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Original Article

Surveillance of carbapenem-resistant *Klebsiella pneumoniae* in Chinese hospitals - A five-year retrospective study

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Abstract

Introduction: Antibiotic consumption is associated with the development of antibiotic resistance. Our aim was to study the relationship between antibiotic consumption and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in three public general tertiary hospitals from 2011-2015 in the eastern, western and central regions of China.

Methodology: Valid data were collected quarterly, and the antibiotic consumption data were expressed as the defined daily dose (DDD) per 100 inpatient days (ID). Bacterial resistance was reported as the percentage of resistant isolates among all tested isolates. Individual trends were calculated by linear regression, while possible correlations between antibiotic consumption and CRKP were evaluated by distributed lags time series analysis.

Results: Over the 5-year period, an overall significant increasing trend ($P < 0.1$, $R^2 > 0.3$) of carbapenems consumption and the prevalence of CRKP was observed in all three hospitals. This correlated with the use of ceftazidime, cefoperazone/sulbactam, cefminox and meropenem at a hospital in eastern China, with the increased use of meropenem at a hospital in eentral China and with the increased use of doxycycline, ceftriaxone, ceftazidime, meropenem and biapenem at a hospital in western China.

Conclusions: We report a high incidence of CRKP in all three hospitals and that an increase in carbapenem usage is associated with this. Further research is needed to elucidate which factors influence the increased consumption of carbapenems.

Key words: antibiotic consumption; resistance; carbapenems; *Klebsiella pneumoniae*.

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Introduction

Antibiotic consumption is associated with the development of antibiotic resistance[1]. China has a high rate of antibiotic use among hospital in-patients [2]. Increase in general public antibiotic consumption (~ 57%) between 2000 and 2010 in Brazil, Russia, India, China and South Africa (BRICS countries) was majorly attributed to China [3].To promote the rational use of antibiotics and contain antimicrobial resistance, the Chinese National Health and Family Planning Commission (NHFPC) implemented a 3-year national campaign in 2011, with a primary focus on public secondary and tertiary hospitals [4]. Despite this campaign, the use of certain antibiotics, such as carbapenems continue to increase in later years [5-7].

Klebsiella pneumoniae is an important pathogen that causes a wide range of infections such as pneumonia and bloodstream infections, commonly in neonates and patients admitted in intensive care units. Carbapenems are the main line of defense against this pathogen, which has resulted in the generation and spread of carbapenem-resistant *K. pneumoniae* (CRKP), a clinically significant carbapenem-resistant *Enterobacteriaceae*. Resistance to carbapenems in *Enterobacteriaceae* is primarily linked to different mechanisms, in particular the production of carbapenemases [8]. Carbapenemases that are

responsible for non-susceptibility to carbapenems, belong to Ambler molecular class A, B, or D. *K. pneumoniae* carbapenemase (KPC) enzymes are currently the most clinically significant enzymes among the class A carbapenemases. CRKP has attracted widespread attention owing to its very limited therapeutic options, and the presence of this strain has increased rapidly in recent years [9]. Patients with CRKP infections have a poor prognosis with a mortality rate of approximately 40-50% [10] and contributes to a significant healthcare-associated cost to the economy [8]. To date, no attempt has been made to investigate the association between antimicrobial consumption and resistance of CRKP in Chinese hospitals.

After CRKP outbreaks in New York City hospitals in the early 2000s, this pathogen has spread throughout the United States and worldwide [11,12]. In China, the prevalence of CRKP has rapidly increased from 2.9% in 2005 to 13.4% in 2014 [13] and the distribution differed greatly by region, with the lowest prevalence in the northeast and the highest prevalence in the eastern region of China [14]. Besides official national reports [13], little has been done to investigate the relationship between hospital antibiotic use and CRKP in Chinese hospitals. Identifying risk factors for CRKP could improve antimicrobial stewardship and infection control and could assist in early recognition and timely intervention. The aim of this study is to investigate the possible relationship between the consumption of broad-spectrum antimicrobial agents and the prevalence of CRKP in major hospitals in China.

