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Full Length Research Paper

The cross-association between antimicrobial consumption and resistance in *acinetobacter baumannii*

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This study was implemented to analyses the association between the regional rates of antimicrobial resistance in *Acinetobacter baumannii (A. baumannii)* isolates and antimicrobial consumption in the hospital districts. The data on the consumption of antimicrobial for systemic use in Liao-Ning North Hospital were obtained from 2005 through 2009. Consumption data were compared with antimicrobial resistance in all isolates of *A. baumannii*. Statistical significance was defined as *p* value < 0.05 for the corresponding correlation coefficient. With the increase of drug resistance, *A. baumannii* isolation rate increased significantly, the proportion of *A. baumannii* infections in the composition of bacteria was also significantly increased (from 2.3% in 2005 year to 17.6% in 2009 year). Yearly rates of resistance to meropenem, cefepime, ceftazidime, piperacillin and amikacin were significantly associated with meropenem or levofloxacin (*P* < 0.05) consumptions in the same year, while consumption of cefepime, ceftazidime and amikacin had no apparent association with resistance. The consumption of Meropenem and levofloxacin significantly correlated with resistance of Meropenem, levofloxacin, cephalosporins, amikacin and piperacillin in *A. baumannii.* The formation of bacterial clones and being prevalent in the local context may be the ideal model for studying antibiotic usage and resistance development.

Keyword: Antimicrobial resistance, *acinetobacter baumannii*, consumption.

INTRODUCTION

The increasing antibacterial consumption is recognized as the main reason for the emergence of resistance in the targeted bacterial population. There were some epidemiological studies that have recorded temporal changes in the frequency of drug-resistance when the volume of drug consumption in the community is deliberately reduced (2,4,5). But there were other investigation that show the decrease in antibiotic use that did not produce a decrease in the resistance levels (3,9,11). These contrasting results indicate that the fate of antimicrobial-resistance determinants, following a significant reduction in the selective pressure, depends on factors other than drug consumption alone.

Acinetobacter baumannii (A. baumannii) is an important nosocomial pathogen, with a rising prevalence. Unfortunately, the emergence of Multi-drug-resistant *A. baumannii* (MDRA) has become a worldwide problem and a troublesome development that threatens the continued successful treatment of *A. baumannii* species infections (1,6,15). The aim of the study described here was to investigate the association between the regional rates of antimicrobial resistance among *A. baumannii* isolates and antimicrobial consumption in Liao-Ning North Hospital of China districts during a 5-year period.

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MATERIALS AND METHODS

Bacterial isolates

A total of 1022 *A. baumannii* isolates were tested for antimicrobial resistance in the Liaoning North hospital of china during a 5-year study period from 2005 through 2009. The isolates were from laboratories reported and only one isolate per patient each year. Identification was performed by using the system (Zhuhai DL Medical Biotech Co.,LTD, China). Our laboratories participate in national quality assurance collaborations (the Chinese National External Quality Assessment Schemes).

Antibiotic susceptibility testing

Antimicrobial susceptibility was determined by the disc diffusion method on Mueller–Hinton agar (Oxoid, Basingstoke, UK) according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). Data on susceptibility to the following antimicrobials were included in the study: amoxicillin, amoxicillin-clavulanate, cephalosporins (cephalothin or cephalexin), fluoroquinolones (norfloxacin or ciprofloxacin), trimethoprim, trimethoprim-sulfamethoxazole, amdinocillin (mecillinam), and nitrofurantoin.

Consumption of antimicrobial agents

Data on the consumption of antimicrobials for systemic use were obtained from the Pharmacy of Liaoning North hospital. Antimicrobial consumption is expressed as defined daily doses (DDD) per 1,000 beds per day. Data of the following antimicrobials were included in the study: meropenem, cefepime, ceftazidime, levofloxacin, amikacin, Piperacillin. The consumptions of imipenem, cefoperazone and other drug were small in their respective categories, so not listed here.

Statistical analysis

The statistical analysis was performed by linear regression (SPSS 11.5). All tests were two-tailed, and a p value of <0.05 was considered significant in linear regression analysis.

RESULTS

The correlation between the levels of antibiotic usage and resistance in *A. baumannii*

These antibiotics commonly used in the treatment of clinical Gram-negative bacteria, such as meropenem, levofloxacin, cefepime, ceftazidime, amikacin, piperacillin, were selected to analyze the associations between antimicrobial consumption and antimicrobial resistance among *A. baumannii* isolates in the North hospital were studied. At the same time, these antibiotics are the most representative, and the biggest consumption in the North hospital. The doses (DDD) per 1,000 beds per day and the rates of drug-resistance each year with each antimicrobial is presented in Table 1.

Of these, two associations were statistically significant. The level of meropenem use was associated with meropenem resistance (r=0.99, t=10.05, P=0.0010), the level of levofloxacin use was associated with levofloxacin resistance (r=0.89, t=3.33,P = 0.0224). The others, cefepime, ceftazidime, amikacin, their consumption was no-associated with drug-resistance respectively. In addition, the association between the specific antibiotics and other antibiotics resistance has been found.

