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Correlation between carbapenem consumption and resistance to carbapenems among Enterobacteriaceae isolates collected from patients with intra-abdominal infections at five medical centers in Taiwan, 2006–2010

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SUMMARY

We investigated the trend in resistance to carbapenems among isolates of Enterobacteriaceae that had been collected from patients with intra-abdominal infections at five medical centers in Taiwan from 2006 to 2010 and evaluated the correlation between resistance to carbapenems and consumption of said agents as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART). During the study period, the usage of ertapenem and that of total carbapenems (ertapenem, imipenem, and meropenem) increased significantly from 6.13 to 13.38 defined daily doses per 1000 patient-days for ertapenem and from 20.43 to 34.25 defined daily doses per 1000 patient-days for total carbapenems. The most common species were *Escherichia coli* ($n = 1095$), *Klebsiella* spp. ($n = 663$), and *Enterobacter* spp. ($n = 202$). The susceptibility of all isolates to ertapenem and to imipenem varied during the study period. For ertapenem, the rates of non-susceptibility ranged from 3.5% to 10.3% and those for imipenem ranged from 3.5% to 10.7%. Although the use of carbapenems increased during the study period, there was no marked increase in resistance to carbapenems. Continuous monitoring of resistance trends is necessary so that antimicrobial prescription policies can be adjusted and infection control intervention programs can be implemented.

Introduction

Antimicrobial resistance is an emerging threat worldwide and is found in both Gram-positive and Gram-negative pathogens. Among Gram-positive bacteria, *Staphylococcus aureus* is notoriously difficult to treat because it is highly resistant to penicillin and methicillin, as well as to glycopeptide antibiotics [1,2]. Among Gram-negative organisms, Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are difficult to treat because many strains produce enzymes that confer multidrug resistance, such as extended-spectrum β-lactamase (ESBL), AmpC β-lactamase, and

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carbapenemase [3]. One of the main reasons for the recent spread and evolution of antibiotic resistance is the increased consumption of antibiotics [4]. Carbapenems, a class of β-lactam antibiotics with a broad spectrum of antibacterial activity, have been used for the treatment of patients with infections due to multidrug-resistant Enterobacteriaceae in Taiwan since 1988 [5]. However, the rate of carbapenem resistance among Enterobacteriaceae has gradually increased over the past decade [6].

In this study, we investigated the trends in resistance to carbapenems among isolates of Enterobacteriaceae that had been collected from patients with intra-abdominal infections at five medical centers in Taiwan from 2006 to 2010 and evaluated the correlation between resistance to carbapenems and consumption of said agents as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART).

Materials and methods

Study centers and antimicrobial agent consumption

A total of 5 hospitals in Taiwan participated in the SMART program during the period 2006 to 2010. Among them, 1 is located in northern Taiwan (National Taiwan University Hospital), 2 in central Taiwan (China Medical University Hospital and Changhua Christian Hospital), and 2 in southern Taiwan (Chi-Mei Medical Center and Kaohsiung Medical University Chung-Ho Memorial Hospital). The defined daily doses (DDDs) per 1000 patient-days of each carbapenem (ertapenem, imipenem, and meropenem) were obtained from the pharmacy department of each hospital.

Bacterial isolates

Each of the participating hospitals prospectively collected up to 100 non-duplicate Enterobacteriaceae isolates from patients with intra-abdominal infections during the study period. Isolates obtained from tissue, fluid, or deep wound cultures during surgical procedures, as well as fluid obtained from paracentesis or percutaneous aspiration of abscesses were included [7–11]. Isolates obtained from drainage bottles, stool, or peri-rectal abscesses, as well as duplicate isolates (i.e., isolates of the same genospecies from the same patient) were excluded. Bacteria were initially identified by standard methods in the clinical microbiology laboratories of each of the participating hospitals.

Antimicrobial susceptibility testing

Procedures for identifying the isolates to the species level, as well as antimicrobial susceptibility testing of all isolates, were performed at the Central Laboratory of International Health Management Associates (International Health Management Associates, Inc., Schaumburg, IL, USA). Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method (Siemens Medical Solutions Diagnostics, MicroScan, West Sacramento, CA, USA) in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines [12]. Both 2010 CLSI breakpoints and 2011 CLSI breakpoints for susceptibility to ertapenem and imipenem were used [13,14]. *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains for each batch of MIC tests.

