapenems. But the effect of carbapenems on CRE was beyond all doubt. Fourthly, genotypic detection of drug resistance genes was not performed in the study. Therefore, multi-center studies with large sample size were necessary in the future to address these limitations to further confirm the relationship between CRE and antibiotic usage.

Conclusion

In conclusion, lactamase inhibitors had different drug resistance inducing effects on CRKP and CREC. The findings will be useful for identify specific antimicrobial agents as targets for interventions. Rational use of antibiotics and infection control measures are urgently needed to reduce the selective pressure of antibiotics, delay the occurrence of CRE 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: Not applicable.

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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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Figures

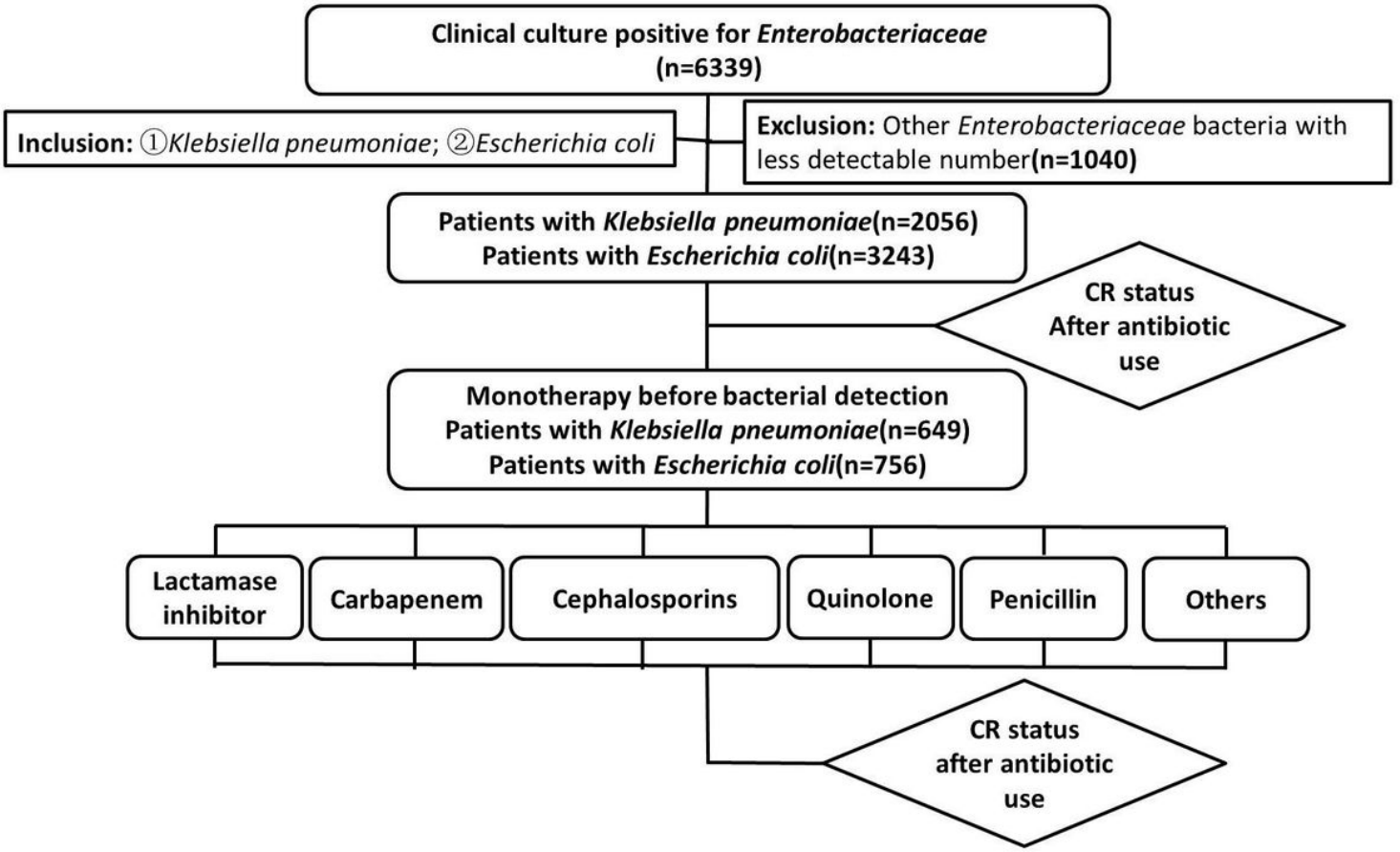

Figure 1

Flow chart of Patients inclusion

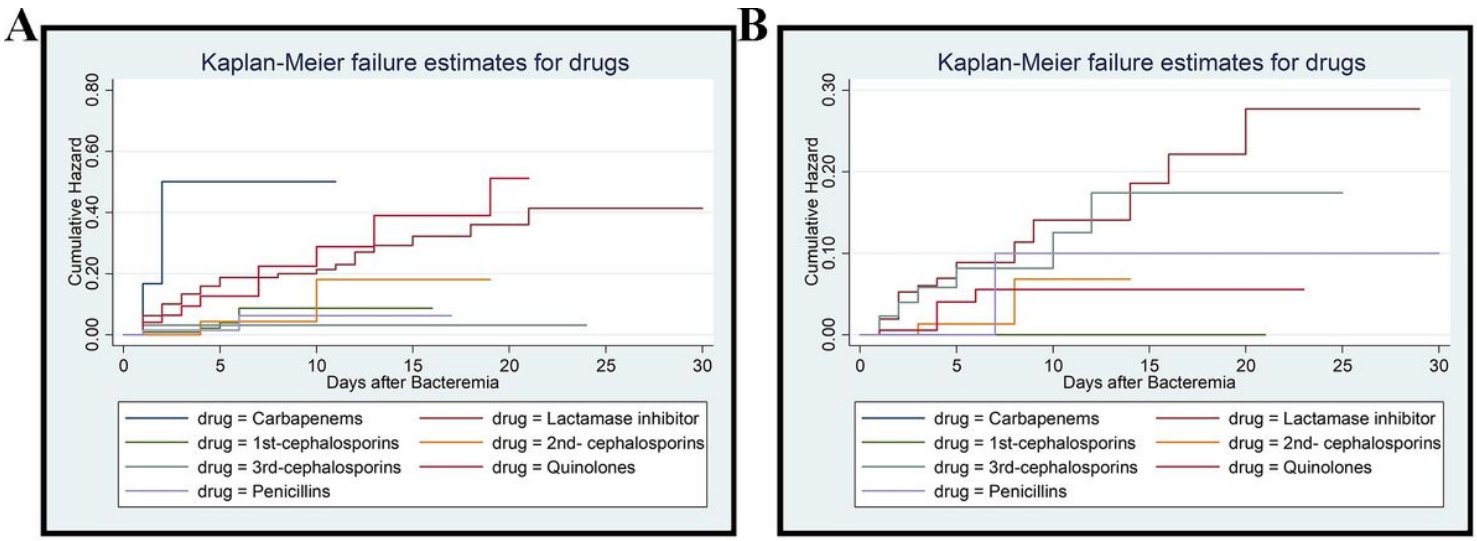

Figure 2

Results of Kaplan-Meier analysis: (A) comparison of CRKP induction between 7 antibiotics; (B) comparison of CR-E.coli induction between 7 antibiotics.

