Journal of Microbiology, Immunology and Infection (2011) 44, 131—138

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ORIGINAL ARTICLE

Changing trends in antimicrobial resistance of major bacterial pathogens, 1985—2005: A study from a medical center in northern Taiwan

Wen-Tsung Lo [a], Wei-Jen Lin [a], Tzong-Shi Chiueh [b], Shi-Yi Lee [c], Chih-Chien Wang [a,*], Jang-Jih Lu [b,d,e,]**

[a] *Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[c] *Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[d] *Department of Laboratory Medicine, China Medical University Hospital, Taichung, Taiwan*
[e] *Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan*

Received 25 September 2009; received in revised form 2 December 2009; accepted 10 February 2010

KEYWORDS
Antimicrobial resistance;
Gram-negative bacteria;
Gram-positive bacteria;
Taiwan;
21 years

Background: Antimicrobial resistance is a major health problem worldwide. We evaluated the antimicrobial resistance trends of 16 major bacterial pathogens at a tertiary medical center in northern Taiwan.
Methods: We conducted a retrospective review of annual summary documents for antimicrobial susceptibility of clinically isolated gram-positive and gram-negative bacteria from 1985 to 2005. The numbers of isolates and susceptibilities were calculated for three 7-year periods: first period, 1985—1991; second period, 1992—1998; and the third period, 1999—2005.
Results: During the 21-year period, 219,715 bacterial pathogens were identified. A significant increase in incidence over time was found for methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *S epidermidis*, penicillin-nonsusceptible *Streptococcus pneumoniae*, erythromycin-resistant *S pneumoniae*, vancomycin-resistant enterococci, cefotaxime/ceftriaxone-resistant *Escherichia coli* and *Klebsiella pneumoniae*, and imipenem-resistant *Acinetobacter baumannii*. Additionally, a significant increase in ciprofloxacin resistance rates over time from 1996 to 2005 was noted for *E coli*, *Enterobacter cloacae*, and *A baumannii* (through 1997 to

* Corresponding author. Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, No. 325 Cheng-Kung Road, Section 2, Nei-hu 114, Taipei, Taiwan.
** Corresponding author. Department of Laboratory Medicine, China Medical University Hospital, No. 2 Yuh-Der Road, Taichung 40447, Taiwan.
E-mail addresses: ndmcccw@yahoo.com.tw (C.-C. Wang), janglu45@gmail.com (J.-J. Lu).

doi:10.1016/j.jmii.2010.02.004

2005). However, a significant decrease in erythromycin resistance rate with time from 1999 to 2005 was found for Groups A and B streptococci, non-A, B, D streptococci, and *S pneumoniae*.
Conclusion: Resistance to antimicrobial agents increased rapidly in the past two decades in Taiwan and has become very common in major bacterial pathogens. Continuous enforcement of policies to limit use of antimicrobial agents and active surveillance of antimicrobial resistance through a nationwide system are both warranted.

Introduction

Antimicrobial resistance is an increasing threat to patients in health care settings as well as in the community, and mortality and morbidity from infection are greater when caused by antimicrobial-resistant bacteria.[1–4] Taiwan has one of the highest levels of antimicrobial resistance in the world, and previous studies in Taiwan clearly demonstrated the remarkably high prevalence of some critically resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSSP), macrolide-resistant streptococci, third-generation cephalosporin-resistant Enterobacteriaceae, imipenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and ciprofloxacin-resistant Enterobacteriaceae.[5–13] Importantly, understanding the hospital antibiogram is mandatory in solving the problem of antimicrobial resistance in hospitals.[14]

In the past, over-the-counter antibiotic use as well as the widespread use of antimicrobial agents in animal husbandry spurred the rapid emergence of resistant bacteria in Taiwan.[5,15] Since 1995, medical payments have been regulated by the National Health Insurance System and a restrictive governmental policy to deny reimbursement through the National Health Insurance System for the costs of antibiotics used for the treatment of acute upper respiratory tract infections without evidence of bacterial involvement was implemented in 2001.[16] In addition, many other measures to control resistance problems were instituted in Taiwan, including more rigorous enforcement of prescription-filling practices in the pharmacy (starting in 1997), educational programs about appropriate antibiotic use for physicians and patients (starting in 1998), prohibition of several antimicrobial agents (such as avoparcin, kanamycin, and spiramycin) in animal husbandry by the Council of Agriculture in 2000, and antibiotic interventions were implemented in most hospitals in recent years.[5,16]

To understand the prevalence and trends of antimicrobial resistance among major bacterial pathogens in the past two decades in Taiwan, a retrospective review of the annual summary documents for antimicrobial susceptibility of clinically isolated gram-positive and gram-negative bacteria (GNB) from 1985 to 2005 in Tri-Service General Hospital (TSGH) were retrieved.