Statistical analysis

Trends in annual consumption of each carbapenem (ertapenem, imipenem, and meropenem), the rate of non-susceptibility to ertapenem and imipenem among Enterobacteriaceae, and the relationship between resistance trends and carbapenem consumption were analyzed by linear regression. A P-value <0.05 was considered to represent statistical significance.

Results

Carbapenem consumption

Data on the annual usage of each carbapenem (ertapenem, imipenem, and meropenem) and total use of carbapenems (DDDs/1000 patient-days) are shown in Table 1. Except for the decrease in consumption of imipenem from 2006 to 2007 (8.88 to 8.29 DDDs/1000 patient-days) and the decrease in consumption of meropenem from 2009 to 2010 (10.35 to 8.05 DDDs/1000 patient-days), there was an incremental increase in carbapenem consumption during the study period. There was also a significant increase in ertapenem ($P = 0.009$) and total carbapenem consumption ($P = 0.002$) during the 5-year period. Ertapenem usage increased from 6.13 DDDs/1000 patient-days in 2006 to 13.38 DDDs/1000 patient-days in 2010. Total carbapenem usage rose from 20.43 DDDs/1000 patient-days in 2006 to 34.25 DDDs/1000 patient-days in 2010.

Trends in carbapenem resistance in Enterobacteriaceae

A total of 2235 non-duplicate isolates of Enterobacteriaceae were collected from the five participating medical centers during the period 2006 to 2010. Trends in resistance to the tested antimicrobial agents among species in the Enterobacteriaceae family are shown in Table 2. *Escherichia* ($n = 1095$, all were *E. coli*), *Klebsiella* ($n = 663$, most were *K. pneumoniae*), and *Enterobacter* ($n = 202$, most were *E. cloacae*) were among the most common genera of bacteria isolated. Isolates of these three genera were more resistant to ertapenem than to imipenem. For *E. coli*, the highest rate of non-susceptibility to ertapenem was 6.6% in 2007 and the lowest rate was 1.3% in 2009. Moreover, the highest rate of non-susceptibility to imipenem was 4.1% in 2007 and the lowest rate was 0.3% in 2010. For *Klebsiella* spp., the highest rate of non-susceptibility to ertapenem was 10% in 2007 and the lowest rate was 3.2% in 2009. Moreover, the highest rate of non-susceptibility

Table 1
Annual consumption of carbapenems at five medical centers in Taiwan, 2006–2010

Antimicrobial agent	Carbapenem consumption (DDDs/1000 patient-days) by year					Correlation[a]		
	2006	2007	2008	2009	2010	γ	P-value[b]	b
Ertapenem	6.13	7.54	11.59	11.86	13.38	0.961	**0.009**	1.882
Imipenem	8.88	8.29	8.97	9.72	12.82	0.819	0.090	0.931
Meropenem	5.42	7.16	8.35	10.35	8.05	0.813	0.094	5.621
Total	20.43	22.99	28.91	31.93	34.25	0.987	**0.002**	3.658

[a] γ = correlation coefficient; b = regression coefficient.
[b] Boldface type indicates significance ($P < 0.05$).

Table 2
Trends in the association of various Enterobacteriaceae not susceptible to the indicated antimicrobial agent at five medical centers, 2006–2010

Organism and carbapenems	Rate (%) of isolates non-susceptible, by year					Correlation[a]		
	2006	2007	2008	2009	2010	γ	*P*-value	b
Escherichia coli								
No. of isolates	186	196	179	238	296			
Ertapenem	4.8	6.6	3.4	1.3	4.4	0.495	0.396	5.930
Imipenem	2.7	4.1	0.6	0.4	0.3	0.790	0.112	4.170
Klebsiella spp.[b]								
No. of isolates	115	140	132	124	153			
Ertapenem	4.3	10	5.3	3.2	3.3	0.496	0.395	7.860
Imipenem	3.5	5.7	1.5	0.8	1.3	0.723	0.168	5.35
Enterobacter spp.[c]								
No. of isolates	35	33	36	41	57			
Ertapenem	17.1	25.7	22.2	14.6	36.8	0.514	0.376	14.790
Imipenem	8.6	11.4	5.6	2.4	19.3	0.304	0.619	5.740
Others[d]								
No. of isolates	40	31	51	53	99			
Ertapenem	2.5	16.1	2	5.7	4	0.202	0.745	-0.740
Imipenem	45	41.9	31.4	24.5	51.5	0.064	0.918	-0.440
Total								
No. of isolates	376	400	398	456	605			
Ertapenem	5.6	10.3	5.5	3.5	7.1	0.238	0.7	7.540
Imipenem	8.0	8.3	5.3	3.5	10.7	0.034	0.957	6.980

