ความสัมพันธ์ระหว่างปริมาณยาโดยเฉลี่ยสำหรับการรักษาต่อวัน ต่อ 1000 รายคนไข้-วัน ของยาต้านจุลชีพ และอัตราดื้อยาของเชื้อ *P. aeruginosa* และ *A. baumannii* : กรณีศึกษาโรงพยาบาลหัวหิน

The Correlation between Defined Daily Dose/1000 Patient-day of Antimicrobials and the Resistance Rate of *P. aeruginosa* and *A. baumannii* : A Case Study at Hua-Hin Hospital

นิพนธ์ต้นฉบับ **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาแนวโน้มของ Defined Daily Dose (DDD)/1000 ราย-วัน ของยาต้านจุลชีพ แนวโน้มการดื้อยาของเชื้อ *P. aeruginosa* และ *A. baumannii* และความสัมพันธ์ระหว่าง DDD/1000 ราย-วัน ของยาต้านจุลชีพกับอัตราดื้อยาของเชื้อ **วิธีการศึกษา:** เก็บข้อมูลการใช้ยาแบบ DDD/1000 ราย-วัน ของยา ceftazidime, imipenem, meropenem, ertapenem, ciprofloxacin, amikacin และ gentamicin และข้อมูลร้อยละของเชื้อ *P. aeruginosa* และ *A. baumannii* ที่ดื้อยากลุ่มคาร์บาพีเนม และเชื้อดื้อยาหลายชนิดในโรงพยาบาลหัวหินระหว่างปี พ.ศ. 2553 - 2557 ทดสอบแนวโน้มทั้งหมดด้วยสัมประสิทธิ์สหสัมพันธ์ (*r*) จาก simple linear regression **ผลการศึกษา:** ในช่วง 5 ปีพบว่า DDD/1000 ราย-วัน ของ meropenem มีแนวโน้มสูงขึ้น ขณะที่ imipenem และ gentamicin ลดลงอย่างมีนัยสำคัญทางสถิติ การใช้ amikacin (r = 0.894, P = 0.041) และ imipenem (r = 0.957, P = 0.011) ที่ลดลงสัมพันธ์กับอัตราดื้อยาหลายชนิดของ *P. aeruginosa* ที่ลดลงด้วย ส่วนการใช้ ertapenem ที่เพิ่มขึ้นสัมพันธ์กับอัตราดื้อยาหลายชนิดของ *P. aeruginosa* ที่ลดลง (r = -0.90, P = 0.037) ส่วนการใช้ amikacin ที่ลดลงสัมพันธ์กับอัตราดื้อยา imipenem ของ *P. aeruginosa* ที่ลดลง (r = 0.891, p = 0.042) แต่สัมพันธ์กับอัตราดื้อยาหลายชนิด (r = -0.948, P = 0.014) ของยา imipenem (r = -0.950, P = 0.013) และ meropenem (r = -0.939, P = 0.018) ของ *A. baumannii* ที่เพิ่มขึ้นด้วย **สรุป:** DDD/1000 ราย-วัน ของยา amikacin, imipenem และ ertapenem สัมพันธ์กับอัตราดื้อยา จึงจำเป็นอย่างยิ่งที่ต้องประเมินการใช้ยาอย่างสมเหตุสมผล เพื่อแก้ปัญหาเชื้อดื้อยาได้ในที่สุด

คำสำคัญ: DDD/1000 patient-day, *P. aeruginosa*, *A. baumannii,* อัตราการดื้อยา

Abstract

Objective: To determine the trends of defined daily dose (DDD) per 1000 patient-day among antimicrobial agents, drug resistance to *P. aeruginosa* and *A. baumannii* and the relationship between DDD per 1000 patient-day of antimicrobial agents and drug resistance rate. **Method:** We collected and defined 1) DDD per 1000 patient-day of ceftazidime, imipenem, meropenem, ertapenem, ciprofloxacin, amikacin and gentamicin and 2) the percentage of carbapenem resistant- and multi drug resistant (MDR) *P. aeruginosa* and *A. baumannii* at Hua-Hin hospital in 2010 - 2014. Correlation coefficients from simple linear regression were used to test the trends. **Results:** DDD/1000 patient-day of meropenem had increased while those of imipenem and gentamicin had decreased with statistical significance. The increased use of amikacin (r = 0.894, P = 0.041) and imipenem (r = 0.957, P = 0.011) each was associated with lower rates of MDR-*P. aeruginosa* while increased ertapenem use was correlated with decreasing MDR-*P. aeruginosa* (r = -0.90, P = 0.037). Moreover, the lesser use of amikacin associated with reducing rates of imipenem resistant *P. aeruginosa* (r = -0.90, P = 0.042) but with increasing rate of MDR (r = -0.948, P = 0.014), imipenem (r = -0.950, P = 0.013) and meropenem (r = -0.939, P = 0.018) resistant *A. baumannii*. **Conclusion:** The use of amikacin imipenem and ertapenem was related to rate of antimicrobial resistance. Thus, drug use evaluation is needed to solve antibiotic resistance.