Methods

Setting

TSGH, a tertiary care medical center located in Taipei city, northern Taiwan, had 1,200 beds in 1985 and 1,700 beds in 2005. The entire hospital moved to new facilities in 2000, with less crowding and larger interbed space, and a smaller proportion of intensive care unit beds to general ward beds. The Nosocomial Infection Control Committee of the hospital was established in 1984. Before 1999, no specific and well-established antibiotic control policies were implemented at the hospital. All attending physicians at the hospital prescribed nearly all antimicrobial agents without consultation with hospital infectious disease specialists.

Data collection

All clinical specimens for bacterial growth and isolation were sent to the central laboratory in the department of clinical pathology at TSGH. These specimens included those from hospitalized in-patients, patients in the emergency services, and patients in the outpatient clinics of all services. In this analysis, there were totally 16 major bacterial pathogens studied, including *S aureus*, coagulase-negative staphylococci (focus on *S epidermidis*), *S pneumoniae*, other streptococci (including Groups A and B streptococci, non-A, B, and D streptococci and viridans streptococci), *Enterococcus* sp (including *E faecalis* and *E faecium*), *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* sp (focus on *E cloacae*), *Serratia marcescens*, *P aeruginosa*, and *Acinetobacter* sp (focus on *A baumannii*). These isolates were nonduplicate samples, as several isolates of one species from each patient recovered within 7 days were considered one isolate. Isolates were identified by standard methods and were confirmed using Vitek or API products (bioMerieux Vitek Inc., Hazelwood, MO, USA). The numbers of isolates were calculated for three 7-year periods: first period, 1985—1991; second period, 1992—1998; and the third period, 1999—2005.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing of the 16 major bacterial pathogens was performed by the disk-diffusion method. Isolates were classified as susceptible or resistant (including intermediate category) by the annually renewed Clinical Laboratory Standards Institute (CLSI; formerly known as the NCCLS) guidelines.[17,18] Screening for extended-spectrum β-lactamase (ESBL) phenotypes among *K pneumoniae* and *E coli* began in 2005. Isolates displaying positive double-disk synergy were considered ESBL producers. Double-disk confirmatory tests were performed using cefotaxime, cefotaxime-clavulanate, ceftazidime, and ceftazidime-clavulanate to confirm the ESBL phenotype.[17] The antimicrobial susceptibilities were summed for each of the 7-year periods indicated above.

The antimicrobial resistance data for *S epidermidis* isolates were not categorized by coagulase negativity and positivity until 2004; isolates of *Streptococcus* sp other than *S pneumoniae* were represented as "other streptococci" before 1997; isolates of Group A streptococci; viridans streptococci; Group B streptococci; and non-A, B, and D streptococci were separated from "other" streptococcal isolates since 1999. In addition, since 1997, isolates of *E cloacae* were separated from *Enterobacter* sp and isolates of *A baumannii* were similarly separated from *Acinetobacter* sp. *E faecalis* and *E faecium* isolates were separated from *Enterococcus* sp when they were isolated from expectedly sterile sites after 1999.

Trends in resistance

To determine the secular resistance trends of major bacterial pathogens at TSGH, the disk-diffusion susceptibility data of these organisms were retrieved from 1985 to 2005 annual summary documents. To calculate the resistance rates, isolates of each species with identical resistance profiles recovered from one patient within 7 days were counted as one isolate.

Statistical analysis

Pearson's correlation coefficient was used to determine the relationship between time series and resistance trends. Annual trends of resistance to each antimicrobial agent for each of the 16 bacteria studied were calculated using Durbin-Watson statistics. An r value greater than 0.72 (or less than -0.72) and a p value less than 0.05 were considered statistically significant.

