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Original Article

Correlational study between discontinuation of the fourth-generation cephalosporin and the dosage of broad-spectrum antibacterial agents as well as resistance rates of pseudomonas aeruginosa against antimicrobials

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Abstract: Objective: To retrospectively investigate the correlation between the discontinuation of the fourth-generation cephalosporin and the dosage of other broad-spectrum antibacterial agents as well as resistance rate of Pseudomonas aeruginosa. Methods: Data on in vitro susceptibilities detected by disk diffusion test, the dosage of various antimicrobial agents which was expressed as defined daily dose (DDD) per 100 patients-days, and the discontinuation of the fourth-generation cephalosporin were collected during 2009 to 2015. The relationship between the use of fourth-generation cephalosporin and the dosage of other broad-spectrum antibacterials as well as the resistance rate of Pseudomonas aeruginosa against broad-spectrum antibacterials were evaluated by the parametric Pearson's or nonparametric Spearman's correlation coefficient. Results: There was a significant negative correlation between the dosage of the fourth-generation cephalosporin and the dosage of piperacillin-tazobactam (P = 0.015), and a significant positive correlation between the antibiotic use density (AUD) of the fourth-generation cephalosporin and the resistance rates of Pseudomonas aeruginosa against cefepime (P = 0.000). Meanwhile, there was also a significant positive correlation between resistance rate of Pseudomonas aeruginosa against levofloxacin and AUD of the fourth-generation cephalosporin (P = 0.001). Conclusion: In those hospitals or regions where Pseudomonas aeruginosa has high resistance rate against cefepime, application of the fourth-generation cephalosporin is the pressure of appearance of multidrug-resistant Pseudomonas aeruginosa.

Keywords: Fourth-generation cephalosporin, gram-negative bacteria, pseudomonas aeruginosa, bacterial resistance

Introduction

Antibiotic resistance has already been known as a global health issue, of which the prevalence is increasing worldwide, especially in China [1]. WHO has suggested that the control of antibiotic resistance should be carried out with administrative strategies combining with national, regional, and institutional strategies at professional levels [2]. In 2011, Chinese Ministry of Health initiated a 3-year special rectification activity of antibiotics use, and carried out strict regulations for varieties, product regulation number, utilization and the intensity of antibacterial use. In terms of variety and product configuration regulation of antibacterial drugs, tertiary hospitals should not keep over 50 types of antibacterials, the third generation and fourth generation of cephalosporins (containing compound preparation) in oral dosage form should not be over 5 product specifications, and the corresponding injectable formulations should not be over 8 product specifications [3].

The main cause for microbial resistance of antibiotics is the inappropriate use [4, 5]. Third- or fourth- generation cephalosporins are key risk factors for the emergence and spread of multidrug-resistant gram-negative bacteria, which

can induce infections associated with substantial morbidity and mortality [6]. Therefore, limited use of variations and product specifications of the third- and fourth-generation of cephalosporin might be helpful to inhibit or avoid the emerging and spread of multidrug-resistant Gram-negative bacteria.

Antibacterial management working group of our hospital organized the screening of varieties and product specifications of antibacterial drugs since October in 2011. They found Pseudomonas aeruginosa was one of the most commonly isolated gram-negative bacteria. According to the monitoring results of hospital bacterial resistance in 2010, the drug resistance rates of Pseudomonas aeruginosa against cefepime (FEP) was 38.67%. The rate was higher than those from America and most countries in Europe [7-9], and also higher than data from bacterial drug resistance monitoring network data of Mohnarin & CHINET in China for the corresponding period [10, 11]. Therefore, antibacterial management working group decided not to put the fourth-generation cephalosporins (such as FEP, cefotaxime Lee, cefpirome and so on) into the procurement catalog. From 2012 to 2015, the hospital has not used the fourth-generation cephalosporin.