Keywords: DDD/1000 patient-day, *P. aeruginosa*, *A. baumannii,* resistant rate

Introduction

Microbial multidrug resistance has been an ever-rising problem, especially gram-negative bacteria including *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii* which poses direct negative treatment outcomes on the patients and the increased overall care expenses.[1] As shown in a study by Evans et al. surgical patients infected with drug-resistant gram-negative bacteria had significantly worse treatment outcomes than those with non-resistant infections regarding infection severity, median numbers of days of hospitalization and ICU stay, and hospitalized care expenses. In addition, they found that the median care expenditure increased by 11,075 US dollars per patient.[2] Resistance to the third generation cephalosporins of *E. coli* and *K. pneumoniae* has been an emerging problem.[1] Data of the National Antimicrobial Resistance Surveillance Center (NARST) of Thailand showed that in 2013, of all isolates

including blood, sputum, and urine, only 55.9% of *E. coli* and 59.3% of *K. pneumoniae* were sensitive to ceftriaxone.[3]

Carbapenem is a major antibacterial drug group for drug-resistant gram-negative bacterial infections.[4] With its ever-increasing use, however, resistance to carbapenems among *P. aeruginosa* and *A. baumannii* has been continuously rising. A study by Surang Dejsirilert found that from 2000 to 2009, incidents of carbapenem-resistant *A. baumannii* increased from 18% to 65%[5], which was consistent with NARST data indicating a rising trend of resistance to imipenem, a carbapenem drug, of *P. aeruginosa* from 14.3% in 2000, to 30.1% in 2013. Recently, Benchamas Rimrang et al. reported a considerable number of resistance incidents to carbapenems of *E. coli* and *K. pneumoniae*.[6] All this evidence suggests that the problem of carbapenem-resistant bacteria in Thailand has become more severe. One of the causes is the extensive use of antimicrobial agents.[7]

In quantifying the extent of drug use, defined daily dose (DDD) has been applied to various drugs with their main indications in adult patients. The DDD for each of the antibiotics has been defined by the World Health Organization (WHO). Once multiplied by the number of hospitalized patient-days, the extent of use of individual antibiotics could be compared across health care settings.[8] DDD was also useful for studying trends by comparing the extent of the use over time. The comparisons of the direct amount of drug used each year could be misleading since it could be rising with the increasing numbers of patients. Thus, to test the association of the antibiotic use and bacterial resistance, DDD was more appropriate than the actual amount of antibiotic use. It has been found that the extent of antibiotic use presented as DDD/1000 patient-days is associated with bacterial resistance.[9,10] As a consequence, the value of DDD/1000 patient-days has been used as an effectiveness index of the hospital infectious control policy.[11]

Hua-Hin hospital, a general hospital, has been facing an increasing number of antibiotic resistance. In 2010, sensitivity to imipenem, a carbapenem drug, was only 3.0% for multi-drug resistant *A. baumannii* and 17.0% for *P. aeruginosa*. In 2013, carbapenem-resistant *Enterobacteriaceae* was first reported in Hua-Hin hospital (interview communication with Praedao Preechachuewong, September 24, 2015. The extent to which the use of antibiotics was associated with the likelihood of resistance among *P. aeruginosa* and *A. baumannii* has not been fully understood. Therefore this study aimed to determine 1) the use of certain antibiotics at Hua-Hin hospital measured as DDD/1000 patient-days from 2010 to 2014 and the trends of use over time, 2) the rates of antibiotic resistance of *P. aeruginosa* and *A. baumannii* from 2010 to 2014 and the trends of the resistance rates over time, and 3) the association between DDD/1000 patient-days and rate of antibiotic-resistance of *P. aeruginosa* and *A. baumannii* over time. Resistance of *P. aeruginosa* and *A. baumannii* included that of multi-drug resistant strains, imipenem non-susceptible strains, and meropenem non-susceptible strains.