Results

Resistance rates

Table 1 shows the years when the selected antibiotics were approved at TSGH. During the 21-year period, 219,715 bacterial pathogens were identified. The sums of isolates by genus and species and antimicrobial susceptibilities of gram-positive bacteria and gram-negative bacteria (GNB) for each of the three 7-year periods are shown in Tables 2 and 3, respectively. Among *S aureus* isolates, the resistances to methicillin, clindamycin, cephazoline, erythromycin, and gentamicin were high ($\geq$75%) and increased substantially after the first period (1985–1991). Vancomycin remained the most active agent for clinical *S aureus* isolates. For *S epidermidis* isolates, the high prevalence of antimicrobial resistance was as the same as that of *S aureus*. Furthermore, susceptibilities to penicillin, ampicillin, clindamycin, and erythromycin among *S pneumoniae* isolates remained low and decreased proportionally after the first period. During the third period (1999–2005), resistance to penicillin, clindamycin, and erythromycin were 75.6%, 67.3%, and 92.0%, respectively. All clinical *S pneumoniae* isolates were susceptible to vancomycin. In contrast to *S pneumoniae*, the antimicrobial susceptibilities of other streptococci did not decrease after the first period. Of the enterococci, 10%–17% was resistant to ampicillin and 63.9% were resistant to high-level gentamicin in the third period. The rate of vancomycin resistance was 22% during the third period. Additionally, *E faecalis* isolates were resistant to ampicillin (2.4%), vancomycin (5.2%), and high-level gentamicin (67.3%); *E faecium* isolates were much more resistant to ampicillin (83.7%), vancomycin (27.5%), and high-level gentamicin (79.1%).

Table 1 Year of approval of selected antimicrobial agents at Tri-Service General Hospital

Antimicrobial agent	Year of approval
Erythromycin	1970
Oxacillin	1972
Gentamicin	1983
Cefotaxime	1984
Vancomycin	1984
Amikacin	1987
Ceftazidime	1989
Imipenem	1989
Ciprofloxacin	1991

Both *E coli* and *K pneumoniae* isolates were highly resistant to cefazolin and gentamicin (Table 3). Increasing resistance to third-generation cephalosporins was observed among these isolates throughout the three periods. *P mirabilis* isolates were highly susceptible to third-generation cephalosporins, amikacin, imipenem, and aztreonam (>95%). In contrast, *Enterobacter* isolates (including *E cloacae*) were less susceptible to third-generation cephalosporins, amikacin, and aztreonam (46.4–89.5%), whereas susceptibility to imipenem remained high (>98%). Although *S marcescens* and *P aeruginosa* isolates remained susceptible to ceftazidime (>90% and >80%, respectively), resistance to ceftazidime was increasing among both pathogens. In the third period, the overall rate of resistance to imipenem was 4.8% for *A baumannii* and 16.8% in *P aeruginosa*. Thus, imipenem was the most active agent for the GNB isolates tested during the study period. Additionally, based on the CLSI guidelines for ESBL confirmation testing,[17] the percentage of ESBL-producing *K pneumoniae* (307/1,858, 16.5%) was greater than that for *E coli* (182/3,326, 5.4%) in 2005.

Resistance trends

Figure 1 shows the secular trends for MRSA, methicillin-resistant *S epidermidis* (MRSE, until 2003), PNSSP, erythromycin-resistant *S pneumoniae* (ERSP), vancomycin-resistant enterococci (VRE, since 1988), and high-level gentamicin resistant enterococci (HLGRE, since 1999). The secular trends for MRSA, MRSE, PNSSP, ERSP, and VRE increased significantly with time ($r > 0.72$ and $p < 0.001$). Peak prevalence for MRSA and ERSP occurred in 2000 and decreased significantly over time during the period of 2000–2005 ($r < -0.72$ and $p < 0.05$). The prevalence of ERSP and HLGRE remained steadily high throughout the studying period. Additionally, the secular trend of various streptococci with erythromycin resistance from 1999 to 2005 is shown in Fig. 2. Erythromycin resistance declined significantly in Groups A and B streptococci; non-A, B, and D

Table 2 Antimicrobial susceptibility rates of common clinical gram-positive bacteria at Tri-Service General Hospital from 1985 to 2005

