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Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991–2003 at a university hospital in Taiwan

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Abstract

This study was conducted to evaluate the relationship between antimicrobial resistance and antimicrobial use in a university hospital in Taiwan. Disk susceptibility data of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia* and other non-fermentative Gram-negative bacilli causing nosocomial infections were evaluated. Data on annual patient-days and annual consumption (defined daily dose (DDD) per 1000 patient-days) of extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, flumoxef, cefepime and cefpirome), β-lactam–β-lactamase inhibitor combinations (ticarcillin/clavulanic acid and piperacillin/tazobactam), carbapenems (imipenem and meropenem), aminoglycosides (amikacin, gentamicin and tobramycin), fluoroquinolones (ciprofloxacin (oral and injectable) and oral levofloxacin and moxifloxacin) from 1991 to 2003 were analysed. Increasing trends of incidences of several of these bacteria causing all nosocomial infections or nosocomial bloodstream infections were noted from 1991 to 2003. The annual patient-days of the hospital significantly increased, from 360 210 in 1991 to 672 676 in 2002 (linear regression analysis, $P < 0.05$), but slightly decreased in 2003 (629 168) owing to the severe acute respiratory syndrome epidemic in Taiwan. The rise in cefotaxime-resistant or ciprofloxacin-resistant *E. coli* and meropenem-resistant *P. aeruginosa* was significantly correlated with increased consumption of extended-spectrum cephalosporins, β-lactam–β-lactamase inhibitor combinations, carbapenems, fluoroquinolones and aminoglycosides (for ciprofloxacin-resistant *E. coli* and meropenem-resistant *P. aeruginosa* only) in the hospital (Pearson's correlation coefficient, $r > 0.72$ (or < -0.72) and P-value < 0.05). Increased ciprofloxacin-resistant *K. pneumoniae* and meropenem-resistant *Acinetobacter* spp. was significantly associated with the increased usage of extended-spectrum cephalosporins but not with the other four classes of antibiotics. This 13-year study in a hospital demonstrated significant changes in antimicrobial use, which may have affected antimicrobial resistance in certain Gram-negative bacteria at the hospital.

Keywords: Antimicrobial use; Antimicrobial resistance; Nosocomial infection; Gram-negative bacteria; Taiwan

1. Introduction

Antimicrobial resistance is an increasing threat in hospitalised patients, and both mortality and morbidity from infection are greater when caused by antimicrobial-resistant bacteria [1–4]. Among these resistant bacteria, extended-

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spectrum cephalosporin-resistant Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and ciprofloxacin-resistant Enterobacteriaceae and non-fermentative Gram-negative bacilli (NFGNB) are of great concern because antimicrobial therapy for infections due to these resistant pathogens remains a clinical dilemma in hospitalised patients [5–11]. Increases in the prevalence of these resistant pathogens in hospitals are frequently related to the high selective pressure of antimicrobials commonly used in hospitalised patients, particularly extended-spectrum cephalosporins, β-lactam–β-lactamase inhibitor combinations, carbapenems, fluoroquinolones and aminoglycosides [12–20]. Importantly, susceptibility profiles of nosocomial pathogens are affected not only by a single agent but also by use of multiple agents [21]. The higher resistance of organisms to some antimicrobial agents is frequently associated with heavy use of fewer antimicrobials [12–22]. Understanding the hospital antibiogram and hospital profile of antimicrobial use is mandatory in solving the problem of antimicrobial resistance in hospitals.

This report aims to evaluate antimicrobial usage and antimicrobial resistance trends for prominent nosocomial Gram-negative pathogens from 1991 to 2003 at a university hospital in Taiwan. For each antimicrobial-resistant pathogen, annual resistance rates and the usage of a single agent and several classes of agents were analysed.

2. Materials and methods

2.1. Setting

National Taiwan University Hospital (NTUH) is a tertiary referral centre and a university-affiliated hospital with 2000 beds. There were 175 beds in the intensive care unit and 150 beds in the haemo-oncology ward of this hospital during the study period. The Nosocomial Infection Control Committee of the hospital was established in 1980 [7]. Prior to 2004, no specific and well-established antibiotic control polices were implemented at the hospital. All attending physicians at the hospital can prescribe nearly all antimicrobial agents (except for liposomal amphotericin B, voriconazole, caspofungin, linezolid and ganciclovir) without the permission of the infection disease specialists.

2.2. Incidence of nosocomial infections caused by Gram-negative bacteria

Definitions for nosocomial infections followed the National Nosocomial Infections Surveillance guidelines [23]. Annual incidences of several major Gram-negative bacteria causing all nosocomial infections (bloodstream, respiratory tract, urinary tract, gastrointestinal, surgical site, and skin and soft tissue infections) and nosocomial bloodstream infections were expressed as episodes per 10 000 discharged. These organisms included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serraba marcescens*, *Proteus* spp., *P. aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and NFGNB other than *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia* (*Pseudomonas fluorescens*, *Pseudomonas putida*, *Acinetobacter junii*, *Acinetobacter haemolyticus*, *Acinetobacter lwoffii*, *Burkholderia cepacia*, *Chryseobacterium indologenes*, *Chryseobacterium meningosepticum* and *Alcaligenes* spp.) (hereafter 'other NFGNB'). These isolates were non-duplicate samples, as several isolates of each species from each patient recovered with 7 days were considered one isolate. Isolates were identified by conventional biochemical tests as well as by two commercial identification kits, VITEK Identification cards (bioMerieux, Hazelwood, MO) and Phoenix System (Becton Dickson, Sparks, MD), if necessary.