As the most common opportunistic pathogen among pseudomonas bacteria, Pseudomonas aeruginosa is widely distributed in nature and spreads through environmental pollution, cross-infection, endogenous infections and iatrogenic infections and so forth; meanwhile, it is also one kind of common pathogens which second only to E. coli and Klebsiella in gram-negative bacilli infection [12]. The epidemic links consists of Pseudomonas aeruginosa, immunocompromised patients and the specific pathogens. Moreover, Pseudomonas aeruginosa may cause infections such as urinary tract infections, burns wounds and bed sores infections, sepsis and lung infections, when the host with immune dysfunction, long-term use of broad-spectrum antibiotics and glucocorticoids, and tumor radiotherapy and chemotherapy [13]. Pseudomonas aeruginosa has natural or acquired antimicrobial resistance, so the treatment is more difficult and should not be ignored [14]. Therefore, in this study, we investigated the changes of the amount of several common antibacterial agents as well as the changes in resistance rate of Pseudomonas aeruginosa before and after the 4-year discontinuation of the fourth-generation cephalosporin.

Materials and methods

Isolates source

This project was approved by the institutional ethics committee of the First Hospital of Quanzhou Affiliated to Fujian Medical University. Informed consents from participants were not obtained because this was a retrospective observational study.

The study was conducted at the First Hospital of Quanzhou Affiliated to Fujian Medical University, Quanzhou, China, an 1810-bed, tertiary care teaching hospital. Nonduplicated Gram-negative bacteria clinical isolates were collected by the Microbiology Department of the hospital from January 2009 to December 2015. Samples composed of blood (45.2%), sputum (28.6%), urine (12.5%) and pus (4.6%). Duplicated isolates regarding to the bacterial species that came from the same patient with the same antibiogram were removed.

Inclusion criteria: Isolates from patients who took fourth-generation cephalosporin during 2009 to 2011, and the samples were taken after the drug administration; isolates from patients who did not take fourth-generation cephalosporin during 2012 to 2015; isolates from patients with complete examination data; isolates that collected and detected with standard operating procedure. Exclusion criteria: Isolates from patients who took fourth-generation cephalosporin during 2012 to 2015; isolates from patients with uncomplete examination data; isolates that did not collect and detect with standard operating procedure.

Basic information

Gender, age, co-commitant diseases, the time from infection to taking medicine were collected.

Antimicrobial consumption data

Data including the dose of ceftazidime (CAZ), cefepime (FEP), meropenem (MEM), Piperacillin/tazobactam (TZP), levofloxacin (LVX) and amikacin (AMK) and the fourth-generation ce-

Table 1. Patients' basic information

Variables	Year 2009 to 2011	Year 2012 to 2015	P
Sex			0.0956
Male	1529	1782	
Female	1517	1801	
Age (year)	35.01 ± 0.82	34.98 ± 0.78	0.128
Time from infection to taking medicine (day)	5.24 ± 1.32	5.78 ± 0.98	0.202

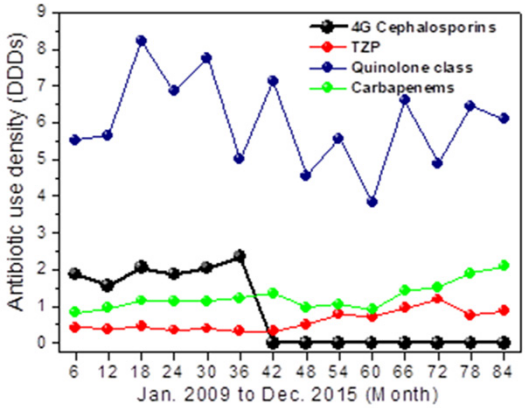

Figure 1. AUD of four types of antibiotics, 2009-2015 Consumption of the fourth-generation cephalosporins, piperacillin-tazobactam (TZP), Quinolones, Carbapenems is expressed as defined daily dose (DDD) per 100 patients-days (DDDs/100 patients/day, y-axis) every half year from 2009 to 2015, and patients stopped consuming the fourth-generation cephalosporins since 2012. Spearman correlation method was used to analyze the correlation of the dosage of fourth-generation cephalosporins and the dosages of piperacillin-tazobactam (TZP), Quinolones or Carbapenems. AUD, antibiotic use density.

phalosporin and the susceptibility of Pseudomonas aeruginosa to antimicrobial agents for each isolate were collected and analyzed.