Pathogen	Period	Number of isolates	Antimicrobial susceptibility (%)							
			P	AM	OX	CC	CZ	E	GM	VA
Staphylococcus aureus	1985—1991	4,455	2.2	2.4	68.6	76.0	—	47.3	66.5	100
	1992—1998	14,098	0.7	0.7	21.5	25.6	—	15.5	22.6	100
	1999—2005	24,976	0.3	—	21.8	23.2	—	17.9	28.9	100
Staphylococcus epidermidis	1985—1991	3,283	6.5	6.9	42.8	77.6	—	45.4	44.9	100
	1992—1998	3,487	5.5	5.4	28.7	57.3	—	29.6	39.1	100
	1999—2003	1,522	2.0	—	16.9	40.4	—	21.7	25.5	100
Coagulase-negative staphylococci	2002—2005	3,093	1.1	—	22.3	50.5	—	33.3	39.6	100
Streptococcus pneumoniae	1985—1991	78	100	98.7	90.3	89.0	—	75.7	25.8	100
	1992—1998	179	60.6	60.1	—	49.2	—	25.5	28.9	100
	1999—2005	610	24.4	24.4	—	32.7	—	8.0	—	100
Other streptococci	1985—1991	2,976	80.1	77.7	71.0	73.7	90.8	70.3	41.1	—
	1992—1997	2,020	87.8	88.2	84.6	78.0	94.5	71.9	72.1	—
Group A streptococcus	1999—2002	145	99.4	98.7	—	63.9	—	59.3	—	100
	2003—2005	198	100	100	—	84.3	—	75.3	—	100
Group B streptococcus	1999—2002	360	90.8	90.6	—	39.6	—	39.8	—	100
	2003—2005	756	99.6	99.6	—	51.1	—	53.2	—	100
Non-A, B, D streptococci	1999—2002	494	89.3	87.9	—	72.0	—	68.3	—	100
	2003—2005	706	99.3	99.7	—	84.9	—	82.1	—	100
Viridans group streptococci	1999—2002	768	82.7	82.3	—	70.8	—	55.8	—	100
	2003—2005	1,243	93.0	93.0	—	72.7	—	63.4	—	100
Enterococcus species	1985—1991	4,154	—	91.8	7.5	3.1	14.9	15.0	13.3	98.8
	1992—1998	5,138	82.8	84.8	3.4	2.6	17.4	13.9	17.4	97.8
	1999—2005	6,549	—	83.4	—	—	—	—	36.1[a]	78.0
Enterococcus faecalis	1999—2005	376	—	97.6	—	—	—	—	32.7[a]	94.8
Enterococcus faecium	1999—2005	345	—	16.3	—	—	—	—	20.9[a]	72.5

[a] Susceptibility to high-dose gentamicin.
AM = ampicillin; CC = clindamycin; CZ = cefazolin; E = erythromycin; GM = gentamicin; OX = oxacillin; P = penicillin; VA = vancomycin.

streptococci; and in *S pneumoniae* isolates ($r < -0.72$ and $p < 0.05$).

Figure 3 demonstrates the secular trends for cefotaxime/ceftriaxone-resistant *E coli* and *K pneumoniae*, ceftazidime-resistant *P aeruginosa* isolates (since 1988), imipenem-resistant *P aeruginosa* isolates (since 1990), and imipenem-resistant *A baumannii* isolates (since 1997). Resistance to cefotaxime/ceftriaxone by *E coli* and *K pneumoniae* isolates and resistance to imipenem by *A baumannii* isolates increased significantly with time ($r > 0.72$ and $p < 0.05$). Resistance to imipenem by *A baumannii* emerged in 2002 and remained at 6.9—8.4% throughout the study periods. Resistance to ceftazidime (9—23%) and imipenem (11—24%) by *P aeruginosa* remained steady over the study periods.

Ciprofloxacin resistance of the major GNB from 1996 to 2005 is shown in Fig. 4. *A baumannii* and *S marcescens* isolates were more resistant to ciprofloxacin from 1996 to 2005 than were other GNB isolates. *E coli* (from 1996 to 2005), *E cloacae* (from 1996 to 2005), and *A baumannii* (from 1997 to 2005) resistance to ciprofloxacin increased significantly with time ($r > 0.72$ and $p < 0.05$).

