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Correlation between a Change of Drug Resistance of *Klebsiella pneumoniae* and Defined Daily Doses of Antimicrobial Agents from 2014 to 2018

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Abstract

Introduction: The prevalence of *Klebsiella pneumoniae* has rapidly increased in recent years and the distribution differed greatly by region, We aimed to study the relationship between antibiotic resistance and *K. pneumoniae*, especially carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in our tertiary hospitals from 2014 to 2018. Methodology: The antibiotic consumption data of *K. pneumoniae* were expressed as the defined daily dose (DDD) per 100 inpatient days (DDDs). *K. pneumoniae* which isolated from clinical samples in hospital between January 2014 and December 2018 were retrospectively analyzed, and the correlation between antibiotic resistance rate and antibiotic frequency was analyzed. Results: From 2014 to 2018, a total of 2295 strains of *K. pneumoniae* were isolated, with the detection rates of 8.2%, 9.2%, 11.9%, 13.4% and 14.0%. There were 423 strains of CRKP, with the detection rates of 7.5%, 5.8%, 17.8% 24.2% and 25.2% respectively. *K. pneumoniae* showed different degrees of resistance to antibiotics and showed an increasing trend year by year to carbapenems. The resistance rate of imipenem was 2.5%, 2.8%, 9.9%, 12.3%, 13.4%, and the resistance rate of meropenem was 2.0%, 3.0%, 8.8%, 12.6%, 12.7%, respectively. The resistance rate of most other drugs decreased. The DDDs values of cefoperazone/sulbactam, piperacillin-tazobactam and gentamicin showed a strong positive correlation with *K. pneumoniae* drug resistance rate ($r > 0.8$, $P < 0.05$). Conclusions: The detection rate of *K. pneumoniae* and CRKP increased year by year, which was closely related to the dose of antibiotics. Strengthening the management of antimicrobial drugs and standardising the use of antimicrobial prescriptions were of great significance for delaying the emergence of drug-resistant bacteria.

Keywords

Klebsiella pneumonia, Antibiotic Consumption, Resistance, Correlation Analysis, Defined Daily Doses

1. Introduction

Klebsiella pneumoniae is a gram-negative bacillus, which is an essential condition pathogenic bacterium and iatrogenic infectious bacterium in *Enterobacteriaceae Klebsiella*. In recent years, the bacterial resistance rate has been increasing with the widespread use of antibacterial drugs and the rapid change of bacteria, especially carbapenem-resistant *K. pneumoniae* (CRKP), CHINET data showed that the detection rate of CRKP was 13.8% in 2007 [1], increasing to 25.0% and 26.3% in 2018 [2]. Therefore, the rational use of antibacterial drugs has become an essential means of curbing bacterial resistance. This study monitored and analysed the drug resistance of *K. pneumoniae* in the hospital from January 2014 to December 2018, and at the same time analysed the frequency of use of antimicrobial drugs among inpatients during this period to provide a basis for the rational use of antimicrobial drugs.

2. Methodology

2.1. Sample Source and Antimicrobial Testing

Klebsiella pneumoniae were isolated from various patient bodily fluids/sites including sputum, urine, pus, blood, sterile body fluid, surgical wound, submitted by the clinical department of the hospital from 2014 to 2018. The samples to exclude the same patient during a hospital and the same strain of the same part were separated and identified by Vitek-2 system (French bio-Merieux company) and the K-B method following guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI), 2011 (M100-S21) [3]. The quality control strain was *Klebsiella pneumoniae* ATCC 700603, which was purchased from the Clinical Laboratory of the Ministry of Health.

2.2. Detecting of the Carbapenem-Resistant *K. pneumoniae* (CRKP)

The modified Hodge test (MHT) was used to dilute the suspension of *K. pneumoniae* ATCC 700603 0.5 M. turbidity bacteria with sterile normal saline at 1:10 and evenly spread on the MH plate. After drying at room temperature for 3 - 10 min, meropenem was pasted in the middle, and the bacteria to be tested were streaked from the edge of the paper sheet to the edge of the plate. The results were observed after 18 - 24 h incubation at 35 C. Result: when the MIC of meropenem ≥ 2 ug/ml, it was a carbapenem-resistant strain.