Data about antimicrobial consumption were obtained from the hospital computer center database. The dosages of the fourth-generation cephalosporin during 2009 to 2015 were auto-summarized for each half year, and a total of 14 periods of dosage including Jan. 2009 to Jun. 2009, Jul. 2009 to Dec. 2009, Jan. 2010 to Jun. 2010, Jul. 2010 to Dec. 2010, Jan. 2011 to Jun. 2011, Jul. 2011 to Dec. 2011, Jan. 2012 to Jun. 2012, Jul. 2012 to Dec. 2012, Jan. 2013 to Jun. 2013, Jul. 2013 to Dec. 2013, Jan. 2014 to Jun. 2014, Jul. 2014 to Dec. 2014, Jan. 2015 to Jun. 2015 and Jul. 2015 to Dec. 2015, were collected.

The resistance rate of Pseudomonas aeruginosa to antimicrobial agents

The susceptibility of Pseudomonas aeruginosa to antimicrobial agents should be tested by using the disk diffusion method, and the resistance rate (%) of Pseudomonas aeruginosa to ceftazidime (CAZ), cefepime (FEP), meropenem (MEM), Piperacillin/tazobactam (TZP), levofloxacin (LVX) and amikacin (AMK) were calculated using WHONET 5.6 software.

Defined daily dose and antibiotic use density

The defined daily dose (DDD) for adults was obtained from the anatomical therapeutic chemical (ATC) classification index from the World Health Organization (WHO), with the DDD unit expressed in grams. Defined daily dose system (DDDs) = consumption of antibiotics (g)/DDD value; AUD (antibiotic use density) = (hospitalized patients DDDs/days of patients admitted to the hospital for the corresponding period) * 100. Days of patients admitted to the hospital in the corresponding period = discharged patients in the corresponding period * their average hospitalization days, which provided by record room of this hospital.

To evaluate the effect of discontinuation of the fourth generation of cephalosporin on dosages of other kinds of antibacterial drugs, this project also collected data concerning the dosages of piperacillin-tazobactam (TZP), quinolones, carbapenems (meropenem, imipenem, panipenem) of hospitalized patients during abovementioned 14 periods.

Main outcomes

The main outcome was the correlation between discontinuation of the fourth generation of cephalosporin and the resistance rate of Pseudomonas aeruginosa to the broad-spectrum anti-bacterial.

Statistical analysis

The relationship between the use of fourth-generation cephalosporin and the dosage of other broad-spectrum antibacterial drugs was ana-

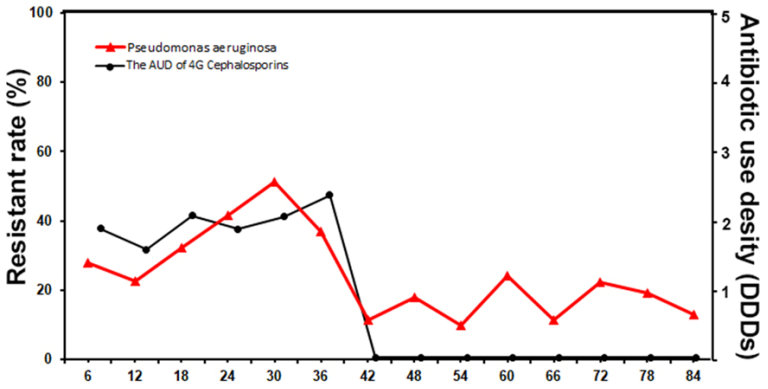

Figure 2. Analysis of the correlation between AUD of the fourth-generation cephalosporins and resistant rate of pseudomonas aeruginosa to cefepime via Spearman correlation method. Consumption of the fourth generation cephalosporins is expressed as defined daily dose (DDD) per 100 patients-days (DDDs/100 patients/day, right y-axis) every six months from 2009 to 2015. The resistance rate of Pseudomonas aeruginosa to cefepime is calculated by dividing the number of resistance strains by the total number of the isolates and multiplying by 100 (%, left y-axis) every six months from 2009 to 2015.