2.3. Antibiotic consumption

Data on annual consumption of extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, flumoxef, cefepime and cefpirome), β-lactam–β-lactamase inhibitor combinations (ticarcillin/clavulanic acid and piperacillin/tazobactam), carbapenems (imipenem and meropenem), aminoglycosides (amikacin, gentamicin and tobramycin) and fluoroquinolones (ciprofloxacin (oral and injectable) and oral levofloxacin and moxifloxacin) from 1991 to 2003 were obtained from the Pharmacy Department of the hospital. Antibiotic consumption was expressed as the number of defined daily doses (DDDs)/1000 patient-days) [24].

2.4. Trends in resistance

To determine the secular trend of resistance in major Gram-negative pathogens causing nosocomial infections at NTUH, data on the disk diffusion susceptibilities of these organisms recovered from 1991 to 2003 were retrieved from the annual summary document [25]. To calculate the resistance rates, isolates of each species with identical resistance profiles recovered from each patient within 7 days were calculated once (non-duplicate isolates). Screening for extended-spectrum β-lactamase (ESBL) phenotypes among *E. coli* and *K. pneumoniae* isolates began in 2003 [26]. *Escherichia coli* and *K. pneumoniae* isolates with an inhibition zone diameter for cefotaxime (30 μg disk) or aztreonam (30 μg disk) of < 27 mm were subjected to the ESBL confirmation method using the following four antimicrobial disks: cefotaxime (30 μg), cefotaxime/clavulanic acid (30/10 μg disk), ceftazidime (30 μg disk) and ceftazidime/clavulanic acid (30/10 μg disk). The results were interpreted based on the National Committee for Clinical Laboratory Standards (NCCLS) criteria [26].

Regular quality assurance was performed among isolates processed using the following American Type Culture Collection (ATCC) strains: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 70063 (for confirmation testing of ESBL-producing

strains) and *P. aeruginosa* ATCC 27853. Isolates were classified as susceptible or resistant (including intermediate category) according to the NCCLS criteria [25,26].

2.5. Statistical analysis

Pearson's correlation coefficient was used to determine the relationship between antibiotic consumption and trends in resistance. Linear regression analysis was used to analyse the trend of hospital patient-days and the trends of rates among Gram-negative pathogens causing all nosocomial infections and nosocomial bloodstream infections with time. Trends of annual resistance rates to each antimicrobial agent for microorganisms were performed using Durbin–Watson statistics. An r-value >0.72 (or <−0.72) and a P-value <0.05 were considered statistically significant. The autoregressive integrated moving average (ARIMA) model was used to demonstrate the time series of antimicrobial resistance and antimicrobial use (cefotaxime resistance in *E. coli* and ceftazidime resistance in *P. aeruginosa*) [27,28].

3. Results

3.1. Incidence of nosocomial infections

Annual rates of major Gram-negative bacilli causing all nosocomial infections and nosocomial bloodstream infections are shown in Fig. 1A and 1B, respectively. For *A. baumannii*, a 3.6-fold increase in nosocomial bloodstream