2.3. Data Collection and Antimicrobial Consumption

The antibacterial drug data was derived from the hospital HIS systems from

January 2014 to December 2018. The antibacterial drug distribution information of the inpatient pharmacy and the relevant information in Excel. The total consumption is calculated and using the defined daily dose (DDD) classification recommended by the World Health Organization (WHO) (http://www.whocc.no/atc_ddd_index/). Inpatient days were calculated by multiplying the quarterly total number of hospital discharges with the mean number of days of hospitalization [4]. Antimicrobial agents tracked include aminoglycosides, β-lactam antibiotics (penicillins, cephalosporins, carbapenems), quinolones, sulfa antibacterial drugs.

2.4. Statistical Analysis

The trend over time for antimicrobial consumption and rates of KP was calculated independently by Pearson's correlation analysis. The Pearson's correlation coefficient (r) between the bacterial resistance rate and the DDDs value of antibacterial drugs was calculated: $r > 0.8$, which was considered to have a strong correlation between them; $r < 0.3$, the relationship between them is considered to be weak; $P < 0.05$ is considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24.0.

3. Results

3.1. Detection Rate of *Klebsiella pneumoniae*

From 2014 to 2018, a total of 2295 strains of *K. pneumoniae* were detected, and the detection rate increased from 8.3% in 2014 to 14.1% in 2018, showing an increasing trend year by year. Among them, 423 CRKP strains were detected, and the isolation rate was from 7.3% in 2014, 5.8% in 2015 to 25.2% in 2018. The specific data are shown in Table 1.

3.2. The Distribution of Species

A total of 2295 *K. pneumoniae* were isolated from sputum, urine and pus, and their composition ratios were 67.2%, 12.3% and 7.8%, respectively. But CRKP was mainly derived from sputum, blood and urine, with a composition ratio of 50.4%, 13.9% and 12.8%, respectively. The specific data are shown in Table 2.

3.3. Antibacterial Drugs Resistance Rate of *K. pneumoniae* and Its Correlation with DDDs

K. pneumoniae have different degrees of resistance to antibacterial drugs, and the resistance to carbapenems has been a significant increasing trend. From 2014 to 2018, The resistance rates of imipenem are 2.53%, 2.80%, 9.90%, 12.30% and 13.41%, the drug resistance rates of meropenem were 2.04%, 3.00%, 8.80%, 12.60%, and 12.72%, respectively. The drugs with the highest DDDs value were cefoperazone/sulbactam and showed an upward trend each year. The smaller values were ciprofloxacin and imipenem. The correlation between the resistance rate of KP to common antibacterial drugs and the changes in the corresponding antibacterial drugs DDDs value from 2014 to 2018 is shown in Table 3.

Table 1. The isolation rates of *Klebsiella pneumoniae* (KP) and CRKP strains from 2014 to 2018 (%).

Year	n/Strain	KP		CRKP	
		Strain	Rate (%)	Strain	Rate (%)
2014	3572	292	8.2	22	7.4
2015	3561	329	9.2	19	5.8
2016	3866	461	11.9	82	17.8
2017	4156	556	13.4	135	24.3
2018	4662	650	14	165	25.2
Total	19,817	2288	11.5	423	18.5

Table 2. Distribution and percentage of KP and CRKP by clinical specimens (%) (2014-2018).

Strain source	KP		CRKP	
	Strain (n = 2295)	Rate (%)	Strain (n = 423)	Rate (%)
sputum	1542	67.2	213	50.4
urine	283	12.3	54	12.8
pus	179	7.8	40	9.5
sterile body fluid	125	5.4	29	6.9
blood	103	4.5	59	13.9
surgical wound	63	2.7	28	6.4

Table 3. Drug resistance rate (%) of the KP strains to the commonly used antbiotics and relationship with the changes of DDDs of antibiotics.