Table 2. Correlation between AUD of the fourth-generation cephalosporins and resistant rate of Pseudomonas aeruginosa to cefepime

Drug Consumed	Pseudomonas aeruginosa resistant rate	
	r	P
4G cephalosporins	0.828	0.000

Note: 4G cephalosporins, fourth-generation cephalosporin; AUD, antibiotic use density.

lyzed by nonparametric Spearman's correlation; the correlation between AUD of the fourth-generation cephalosporins and drug resistance rates of Pseudomonas aeruginosa to other six antibacterial drugs was analyzed by nonparametric Spearman's correlation as well as parametric Pearson's correlation and the correlation between the AUD of other antibacterial drugs and drug resistance rate of Pseudomonas aeruginosa was analyzed by parametric Pearson's correlation.

Statistical analysis was performed with SPSS (version 17.0; SPSS, Inc, an IBM Company, Chicago, Illinois). The measurement data were expressed as mean ± standard deviation and the count data were expressed as percentage or rate. A *P* value of <0.05 was considered statistically significant. Spearman's correlation coefficient (r): $|r|\geq 0.8$ as strong, $0.5\leq|r|<0.8$ as moderate and $0.3\leq|r|<0.5$ as weak.

Results

Basic information

A total of 83 and 106 cases were included during 2009 to 2011 and 2012 to 2015, respectively and the disease distribution was insignificantly different (P>0.05). Besides, the other basic data including the sex, age, the time from infection to taking medicine had no significant difference between the two phases (all P>0.05). See **Table 1**.

Correlation between the dosage of the fourth-generation cephalosporin and dosages of piperacillin-tazobactam, quinolones and carbapenems

Spearman correlation method was applied to analyze the correlation between the dosage of the fourth-generation cephalosporin and dosages of piperacillin-tazobactam, quinolones and carbapenems. The AUD of piperacillin-tazobactam was significantly correlated to the AUD of the fourth-generation cephalosporin (r = 0.635, P = 0.015), while the AUD of quinolones and carbapenems illustrated no significant correlation to AUD of the fourth-generation cephalosporin (r = -0.312, P = 0.278; r = -0.282, P = 0.328). The AUD of 4 types of antibacterial drug were detailed in **Figure 1**.

The correlation between AUD of the fourth-generation cephalosporins and drug resistance rates of Pseudomonas aeruginosa to FEP

There was a significant positive correlation between AUD of the fourth-generation cephalosporin and drug resistance rate of Pseudomonas aeruginosa (r = 0.828, P = 0.000). The results were detailed in **Figure 2**, **Table 2**.

Drug resistance rate of Pseudomonas aeruginosa against other antibacterial drugs

Besides FEP, the correlation between drug resistance rate changes of against other five antibacterial drugs (ceftazidime (CAZ), meropenem (MEM), piperacillin/tazobactam (TZP), levofloxacin (LVX), amikacin (AMK)) and AUD of the fourth-generation cephalosporin was fur-