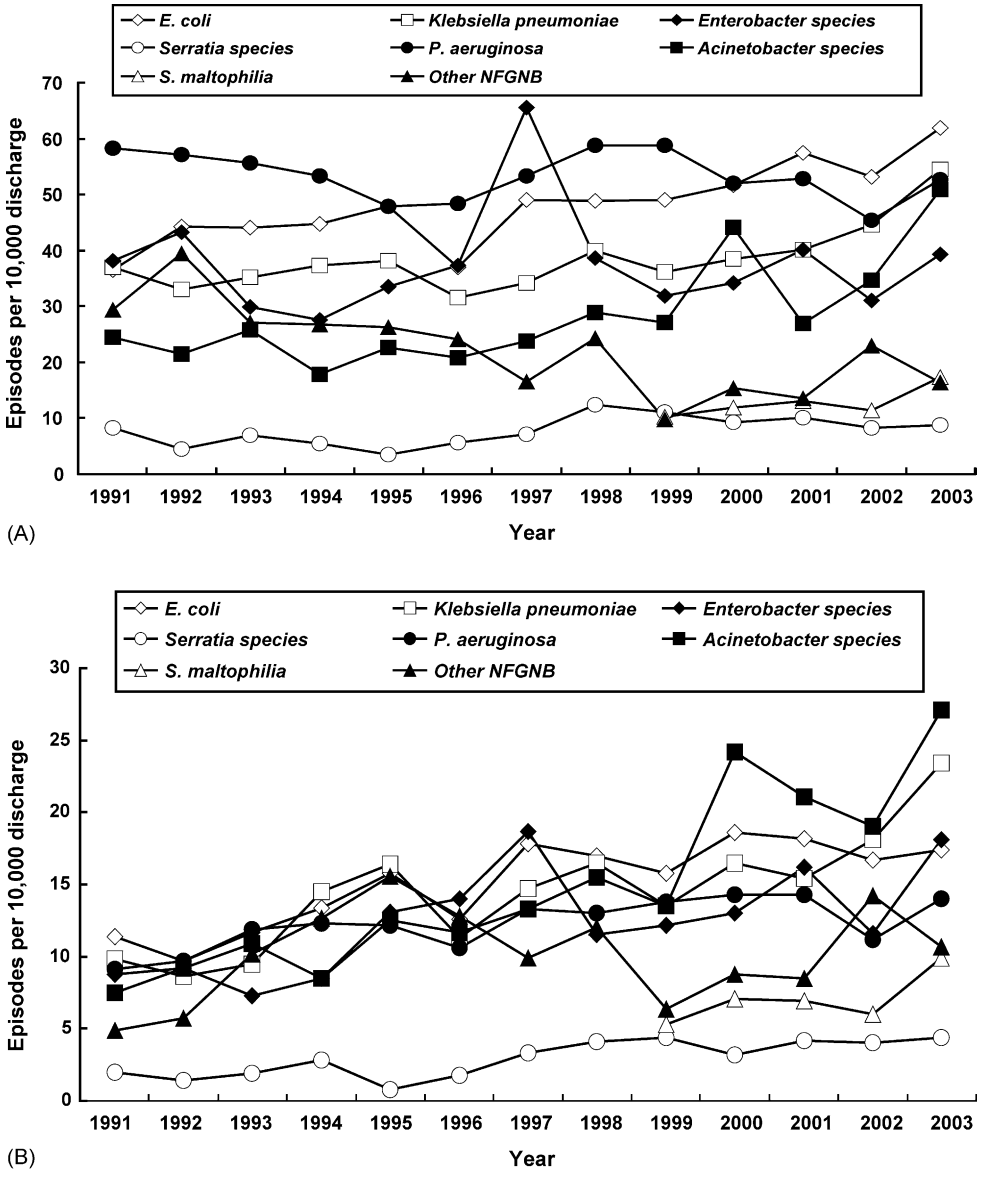

Fig. 1. Incidence (episodes per 10 000 discharged) of (A) all nosocomial infections and (B) nosocomial bloodstream infections caused by major Gram-negative bacilli isolated from patients treated at a university hospital in Taiwan from 1991–2003. NFGNB, non-fermentative Gram-negative bacilli.

Table 1
Trends of incidence rates among Gram-negative pathogens causing all nosocomial infections and nosocomial bloodstream infections at National Taiwan University Hospital, 1991–2003

Microorganism	All nosocomial infections		Nosocomial bloodstream infection	
	r	*P*	*r*	*P*
Escherichia coli	0.850	<0.001*	0.846	<0.001*
Klebsiella pneumoniae	0.696	0.008	0.829	<0.001*
Enterobacter spp.	0.013	0.968	0.669	0.012*
Serratia spp.	0.555	0.049	0.810	<0.001*
Proteus spp.	0.628	0.096	0.912	0.002*
Pseudomonas aeruginosa	0.367	0.005	0.904	0.006*
Acinetobacter spp.	0.730	0.218	0.729	<0.001*
Stenotrophomonas maltophilia	0.778	0.113	0.730	0.161
Other NFGNB	0.758	0.003*	0.258	0.395

NFGNB, non-fermentative Gram-negative bacilli.
* Statistically significant association ($r > 0.72$, $P < 0.05$).

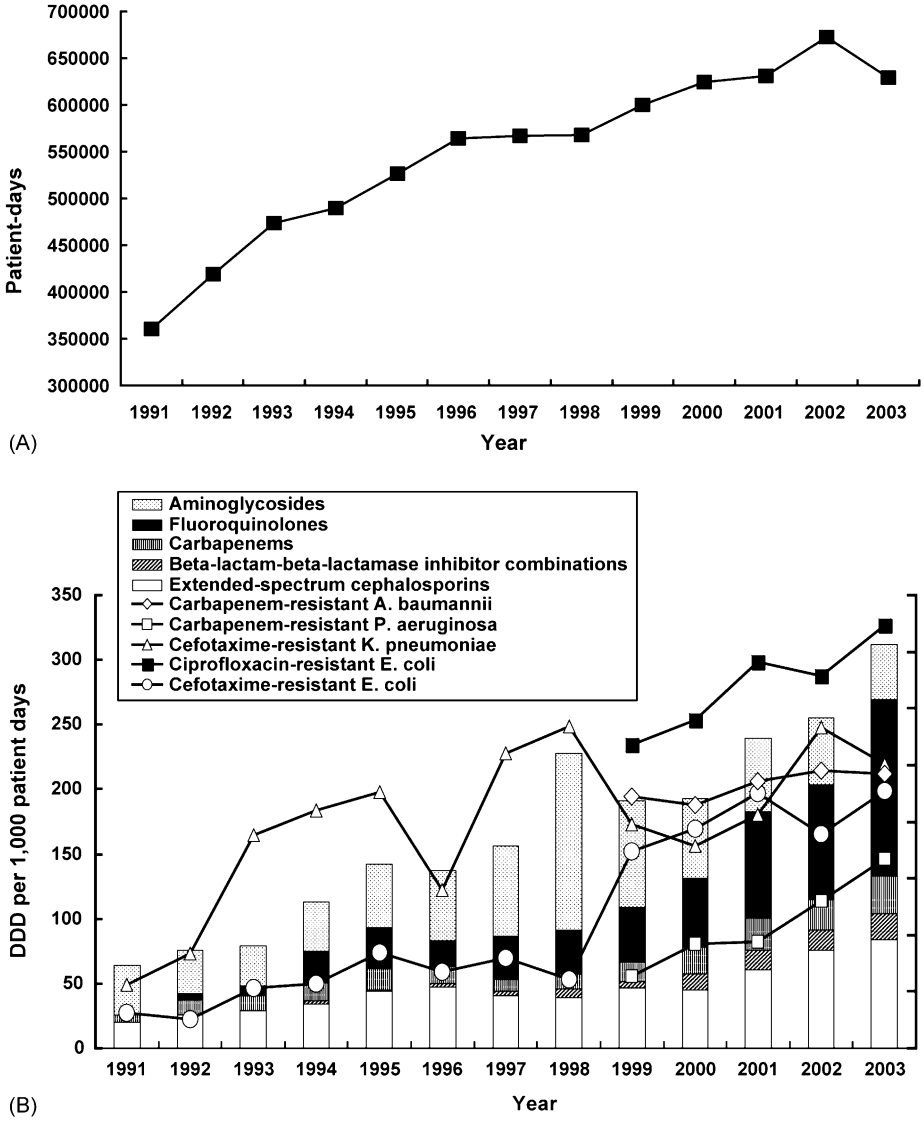

Fig. 2. (A) Annual patient-days and (B) annual consumption (defined daily dose (DDD) per 1000 patient-days) of five classes of antimicrobial agents and resistance trends for five drug/organism combinations at a university hospital in Taiwan from 1991–2003.