Methodology

Data collection and sample source

We retrospectively obtained the antimicrobial use and resistance data (between 2011 and 2015) from a total of 230,650,000 inpatients from three major tertiary public hospitals in the eastern (ECH), central (CCH) and western (WCH) regions of China. This was done through the Center for Antibacterial Surveillance (CAS) and the Chinese Antimicrobial Resistance Surveillance System (CARSS), Ministry of Health implemented surveillance systems intended to monitor the consumption and resistance of antimicrobial in Chinese public hospitals. Specifically, data on antimicrobial use were obtained from all clinical departments in each hospital except for pediatric wards, using the Anatomic Therapeutic Chemical (ATC) and defined daily dose (DDD) classification as recommended by the World Health Organization Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atc_ddd_index/). CRKP were isolated from various patient bodily fluids/sites including sputum, urine, blood, pus, bile, throat, surgical wound, catheter and stool samples. Ethics committee involvement was not necessary as no data on individual patients were used.

Antimicrobial consumption

Antimicrobials used were expressed in DDD per 100 inpatient-days for each hospital. Inpatient days were calculated by multiplying the quarterly total number of hospital discharges with the mean number of days of hospitalization [7]. Antimicrobial agents tracked include tetracyclines (doxycycline); second generation cephalosporins (cefoxitin, cefminox, cefuroxime); third generation cephalosporins (ceftazidime, ceftriaxone, cefodizime, cefoperazone/sulbactam, cefoperazone/tazobactam), fourth generation cephalosporins (cefepime); other cephalosporins (cefminox); carbapenems (include meropenem, imipenem/cilastatin, doripenem and ertapenem).

Antimicrobial susceptibility testing

Microbiological data were obtained from the CRASS database. Duplicate isolates — defined as the same bacterial species from the same inpatient during the same inpatient stay — were excluded from analysis, and only the first isolate was included in the analysis. Identification and susceptibility testing were performed using the automated Vitek-2 system (Biomérieux, l'Etoile, France) and further confirmed by the Kirby Bauer Disk Diffusion Agar method following guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI), 2011 (M100-S21) [15]. The susceptibility of CRKP isolates to 12 antibiotics; doxycycline, ceftazidime, cefoperazone/sulbactam, cefoperazone/tazobactam, cefoxitin, cefminox, cefuroxime, cefepime, ceftriaxone, cefodizime, meropenem, imipenem and cilastatin/biapenem were tested. Bacterial resistance is calculated as the percentage of resistant isolates (percentage of all resistant and intermediate resistant strains) among all tested isolates. Isolates were defined as CRKP if they were not susceptible to 1 or more carbapenems. Results were interpreted according to CLSI guidelines [15].

Statistical analysis

Trend over time for quarterly antimicrobial consumption and rates of CRKP were calculated independently by linear regression analysis. If linear regression analysis was statistically significant ($P <$

0.05, $R^2 > 0.3$) the relationship between the trend in quarterly antimicrobial consumption over time was further explored using distributed lags time series analysis, a specialized dynamic regression technique for examining the relationship between variables that involve some delay [16]. Here, the dependent variable is the quarterly rates of CRKP and antimicrobial consumption (expressed as DDD/100 inpatient-days quarterly) as is the independent variable. An association was deemed to be present and significant if the coefficient of determination (R^2) was less than 0.3 at any one time lag and the highest correlation for each pair determined the most likely time lag where antibiotic usage affected resistance or *vice versa* for that particular pair [17]. Trend correlated at zero-time lag meant that antibiotic consumption had influence bacterial resistance in the same quarter, at one time lag means that bacterial resistance was influenced by antibiotic consumption at last quarter. Furthermore, series were reviewed using the autocorrelation function and the partial autocorrelation function plots to exclude serial dependencies and to ensure appropriateness of the model. All statistical analyses were performed using IBM SPSS Statistics 24.0.

