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ORIGINAL ARTICLE

Antimicrobial consumption and resistance in five Gram-negative bacterial species in a hospital from 2003 to 2011

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antimicrobial agents;
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Background: The misuse of antimicrobial agents increases drug resistance in bacteria.
Methods: The correlation between antimicrobial agent consumption and related resistance in the Gram-negative bacteria *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus mirabilis* was analyzed during the period 2003–2011.
Results: Among these five bacteria, overall *E. coli* and *K. pneumoniae* were more commonly isolated from bloodstream than the other species. Regarding Enterobacteriaceae, *E. coli* and *K. pneumoniae* showed annual increases of resistance to the tested antimicrobial agents; conversely, *P. mirabilis* exhibited reduced resistance to cefuroxime, ceftriaxone and cefepime. In contrast to the relatively low antimicrobial resistance in *P. aeruginosa*, *A. baumannii* revealed high resistance, which was over 85% resistant rate to the tested antimicrobial agents and over 80% carbapenem resistance in 2011. *E. coli*, *K. pneumoniae*, and *P. mirabilis* differed in development of antimicrobial resistance after consumption of the antimicrobial agents. *K. pneumoniae* developed resistance to all antimicrobial groups, whereas resistance in *P. mirabilis* was not related to any antimicrobial consumption. *P. aeruginosa* developed resistance to β-lactam antimicrobials and aminoglycosides, whereas *A. baumanii* developed resistance to carbapenems after their use.

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Conclusion: The development of antimicrobial resistance was related to antimicrobial agents and bacterial species.

Introduction

Extended-spectrum cephalosporins, β-lactam with β-lactamase inhibitor, carbapenems, fluoroquinolones, and aminoglycosides are common antimicrobial agents used in the treatment of bacterial infections. However, application of these antimicrobial agents can induce antimicrobial resistance through mutations and the transfer of mobile elements harboring resistance genes, thus increasing the incidence of drug-resistant bacteria. Some examples include extended-spectrum β-lactamase (ESBL)-producing bacteria carrying *bla* genes for cephalosporin resistance[1,2] and fluoroquinolone-resistant bacteria with mutations in topoisomerases II and IV and altered expression of efflux pumps.[3,4]

The emergence of multidrug resistant (MDR) bacteria not only causes public health problems but also increases medical costs and the hospitalization, morbidity and mortality of patients.[5] MDR Gram-negative bacteria are major nosocomial pathogens and are increasing annually worldwide[6–11] and in Taiwan[12,13]; these species include ESBL-producing *Klebseiella pneumoniae* and *Escherichia coli*, MDR *Pseudomonas* aeruginosa,[14,15] and pan-drug resistant *Acinetobacter baumannii*.[16] Carbapenems have recently been replaced the extended-spectrum cephalosporins to treat ESBL-producing bacteria; accordingly, carbapenem resistance has been observed in *P. aeruginosa* (i.e., imipenem)[17] and *A. baumannii* (CRAB).[18,19] In Taiwan, CRAB isolates have increased gradually, with the highest in central Taiwan.[20] In this study, we analyzed the resistance profile of major Gram-negative bacteria, the consumption of antimicrobial agents and the correlation between antimicrobial usage and development of resistance.

Materials and methods

Retrospective study

All information was collected from Chiayi Branch, Taichung Veterans Hospital from 2003 to 2011. The hospital has 445 beds, including 24 beds for intensive care units, 40 beds for the respiratory care ward, 250 beds for general in-patients, and 225 beds for psychiatry patients. The hospital also has a 246-bed nursing home.