Discussion

Our results demonstrate that resistance to antimicrobial agents increased rapidly during the past two decades in Taiwan. MRSA was first documented in Taiwan in the early 1980s.[19] Since then, the prevalence of MRSA infections markedly increased for both nosocomial- and community-acquired infections.[20—25] Several dominant clones are prevalent in hospitals and in the community.[20—25] A nationwide survey showed that MRSA isolates increased from 52% to 61% between 1998 and 2000.[6] MRSA isolates increased rapidly in our hospital from 33% in 1990, peaking at 87.4% in 2000, and decreasing significantly thereafter to 75.2% in 2004. The rate of MRSA in this report is higher than in previously reported studies in Taiwan and other countries.[5—7,11,20,26] Although MRSA isolates are still largely susceptible to vancomycin, the first *S aureus* isolate with intermediate resistance to vancomycin (minimum inhibitory concentration, 8 μg/mL) isolated from synovial fluid and a knee wound from a patient with septic arthritis in our hospital was reported in 2005.[27] Furthermore, the increase in MRSE in our report is worrisome because coagulase-negative staphylococci are the leading cause of blood stream infections, as revealed in the 1999 National Nosocomial Infections Surveillance study.[28]

Taiwan has a relatively low prevalence of VRE (3—7% of isolates),[5—7,10,11] in contrast to the high prevalence of VRE in United States intensive care units, where the rate was about 28% from 2001 and 2004.[29] The high prevalence of VRE (22% in the third study period) in our analysis could be

Table 3 Antimicrobial susceptibility rates of common clinical gram-negative bacteria at Tri-Service General Hospital from 1985 to 2005

Pathogen	Period	Number of isolates	Antimicrobial susceptibility (%)											
			AM	CZ	PIP	CTX/CRO	CAZ[a]	GM	AN[b]	IPM[c]	SXT[d]	CIP	ATM	NA[d]
Escherichia coli	1985–1991	7,672	23.4	57.6	—	98.4	99.2	74.2	95.1	99.5	57.2	—	99.0	88.7
	1992–1998	6,533	21.9	58.2	—	97.6	98.0	64.0	96.7	99.8	44.3	81.2	96.8	76.2
	1999–2005	14,322	19.4	38.7	—	80.9	84.6	65.5	96.3	99.9	38.9	67.1	84.6	43.7
Klebsiella pneumoniae	1985–1991	6,434	1.1	69.8	—	97.5	98.5	68.1	91.2	100	63.7	—	97.5	77.5
	1992–1998	5,648	—	60.2	—	89.1	89.1	74.0	89.4	99.7	62.0	76.9	78.7	65.3
	1999–2005	9,429	—	62.6	—	73.6	74.9	72.0	87.6	99.8	60.2	68.2	74.7	40.3
Proteus mirabilis	1985–1991	2,117	31.4	69.0	—	98.3	99.5	68.9	98.2	100	51.6	—	99.0	89.1
	1992–1998	1,524	35.9	81.5	—	99.4	99.3	74.5	100	99.3	44.3	93.8	97.1	85.9
	1999–2005	2,312	36.3	72.5	—	95.4	99.5	65.6	95.6	100	37.8	85.3	99.8	56.1
Enterobacter species	1985–1991	3,566	5.7	7.5	—	61.6	74.3	45.2	77.0	98.1	50.7	—	71.5	78.6
	1992–1996	2,336	2.8	2.9	—	52.2	56.7	52.6	89.5	98.8	50.5	77.0	55.0	62.0
Enterobacter cloacae	1997–1998	925	0.5	0.5	—	49.4	48.7	42.9	84.1	100	44.3	80.7	46.7	39.5
	1999–2005	3,477	0.3	0.5	—	46.9	56.5	59.5	77.7	100	51.0	64.2	46.4	28.4
Serratia marcescens	1985–1991	1,691	0.6	0.9	—	74.1	96.5	39.0	60.2	99.2	45.7	—	87.4	37.4
	1992–1998	3,773	1.1	0	—	70.0	93.2	34.2	83.5	99.6	54.8	40.5	83.5	26.4
	1999–2005	3,798	0.1	0.2	—	42.9	91.2	44.2	83.8	99.9	40.2	38.7	75.1	15.3
Pseudomonas aeruginosa	1985–1991	11,252	—	—	73.6	7.1	85.8	49.6	71.9	87.4	—	—	63.4	92.0
	1992–1998	15,751	—	—	83.0	17.8	84.2	51.6	81.0	83.6	—	71.3	64.4	—
	1999–2005	17,338	—	—	76.2	—	81.0	65.9	87.9	83.2	—	65.7	59.8	—
Acinetobacter species	1985–1991	3,210	7.6	2.4	53.3	13.9	74.2	40.5	63.7	96.0	50.8	—	12.4	73.4
	1992–1996	4,227	2.9	1.4	53.6	27.5	65.2	30.2	60.6	97.3	48.3	89.0	8.2	77.4
Acinetobacter baumannii	1997–1998	2,071	1.0	—	42.4	25.3	54.8	21.3	43.6	98.0	30.7	52.2	7.4	16.7
	1999–2005	9,021	0	—	—	1.7	31.6	19.7	32.9	95.2	—	26.1	1.0	7.5