Results

A total of 11016 CRKP were isolated from three major tertiary public hospitals in the eastern, central and western regions of China (2907 in ECH, 5005 in CCH and 3104 in WCH). In summary, the total percentage of CRKP isolates detected over the 5-year period in the ECH was 8.58%, 10.48% in CCH the and 11.92% in WCH. CRKP were isolated from patient sputum (1614 in ECH,55.53%,2972in CCH,59.38%,2482in WCH,79.98%) (Figure 1). In ECH, there was a high consumption of third generation cephalosporins (ceftazidime and cefoperazone/sulbactam), carbapenems (meropenem and imipenem and cilastatin) and other cephalosporins (cefminox) ($R^2 > 0.3$, $P < 0.05$) (Table 1). In contrast, a significant increase in meropenem ($R^2 > 0.3$, $P < 0.05$) and a notable decrease in second generation cephalosporins (cefoxitin and cefuroxime) use were observed in the CCH. There was an increased use of doxycycline, meropenem and biapenem at the WCH. Although consumption of third generation cephalosporins have reduced over the years in this hospital, consumption of third generation cephalosporins (ceftazidime and ceftriaxone) have increased. Alarmingly, we observed an overall increasing trend of the CRKP presence ($P < 0.1$, $R^2 > 0.3$) in the three hospitals over the 5-year period (Figure 2, Table 2). We then determined whether there was an association between the rates of CRKP prevalence and quarterly consumption of antimicrobial of different classes in the three hospitals over the 5-year period. Using distributed lags time series analysis, the increased prevalence of CRKP correlated with the use of second generation cephalosporins (cefminox), third generation cephalosporins (ceftazidime and cefoperazone/sulbactam) and carbapenem (meropenem) at ECH (Table 3). In CCH, CRKP prevalence correlated with the increased use of meropenem. On the other hand, increased use of tetracyclines (doxycycline), third generation

Table 1. Antibiotic consumption from three major hospitals, 2011-2015.

Hospital	Antibiotics	Beta	R^2	P value	95% CI
ECH	Ceftazidime	0.063	0.348	< 0.01	0.019-0.108
	Cefoperazone/sulbactam	0.109	0.646	< 0.01	0.068-0.151
	Meropenem	0.103	0.664	< 0.01	0.065-0.140
	Imipenem and Cilastatin	0.046	0.283	< 0.05	0.009-0.084
	Cefminox	0.161	0.719	< 0.01	0.111-0.210
CCH	Cefoxitin	-0.045	0.071	0.270	-0.128-0.038
	Cefuroxime	-0.006	0.003	0.823	-0.063-0.051
	Meropenem	0.313	0.705	< 0.01	0.209-0.417
	Imipenem and Cilastatin	0.004	0.024	0.529	-0.009-0.017
WCH	Doxycycline	0.036	0.715	< 0.01	0.025-0.047
	Ceftazidime	0.077	0.561	< 0.01	0.042-0.112
	Ceftriaxone	0.081	0.652	< 0.01	0.051-0.111
	Cefodizime	-0.124	0.353	< 0.01	-0.209-0.038
	Cefoperazone/tazobactam	-0.161	0.072	0.267	-0.456-0.135
	Cefepime	-0.068	0.308	< 0.05	-0.136-0.000
	Meropenem	0.105	0.762	< 0.01	0.075-0.136
	Biapenem	0.019	0.787	< 0.01	0.014-0.024
	Imipenem and Cilastatin	0.016	0.148	0.104	-0.004-0.035

cephalosporins (ceftriaxone and ceftazidime), carbapenems (meropenem and biapenem) is associated with the increased prevalence of CRKP in WCH. In all cases, the increase in carbapenem usage is associated with the increasing prevalence of CRKP.

Figure 1. Distribution of KPN by clinical specimens, percentage (2011-2015).