The level of meropenem use was associated with Imipenem resistance (r=0.95, t=5.03,P=0.0076), cefepime (r=0.98,t=9.69,P=0.0023), ceftazidime (r=0.98,t=9.69,P=0.0032), amikacin (r=0.93, t=4.46,P=0.0209), piperacillin (r=0.98,t=7.62,P=0.0047), levofloxacin (r=0.979, t=8.33,P=0.0036).The level of levofloxacin use was associated with Imipenem resistance (r=0.95, t=5.03,P=0.0076), cefepime (r=0.93,t=4.34,P=0.0225), ceftazidime(r=0.92, t=3.99,P=0.0032), amikaci n(r=0.91, t=3.84,P=0.0312), piperacillin (r=0.98, t=7.62,P=0.0282), meropenem (r=0.91, t=3.80,P=0.0320).

Observation of the emergence of *A.baumannii* with nosocomial infection rates

With drug-resistance rates increasing, the detection rate of *A. baumannii* was significantly higher in overall infection rates. However, meropenem resistant *A. baumannii* were very low in 2005 and 2007 year, but significantly increased in 2007 year. As showed in table 2.

DISCUSSION

In this study, two associations were statistically significant among *A. baumannii*. The level of meropenem use was associated with meropenem resistance. The level of levofloxacin use was associated with levofloxacin resistance. The others, amikacin, cefepime, ceftazidime, amikacin, their consumption was no-associated with drug-resistance respectively. In addition, the association between the specific antibiotics and other antibiotics resistance has been found. The level of meropenem use was associated with resistance to Imipenem, cefepime, ceftazidime, amikacin, piperacillin, levofloxacin (P<0.05, respectivly) in *A. baumannii.* The level of levofloxacin use was also associated with resistance to Imipenem, cefepime, ceftazidime, amikacin, piperacillin, meropenem (P<0.05, respectivly) in *A.*

Table 1. The defined daily doses (DDD) per 1,000 beds AND the rates of drug-resistance during a 5-year study period from 2005 through 2009.

Year	meropenem		levofloxacin		cefepime	amikacin		ceftazidime		Piperacillin		
	DDDs	R(%)	**DDDs**	R(%)	**DDDs**	R(%)	**DDDs**	R(%)	**DDDs**	R(%)		
2005	12.7	2	9.7	30	0.77	23.2	2.5	25	27	26.5	-	21.7
2006	15.2	1	13.4	39	0.5	29.3	2.8	47	10.5	32.2	-	38.0
2007	24.4	35	14.4	58	7.9	50.9	3.1	60	8.8	55.4	-	63.2
2008	43	70	19.2	75	20.7	75.1	2.9	74	2.8	75.8	-	88.8
2009	42.5	83.4	28	78.7	0.73	86.4	2.2	83.7	26	85.8	-	88.6

Table2. The isolate rates of A. baumannii from 2005 year to 2009 year.

Year	Isolatesn（Proportions %）	In the ranking of all bacteria isolates in the hospital
2005	58（2.3%）	10(tenth)
2006	59（2.6%）	11（eleventh）
2007	175（8.6%）	5(fifth)
2008	307（15.7%）	2(second)
2009	423(17.6%)	2(second)

baumannii. Thus the positive associations found between antimicrobial resistance in *A. baumannii* and antimicrobial use concerned mainly meropenem and levofloxacin.

The results presented in this paper are in line with those presented in several other papers. LUO Yan-ping et al. (8) reported, from 1994 to 2003, a significant positive correlation between the resistance and DDDs of ceftazidime and ciprofloxacin (r=0.88,P≤0.01 and r=0.65,P≤0.05) were found. The consumption of ceftazidime and ciprofloxacin was also related to the resistance of *A. baumannii* to piperacillin and cefotaxime respectively. During the study period, imipenem consumption was very small, its resistance of *A. baumannii* was low, the link between the two was not statistically significant, imipenem on *A. baumannii* impact of other drug resistance was not significant. Meyer et al. (10) reported increased carbapenem consumption was associated with carbapenem-resistant *K. pneumoniae* carbapenemase-producing bacteria and imipenem-resistant *A. baumannii*. However, several other studies have shown the associations between antimicrobial resistance in *A. baumannii* and antimicrobial consumption was no significant. Thab et et al. (13) reported the consumption of ciprofloxacin was also correlated (P<0.05) with resistance of ceftazidime in *K. pneumoniae*. However, there is not a correlation (P> 0.05) between fluoroquinolones use and resistance in *A. baumannii* as well in ciprofloxacin, imipenem and ceftazidime.

It is interesting that during the Five-year study period, there were no significant correlation between the resistance rates and consumption of the major antibiotic in *P. aeruginosa* which ranked first in all bacteria isolated in our hospital (Negative results, not showed in this article). This result is inconsistent with other report (7). In addition, our previous studies have shown that the emergence of Acinetobacter carbapenem resistance in our Hospital is associated with the spread of *Abaumannii* strains of major clone A during the period of this study (14). Nemec A (12) reported that the emergence of Acinetobacter resistance to carbapenems in the Czech Republic was associated with the spread of MDR *A. baumannii* strains belonging to EU clone II. So, it may be infer that the formation of bacterial clones and being prevalent in the local context is the ideal model for studying antibiotic usage and resistance development.

In conclusion, the consumption of meropenem and levofloxacin was significantly associated with drugs resistance. The consumption of Meropenem and levofloxacin significantly also correlated with resistance of cephalosporins, amikacin and piperacillin in *A. baumannii.* When adjusting drug use patterns in order to reduce the selection pressure that aids the development of resistance, the cross effect of Meropenem and levofloxacin on other drugs must be taken into account. The formation of bacterial clones and being prevalent in the local context may be the ideal model for studying antibiotic usage and resistance development.

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