Bacterial identification and antimicrobial susceptibility test

Clinical isolates of *A. baumannii*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis* were identified using the Phoenix and VITEK system in the Medical Laboratory Division. The antimicrobial susceptibility to the antimicrobial agents was determined according to the guidelines of Clinical and Laboratory Standards Institute.[21] The antimicrobial agents analyzed included: amikacin, gentamicin, and isepamicin (aminoglycosides); cefazolin, cephradine, and cephalexin (first-generation cephalosporins); flomoxef, cefuroxime, cefoxitin, ceftazidime, ceftriaxone, and cefepime (extended-spectrum cephalosporins); imipenem, meropenem, and ertapenem (carbapenems); ciprofloxacin, levofloxacin, and moxifloxacin (fluoroquinolones); ampicillin/sulbactam, amoxicillin/clavulanic acid, piperacillin, piperacillin/tazobactam (penicillins and penicillin with β-lactamase inhibitor); and tigecycline. The defined daily dose represents the antimicrobial usage of 1000 patients and was used for the statistical analysis.

Statistical analysis

Linear regression was performed to determine the correlation coefficient (r) of antimicrobial agent consumption and antimicrobial resistance of each species associated with specific years. Furthermore, correlation coefficients of antimicrobial agent consumption and antimicrobial resistance in each species were calculated, and a t test for was applied to ascertain significant differences ($p < 0.05$).

Results

Clinical isolates of five Gram-negative bacteria

The number of clinical isolates differed among the species with the highest for *P. aeruginosa*, followed by *E. coli*, *A. baumannii*, *K. pneumoniae*, and *P. mirabilis* (Table 1). Although the clinical isolates of each species differed annually, maximal number was observed for *P. aeruginosa*, *E. coli*, and *K. pneumoniae* in 2008 and for *P. mirabilis* in 2009. *A. baumannii* clinical isolates increased annually from 2003 to 2011. These five species differed in prevalence of bloodstream isolates from the highest for *E. coli* (13.5%), followed by *K. pneumoniae* (9.8%), *A. baumannii* (5.9%), *P. mirabilis* (5.9%) and *P. aeruginosa* (3.6%). Interestingly, *A. baumannii* showed an increase in bloodstream isolates and mainly were CRAB (88%).

Consumption of antimicrobial agents

The consumption level of five major antimicrobial groups differed with a gradual reduction in aminoglycosides ($r = -0.88$, $p < 0.01$) and first-generation cephalosporins ($r = -0.92$, $p < 0.01$), an annual increase in extended-spectrum cephalosporins ($r = 0.92$, $p < 0.01$) and carbapenems ($r = 0.93$, $p < 0.01$), with an exceptional use of fluoroquinolones and penicillins in 2006 and 2007,

Table 1 Clinical and bloodstream isolates of five prevalent bacterial species from 2003 to 2011

Year	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Acinetobacter baumannii*	*Proteus mirabilis*	Total
Total clinical isolates						
2003	394	453	152	271	105	1375
2004	459	561	226	268	90	1604
2005	653	748	371	310	224	2306
2006	570	800	458	442	296	2566
2007	497	551	417	416	165	2046
2008	545	638	482	348	218	2231
2009	546	569	445	380	333	2273
2010	527	496	346	396	202	1967
2011	712	620	468	612	320	2732
Total	4903	5436	3365	3443	1953	19,100
Mean	544.8	604	373.9	382.6	217	2122.2
From bloodstream isolates						
2003	60	16	15	23	7	121
2004	67	11	18	11	7	114
2005	86	16	45	11	16	174
2006	53	15	40	15	12	135
2007	53	16	29	14	18	130
2008	51	18	44	12	13	138
2009	93	47	30	19	15	204
2010	65	23	38	32	12	170
2011	132	32	70	67	15	316
Total	660	194	329	204	115	1502
Mean	73.3	21.6	36.6	22.7	12.8	166.9
Bloodstream isolate rate (%)	13.5	3.6	9.8	5.9	5.9	7.9

respectively (Table 2). Furthermore, the consumption level of antimicrobial agents in each group varied. For the aminoglycosides, an increase in amikacin and reduction in gentamicin were observed. With regard to the fluoroquinolones, a significant reduction in ciprofloxacin and increase in levofloxacin were found ($p < 0.05$). Of penicillins, ampicillin/sulbactam and piperacillin reached the maximal consumption in 2007 and 2008, respectively, and then decreased in contrast to the increase in the use of amoxicillin/clavulanic acid and piperacillin/tazobactam annually. For the extended-spectrum cephalosporins, a significant increase in ceftriaxone, cefoxitin, and flomoxef and decrease in cefuroxime were observed. The consumption level of imipenem and meropenem was decreased since 2008 and 2009, respectively, while an increase in ertapenem was observed at the same period.