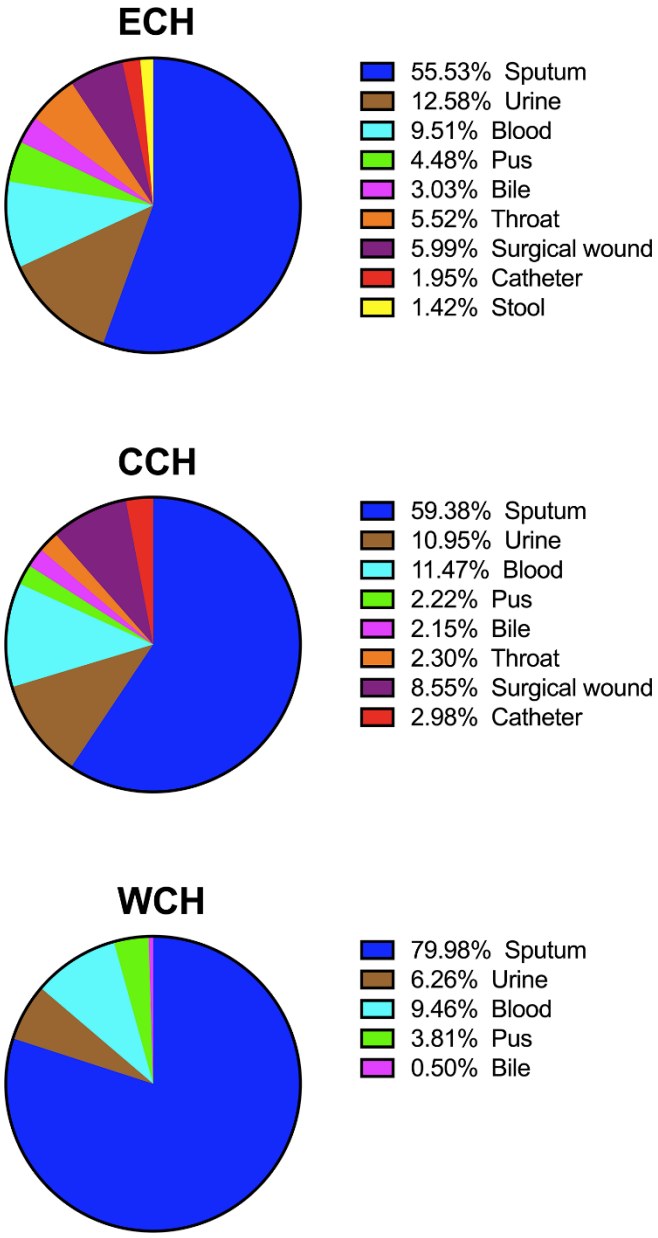

Figure 2. Prevalence of CRKP in three hospitals, percentage in each annual quarter (2011-2015).

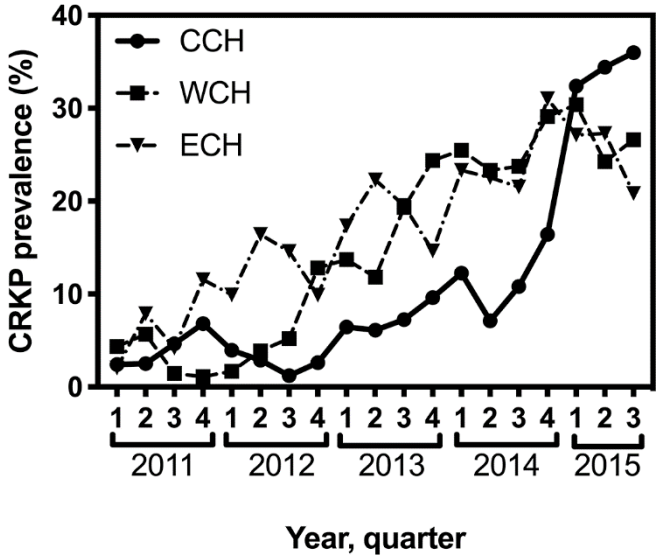

Table 2. CRKP prevalence in three major hospitals, 2011-2015.

Hospital	Beta	R^2	P value	95% CI
WCH	0.013	0.798	< 0.01	0.009-0.016
CCH	0.016	0.647	< 0.01	0.010-0.022
WCH	0.017	0.875	< 0.01	0.014-0.021

Discussion

Our study highlights the increasing consumption of different broad-spectrum antimicrobial agents coupled with rising resistance rates of *K. pneumoniae* to carbapenem. Overall, we found a significant decrease for antimicrobial usage in the three hospitals over the study period. From 2011 onwards, it is a requirement for all Chinese hospitals to form an antibiotic administrative group with the aim of enforcing formulary restrictions and total inpatient consumption of antibiotics (> 40 defined daily doses/100 inpatient days) [4]. Our study revealed an increase in the usage of carbapenems in the three hospitals. Meropenem was considered as the preferred carbapenem in treating serious infectious in the three hospitals. The possible reason is to compensate the loss of income from controlled drug usage in the hospitals. In Chinese public hospitals, drug revenue is the main source of income, and the use of expensive drugs in the context of reducing drug use is conducive to ensuring income [18].

