

Changes in the rates of antimicrobial resistance among clinical isolates of *Pseudomonas aeruginosa* between 2002 and 2004 in a tertiary-care teaching hospital in Turkey

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SUMMARY

Pseudomonas aeruginosa is an important opportunistic pathogen usually resistant to most antimicrobials. We present changes in the resistance pattern of *P. aeruginosa* to amikacin (AK) and ciprofloxacin (CIP) between January 2002 and June 2004. The physicians of each unit were given information on antibiotic resistance rates of *P. aeruginosa* isolated from ward patients at regular intervals. The antibiotic resistance of 161 *P. aeruginosa* isolates isolated from intensive care units (ICUs) and non-ICUs were tested by disk diffusion method, and the results were interpreted according to the guidelines of National Committee for Clinical Laboratory Standards. Thirty-five percent of all the *P. aeruginosa* isolates were resistant to AK in 2002, 18% in 2003, and 20% in 2004. The CIP resistance rates were 4% in 2002, 26% in 2003, and 20% in 2004. In that period, resistance to AK decreased, whereas resistance to CIP increased. The usage rate of AK in 2002 was 32%, which fell to 26% in 2003 ($p < 0.05$). This rate increased to 27% in 2004 ($p < 0.05$). The usage rate of CIP was very low in 2002 (3%). Subsequently, it increased to 8% in 2003 and 2004 ($p < 0.05$). The changes in resistance rates may have been due to alteration in drug usage policy in our hospital. It is important to provide physicians with information on antibiotic resistance rates at regular intervals to guide therapy for critical *P. aeruginosa* infections.

KEY WORDS: *Pseudomonas aeruginosa*, Antimicrobial resistance, Therapy policy

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INTRODUCTION

P. aeruginosa is an important opportunistic pathogen. It has high intrinsic resistance to most antimicrobials used in therapeutic practice (Segatore *et al.*, 1999; Kiffer *et al.*, 2005; Bayram *et al.*, 2006). Antimicrobial agents with reliable

activity against *P. aeruginosa* include antipseudomonal penicillins and cephalosporins, carbapenems, aminoglycosides and fluoroquinolones, particularly ciprofloxacin. Nowadays, recommended treatments for systemic *P. aeruginosa* infections are combined therapy, which may increase the chance of successful therapy and minimize the risk of developing resistance (Burgess *et al.*, 2005). Aminoglycosides and fluoroquinolones are important components of combined therapy. They exhibit synergy with other antimicrobials (Poole *et al.*, 2005). The combinations involving an aminoglycoside plus β -lactam with antipseudomonal activity or antipseudomonal fluoroquinolon plus β -lactam with

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antipseudomonal activity are important alternatives for treatment of *P. aeruginosa* infections (Drago *et al.*, 2005; Burgess *et al.*, 2002). For each of the antipseudomonal agents, emergence of resistance during therapy has been described. Regional variations in resistance pattern were observed and most probably related to antibiotic treatment regimens (Eldere *et al.*, 2003; Dzieranowska-Fangrat *et al.*, 2005; Bouza *et al.*, 1999).

In this study, the ward doctors were given information about antibiotic resistance rates of *P. aeruginosa* isolated from ward patients at regular intervals and the changes in resistance rates to amikacin and ciprofloxacin between January 2002 and June 2004.

METHOD

Bacterial isolates

The study was performed at Inonu University Hospital, a 700-bed tertiary-care teaching hospital in Malatya, Turkey. One hundred and sixty-one bacterial isolates were obtained from various biological materials, collected from in-patients according to the decision of the attending physicians between January 2002 and June 2004.

A total of 161 isolates were studied. Forty-three bacterial isolates were isolated from intensive-care units (ICU) (neurosurgery, cardiovascular surgery, neonatal, pediatric, surgical and general high care). The other 118 strains were isolated from different non-intensive-care-units (non-ICU) (general surgical, neurosurgery, cardiovascular surgery, neonatal, pediatric, orthopedics, urology, nephrology, gastroenterology, chest diseases). The samples were obtained from urine (60 isolates), tracheal aspirates (48 isolates), surgical wound (20 isolates), blood (14 isolates), sputum (9 isolates), and other samples (10 isolates). All of them were isolated from clinical species in different years as follows: 46 in 2002; 85 in 2003, and 30 in 2004. The bacterial isolates were identified by conventional biochemical tests. Multiple isolates of the same species from a single origin (same patient) were excluded. If more than one *P. aeruginosa* isolate were recovered from different species of the same patient, only one of the isolates with the same antimicrobial resistance pattern was selected.