Antimicrobial susceptibility

The antimicrobial agent selected to treat infections depend on the bacterial species involved. Therefore, antimicrobial resistance and its prevalence differed among these five species (Table 3). Comparing the antimicrobial resistance of *E. coli*, *K. pneumoniae*, and *P. mirabilis* of Enterobacteriaceae, *E. coli* showed significant increase in the resistance (over 40%; $r > 0.9$, $p < 0.05$) to ampicillin/sulbactam, cefazolin, cefoxitin, ceftazidime, and ceftriaxone of the β-lactam antimicrobials, and to ciprofloxacin and levofloxacin of the fluoroquinolones. In contrast, the average resistance rate (≤20%) was for cefepime, meropenem, and piperacillin/tazobactam. All *K. pneumoniae* isolates exhibited significantly increased resistance ($r > 0.70$, $p < 0.05$) to all antimicrobial agents, except gentamicin, cefepime, levofloxacin, and meropenem. These two species differed in the antimicrobial resistance rate. Higher resistance rates were observed in *E. coli* for ampicillin/sulbactam, ceftriaxone, ciprofloxacin and levofloxacin and in *K. pneumoniae* for cefepime, meropenem and piperacillin/tazobactam. In contrast to the above two species, *P. mirabilis* displayed annual increases in resistance only to amikacin ($r = 0.70$, $p < 0.05$).

In *P. aeruginosa*, resistance rate was increased in ceftazidime, piperacillin/tazobactam, and carbapenems of meropenem ($p = 0.03$) and imipenem ($p = 0.08$), but reduced in aminoglycosides ($r < -0.8$, $p < 0.05$). All *A. baumannii* isolates showed the highest resistance rate to all antimicrobials examined, particularly ampicillin/sulbactam, meropenem, ciprofloxacin, and levofloxacin, with nearly 90% in recent years. However, an annual increase in resistance was only found to be significant for imipenem and meropenem ($r > 0.9$, $p < 0.05$), ciprofloxacin ($r = 0.96$, $p < 0.001$) and ampicillin/sulbactam ($r = 0.95$, $p < 0.001$).

Association of antimicrobial resistance rate and antimicrobial dosage

Although 26 antimicrobial agents and five bacterial species were investigated, a significant correlation between the antimicrobial resistance rate of six antimicrobial agent