infections was noted (7.5 episodes/10 000 discharges in 1991 versus 27.1 episodes/10 000 discharges in 2003), along with a 2.1-fold increase in all nosocomial infections (24.5 episodes/10 000 discharges in 1991 versus 50.8 episodes/10 000 discharges in 2003). There was a 2.2-fold increase in other NFGNB causing nosocomial bloodstream infections (4.9 episodes/10 000 discharges in 1991 versus 10.7 episodes/10 000 discharges in 2003). Among the eight Gram-negative bacterial species and other NFGNB isolates, trends of increased incidences were significant ($r > 0.72$ and $P < 0.05$) among *E. coli* and other NFGNB causing all nosocomial infections, and among *E. coli*, *K. pneumoniae*, *Serratia* spp., *Proteus* spp., *P. aeruginosa* and *Acinetobacter* spp. causing nosocomial bloodstream infections (Table 1).

3.2. Annual antibiotic consumption

The annual patient-days of the hospital significantly increased, from 360 210 in 1991 to 672 676 in 2002 (linear regression analysis, $P < 0.05$), but slightly decreased in 2003 (629 168) owing to the severe acute respiratory syndrome epidemic in Taiwan (Fig. 2A). Table 2 shows the annual consumption of several commonly used antimicrobial agents, and Fig. 2B illustrates the annual consumption of five classes of agents from 1991 to 2003. In general, the usage of each individual antimicrobial agent varied with years. A significant stepwise increase in consumption ($r > 0.72$ and $P < 0.05$) was found for piperacillin/tazobactam, cefepime, meropenem and ciprofloxacin (Table 2). Antibiotics with significantly decreased annual use in the past 4 years (2000–2003) were amikacin and sulphamethoxazole/trimethoprim ($r < -0.72$ and $P < 0.05$). For the five classes of agents, a 4.2-fold, 5.1-fold and 801.3-fold increase in usage was noted for extended-spectrum cephalosporins, carbapenems and fluoroquinolones, respectively, in 2003 compared with 1991. An 8.8-fold increase in usage of β-lactam–β-lactamase inhibitor combinations was noted in 2003 (19.55 DDD per 1000 patient-days) compared with 1994 (2.22 DDD per 1000 patient-days).

3.3. Relationship between antibiotic consumption and rates of resistance

In 2003, the overall rate of resistance to cefotaxime was 22.7% in *E. coli* and 25.1% in *K. pneumoniae*. However, based on the NCCLS guidelines for ESBL confirmation testing [26], the rate of ESBL-producing isolates of *E. coli* and *K. pneumoniae* in 2003 was 14.2% and 14%, respectively. Table 3 shows the trends of resistance rates among Gram-negative pathogens. A significant increase in resistance rate with time ($r > 0.72$ and $P < 0.05$) was found for cefotaxime- and ciprofloxacin-resistant *E. coli*, cefepime- and ciprofloxacin-resistant *K. pneumoniae*, cefepime- and meropenem-resistant *P. aeruginosa*, ceftazidime-, piperacillin/tazobactam-, gentamicin- and amikacin-resistant *A. baumannii*, and cefepime- and piperacillin/tazobactam-

Table 2
Annual consumption of several representative antimicrobial agents at National Taiwan University Hospital, 1991–2003

Antimicrobial agent	Antibiotic consumption (DDD/1000 patient-days) by year													Correlation	
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	r	P
Ceftazidime	7.94	9.13	13.24	15.83	23.03	25.25	24.50	19.04	18.65	15.55	14.35	14.74	13.81	0.206	0.250
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	4.88	6.57	10.17	16.22	0.968	0.016*
Ticarcillin/clavulanic acid	–	–	–	2.21	0.86	2.46	3.38	6.48	5.32	7.95	8.31	5.20	3.33	0.601	0.033
Cefepime	–	–	–	–	–	–	–	0.92	7.75	14.72	22.88	35.17	39.37	0.994	0.028*
Imipenem	5.75	11.305	11.51	14.125	16.81	13.21	9.24	12.09	11.58	14.95	14.9	12.00	19.11	0.560	0.046
Meropenem	–	–	–	–	–	–	–	0.10	3.40	5.66	10.10	11.28	10.39	0.943	0.005*
Imipenem + meropenem	5.75	11.31	11.51	14.13	16.81	13.21	9.24	12.19	14.98	20.61	25	23.275	29.50	0.851	<0.001*
Ciprofloxacin	0.32	5.18	7.32	10.80	14.12	25.84	13.86	15.38	20.04	22.86	24.26	26.78	34.36	0.916	<0.001*
Gentamicin	13.71	10.46	10.00	15.00	24.25	30.96	52.79	58.33	71.25	48.83	45.75	42.21	35.00	0.702	0.004
Amikacin	12.7	13.62	13.2	13.71	12.64	13.53	6.76	6.82	5.78	5.84	5.63	6.63	6.19	−0.867	<0.001*
Sulphamethoxazole/trimethoprim	305.43	325.47	229.51	296.22	284.14	166.11	274.32	293.74	264.62	219.2	208.77	131.11	135.53	−0.727	0.002*

DDD, defined daily dose.
* Statistically significant association ($r > 0.72$, $P < 0.05$).