[a] During the first period (1985–1991), disk-susceptibility data of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* species, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Acinetobacter* species were evaluated from 3,488; 2,857; 952; 1,379; 792; 5,219; and 1,378 isolates, respectively

[b] During the first period (1985–1991), disk-susceptibility data of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* species, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Acinetobacter* species were evaluated from 5,480; 4,595; 1,512; 2,643; 1,254; 7,836; and 2,486 isolates, respectively

[c] During the first period (1985–1991), disk-susceptibility data of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* species, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Acinetobacter* species were evaluated from 2,786; 2,321; 763; 975; 541; 3,864; and 982 isolates, respectively

[d] SXT and NA were only tested for isolates obtained from urine samples.

AM = ampicillin; AN = amikacin; ATM = aztreonam; CAZ = ceftazidime; CIP = ciprofloxacin; CRO = ceftriaxone; CTX = cefotaxime; CZ = cefazolin; GM = gentamicin; IPM = imipenem; NA = nalidixic acid; PIP = piperacillin; SXT = trimethoprim/sulfamethoxazole.

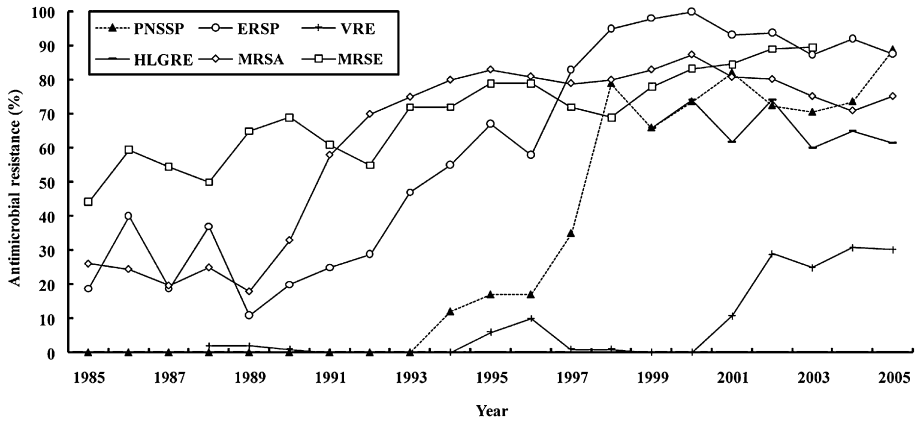

Figure 1. Secular trend of selected gram-positive bacterial isolates resistant to various antimicrobial agents at Tri-Service General Hospital from 1985 to 2005. ERSP = erythromycin-resistant *Streptococcus pneumoniae*; HLGRE = high-level gentamicin resistant enterococci; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSE = methicillin-resistant *Staphylococcus epidermidis*; PNSSP = penicillin-nonsusceptible *Streptococcus pneumoniae*; VRE = vancomycin-resistant enterococci.

because of the policy of routinely screening every patient admitted to the intensive care units in our hospital for VRE; thus, enterococci isolates included in this report are colonizing and infecting isolates. Additionally, a previous nationwide study in Taiwan showed that the rate of high-level gentamicin resistance among *E faecalis* and *E faecium* isolates was 66% and 62%, respectively.[6] The higher rates of HLGRE (around 65—75%) in the present report could correlate with administration of aminoglycosides because they are the second most frequently used antimicrobial category in Taiwan hospitals.[14,30]

The prevalence of PNSSP increased rapidly from 0% in 1993 to very high levels of 73.3% in 2004 and 88.9% in 2005 in our hospital. Although our PNSSP rate was lower than that reported for Vietnam where the PNSSP prevalence was 92% among clinical isolates during the 2000—2001 period,[8] we report the highest prevalence of PNSSP in Taiwan.[5,6,9,15] Hsueh[31] reported a 16% decline in rate of PNSSP from the 1998—1999 period to 2001, after a 46% decrease in total penicillin and other cephalosporin usage in 2001 compared with 1999. However, we did not find such a decreasing trend. In addition, we report a significantly declining trend in erythromycin resistance in Groups A and B streptococci; non-A, B, and D streptococci; and *S pneumoniae* from 1999 to 2005. During the period of 1999—2003, Hsueh et al.[16,31] also demonstrated a decline in erythromycin consumption and resistance rates of Group A streptococci, but a continued increase in erythromycin resistant *S pneumoniae* was found. The relatively small numbers of *S pneumoniae* isolates in our report could contribute to the differing results between two hospitals.