Table 2 Annual consumption of antimicrobial agents from 2003 to 2011

Antimicrobial agents	Antibiotic consumption (DDD/1000 patient-days) by year[a]											
	2003	2004	2005	2006	2007	2008	2009	2010	2011	Mean	*r*	*p*
Aminoglycosides	68.9	73.7	54.3	44.1	46.4	43.9	32.6	32.8	40.0	48.5	−0.88	0.00
Amikacin	4.0	4.7	3.9	4.7	7.5	11.6	11.2	11.6	12.7	8.0	0.96	0.00
Gentamicin	65.0	69.0	50.7	39.4	38.9	32.2	21.3	21.2	25.6	40.4	−0.94	0.00
First-generation cephalosporins	172	189	165	132	135	128	105	110	112	139	−0.92	0.00
Extended-spectrum cephalosporins	29.2	26.9	48.3	61.1	40.6	68.0	67.6	72.4	91.1	56.1	0.92	0.00
Ceftazidime	1.3	6.9	18.5	29.2	16.3	14.9	11.4	4.8	3.5	11.9	−0.13	0.73
Ceftriaxone	1.6	2.9	7.1	8.4	10.6	16.2	13.8	17.3	25.9	11.5	0.96	0.00
Cefepime	11.3	4.9	6.3	5.2	1.9	6.5	12.8	15.3	21.9	9.5	0.64	0.07
Cefoxitin	0.7	2.8	3.5	1.5	6.1	8.8	18.1	21.0	20.0	9.2	0.93	0.00
Flomoxef	0.8		0.2		1.2	4.3	6.4	10.5	17.5	4.6	0.86	0.01
Cefuroxime	13.5	9.4	12.9	16.1	4.6	17.3	5.1	2.0	0.1	9.0	−0.65	0.06
Carbapenems	4.9	6.5	7.2	13.0	14.6	19.7	42.5	49.4	44.1	22.4	0.93	0.00
Imipenem	2.3	4.7	4.9	11.2	12.4	16.9	7.7	5.7	4.8	7.8	0.24	0.54
Meropenem	2.6	1.8	2.2	1.9	2.3	2.8	13.9	7.2	1.5	4.0	0.41	0.28
Ertapenem							20.9	36.5	37.8	10.6	0.90	0.29
Quinolones	30.9	37.8	54.8	76.6	66.7	67.4	53.8	44.2	36.3	52.0	0.08	0.83
Ciprofloxacin	27.7	33.4	47.0	69.4	58.1	47.7	29.6	17.2	11.0	37.9	−0.41	0.27
Levofloxacin	3.2	4.4	7.7	7.1	8.6	19.8	19.2	21.6	20.6	12.5	0.94	0.00
Penicillins												
Ampicillin/sulbactam	13.7	38.1	68.9	92.5	117	76.9	80.3	48.9	30.0	62.9	0.15	0.71
Amoxicillin/clavulanic acid		6.0	4.7	11.5	14.8	26.7	35.2	42.7	56.9	22.1	0.97	0.00
Piperacillin	7.6	9.8	4.5	5.5	12.4	16.4	9.0	6.0	7.4	8.7	0.09	0.81
Piperacillin/tazobactam	1.1	2.8	4.2	8.7	15.6	23.6	24.4	33.5	39.5	17.0	0.98	0.00
Tigecycline					0.2	0.3	4.1	2.3	3.0	1.1	0.79	0.01

[a] Patient-days are only for patients from intensive care units, respiratory care ward, and general inpatients.
DDD = defined daily dose.

groups and antimicrobial consumption was observed; for examples, use of extended-spectrum cephalosporins as well as reduced use of aminoglycoside and first-generation cephalosporins and development of related resistance in *E. coli*; development of resistance to all five antimicrobial groups used and reduced consumption of aminoglycosides in *K. pneumoniae*; use of aminoglycosides, extended-spectrum cephalosporins, and piperacillin/tazobactam to develop resistance to these antimicrobial agents in *P. aeruginosa*; use of carbapenem and development of resistance to imipenem and meropenem in *A. baumannii* (Table 4).

Discussion

Antibiotic-resistant bacteria in humans have been related to maternal and environmental microbial origins[22] and can transfer from animals to humans through consumption of contaminated meats and other products. In this study, the major antimicrobial agents, for which significant increases in consumption were found, included extended-spectrum cephalosporins and carbapenems, although aminoglycoside and first-generation cephalosporins consumption significantly decreased (Table 2). The association of antimicrobial consumption with the development of antimicrobial resistance has been reported to be dependent on the species and antimicrobial agent. The aminoglycoside consumption developed resistance to amikacin in *K. pneumoniae* and resistance to gentamicin in *E. coli*, resistance to both antimicrobials in *P. aeruginosa*, no resistance to both in *A. baumannii* and *P. mirabilis* (Table 4). These results also partially confirmed the report that aminoglycoside resistance was not associated with its consumption in Gram-negative bacteria.[23]

Despite decreases in the consumption of fluoroquinolones, gentamicin and trimethoprim/sulfonamide, the resistance to these agents increased in *E. coli*.[24] Ciprofloxacin consumption could significantly increase the resistance to ceftazidime in *K. pneumoniae*, resistance to ceftazidime, ciprofloxacin or imipenem in *A. baumannii* and resistance to imipenem, ceftazidime and ciprofloxacin in *P. aeruginosa*.[25] Consumption of antimicrobial agents to develop resistance to other antimicrobial agents also occurred in *E. coli*; for example: cephalosporin use and nitrofurantoin resistance; amoxicillin use and fluoroquinolone resistance; and fluoroquinolone use and ampicillin resistance.[26]