Table 3
Trends of resistance rates among Gram-negative pathogens causing nosocomial infections at National Taiwan University Hospital, 1991–2003

Organism/antimicrobial agent	Antimicrobial resistance (%) by year													Correlation	
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	*r*	*P*
Escherichia coli															
No. of isolates	112	161	180	204	230	196	284	282	313	356	409	415	434		
Cefotaxime	3.1	2.6	5.3	5.7	8.5	6.7	8	6.1	17.4	19.4	22.5	18.9	22.7	0.918	<0.001*
Cefepime	–	–	–	–	–	–	–	–	8.4	10.2	11.1	6.9	8.5	−0.297	0.314
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	–	8.9	12.7	12.7	0.866	0.167
Ciprofloxacin	–	–	–	–	–	–	–	–	26.8	29.0	34.1	32.9	37.3	0.946	0.008*
Gentamicin	23.8	30.4	36.0	32.0	45.4	42.5	36	36.5	37.7	36.4	37.6	34.0	34.6	0.327	0.138
Klebsiella pneumoniae															
No. of isolates	113	121	144	170	184	167	198	232	228	267	285	350	382		
Cefotaxime	5.6	8.4	18.8	21.0	22.6	14.0	26.0	28.4	19.8	17.9	20.6	28.3	25.1	0.68	0.005
Cefepime	–	–	–	–	–	–	–	–	8.9	13.6	18.1	22.5	18	0.83	0.041*
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	–	19.5	15.1	15.9	−0.768	0.221
Ciprofloxacin	–	–	–	–	–	–	–	–	8.9	16.2	20.2	28.8	23.1	0.868	0.028*
Gentamicin	15.4	17.5	24.8	23.5	25.0	18.7	27.3	32.8	25.4	17.3	21.7	31.1	19.7	0.31	0.151
Enterobacter cloacae															
No. of isolates	117	155	124	126	161	197	235	222	203	236	289	244	276		
Cefotaxime	44.7	48.0	50.4	48.3	51.9	63.0	60.5	62.7	62.7	48.9	60.1	58.7	51.3	0.498	0.042
Cefepime	–	–	–	–	–	–	–	–	7.8	7.6	10.6	16.2	9.2	0.512	0.189
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	–	30.7	34.8	29.3	−0.245	0.421
Ciprofloxacin	–	–	–	–	–	–	–	–	6.4	15.8	14.5	19.5	15.4	0.712	0.089
Gentamicin	38.0	37.4	32.2	22.2	22.2	34.5	34.2	39.6	35.6	29.7	34.1	29.9	26.9	−0.160	0.300
Amikacin	22.6	21.9	19.2	7.9	5.6	12.8	18.8	18.6	23.9	13.2	23.6	17.6	10.2	−0.07	0.410
Serratia marcescens															
No. of isolates	24	15	29	24	17	29	41	70	70	63	72	64	61		
Cefotaxime	28.6	8.3	12.0	20.8	17.6	34.4	51.2	57.1	61.1	45.2	34.7	38.1	41.0	0.635	0.010
Cefepime	–	–	–	–	–	–	–	–	5.6	6.0	9.2	9.5	6.6	0.474	0.210
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	–	23.1	26	23.9	0.267	0.414
Ciprofloxacin	–	–	–	–	–	–	–	–	32.4	33.3	20.0	30.6	30.0	−0.222	0.360
Gentamicin	11.8	20.0	11.5	12.5	11.8	34.5	48.8	51.4	40.0	40.3	25.3	26.6	31.1	0.542	0.280
Amikacin	23.8	13.3	11.1	12.5	0.0	10.3	35.9	23.2	20	17.7	11.1	10.9	13.1	−0.019	0.476
Proteus spp.															
No. of isolates	30	29	24	36	37	40	57	51	68	68	84	64	86		
Cefotaxime	0.0	0.0	9.1	0.0	8.1	2.5	1.8	3.9	3.3	1.5	1.2	4.7	5.9	0.168	0.292
Cefepime	–	–	–	–	–	–	–	–	0.0	1.6	0.0	0.0	2.3	0.433	0.233
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	–	–	2.7	0.0	0.0	−0.866	0.167
Ciprofloxacin	–	–	–	–	–	–	–	–	6.2	5.9	7.1	4.7	14.0	0.617	0.134
Gentamicin	21.4	24.1	13	25	10.8	17.5	18.2	37.3	19.1	26.9	25	23.4	24.4	0.334	0.132
Amikacin	0.0	0.0	4.3	0.0	0.0	2.5	1.8	5.9	1.5	1.5	1.2	1.6	3.5	0.322	0.141
Pseudomonas aeruginosa															
No. of isolates	179	204	230	243	231	255	309	324	372	358	376	357	369		
Ceftazidime	13.6	22.4	18.8	9.2	10.3	11.7	8.4	10.1	12.2	9.3	10.3	11.5	9.5	−0.578	0.019
Cefepime	–	–	–	–	–	–	–	–	6.0	8.9	9.3	12.1	11.6	0.934	0.010*
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	23.4	11.0	10.0	15.0	17.0	−0.259	0.337
Meropenem	–	–	–	–	–	–	–	–	6.4	9.2	9.4	13.0	16.7	0.969	0.003*
Ciprofloxacin	–	–	–	–	–	–	–	–	8.2	9.5	6.4	11.6	16.1	0.759	0.068
Gentamicin	19.8	26.4	20.9	14.2	18.9	13.4	22.7	20.2	15.9	17.6	12.3	15.1	13.7	−0. 598	0.016
Amikacin	13.3	17.6	13.4	7.9	9.6	6.7	12.3	8.0	7.1	6.5	4.8	7.3	4.9	−0.803	<0.001*
Acinetobacter baumannii															
No. of isolates	75	76	103	74	103	106	132	158	170	302	294	272	356		
Ceftazidime	24.3	13.9	21.3	17.4	21.2	17.5	34.5	37.8	52.4	47.3	49.8	44.3	47.9	0.871	<0.001*
Cefepime	–	–	–	–	–	–	–	–	48.5	46.2	43.0	45.8	46.5	−0.353	0.280
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	40.8	41.1	43.0	45.2	48.6	0.962	0.004*
Meropenem	–	–	–	–	–	–	–	–	22.2	21.5	23.6	24.5	24.2	0.853	0.033
Ciprofloxacin	–	–	–	–	–	–	–	–	46.2	42.2	44.9	48.7	48.9	0.673	0.106
Gentamicin	20.8	18.4	26.8	17.6	25.5	17.9	33.6	40.5	49.4	47.0	53.2	53.1	54.2	0.921	<0.001*
Amikacin	19.4	15.8	19.6	14.1	12.9	6.7	22.3	30.1	47.0	44.4	40.7	43.9	44.9	0.825	<0.001*