Antimicrobial susceptibility

Antibiotic susceptibility was determined using the disk diffusion method described by National Committee for Clinical Laboratory Standards (NCCLS 2000). The quality control was carried out using standard strains of *P. aeruginosa* (ATCC 27953). All the isolates were tested against amikacin (AK) (30 µg) and ciprofloxacin (CIP) (5 µg) (oxid UK). The isolates displaying intermediate susceptibility according to the NCCLS guidelines were considered as resistant.

Statistical analysis

Statistical analysis was performed using Chi square test and $p < 0.05$ was considered statistically significant. Statistical Package for Social Sciences, version 10.0 software, was used for the data analyses.

RESULTS

In the whole hospital:

Thirty-five percent of total *P. aeruginosa* isolates were resistant to AK in 2002; 18%, in 2003, and 20%, in 2004. In all the units, the CIP resistance rates were 4% in 2002, 26% in 2003, and 20% in 2004.

In ICUs:

The AK resistance rates of *P. aeruginosa* obtained from ICU decreased to 9% in 2004 from 30% in 2002 (30% in 2002, 23% in 2003, and 9% in 2004; Table 1).

In non-ICUs:

The AK resistance rates of isolates obtained from non-ICUs also fell to 16% in 2003 from 36% in 2002, but increased again to 26% in 2004. The decline in the rates in non-ICUs was statistically significant. The CIP resistance rates of strains from non-ICUs increased from 6% in 2002 to 26% in 2003 and 2004 ($P=0.01$, $P=0.02$).

The resistance rates to AK and CIP of *P. aeruginosa* isolates are presented in Table 1.

Two out of 16 AK-resistant strains were resistant to CIP in 2002; 6 out of 15 AK-resistant strains, in 2003, and 5 out of 6 AK-resistant strains in 2004 (Table 1).

AK was the most commonly preferred drug in the hospital between 2002 and 2004. The usage rate

TABLE 1 - Resistance rates of *P. aeruginosa* isolates to antimicrobials.

	Years (n)	2002 (10)	2003 (22)	2004 (11)	Total (43)
Antibiotic resistance in ICUs % (n)	AK % (r)	30 (3)	23 (5)	9 (1)	21 (9)
	CIP % (r)	0 (0)	32 (7)	9 (1)	19 (8)
Non-ICUs	Years (n)	2002 (36)	2003 (63)	2004 (19)	Total (118)
	AK % (r)	36 (13)	16 (10)	26 (5)	24 (28)
	CIP % (r)	6 (2)	26 (15)	26 (5)	19 (22)
Total Units (ICU and non-ICU)	Years (n)	2002 (46)	2003 (85)	2004 (30)	Total (161)
	AK % (r)	35 (16)	18 (15)	20 (6)	23 (37)
	CIP % (r)	4 (2)	26 (22)	20 (6)	19 (30)
	Resistance to both AK and CIP % (r)	4 (2)	7 (6)	17 (5)	8 (13)

TABLE 2 - The amikacin and ciprofloxacin usage rates in our hospital between 2002 and 2004.

Years	Drugs	Annual usage % (n)
2002 (Total antibiotic usage: 49000 doses)	Ciprofloxacin	3 (1688)
	Amikacin	32 (15561)
	Total	35 (17249)
2003 (Total antibiotic usage: 33737 doses)	Ciprofloxacin	8 (2687)
	Amikacin	26 (8679)
	Total	34 (11366)
2004 (Total antibiotic usage: 36376 doses)	Ciprofloxacin	8 (2901)
	Amikacin	27 (9893)
	Total	35 (12794)

In this study, the term 'dose' refers to each of the pharmaceutical dosages forms such as one tablet, one capsule, one flacon; n: number of dose.

of AK in 2002 was 32%, and it fell to 26% in 2003 ($p < 0.05$). This rate increased to 27% in 2004 ($p < 0.05$). The usage rate of CIP was very low in 2002 (3%). However, it increased to 8% in 2003 and 2004 ($p < 0.05$) (Table 2).