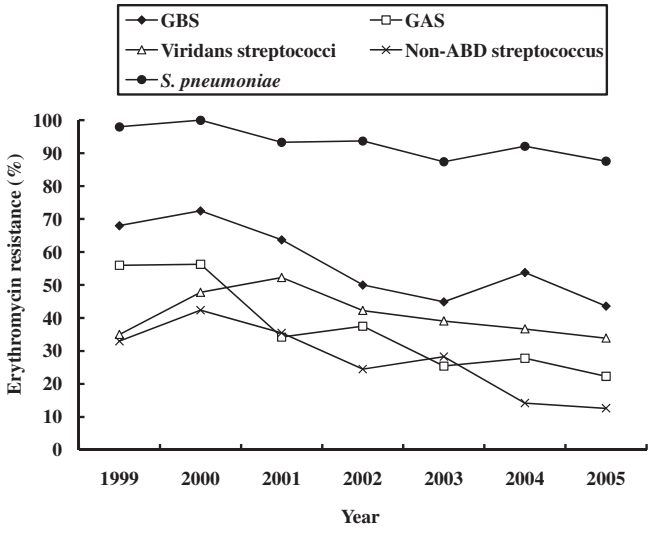

Figure 2. Secular trend of various streptococci resistant to erythromycin at Tri-Service General Hospital from 1999 to 2005. GAS = group A streptococcus; GBS = group B streptococcus.

A previous study in Taiwan conducted by Jean et al.[32] stated that cefotaxime-resistant *E coli* (33.3%) and *K pneumoniae* isolates (58.4%) exhibited ESBL. In our hospital, among ceftriaxone-resistant *E coli* and *K pneumoniae* isolates tested in 2004, 27.5% and 58.2%, respectively, exhibited the ESBL phenotype. In the Asia-Pacific region, ESBL-producing isolates showed high levels of coresistance to aminoglycosides, tetracycline, trimethoprim-sulfamethoxazole, and ciprofloxacin.[33] Although all the ESBL-producing isolates were susceptible to imipenem at our hospital, indiscriminate use of imipenem could promote imipenem resistance.[32—35] Thus, establishment of alternative agents for use against ESBL producers is crucial at the individual hospital level because interhospital variation of these data occur.[34]

Ciprofloxacin was launched in Taiwan in 1991, and a dramatic increase in the prescription of fluoroquinolones in Taiwan has occurred thereafter.[13] Sheng et al.[13] reported the rapid increase in ciprofloxacin-resistant *E coli*, *Morganella morganii*, *S marcescens*, *P aeruginosa*, and *E cloacae* in 1996—1997, following the widespread use ciprofloxacin in Taiwan. Additionally, we also report a significantly increasing trend in ciprofloxacin resistance over time for *E coli* (1996—2005), *E cloacae* (1996—2005), and *A baumannii* (1997—2005).

An effective strategy to limit the effects of increasing high antimicrobial resistance must be multifaceted and must include education of patients and physicians about