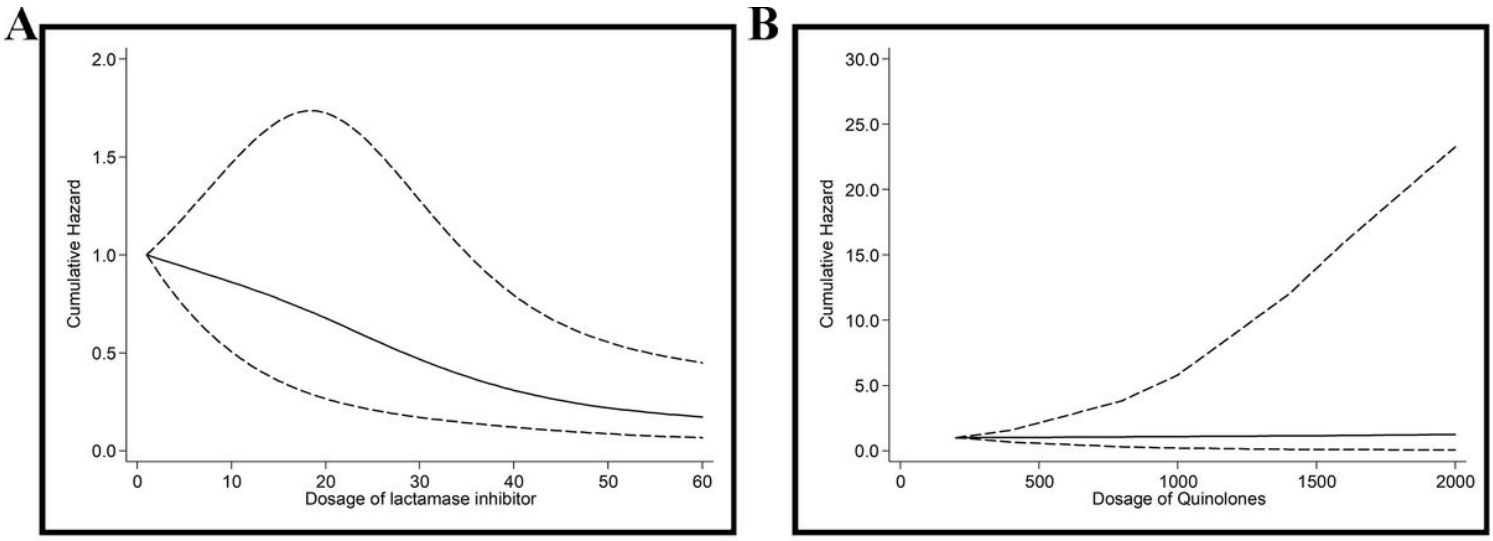

Figure 3

Results of restricted cubic spline regression on KP: (A) the hazard of CRKP induction decreased with the increase dose of lactamase inhibitors; (B) There was no significant change in the hazard ratio of CRKP induction with the increase dose of quinolones.

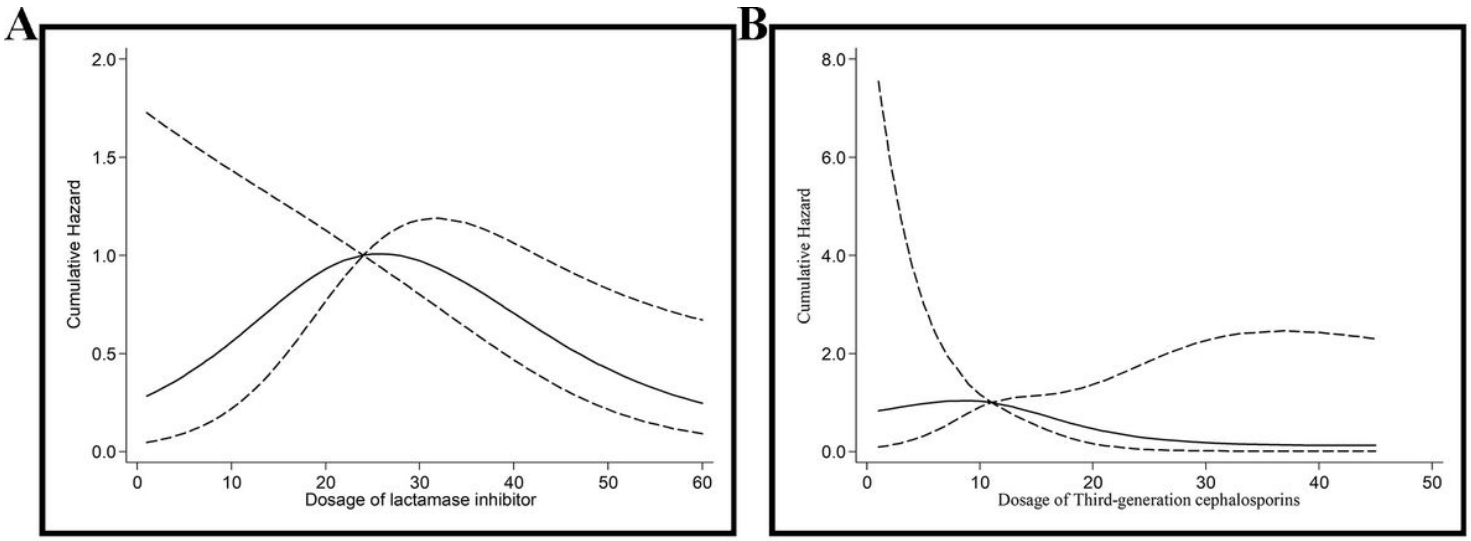

Figure 4

Results of restricted cubic spline regression on E. coli: (A) there was a clear threshold (24g) for the hazard of CR-E.coli induction due to lactamase inhibitors; (B) There was no significant change in the hazard ratio of CR-E.coli induction with the increase dose of 3rd-cephalosporins.

Supplementary Files

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- SupplementaryFigureS1.docx