An increasing use of extended-spectrum cephalosporins (particularly ceftazidime) could develop ceftazidime resistance in *K. pneumoniae*, *Enterobacter* spp. and *P. aeruginosa* in humans.[27–31] Such correlation between application of third- and fourth-generation cephalosporins and increase of extended-spectrum cephalosporinase-producing *E. coli* has been reported in pigs,[32] implying that the ESBL-producing *E. coli* can transfer from the contaminated meat and products to humans. In the present study, correlation between extended-spectrum cephalosporin use and development of resistance to these antimicrobials were

Table 3 Trends of resistance rates among five Gram-negative pathogens from 2003 to 2011

Species	Antimicrobial agent	2003	2004	2005	2006	2007	2008	2009	2010	2011	Mean	*r*	*p*
Escherichia coli	Amikacin	7	8	10	15	10	18	18	9	11	11	0.35	0.36
	Gentamicin	46	51	59	59	57	62	61	58	56	57	0.63	0.07
	Ampicillin/sulbactam	42	46	56	57	69	79	80	72	79	65	0.93	0.00
	Piperacillin/tazobactam	3	11			14	19				11.6	0.93	0.07
	Cefazolin	31	38	53	51	64	71	72	70	(81)[a]	56 (59)	0.95 (0.96)	0.00
													0.00
	Cefoxitin	15	25	50		55	59	65	65	64	50	0.91	0.00
	Ceftazidime	11	19	33	35	47	47				32	0.97	0.00
	Ceftriaxone	21	28	40		53	61	61	61	(69)	46 (49)	0.96 (0.97)	0.00
	Cefepime	3	4	11	22	27	40	31	24	17	20	0.63	0.07
	Ciprofloxacin	29	36	49	55	58	62	71			52	0.98	0.00
	Levofloxacin	35					51	70	65	65	57	0.92	0.03
	Meropenem		0	0	0	0	0	0	0.2	(0)	0.03	(0.41)	0.00
													(0.27)
	Tigecycline								0	0	0		
Klebsiella pneumoniae	Amikacin	17	12	22	19	29	36	39	35	35	27	0.90	0.00
	Gentamicin	40	35	42	53	59	62	62	51	52	51	0.67	0.05
	Ampicillin/sulbactam	38	43	49	60	70	73	74	68	67	60	0.86	0.00
	Piperacillin	45	33			93	98				67	0.90	0.01
	Piperacillin/tazobactam	10	22			32	40				26	0.97	0.03
	Cefazolin	40	38	47	61	69	69	70	67	(67)	58 (59)	0.90 (0.86)	0.00
	Cefoxitin	33	23			57	64	66	63	50	51	0.78	0.04
	Ceftazidime	13	16	25	43	41	47				31	0.96	0.00
	Ceftriaxone	26	22	30		40	44	41	43	(40)	35 (36)	0.92 (0.86)	0.00
	Cefepime	5	6	15	36	33	41	34	36	22	25	0.67	0.05
	Ciprofloxacin	20	17	35	46	47	50	39			36	0.80	0.03
	Levofloxacin	22					45	53	42	39	40	0.74	0.16
	Meropenem			1	1.5	0.9	0	0.3	1.3	(0.5)	0.8	0.137 (0.04)	0.77
													(0.93)
	Tigecycline								0	0	0		
Proteus mirabilis	Amikacin	27	30	30	23	23	35	33	36	41	31	0.70	0.04
	Gentamicin	74	77	83	81	90	80	81	84	82	81	0.49	0.18
	Ampicillin/sulbactam	59	47	64	66	74	62	56	55	65	61	0.17	0.67
	Cefazolin	65	67	80	81	80	76	78	75	(92)	75 (77)	0.54 (0.70)	0.17
													(0.03)
	Cefoxitin	0	0	50	—	49	42	33	38	38	31	0.60	0.12
	Cefuroxime	37	41	38	30	30	31				35	−0.80	0.06
	Ceftazidime	10	14	12	12	14	10				12	0.00	1
	Ceftriaxone	27	32	24	17	17	28	20	16	(35)	23 (24)	−0.61	0.11
												(−0.09)	(0.83)
	Cefepime	12	9	10	9	3	5	7	4	12	8	−0.34	0.37
Pseudomonas aeruginosa	Amikacin	22	20	15	11	13	10	9	14	6	13	−0.84	0.00
	Gentamicin	55	52	45	49	48	43	44	36	35	45	−0.93	0.00
	Piperacillin	14	12	12	20	22	16	—	24	29	19	0.87	0.01
	Piperacillin/tazobactam	8	10	11	16	15	12	11	20	23	14	0.79	0.01
	Ceftazidime	4	2	5	8	9	11	7	10	10	7	0.81	0.01
	Cefepime	3	5	6	9	15	18	7	10	8	9	0.44	0.24
	Ciprofloxacin	39	40	38	45	45	49	48	35	44	43	0.28	0.47
	Levofloxacin	33					49	50	37	46	43	0.57	0.31
	Imipenem	15	16	9	9	15	17	15	17	28	16	0.62	0.08
	Meropenem	—	16	16	15	15	18	15	26	29	19	0.76	0.03
Acinetobacter baumannii	Amikacin	83	85	83	82	80	83	80	83	89	83	0.22	0.57
	Gentamicin	95	91	93	93	95	95	88	92	95	93	−0.13	0.74
	Ampicillin/sulbactam	36	22	34	36	48	55	66	71	85	50	0.95	0.00
	Piperacillin/tazobactam	82	89	87	93	—	80				86	−0.18	0.77
	Ceftazidime	85	89	87	90	95	86				89	0.39	0.45
	Cefepime	83	86	83	88	87	93	88	85	89	87	0.53	0.14