Materials and Methods

This retrospective study was set at Hua-Hin hospital, a general hospital with 400 beds, in Prachuabkhirikhan province, Thailand. We collected data on the use of antibiotics and percentages of antibiotic resistance between 2010 and 2014. Specifically the following data were collected: 1) the use amount in grams of ceftazidime, imipenem, meropenem, ertapenem, ciprofloxacin, amikacin, and gentamicin, 2) numbers of hospitalization days in each study year, and 3) rate of multi-drug resistant *P. aeruginosa* and *A. baumannii* and carbapenem-resistant strains, specifically non-susceptible to imipenem or meropenem.

Study patients

We recruited all patients in the in-patient department (IPD) from 2010 to 2014. Patients with visits at the out-patient department, emergency room, and observation room were not eligible. The number of hospitalization days of each patient in a given year was summed. In a special case of hospitalization period covering two calendar years, two separate durations according to each calendar year were counted. For example, for a hospitalization from December 1, 2011, to January 31, 2012, 31 hospitalization days for 2011, and another 31 hospitalization days for 2012 were counted. Data of hospitalization days were retrieved and extracted from the hospital-computerized database entitled Medical2000. This study was approved by the Ethical Committee for Human Study of Hua-Hin hospital (approval number 11/2015).

Study antibiotics

We collected the use of a set of antibiotics including ceftazidime, imipenem, meropenem, ertapenem, cipro-

floxacin, amikacin and gentamicin from 2010 to 2014 from the computerized database Medical2000. Only the use of injection dosage forms with all strengths available in the hospital were collected to calculate the DDD. The use was excluded if it was in oral dosage form, eye drops or nebulizations, or prescribed for patients in the out-patient department, emergency room, or observation room.

Antibiotic Sensitivity Data

Data on susceptibility of *P. aeruginosa* and *A. baumannii* to antibiotics were obtained from the hospital antibiogram of all isolates from 2010 to 2014. Sensitivity results in antibiogram were based on the standards provided by the *Clinical and Laboratory Standards Institute* (*CLSI*) with disk diffusion method.[12] Susceptibility results consisted for susceptible to antibiotics (S), intermediately resistant (I), and resistant (R). In our study, sensitivity status was classified only to susceptible (or sensitive), and non-susceptible strain of bacteria (intermediately resistant and resistant combined) to each of antipseudomonal carbapenems (i.e., imipenem and meropenem). In addition, multi-drug resistance was defined as non-susceptible to at least three groups of antibiotics. All sensitivity results for each of the antibiotics were converted to rates as percentages.

Estimation of defined daily dose per 1000 patient-days

Data on the use of ceftazidime, amikacin, gentamicin, ciprofloxacin, ertapenem, imipenem and meropenem were collected. In addition, the use of imipenem and meropenem as antipseudomonal agents were also specified and collected. Hospitalization days in relation to the use of these antibiotics were used to calculate DDD/1000 patient-days for each of antibiotics as follows.

$$\text{DDD per 1,000 patients-days} = \frac{\text{the use amount in grams of the antibiotics in a given year} \times 1{,}000}{\text{DDD of the antibiotics} \times \text{number of hospitalization days in a given year}}$$

The value of DDD of each antibiotics was provided by WHO as an average daily dose for main indication in adult patients. DDD values for ceftazidime, imipenem, meropenem, ertapenem, ciprofloxacin, amikacin and gentamicin were 4, 2, 2, 1, 0.5, 1 and 0.24 grams, respectively.[8]

Data analysis

Defined daily dose per 1000 patient-days of each study of antibiotics from 2010 to 2014, was presented as number of doses. For each antibiotics, the association between DDD per 1000 patient-days and the four consecutive study years, 2010 to 2014, was tested by linear regression for the trend of use over time with a corresponding *P*-value.

Rates of antibiotic resistance of *P. aeruginosa* and *A. baumannii* from 2010 to 2014 were presented as percent. For each of *P. aeruginosa* and *A. baumannii*, rates of multi-drug resistant strains, imipenem non-susceptible strains, and meropenem non-susceptible strains were presented separately. For each strain, the association between percents of resistance and the four consecutive study years, 2010 to 2014, was also tested by linear regression for the trend of resistance over time with a corresponding *P*-value.