In this study, the term 'dose' has been used to refer to each of the pharmaceutical dosage forms such as one tablet, one capsule, one flacon. The total doses of antibiotics used in the hospital in different years were 49000 doses in 2002, 33737 in 2003, and 36376 in 2004. The ciprofloxacin usage rates in different years were 3%, 8%, 8% of the total dose of all the antibiotics used, and the usage rates for amikacin were 32%, 26%, and 27% in 2002, 2003, and 2004 respectively (Table 2).

DISCUSSION

The effect of physicians' awareness of the changes in antibacterial resistance rates of bacteria was evaluated. Recent studies have focused on the increased resistance of *P. aeruginosa* to anti-pseudomonal agents (Obritsch *et al.*, 2004; Andrade *et al.*, 2003). From different countries, the antibiotic resistance rates of *P. aeruginosa* have been reported to be 4-17% to AK, and 18-26% to CIP (Eldere *et al.*, 2003; Bouza *et al.*, 1999; Karlowsky *et al.*, 2003; Rodriguez *et al.*, 2006). In some reports from our country, the rates have been noted as 20-42% for AK and 16-59% for CIP, (Bayram *et al.*, 2006; Gönlugur *et al.*, 2003; Küçükate *et al.*, 2005; Gençer *et al.*, 2002). This study aimed to investigate the effects of providing physicians with data on antibacterial resistance rates of *P. aeruginosa* at different clinics.

The resistance rates of our isolates were quite similar to other results from foreign countries and the results of some studies from our country. On the other hand, in our study, the CIP resistance rate was very low in 2002. The isolates obtained from ICU patients in 2002 were not resistant to CIP, while the resistance rate increased to 32% in 2003 and decreased to 9% in 2004 in ICUs (Table 1).

The AK resistance rate in all our hospital units was 35% in 2002. The CIP resistance rate increased from 4% in 2002 to 26% in 2003, while the AK resistance rate decreased from 35% to 18% in 2003. However, the AK resistance rate slightly increased in 2004, and the CIP resistance started

to decrease again. The relationship between the CIP and AK-resistant strains was interesting. Two out of 16 AK-resistant strains were resistant to CIP in 2002, 6 out of 15 AK-resistant strains in 2003, and 5 out of 6 AK-resistant strains in 2004 (Table 1). The AK and CIP resistance rates increased from 4% in 2002 to 17% in 2004. This was an undesirable result. What caused the changes in resistance rates is a matter of speculation.

The physicians of each unit were provided with information on antibiotic resistance rates of *P. aeruginosa* isolated from the ward patients at regular intervals, and the antimicrobial susceptibility results were followed by the Infection Control Committee of the hospital between 2002 and 2004. The changes in the resistance rates of *P. aeruginosa* to antimicrobials may have been due to constant warnings of the hospital control committee of the physicians based on our data and thus, the alterations made in the drug regimens of use accordingly.

The data collected from the pharmacy of our hospital on the amount of antibiotics prescribed or consumed have been shown in Table 2. Such data supported our notion.

The usage of AK was most frequent in 2002 (32%). Therefore, sensitive strains had died, but resistant strains had increased in number. The rate of CIP usage was very low (3%) in 2002. The rate of CIP-resistant strains was also very low (4%) in 2002, and 96% of *P. aeruginosa* strains causing infections were CIP-sensitive. Therefore, the physicians preferred the use of CIP to AK in 2003 and 2004. The CIP usage rate increased to 8% in 2003 and 2004. The AK usage rate declined significantly in 2003 (26%) and slightly increased again in 2004 (27%).

The resistance rate to AK also decreased from 35% in 2002 to 18% in 2003 ($p < 0.05$) and slightly increased in 2004 (20%). The resistance rate to CIP also increased from 4% in 2002 to 26% in 2003 ($p < 0.05$). In 2004, the CIP usage rate sustained, while the AK usage rate increased to 27%. In that year, the resistance rates of *P. aeruginosa* to both drugs were the same (20%), but the rates of both CIP and AK-resistant strains increased to 17% from 7% in 2004.

In conclusion, it is necessary to provide physicians with information on antibiotic resistance rates at regular intervals since prescribing practices in our study changed the drug resistance

rates between 2002 and 2004. This information affected the practice of antibiotics usage and the resistance profile of *P. aeruginosa* to antibiotics in our hospital. Continued surveillance is important to guide therapy for critical *P. aeruginosa* infections.

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