(*continued on next page*)

Table 3 (*continued*)

Species	Antimicrobial agent	2003	2004	2005	2006	2007	2008	2009	2010	2011	Mean	*r*	*p*
	Ciprofloxacin	83	83	84	88	89	94	97			88	0.96	0.00
	Levofloxacin	81					90	88	84	87	86	0.62	0.27
	Imipenem	3	8	6	22	25	40	77			26	0.91	0.01
	Meropenem		2	15	32	53	52	69	78	90	49	0.99	0.00
	Tigecycline								9	6	7.5		

[a] Resistance rates in parentheses were determined by 2010 Clinical and Laboratory Standards Institute (CLSI) guideline and others were determined by 2003–2009 CLSI guideline. Resistance criteria in Enterobacteriaceae between 2003 and 2009 and 2010 CLSI guidelines changed from ≤14 mm to ≤19 mm for cefazolin, from ≤13 mm to ≤19 mm for ceftriaxone, from ≤15 mm to ≤19 for ertapenem, from ≤13 mm to ≤19 mm for imipenem and from ≤13 mm to ≤19 mm for meropenem.

only observed in *P. aeruginosa*, *E. coli*, and *K. pneumoniae*, not in *P. mirabilis* and *A. baumanii* (Table 4).

Because of the dissemination and spread of ESBL-producing bacteria, carbapenem has been replaced extended-spectrum cephalosporins as therapeutic drugs for the bacterial infection. In Germany, an increase in third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* was accompanied by a twofold increase in carbapenem consumption and then increased carbapenem resistance in *K. pneumoniae* and *A. baumannii*.[33] In the present study, a significant correlation between carbapenem consumption and resistance to these agents was also observed in *K. pneumoniae* and *A. baumannii* (Table 4). In Taiwan, CRAB was found to be, on average, 46% in hospitals[20] and has increased meropenem resistance to 48.4%.[34] Our data demonstrated a higher resistance to meropenem and imipenem in *A. baumannii*, with a prevalence of 69% and 77%, respectively. This higher CRAB rate is possibly because the patients are mainly veterans with an average age of 66 years in the nursing home of our hospital. Additionally, the gradually increasing consumption of piperacillin/tazobactam for treatment was correlated with an increase in piperacillin/tazobactam resistance in *K. pneumoniae* and *P. aeruginosa* (Table 4).