Finally the relationships between DDD per 1000 patient-days of each antibiotics and rates of antibiotic resistance of each resistant strains of *P. aeruginosa* and *A. baumannii* were tested. Data of DDD per 1000 patient-days and percents of resistance strains were tested for normal distribution using Shapiro-Wilk test. The relationship was presented as Pearson's correlation coefficient or Spearman rank correlation (*r*) with a corresponding *P*-value.

All correlation tests were conducted using a significant level set at $P < 0.05$. All analyses were performed using PSPP free software version 0.8.4.

Results

DDD per 1,000 patient-days of antibiotics

A total numbers of patient-days in 2010 to 2014 were considerably comparable, i.e., 111,855, 132,732, 134,738, 134,423, and 127,759 days, respectively. Numbers of isolates tested for strains of *P. aeruginosa* and *A. baumannii* were 202 and 179 respectively in 2010, 370 and 204 in 2011, 376 and 316 in 2012, 379 and 385 in 2013, and 397 and 392 in 2014. It was found that DDD/1000 patient-days of ceftazidime increased the most (1.88 folds) from 19.60 doses in 2012 to 36.75 doses in 2014, followed by ciprofloxacin, with a 1.35-fold increase, from 15.07 doses in 2010 to 20.33 doses in 2014. On the other hand, a decrease was found in amikacin and gentamicin (Table 1). In terms of carbapenem use rate, it was found that DDD/1000 patient-days increased, of which meropenem from 13.54 doses in 2010 to 54.13 doses in 2014, and ertapenem from 0.08 doses in 2010 to 4.56 doses in 2014. On the other hand, imipenem decreased from 27.02 doses in 2010 to 9.01 doses in 2014. Once

antipseudomonal carbapenems were considered, DDD per 1,000 patient-days were high and increased from 40.64 doses in 2010 to 67.70 doses in 2014.

Regarding trends of change, only gentamicin (r = -0.89, *P* = 0.044) and imipenem (r = -0.99, *P* = 0.002) had statistically significant negative associations of DDD per 1,000 patient-days with the five consecutive years from 2010 to 2014. In contrast, meropenem had a significant positive association (r = +0.88, *P* = 0.045).

Table 1 Defined daily dose/1000 patient-days of antibiotics used from 2010 to 2014 at Hua-Hin hospital.

Antimicrobial agents	DDD per 1,000 patient-days (doses) by year					*r* *	*P*-value†
	2010	2011	2012	2013	2014		
Ceftazidiime	19.60	9.58	29.51	23.42	36.75	+0.74	0.151
Amikacin	9.85	5.70	6.70	6.34	5.46	-0.73	0.164
Gentamicin	35.20	28.49	16.38	16.22	16.68	-0.89	**0.044**
Ciprofloxacin	15.07	18.96	15.82	12.99	20.33	+0.24	0.696
Ertapenem	0.08	0.26	0.41	1.41	4.56	+0.85	0.065
Imipenem	27.02	20.14	16.70	14.13	9.01	-0.99	**0.002**
Meropenem	13.54	27.83	51.53	65.37	54.13	+0.89	**0.045**
Antipseudomonal carbapenems‡	40.64	48.23	68.64	80.91	67.70	+0.84	0.077

* Correlation coefficient (*r*) between DDD per 1,000 patient-days and years (2010 – 2014) from linear regression analysis.

† *P*-value corresponding to correlation coefficient (*r*).

‡ Antipseudomonal carbapenems = imipenem + meropenem.

Rates of antibiotic resistance of *P. aeruginosa* and *A. baumannii*

Rates of serious antibiotics resistance of *P. aeruginosa* had been decreased over time from 2010 to 2014 as follows (Table 2). Multi-drug resistant strains of *P. aeruginosa* had decreased from 31.19% in 2010 to 20.65% in 2014; while a decrease from 41.02% to 35.49% of imipenem non-susceptible strains, and a slight decrease from 37.46% to 34.52% of meropenem non-susceptible strains were found. On the other hand, *A. baumannii* were found to have high rates of resistance throughout study periods, and the rates had been increased over time. First, multi-drug resistant strains of *A. baumannii* had increased from 68.16% in 2010 to 83.93% in 2014. Second, an increase in imipenem non-susceptible strains *A. baumannii* was found, from 67.70% to 83.41%. Finally, an increase from 71.27% to 83.41% of meropenem non-susceptible strains *A. baumannii* was found. Despite all changes mentioned above, only changes in rates of multi-drug resistant strains of *P. aeruginosa* over the study period were statistically significant (r = -0.90; *P* = 0.037).