Antibacterial drugs	Drug resistance rate of KP (%)					DDDs					r	P
	2014	2015	2016	2017	2018	2014	2015	2016	2017	2018		
Amikacin	20.5	18.5	14.4	13	13.1	248	253	336.2	416.4	452.6	−0.932	0.021
Ampicillin	100	99.6	100	99.8	99.7	-	-	-	-	-	-	-
Ciprofloxacin	23.8	23.5	26.5	30.5	30.4	185.5	172.4	147.2	132.8	165.8	−0.682	0.205
Ceftriaxone	56.6	54.6	62.9	47.2	46.3	6831	7184	9374	14634	15494	−0.772	0.126
Cefoperazone/sulbactam	10.8	9.8	13.9	20.5	22.3	25,642	27,283	36,402.7	41,241.4	46,848.6	0.964	0.008
Cefuroxime	62.5	59.5	73.4	49.2	48	465.3	495.7	2221	5105.7	5865.5	−0.697	0.191
Cefazolin	65.6	62.6	54.4	54.3	58.5	5869.2	5511.7	4627.3	9294	10,684	−0.277	0.651
Cefepime	39.5	39.4	29.7	26.1	25.6	-	-	-	182.4	-	-	-
Cefoxitin	31.6	29.6	35.9	22.1	23.1	-	-	-	-	-	-	-
Gentamicin	43.4	42.4	30.4	22.6	21.9	4754.8	4563.3	3024.3	2989.7	2579.6	0.967	0.007
Imipenem	2.5	2.8	9.9	12.3	13.4	123.8	132.5	389.3	306.8	314.4	0.873	0.053
Levofloxacin	25.2	22.2	23.9	26	25.9	15,483.7	16,539.8	21,092.4	20,170.4	25,367.5	0.48	0.413
Meropenem	2	3	8.8	12.6	12.7	6537.9	4970.8	6750.7	10,914.4	12,835.8	0.876	0.052
Piperacillin/tazobactam	9.4	10.4	13.2	17.1	17.2	2146.6	2395.6	5356.2	6733.5	7483.4	0.98	0.003
Fuxin Xinming	46.5	48.5	42.7	28.1	27.6	-	-	-	-	-	-	-

Note: - indicates that this item has no data.

3.4. Correlation Analysis of the Changing Trend of Antibacterial Drugs DDDs Value and Resistance Rate of *K. pneumoniae*

The strength of association between DDDs of cefoperazone/sulbactam, piperacillin/tazobactam, gentamicin and resistance rate of *K. pneumoniae* were very high (r = 0.964, 0.980, 0.967), and that the correlation coefficient is very highly significantly different from zero ($P < 0.01$). The values of DDDs of amikacin and ciprofloxacin were negatively correlated with the resistance rate of *K. pneumoniae* (r = −0.965, −0.972, $P < 0.05$). The DDDs of levofloxacin had a correlation with the *K. pneumoniae* resistance rate of $0.8 > r > 0.6$, $P < 0.01$. The DDDs of meropenem had a strong positive correlation with *K. pneumoniae* resistance rate $r > 0.8$, but $P > 0.05$ showed no difference. Imipenem $0.5 < r < 0.8$, $P > 0.05$, its correlation is not large. For other antibacterial drugs, $r < 0.8$, $P > 0.05$, the correlation is not great.

4. Discussion

Our study highlights the rising resistance rates of *K. pneumoniae* which isolated our hospital from 2014 to 2018, especially the resistance rates of CRKP has rapidly increased from 7.5% in 2014, 5.8% in 2015 and 17.8% in 2016, 24.2% in 2017 to 25.2% in 2018. In our study our hospital should pay attention to the resistance of CRKP because carbapenems are the last line in defence against the pathogen, clinical drug treatment is facing severe challenges and changes, and it is a wake-up call for clinicians and pharmacists. This article wants to provide valid data for the clinic by counting the correlation between the drug resistance rate of bacteria and the frequency of use of antibacterial drugs DDDs. Reasonable norms, to eliminate the phenomenon of unindicated medication and medication for too long [5].