[a] γ = correlation coefficient; b = regression coefficient.
[b] *K. pneumoniae* (*n* = 613); *K. oxytoca* (*n* = 48); *K. ornithinolytica* (*n* = 2); *K. terrigena* (*n* = 1).
[c] *E. cloacae* (*n* = 162); *E. aerogenes* (*n* = 34); *E. sakazakii* (*n* = 2); *E. amnigenus, E. agglomerans, E. cancerogenus, E. asburiae* (*n* = 1).
[d] *Citrobacter amalonaticus* (*n* = 2), *Citrobacter braakii* (*n* = 2), *Citrobacter freundii* (*n* = 38), *Citrobacter koseri* (*n* = 21), *Citrobacter* spp. (*n* = 1), *Edwardsiella ictaluri* (*n* = 1), *Kluyvera ascorbata* (*n* = 1), *Morganella morganii* (*n* = 35), *Plesiomonas shigelloides* (*n* = 1), *Proteus mirabilis* (*n* = 95), *Proteus penneri* (*n* = 1), *Proteus vulgaris* (*n* = 15), *Providencia alcalifaciens* (*n* = 1), *Providencia rettgeri* (*n* = 4), *Salmonella enteritidis* (*n* = 1), *Salmonella* spp. (*n* = 20), *Serratia marcescens* (*n* = 33), *Serratia odorifera* (*n* = 1).

to imipenem was 5.7% in 2007 and the lowest rate was 0.8% in 2009. The rates of non-susceptibility among *Enterobacter* spp. were markedly higher than those among *E. coli* or *Klebsiella* spp., with the highest rates being 36.8% for ertapenem and 19.3% for imipenem in 2010. Higher rates of imipenem resistance were found in *Proteus* and *Morganella* spp. (71/111 = 65.8% and 31/35 = 88.6%, respectively) than those of resistance to ertapenem. The overall non-susceptibility rates among all isolates to ertapenem were 5.6% in 2006, 10.3% in 2007, 5.5% in 2008, 3.5% in 2009, and 7.1% in 2010. The overall non-susceptibility rates among all isolates to imipenem were 8.0% in 2006, 8.3% in 2007, 5.3% in 2008, 3.5% in 2009, and 10.7% in 2010. Overall, there was no significant increase in the rate of carbapenem resistance among species in the Enterobacteriaceae family of bacteria during the period 2006 to 2010.

Relationship between carbapenem consumption and resistance to carbapenems

Table 3 shows the correlation between resistance to ertapenem or imipenem and carbapenem usage. We found that there was no significant change in ertapenem resistance among the isolates of Enterobacteriaceae. This lack of correlation between consumption and resistance was also observed between imipenem resistance and total carbapenem consumption.

Discussion

Carbapenems are more potent β-lactams than penicillins or cephalosporins because they act as slow substrates or inhibitors of β-lactamase. This is because of their special molecular characteristics, such as a carbon atom at the C-1 position, an *R* configuration on the hydroxyethyl side chain, and a *trans* configuration of the β-lactam ring at C-5 and C-6 [15]. Metallo-β-lactamase production, oxacillinase production, efflux pumps, and the ability to down-regulate porin are well-known mechanisms that confer carbapenem resistance among non-fermenting Gram-negative bacteria, such as *Pseudomonas* spp., *Acinetobacter* spp., and *Stenotrophomonas* spp. [15,16]. Before the year 2000, carbapenem resistance in Enterobacteriaceae was rare and, therefore, carbapenems were the drugs of choice for the treatment of infections due to ESBL- or AmpC β-lactamase-producing Enterobacteriaceae [16,17]. However, carbapenem resistance in Enterobacteriaceae is no longer a rare event, mainly because growing numbers of Enterobacteriaceae exhibit resistance mechanisms mediated by ESBL or AmpC enzymes in combination with reduced permeability due to mutations that cause porin loss, or expression of true carbapenemases such as KPC, NDM-1, and VIM (*K. pneumoniae* carbapenemase, New Delhi metallo-β-lactamase 1, and Verona integron-encoded metallo-β-lactamase, respectively) [6,18].