The usage of other antimicrobials has also increased in the three hospitals. The Chinese government urges different regions to establish local guidelines for antimicrobial drug use. This could be due to various factors such as, differences in bacteria resistance, hospital health insurance policies and benefit packages, region-specific drug prescription practices to avoid the over-concentration and aggravation of drug resistance risk. Reynolds *et al.,* argued that this practice is insufficient, and that China has made limited progress in containing antibiotic resistance [19]. CRKP outbreaks have become increasingly common in China [20,21]. We found an increasing prevalence of CRKP in the three hospitals, consistent with findings from previous large surveillance studies [13]. High rates of bacterial resistance are often correlated with high rates of antibiotic use and intra- and inter-hospital spread of antibiotic resistant bacteria [22].

We found differences in the time lag of correlation between antimicrobial use and the prevalence of CRKP. Carbapenem prescription showed significant correlation with CRKP at no time lag in ECH and WCH. It is known that carbapenem use correlates significantly with CRKP prevalence rates [23,24]. In WCH, we found rising CRKP prevalence correlated at no time lag with use trends of ceftazidime and cefoperazone/sulbactam, and at 1 quarter lag with consumption of cefminox and ceftriaxone. Ceftazidime, ceftriaxone and cefminox are commonly used to treat infections caused by sensitive gram-negative bacteria and its use is highly restricted in these hospitals. In CCH, only meropenem use correlated with the increasing prevalence of CRKP at one time lag. Previous epidemiological studies support our findings. An ecological study conducted at teaching hospitals in Brazil from 2007-2016 showed that increase consumption of β-lactam/β-lactamase inhibitors increased the frequency of carbapenem-resistant *Klebsiella spp.* with a 1-year time delay [25]. Indeed, increased usage of third-generation cephalosporins was found to be the main independent risk factors of CRKP infections in a retrospective cohort study done in Turkey [26]. The study found that the propensity for CRKPs to emerge is likely the result of a multifactorial process with respect to antibiotic exposure. Our study corroborates these results and may indicate that replacing several antibiotics with carbapenems could potentially be problematic.

There are several limitations in this work. As this study is retrospective in nature, potential confounders such as changes in length of stay, shift of patients from the ICU to the ward and vice versa, case stratification, time of collection of blood samples could not be ascertained while observing the trends. The results of a previous study showed that age, gender, recent admission to ICU for more than 24 hours, indwelling urinary catheter, mechanical ventilation, exposure to β-

Table 3. Distributed lags time series analysis between CRKP prevalence rate and quarterly consumption of antimicrobials.

Hospital	Antibiotics	R^2	SE	t	R^2	Lag[a]	P value
ECH	Ceftazidime	0.090	0.024	3.78	0.456	0	0.001
	Cefoperazone/sulbactam	0.085	0.015	5.69	0.656	0	0.000
	Meropenem	0.081	0.019	4.29	0.520	0	0.000
	Cefminox	0.064	0.010	6.37	0.705	1	0.000
CCH	Meropenem	0.060	0.004	8.76	0.936	1	0.000
WCH	Doxycycline	0.375	0.067	5.55	0.672	2	0.000
	Ceftazidime	0.122	0.033	3.71	0.448	0	0.002
	Ceftriaxone	0.142	0.032	4.41	0.549	1	0.000
	Meropenem	0.130	0.021	6.34	0.703	0	0.000
	Biapenem	0.760	0.111	6.85	0.734	0	0.000

[a] only the most significant lags are mentioned.

lactam-β-lactamase inhibitors, treatment with fourth-generation cephalosporins and carbapenems, were associated with CRKP infection in a tertiary care hospital in Beijing [27]. Secondly, differences in infection control measures in the three hospitals over the study period were not assessed. By understanding infection control measures in each hospital, we can better explain the association of certain antimicrobial use and increasing CRKP prevalence. The increased prevalence in CRKP might also be a result of the increased rates of use of other antimicrobial hence causing bias in our interpretation of our time lag association data. It is also important to note that data is representative of only a single isolate taken from each patient. Changes in antimicrobial susceptibility or resistance for a particular isolate over time was not followed up in this study. Finally, we were unable to obtain the exact length of patient stay in each hospital as data was extracted from the CAS database. Although there could be some deviation in our antimicrobial consumption data, the impact of bias is limited as we analyzed a large dataset in this study.

Conclusion

Our data demonstrate a significant increase in prevalence of CRKP and consumption of carbapenems in three Chinese public general tertiary hospitals. We found that the high incidence of CRKP associated with increased carbapenem usage in all three hospitals. Future work is needed to elucidate the factors which influence the increased consumption of carbapenems in these hospitals.

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