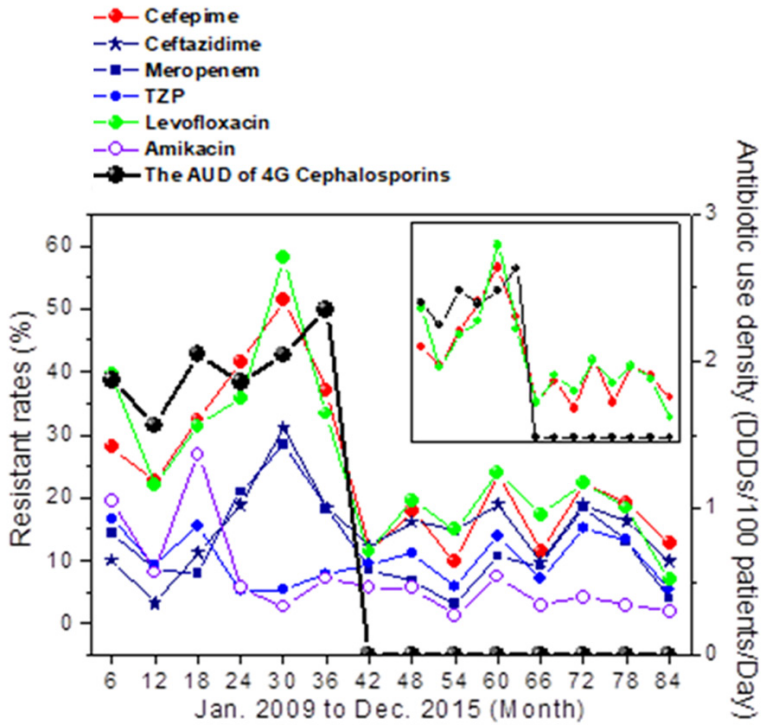

Figure 3. Correlation between AUD of the fourth generation cephalosporins and resistant rates of Pseudomonas aeruginosa against other five antibacterial drugs. Consumption of the fourth generation cephalosporins is expressed as defined daily dose (DDD) per 100 patients-days (DDDs/100 patients/day, right y-axis) every half year from 2009 to 2015. The resistance rate of Pseudomonas aeruginosa to cefepime, cefepime, meropenem, Piperacillin/tazobactam, levofloxacin and amikacin is calculated by dividing the number of resistance strains by the total number of the isolates multiplied by 100 (%, left y-axis) every half year from 2009 to 2015. The spearman correlation method was used to analyze the relationship between the amount of the fourth-generation cephalosporin and the resistance rate of Pseudomonas aeruginosa to these six antimicrobial agents. AUD, antibiotic use density.

ther analyzed. As the result showed, except FEP, drug resistance rate of Pseudomonas aeruginosa against Levofloxacin was significantly positively correlated to the AUD of the fourth-generation cephalosporin ($r = 0.786$, $P = 0.001$) and no correlation was shown between drug resistance against ceftazidime, meropenem, piperacillin/tazobactam, amikacin and the AUD of fourth generation cephalosporin (all $P>0.05$, **Figure 3** and **Table 3**).

Correlation between the AUD of other antibacterial drugs and drug resistance rate of Pseudomonas aeruginosa

The drug resistance rate of Pseudomonas aeruginosa against FEP was negatively correlated to AUD of TZP ($r = -0.541$, $P = 0.046$); drug resistance rate of Pseudomonas aeruginosa against LVX was only significantly positively correlated to intensity of use of the fourth-generation cephalosporin ($r = 0.786$, $P = 0.001$), but it had no correlation to AUD of TZP, fluoroquinolones and carbapenems (all $P>0.05$). While drug resistance rate of Pseudomonas aeruginosa against ceftazidime, meropenem, piperacillin-tazobactam and amikacin had no correlation to intensity of use of 4 types of antibacterial drugs (all $P>0.05$). See **Table 3**.

Discussion

The association of antimicrobial consumption with the development of antimicrobial resistance has been reported to be dependent on the species and antimicrobial agent. The main drug resistance mechanisms of bacteria including that antibacterial drugs can induce hypermutator to cause some genetic mutations and susceptible strains become resistant strain by receiving the lateral transfer of exogenous plasmids and transposons with drug resistance gene and so forth [15-19]. Wherein, producing drug resistant mutant strain and obtain reasonable application of selective advantage amplification and antibacterial drug from strains is particularly correlated.

FEP was used for moderate/severe infection, for example, the recommended dosages for streptococcus pneumonia and (or) gram-negative bacteria caused pneumonia are 1-2 g intravenously every 12 h for 10 days, which is sufficient to achieve the treatment goal for |susceptible organisms [20]. But if the standard treatments are able to achieve such targets and cure serious infections caused by Pseudomonas aeruginosa was concerned [20].

This research illustrated that there was significant strong correlation between AUD of the

Table 3. Correlation between AUD of the fourth-generation cephalosporin and resistant rates of Pseudomonas aeruginosa against other five antibacterial drugs

Drug consumed	Pseudomonas aeruginosa resistant rate					
	FEP	CAZ	MEM	TZP	LVX	AMK
	r, P	r, P	r, P	r, P	r, P	r, P
4G cephalosporins	0.828, 0.000	0.090, 0.759	0.426, 0.129	-0.022, 0.941	0.786, 0.001	0.520, 0.057
TZP	-0.541, 0.046	-0.086, 0.771	-0.286, 0.322	-, -	-0.431, 0.124	-0.512, 0.061
Quinolones	0.147, 0.615	-0.191, 0.513	0.077, 0.794	-0.336, 0.240	0.020, 0.946	-0.075, 0.799
Carbapenems	-0.305, 0.288	-0.051, 0.864	0.011, 0.970	-0.204, 0.483	-0.486, 0.078	-0.493, 0.073