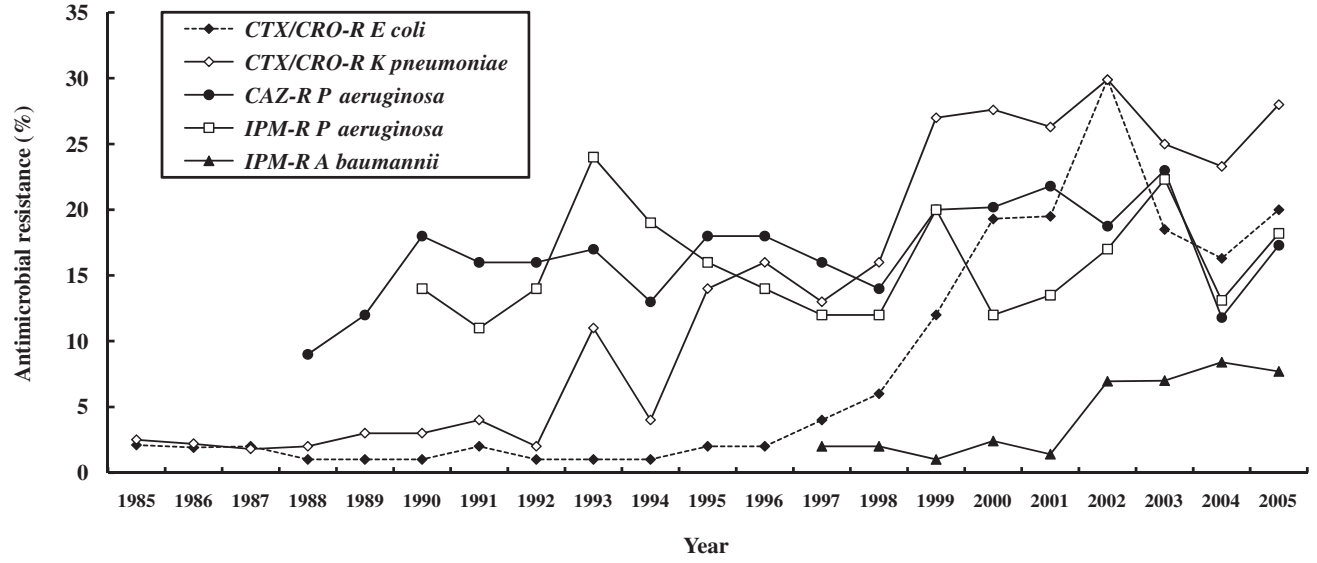

Figure 3. Secular trend of selected gram-negative bacterial isolates resistant to various antimicrobial agents at Tri-Service General Hospital from 1985 to 2005. CAZ = ceftazidime; CRO = ceftriaxone; CTX = cefotaxime; IPM = imipenem.

appropriate antimicrobial use, use of effective infection control practices to prevent transmission from infected to uninfected patients, surveillance of antimicrobial resistance and antimicrobial use, improved use of immunization, and development of alternative therapies that would circumvent the need for antimicrobial therapy.[29,30,36] The government policy of restricting antibiotic use for acute respiratory tract infections without evidence of bacterial infection in Taiwan in 2001 resulted in a decrease in the use of penicillins, cephalosporins, and macrolides and also reduced macrolide-resistant Group A streptococcus.[16] In addition, the hospital moved to new facilities with a smaller proportion of intensive care units beds and wider interbed spaces, which could have contributed to the significant decrease in the rate of MRSA after 2000 and the relatively low prevalence of imipenem-resistant *A baumannii* in our hospital.

In conclusion, this 21-year study in a medical center in northern Taiwan demonstrated significant changes in antimicrobial resistance among major bacterial pathogens.

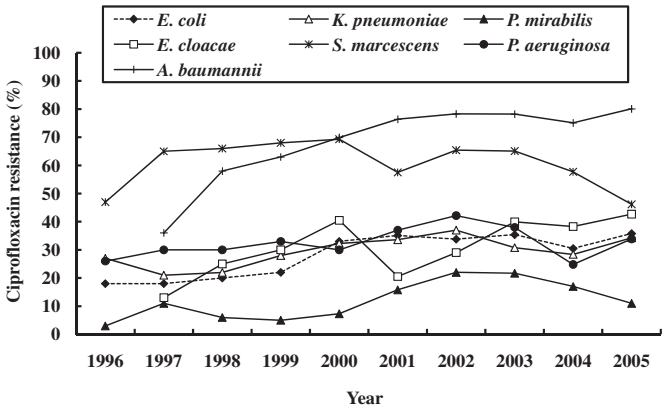

Figure 4. Secular trend of major gram-negative bacterial isolates resistant to ciprofloxacin at Tri-Service General Hospital from 1996 to 2005.

Dissemination and feedback of these data to clinicians and decision makers at our hospital and others is crucial to improve antibiotic prescribing and to implement effective infection control.

Acknowledgment

This work was supported by grants NSC 95-2320-B-016-023-MY3 from the National Science Council and TSGH-C96-62 from Tri-Service General Hospital, Taiwan, Republic of China.

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