Table 3 (*Continued*)

Organism/antimicrobial agent	Antimicrobial resistance (%) by year													Correlation	
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	*r*	*P*
Stenotrophomonas maltophilia															
No. of isolates	–	–	–	–	–	–	–	–	65	82	94	89	121		
Ceftazidime	–	–	–	–	–	–	–	–	60	37.5	50	47.2	56.6	0.052	0.467
Cefepime	–	–	–	–	–	–	–	–	80.6	79	89.4	92.1	89.9	0.841	0.037*
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	70.6	78.7	83.1	84.1	89.8	0.968	0.003*
Ticarcillin/clavulanic acid	–	–	–	–	–	–	–	–	47.4	29.3	39.3	32.6	42.9	−0.122	0.423
Ciprofloxacin	–	–	–	–	–	–	–	–	15.2	26.8	55.4	36.4	21.7	0.228	0.356
Sulphamethoxazole/trimethoprim	–	–	–	–	–	–	–	–	–	15.9	10.8	26.7	26.9	0.785	0.107
Other NFGNB															
No. of isolates	91	80	111	122	132	132	100	78	63	104	97	178	113		
Ceftazidime	35.4	46.2	18.8	43.4	35.5	40	49.5	46.8	35	37.6	45.2	34.9	35.7	0.106	0.366
Cefepime	–	–	–	–	–	–	–	–	25.7	34.6	34.1	35.6	30.1	0.377	0.266
Piperacillin/tazobactam	–	–	–	–	–	–	–	–	11.8	22.3	30.8	27.2	18.2	0.375	0.267
Meropenem	–	–	–	–	–	–	–	–	29.6	40.8	53.7	42.7	57.8	0.683	0.159
Ciprofloxacin	–	–	–	–	–	–	–	–	44.7	34.9	38.1	43.8	31.9	−0.476	0.209
Gentamicin	73.8	75.9	82.9	80.2	68.7	71	22.7	74.4	68.3	69.2	73.2	80.2	69.9	−0.101	0.371
Amikacin	61	73.1	75.5	73.1	56.9	63.9	12.3	8	57.1	59.6	68	70.6	65.5	−0.109	0.361

NFGNB, non-fermentative Gram-negative bacilli (other than *P. aeruginosa*, *A. baumannii* and *S. maltophilia*).

* Statistically significant association ($r > 0.72$ or < -0.72, $P < 0.05$).

resistant *S. maltophilia*. A significantly increased susceptibility with time ($r < -0.72$ and $P < 0.05$) was found to ceftazidime and amikacin for *P. aeruginosa* (Table 3).

Relationships between rates of resistant Gram-negative pathogens causing nosocomial infections and the annual consumption of the corresponding antibiotic in the hospital from 1991 to 2003 are shown in Table 4. Significant positive associations (increased resistance associated with increased consumption) ($r > 0.72$ and $P < 0.05$) were found in cefotaxime- and ciprofloxacin-resistant *E. coli*, cefotaxime- and gentamicin-resistant *S. marcescens*, ciprofloxacin-resistant *P. aeruginosa*, and piperacillin/tazobactam-, amikacin- and meropenem-resistant *A. baumannii*. Significant negative associations ($r < -0.72$ and $P < 0.05$) were found in cefepime- and gentamicin-resistant *A. baumannii.*