To inhibit the development of antimicrobial resistance due to antimicrobial agent-inducing mutations, the lowest concentration (mutant prevention concentration, MPC) that prevents the growth of resistant colonies is commonly used. Therefore, an antimicrobial concentration above MPC during therapy can inhibit mutant subpopulation amplification.[35] An analysis of MPC for *E. coli* ATCC 25922 varied from 2 × minimal inhibitory concentration (MIC) for trovafloxacin, 4 × MIC for ciprofloxacin, norfloxacin and ofloxacin, 8 × MIC for clinafloxacin and levofloxacin, 16 × MIC for sparfloxacin and 32 × MIC for nalidixic acid at 37°C under aerobic conditions.[34] The MPC/MIC value of urinary tract infection *E. coli* was 16 for ciprofloxacin resistance (4 mg/L) and up to 5 for ciprofloxacin susceptibility (1 mg/L).[36] Furthermore, *P. aeruginosa* showed significant correlation between ciprofloxacin use and its resistance development.[35] In our study, the decrease in quinolone consumption since 2006 was associated with an increase in its resistance in *A. baumannii*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, possibly due to the increasing levofloxacin consumption (Table 2). The ciprofloxacin MPC was two-fold lower than that of levofloxacin; therefore, the increased use of levofloxacin possibly induced bacterial resistance. In an effort to reduce antimicrobial-resistant bacteria, the extensive implementation of antimicrobial stewardship has

Table 4 Relationship between annual antimicrobial agent consumption and antimicrobial resistance in four bacterial species

Antimicrobial agent group	Species	Resistance to	*r*	*p*
Aminoglycosides	*Klebsiella pneumoniae*	Amikacin	−0.970	0.000
	Escherichia coli	Gentamicin	−0.796	0.001
	Pseudomonas aeruginosa	Amikacin	0.836	0.005
		Gentamicin	0.776	0.014
First-generation cephalosporins	*E. coli*	Cefazolin	−0.880	0.004
Extended-spectrum cephalosporins	*K. pneumoniae*	Ceftazidime	0.858	0.029
		Ceftriaxone	0.869	0.011
	E. coli	Ceftriaxone	0.900	0.006
		Cefazolin	0.845	0.008
	P. aeruginosa	Ceftazidime	0.792	0.019
Carbapenems	*K. pneumoniae*	Imipenem	0.936	0.002
	Acinetobacter baumannii	Imipenem	0.993	0.000
	A. baumannii	Meropenem	0.886	0.008
Quinolone	*K. pneumoniae*	Ciprofloxacin	0.934	0.002
Piperacillin/tazobactam	*K. pneumoniae*	Piperacillin/tazobactam	0.958	0.042
	P. aeruginosa		0.792	0.011

significantly decreased the consumption of second-generation cephalosporins, carbapenems, and aminoglycoside and reduced the appearance of methicillin-resistant *Staphylococcus aureus* and antimicrobial-resistant *Serratia marcescens*.[37] Therefore, a effective implementation of antimicrobial use and MPC are needed to reduce the development of antimicrobial resistance.

In Enterobacteriaceae, *K. pneumoniae* developed resistance to all antimicrobial groups most easily, followed by *E. coli*. This higher resistance may be due to the thick polysaccharide capsule in general around *K. pneumoniae*. No correlation between antimicrobial consumption and its resistance was observed in *P. mirabilis*, which is frequently considered to be contamination. However, MDR *P. mirabilis* is commonly identified in this hospital. *P. aeruginosa* developed resistance to β-lactam antimicrobials and aminoglycosides, while *A. baumanii* only developed resistance to carbapenems associated with their use.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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