In our study, we found that the consumption of each carbapenem gradually increased during the period 2006–2010, with the exception of imipenem usage during 2006–2007 and meropenem usage during 2009–2010. A significant increase in usage was only observed for ertapenem and total carbapenems, but not for imipenem and meropenem during the study period. Because of the adoption of new CLSI carbapenem breakpoints for Enterobacteriaceae in 2010 (the susceptible breakpoint for

Table 3
Relationship between annual consumption of carbapenems and resistance to ertapenem and imipenem among Enterobacteriaceae isolates collected at five medical centers in Taiwan, 2006–2010

	Correlation[a]														
	E. coli			*Klebsiella* spp.[b]			*Enterobacter* spp.[c]			Others[d]			Total		
	γ	*P*	b	γ	*P*	b	γ	*P*	b	γ	*P*	b	γ	*P*	b
Ertapenem resistance															
Ertapenem	0.587	0.298	−0.369	0.527	0.361	−0.477	0.424	0.476	1.193	0.348	0.566	−0.651	0.350	0.564	−0.285
Total carbapenems	0.605	0.280	−0.201	0.561	0.326	−0.268	0.412	0.491	0.612	0.304	0.619	−0.301	0.360	0.552	−0.155
Imipenem resistance															
Imipenem	0.636	0.249	−0.602	0.574	0.312	−0.649	0.677	0.210	2.426	0.453	0.443	2.730	0.498	0.393	0.776
Total carbapenems	0.867	0.057	−0.252	0.810	0.097	−0.281	0.179	0.773	0.197	0.181	0.771	−0.335	0.092	0.883	−0.044

[a] γ = correlation coefficient; b = regression coefficient.
[b] *K. pneumoniae* (*n* = 613); *K. oxytoca* (*n* = 48); *K. ornithinolytica* (*n* = 2); *Klebsiella terrigena* (*n* = 1).
[c] *E. cloacae* (*n* = 162); *E. aerogenes* (*n* = 34); *E. sakazakii* (*n* = 2); *E. amnigenus*, *E. agglomerans*, *E. cancerogenus*, *E. asburiae* (*n* = 1).
[d] *Citrobacter amalonaticus* (*n* = 2), *Citrobacter braakii* (*n* = 2), *Citrobacter freundii* (*n* = 38), *Citrobacter koseri* (*n* = 21), *Citrobacter* spp. (*n* = 1), *Edwardsiella ictaluri* (*n* = 1), *Kluyvera ascorbata* (*n* = 1), *Morganella morganii* (*n* = 35), *Plesiomonas shigelloides* (*n* = 1), *Proteus mirabilis* (*n* = 95), *Proteus penneri* (*n* = 1), *Proteus vulgaris* (*n* = 15), *Providencia alcalifaciens* (*n* = 1), *Providencia rettgeri* (*n* = 4), *Salmonella enteritidis* (*n* = 1), *Salmonella* spp. (*n* = 20), *Serratia marcescens* (*n* = 33), *Serratia odorifera* (*n* = 1).

ertapenem was 0.25 μg/mL and that for imipenem was 1 μg/mL) in this study, the carbapenem non-susceptible rate in this study was higher than that in previous reports [19,20]. The high rate of non-susceptibility to imipenem in the 'others' group is attributed to *Proteus* and *Morganella* spp., because they have greater MIC distributions for imipenem than ertapenem. A previous study also reported similar findings (imipenem MIC_{50} 1–2 μg/mL, ertapenem MIC_{50} <0.06 μg/mL) [21].

In our study, the rate of non-susceptibility to carbapenems among Enterobacteriaceae did not increase proportionally during the study period, even though total carbapenem consumption increased significantly. This lack of correlation might be explained by the limitations of this study. First, the different breakpoints adopted for the interpretation of susceptibility might have had a negative influence on our results [10]. Second, antibiotic consumption over a threshold (15–25 DDDs/1000 patient-days) might result in a rise in resistance [22]. Whether this is the case for carbapenems is unknown. Third, all of the bacterial strains had been isolated from patients with intra-abdominal infections. Whether our findings can be extrapolated to bacteria isolated from patients with infections other than intra-abdominal infections is not clear. In addition, outbreaks of resistant strains and different infection control interventions in various hospitals were not taken into consideration. Fourth, the difference in prescribing profiles and lower dose prescriptions in pediatric patients or patients with renal function impairment were not analyzed. Furthermore, 5 years might not have been long enough to detect the emergence of antibiotic resistance.

In conclusion, although the use of carbapenems increased during the study period, there was no marked increase in resistance to carbapenems. Continuous monitoring of resistance trends is necessary so that antimicrobial prescription policies can be adjusted and infection control intervention programs can be implemented.

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