The rise in cefotaxime-resistant *E. coli* was significantly correlated with the increased consumption of extended-spectrum cephalosporins ($r = 0.8409$, $P < 0.0001$), β-lactam–β-lactamase inhibitor combinations ($r = 0.9148$, $P < 0.0001$), carbapenems ($r = 0.8929$, $P < 0.0001$) and fluoroquinolones ($r = 0.8877$, $P < 0.0001$). The rise in cefotaxime-resistant *K. pneumoniae* was significantly associated with the use of extended-spectrum cephalosporins ($r = 0.7223$, $P = 0.0281$) and fluoroquinolones ($r = 0.7810$, $P < 0.0373$) only. The increase in rates of ciprofloxacin-resistant *E. coli* and meropenem-resistant *P. aeruginosa* was significantly correlated with increased consumption of extended-spectrum cephalosporins ($r = 0.89446$, $P = 0.0404$ and $r = 0.9283$, $P = 0.0218$, respectively), β-lactam–β-lactamase inhibitor combinations ($r = 0.9323$, $P = 0.0209$ and $r = 0.8991$, $P = 0.0379$, respectively), carbapenems ($r = 0.8933$, $P = 0.0412$ and $r = 0.9283$, $P = 0.0218$, respectively) and fluoroquinolones ($r = 0.9612$, $P = 0.0091$ and $r = 0.9523$, $P = 0.0124$, respectively). Decreased use of aminoglycosides was significantly associated with an increased incidence of ciprofloxacin-resistant *E. coli* ($r = -0.9221$, $P = 0.0258$) and meropenem-resistant *P. aeruginosa* ($r = -0.9082$, $P = 0.0264$). An increase in meropenem-resistant *Acinetobacter* spp. was significantly associated with increased usage of extended-spectrum cephalosporins ($r = 0.9316$, $P = 0.0212$) and carbapenems ($r = 0.9026$, $P = 0.0412$) but not with the other four classes of antibiotics. The relationships between rates of ciprofloxacin resistance in *K. pneumoniae* and *P. aeruginosa* and the five classes of antimicrobials were not significant.

3.4. Time series analysis with ARIMA model

Table 5 shows ARIMA and transfer function models for estimating the percentage of cefotaxime resistance among *E. coli* isolates. An increase of 1 DDD/1000 patient-days for cefotaxime resulted in an increase of 0.98% in the cefotaxime resistance rate. A forecast of cefotaxime resistance in *E. coli* and ceftazidime resistance in *P. aeruginosa* up to 2011 is shown in Fig. 3. In 2011, the predicted cefotaxime resistance percentage for *E. coli* is 36.3% (95% confidence interval (CI), 26.6–42.5%) and the predicted ceftazidime resistance percentage for *P. aeruginosa* is 8.79% (95% CI, 3.9–10.6%).

4. Discussion

This study regarding the association between antimicrobial resistance in Gram-negative bacteria that cause nosocomial infections and antibiotic use at a Taiwanese teaching hospital with an increase of annual patient-days during a 13-year period discloses three important points. First, the incidence of nosocomial bacteraemia due to the major Gram-negative bacteria generally increased over time. Notable trends in antimicrobial usage demonstrated sharp increases in the use of piperacillin/tazobactam, cefepime, ciprofloxacin

Table 4
Relationship between annual consumption of individual antibiotics and rates of key resistant Gram-negative pathogens causing nosocomial infections at National Taiwan University Hospital, 1991–2003

Antimicrobial agent	*Escherichia coli*		*Klebsiella pneumoniae*		*Enterobacter cloacae*		*Serratia marcescens*		*Proteus* spp.		*Pseudomonas aeruginosa*		*Acinetobacter baumannii*		*Stenotrophomonas maltophilia*		Other NFGNB	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Cefotaxime	0.764	0.002*	0.480	0.097	0.437	0.136	0.777	0.002*	0.011	0.971	–	–	–	–	–	–	–	–
Ceftazidime	–	–	–	–	–	–	–	–	–	–	−0.543	0.045	0.008	0.980	0.327	0.591	0.245	0.420
Cefepime	0.787	0.114	0.345	0.576	0.064	0.919	0.555	0.332	−0.147	0.814	0.142	0.82	−0.952	0.012*	0.25	0.684	0.601	0.284
Piperacillin/tazobactam	0.784	0.426	−0.667	0.469	0.535	−0.303	0.124	0.921	−0.784	0.426	0.931	0.069	0.993	0.007*	0.963	0.037	−0.587	0.413
Ciprofloxacin	0.903	0.036*	0.674	0.212	0.527	0.361	−0.069	0.912	0.819	0.090	0.881	0.049*	0.647	0.238	−0.025	0.968	−0.627	0.257
Gentamicin	0.342	0.252	0.465	0.109	0.260	0.391	0.851	<0.001*	0.350	0.241	−0.261	0.388	−0.721	0.005*	1		−0.404	0.171
Amikacin	–	–	–	–	−0.264	0.384	−0.376	0.206	−0.322	0.283	−0.581	0.037	0.896	<0.001*	1		0.394	0.183
Meropenem	–	–	–	–	–	–	–	–	–	–	0.771	0.127	0.899	0.038*	–	–	0.786	0.214
Ticarcillin/clavulanic acid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−0.470	0.424	–	–
Sulphamethoxazole/trimethoprim	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−0.937	0.063	–	–

NFGNB, non-fermentative Gram-negative bacilli.
* Statistically significant association ($r > 0.72$ or < -0.72, $P < 0.05$).

Table 5
Autoregressive integrated moving average (ARIMA) and transfer function models for estimating percentage of cefotaxime resistance among *Escherichia coli* isolated at National Taiwan University Hospital, 1991–2003

Antibiotic use	Parameter (SE)[a]	*T*-ratio	*P*
ARIMA model for percentage of cefotaxime resistance			
MA	0.9814 (0.0346)	28.36448	<0.001
Transfer function for cefotaxime resistance			
Cefotaxime use	0.9815 (0.03447)	28.4748	<0.001
MA	0.9814 (0.03675)	26.7021	<0.001

SE, standard error; MA, moving average term, representing disturbance and abrupt changes of resistance.
[a] Size and direction of the effect.

and carbapenems, but decreases in the use of amikacin and sulphamethoxazole/trimethoprim.