Antimicrobial resistance (AMR) is currently one of the most urgent public health issues in the world [6]. The resistance of *K. pneumoniae* is mediated by a series of mechanisms, which are mainly related to the widespread use of broad-spectrum antibacterial drugs. Catalytic hydrolysis to produce KPC carbapenemase or NDM-1 metalloenzyme can hydrolyze carbapenems to produce CRKP. Resistance to other antibacterial drugs is related to the combined action of biofilm formation, loss or alteration of membrane pore proteins, and efflux pumps [7] [8] [9].

From the data, it was found that 15 antibacterial drugs of *K. pneumoniae* were tested for in vitro susceptibility. The increase in drug resistance rate was directly related to the amount of clinical use. The DDDs of cefoperazone/sulbactam rose from 27,283.0 to 41,241.4. The resistance rate of cefoperazone/sulbactam to *K. pneumoniae* increased from 9.8% to 20.5%, and the DDDs of piperacillin sodium/tazobactam sodium increased from 2395.6 to 6733.5 and *K. pneumoniae* to cefoperazone/sulbactam The rate increased from 10.43% to 17.09%, and the DDDs of gentamicin decreased from 4563.3 to 2989.7, which was highly corre-

lated with the resistance rate of *K. pneumoniae* to gentamicin from 42.4% to 22.6% ($r = 0.953, 0.938, 0.928$, $P < 0.05$); the values of DDDs of amikacin and ciprofloxacin were strongly negatively correlated with the resistance rate of *K. pneumoniae* ($r = -0.965, -0.972$, $P < 0.05$). The meropenem DDDs values were not significantly correlated with *K. pneumoniae* drug resistance rate ($r > 0.8$, $P > 0.05$). Imipenem $0.5 < r < 0.8$, $P > 0.05$, its correlation is not large. It is suggested that the emergence of bacterial resistance is not only related to antibacterial drugs DDDs but may also be related to factors such as cross-resistance of bacteria. Among them, the widespread use of broad-spectrum β-lactamase inhibitors affects the effect of carbapenem drugs on the Antibacterial activity of *K. pneumoniae*. Zhan [10] studies have consistent with the study of the exhibition champion. Piperacillin/tazobactam DDDs are highly correlated with imipenem resistance. Meng [11] studies considered that Piperacillin tazobactam, cefoxitin, imipenem, Meropenem and amikacin are still the first choice for the treatment of *K. pneumoniae* infection. because the drug resistance rate of *K. pneumoniae* to piperacillin was significantly positively correlated with AUD of ceftazidime. The drug resistance rate of imipenem was positively correlated with AUD of amoxicillin clavulanate.

In the study, the monitoring data shows that the resistance of *K. pneumoniae* to carbapenem antibacterial drugs is on the rise because carbapenem antibacterial drugs are the most effective antibacterial drugs for the treatment of *K. pneumoniae* infections [8]. Therefore, Our hospital establishes an fore-warning mechanism for different bacteria every quarter to cope with the difficult drug resistance situation and improving the level of anti-infective treatment and controlling the clinical application of antibacterial drugs refers to the Guidelines for the Clinical Application of Antibacterial Drugs to increase the rate of clinical specimen submission and detection, Choose appropriate antibacterial drugs according to the susceptibility of bacteria.

After 5-year period analysis of drug resistance rates, although *K. pneumoniae* has aminoglycosides (amikacin), enzyme-inhibitors (piperacillin/tazobactam, cefoperazone/sulbactam), The sensitivity of cephalosporins (cefoxitin) and carbapenems (imipenem, meropenem) has remained at a high level, and the resistance rate of the third and fourth generation cephalosporins has increased, especially CRKP is gradually increasing. Therefore, the drug resistance rate of *K. pneumoniae* is highly correlated with the use of various antibacterial drugs. Rotation of antibacterial drugs can reduce the drug resistance rate of bacteria.

5. Conclusion

Our data demonstrate a significant increase in the prevalence of *K. pneumoniae* and the consumption of enzyme-inhibitors in our hospital. We found that the high incidence of CRKP is associated with increased enzyme-inhibitors usage in our hospital. Future work is needed to elucidate the factors which influence the increased consumption of enzyme-inhibitors usage in our hospital.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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