Note: FEP, cefepime; CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin-tazobactam; LVX, levofloxacin; AMK, amikacin; 4G cephalosporins, fourth-generation cephalosporin; AUD, antibiotic use density.

fourth-generation cephalosporin and drug resistance rate of Pseudomonas aeruginosa. In a study by Lee HS et al., correlation between broad-spectrum cephalosporin use and development of resistance to these antimicrobials were also observed in Pseudomonas aeruginosa [21]. Increasing the administrated dosage or extend infusion time of Pseudomonas aeruginosa is required to achieve the pharmacodynamic target [22]. Before the massive use of FEP, the sensitivity of Pseudomonas aeruginosa against CAZ and FEP were usually the same; after that, it can be observed that Pseudomonas aeruginosa is resistance to FEP and susceptibility to ceftazidime, which may cause by over-expression of the MexXY-OprM efflux system [23]. According to the monitoring results from 2009 to 2015 in our hospital, the drug resistance rates of Pseudomonas aeruginosa against FEP were all higher than CAZ, especially when the massive use of FEP from 2009 to 2011 (see **Figure 3**). According to our investigation, when physicians use FEP to treat Pseudomonas aeruginosa, they usually use conventional dosing regimen, which can cause enrichment, expansion and dissemination of drug resistant strain, and finally the sensitivity of bacteria to antibacterial drug is lost.

This study demonstrated that drug resistance rate of Pseudomonas aeruginosa against levofloxacin also showed a significant positive correlation to intensity of use of the fourth-generation cephalosporin. Therefore, the application of the fourth-generation cephalosporin can not only affect the drug resistance rate of bacteria against FEP, but also affect the drug resistance rate of Pseudomonas aeruginosa against levofloxacin.

Further analysis of the effect of three antibacterial drugs (TZP, fluoroquinolones and carbapenems) on drug resistance rate of Pseudomonas aeruginosa were performed. According to the result, drug resistance rate of Pseudomonas aeruginosa against levofloxacin was significantly positively correlated to AUD of the fourth-generation cephalosporin, while that was not correlated with abovementioned three antibacterial drugs. Drug resistance rates of Pseudomonas aeruginosa against CAZ, MEM, TZP, AMK also had no correlation to the dosage of abovementioned three antibacterial drugs. That illustrated the application of the fourth-generation cephalosporin was the main selective pressure of emerging of multi-drug resistant Pseudomonas aeruginosa, therefore, when treating Pseudomonas aeruginosa infection with the fourth-generation cephalosporin, administrated dosage should be increased or the infusion time should be extended to optimize treatment solutions, in the meanwhile, multisectoral and powerful national plan of action is the guarantee of preventing bacterial resistance, and establishment normalized drug regulatory mechanism is necessary.

There are some limitations of this work. Firstly, this is a retrospective study, there might be variations in antibacterial drugs for different types of diseases and basic situation of patients in each time period. Secondly, our hospital initiated Special Rectification Activities of National Clinical Use of Antibiotics in 2011, the medication rationality increased gradually, and it also had impact on the emerging of bacterial resistance. Thirdly, no other risk factor evaluation affecting bacterial resistance was performed, such as controlling of hospital infection. Hence, a prospective study without these limitations is necessary to further exp-

lore the association between resistance of Gram-negative bacteria and the usage of fourth-generation cephalosporins in certain hospital.

In conclusion, the AUD of the fourth-generation cephalosporin was significantly negatively correlated with AUD of piperacillin-tazobactam and there were significantly positive correlations between AUD of the fourth-generation cephalosporin and drug resistance rates of Pseudomonas aeruginosa against FEP and LVX. Therefore, application of the fourth-generation cephalosporin was the main selective pressure of multi-drug resistant Pseudomonas aeruginosa.

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Disclosure of conflict of interest

None.

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