Second, widespread use of four major classes of antimicrobial agents in the hospital were significantly associated with the increase in cefotaxime and ciprofloxacin resistance in *E. coli* and carbapenem resistance in *P. aeruginosa*. Increased use of extended-spectrum cephalosporins was also significantly related to the increased incidence of cefotaxime resistance in *K. pneumoniae* and carbapenem resistance in

Fig. 3. Yearly percentage of (A) cefotaxime-resistant *Escherichia coli* and (B) ceftazidime-resistant *Pseudomonas aeruginosa* observed between 1991 and 2003 and predicted values up to 2011 with 95% confidence intervals according to autoregressive integrated moving average (ARIMA) and transfer function models.

Acinetobacter spp. The increased use of fluoroquinolones is also significantly associated with the increased incidence of cefotaxime resistance in *K. pneumoniae* and carbapenem resistance in *P. aeruginosa*. Third, the decreasing use of gentamicin and amikacin in recent years is associated with increasing susceptibility of *S. marcescens* to gentamicin and of *P. aeruginosa* to amikacin; however, resistance to gentamicin and amikacin in *A. baumannii* remained high.

The relationship between antimicrobial resistance and antimicrobial usage for a particular drug, or classes of drug, and organism combination is partly in line with other previous studies [12–22]. A significant positive correlation between the increase in the use of extended-spectrum cephalosporins (particularly ceftazidime) and the increased prevalence of ceftazidime-resistant *K. pneumoniae*, *Enterobacter* spp. and *P. aeruginosa* has been described in many previous reports [17,29–32]. Our study further demonstrated this positive association with cefotaxime use and cefotaxime-resistant *S. marcescens*. However, a significantly increased use of cefepime in NTUH failed to result in an increased rate of cefepime resistance in *A. baumannii* and even exerted a protective effect against this resistance ($r = -0.952$ and $P = 0.012$). Use of piperacillin/tazobactam has been demonstrated to reduce rates of ceftazidime-resistant or ESBL-producing *K. pneumoniae* [12,29,32]. However, our study showed a significantly positive association between piperacillin/tazobactam use and piperacillin/tazobactam-resistant *A. baumannii*.

Although the consumption of ceftazidime in 2003 decreased to approximately one-half of that in 1996, and although piperacillin/tazobactam use increased dramatically, cefotaxime resistance in *K. pneumoniae* remained high (25.1% in 2003), and rates of piperacillin/tazobactam resistance in these Gram-negative bacteria remained stable. However, cefotaxime resistance in *Enterobacter* spp. and ceftazidime-resistant *P. aeruginosa* declined gradually. Because the incidence of ESBL-producing *E. coli* and *K. pneumoniae* was not available prior to 2003, it was not possible to define the relationship between antimicrobial usage and the incidence of ESBL-producing isolates.

Previous reports demonstrated that fluoroquinolones were protective against isolation of third-generation cephalosporin-resistant pathogens [31,33]. A recent study further demonstrated that higher hospital-level use of fluoroquinolones was associated with an increased proportion of ciprofloxacin resistance among *P. aeruginosa* isolates causing hospital-acquired infections [34] but not in *E. coli* isolates. However, MacDougall et al. demonstrated that there was no significant relationship between total hospital fluoroquinolone use and resistance in *E. coli* [35]. In this study, increased use of fluoroquinolones was not only associated with the increased incidence of cefotaxime-resistant *E. coli* and *K. pneumoniae* but also correlated with varying degrees of increase in ciprofloxacin resistance among these Gram-negative bacteria, except for *S. maltophilia* isolates.

The root causes of the rapid emergence and dissemination of drug-resistant bacteria in hospitals are multifactorial [36], including the high selective pressure that results from inappropriate and widespread use of antimicrobial agents particularly in intensive care units, cross transmission from patient to patient owing to inconsistent application of appropriate infection control measures, interhospital transfer of resistance (clonal spreading of resistant bacteria or horizontal transfer of resistance genes), a community contribution to resistance, or a complex relationship between resistance and the use of a variety of antimicrobials [33,36–38]. However, increasing resistance may further drive increased consumption of several so-called ‘last-line’ antimicrobial agents. In this study, the increase in the incidence of nosocomial infections due to multidrug-resistant *P. aeruginosa* and *A. baumannii* and cefotaxime-resistant *E. coli* and *K. pneumoniae* resulted in an increase in the use of carbapenems. The increased use of these agents was significantly associated with an increase in the incidence of nosocomial infections due to carbapenem-resistant *A. baumannii* and *P. aeruginosa*, *S. maltophilia* and other NFGNB, particularly among patients hospitalised in intensive care units (data not shown). Previous studies have demonstrated that the spread of pauci-clones of carbapenem-resistant or pandrug-resistant *A. baumannii* and poly-clones of carbapenem-resistant *P. aeruginosa* in intensive care units and other wards at the hospital contributes significantly to the increased rates of carbapenem resistance among these isolates [6,10–12].

Recently, the ARIMA model has been widely used to investigate the relationship between antibiotic use and antibiotic resistance and provides forecasts of resistance based on past antibiotic use and resistance data [27,28]. Owing to the huge database in this study, this model was used to analyse both cefotaxime resistance in *E. coli* and ceftazidime resistance in *P. aeruginosa*. Our results clearly demonstrated the trends of worsening cefotaxime resistance in *E. coli* and favourable susceptibility in *P. aeruginosa* to ceftazidime in the next 6 years.

In conclusion, this 13-year study in a hospital demonstrated that significant changes in antimicrobial use might have affected antimicrobial resistance in certain Gram-negative bacteria at the hospital. The changes could have been due to several other factors, most likely in conjunction with one another. Dissemination and feedback of these data to clinicians and decision-makers at the hospital is crucial to improve antibiotic prescribing and to implement effective infection control. More judicious use of antimicrobial agents will be necessary to limit this trend.

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