Table 2 Rates of antibiotic resistance of *P. aeruginosa* and *A. baumannii* from 2010 to 2014.

Microbial strains	Rate as % of resistance by year					*r* *	*P*-value†
	2010	2011	2012	2013	2014		
P. aeruginosa							
Multi-drug resistant strains	31.19	25.68	24.73	25.33	20.65	-0.90	**0.037**
Imipenem non-susceptible strains	41.02	32.61	35.57	33.00	35.49	-0.50	0.388
Meropenem non-susceptible strains	37.46	29.78	36.05	33.78	34.52	-0.10	0.870
A. baumannii							
Multi-drug resistant strains	68.16	87.25	76.90	81.04	83.93	+0.54	0.344
Imipenem non-susceptible strains	67.70	85.51	75.59	80.42	83.41	+0.59	0.299
Meropenem non-susceptible strains	71.27	85.45	77.13	80.80	83.41	+0.55	0.333

* Correlation coefficient (*r*) between DDD per 1,000 patient-days and years (2010 – 2014) from simple linear regression analysis.

† *P*-value corresponding to correlation coefficient (*r*).

Relationships between DDD per 1000 patient-days and rates of antibiotic resistance

As indicated in Table 1 that DDD per 1000 patient-days of amikacin and imipenem had decreased over time, the findings in Table 3 suggested that such decrease in DDD per 1000 patient-days in each of the two drugs were significantly associated with the decrease in the rates of multi-drug resistant strains of *P. aeruginosa* (r = +0.90, *P* = 0.041 for amikacin, and r = +0.96, *P* = 0.011 for imipenem). This association is also graphically visualized in Figure 1. On the other hand, while ertapenem's DDD per 1000 patient-days had increased over time, the rates of multi-drug resistant strains of *P. aeruginosa* had decreased significantly (r = -0.90, *P* = 0.037) (Table 3 and Fig. 1).

For amikacin, it was further found that the decrease of amikacin's DDD per 1000 patient-days over time was significantly associated with the decrease in the rates of imipenem non-susceptible strains of *P. aeruginosa* (r = +0.89, *P* = 0.042). However, the resistance trends relating to *A. baumannii* were different. The decrease of amikacin's DDD per 1000 patient-days over time was significantly associated with the increase in the rates of multi-drug resistant strains (r = -0.95, *P* = 0.014), imipenem non-susceptible strains (r = -0.95, *P* = 0.013), and meropenem non-susceptible strains of *A. baumannii* (r = -0.94, *P* = 0.018). For ceftazidime, gentamicin and ciprofloxacin, the changes in DDD per 1000 patient-days of these antibiotics over time were not significantly associated with the changes in resistance rates.

Table 3 Correlation coefficient (*r*) between DDD per 1000 patient-days and rates of resistance.

Antimicrobial agents		*P. aeruginosa*			*A. baumannii*		
		Multi-drug resistant strains	Imipenem non-susceptible strains	Meropenem non-susceptible strains	Multi-drug resistant strains	Imipenem non-susceptible strains	Meropenem non-susceptible strains
Ceftazidime	*r*	-0.61	+0.14	+0.54	-0.07	-0.03	-0.06
	P-value	0.278	0.823	0.350	0.913	0.964	0.925
Imipenem	*r*	+0.96	+0.59	+0.21	-0.65	-0.68	-0.65
	P-value	**0.011**	0.295	0.732	0.240	0.207	0.235
Meropenem	*r*	-0.74	-0.61	-0.08	+0.45	+0.47	+0.43
	P-value	0.156	0.272	0.903	0.453	0.421	0.468
Ertapenem	*r*	-0.90	-0.30	-0.30	+0.40	+0.40	+0.40
	P-value	**0.037**	0.624	0.624	0.505	0.505	0.505
Amikacin	*r*	+0.90	+0.89	+0.70	-0.95	-0.95	-0.94
	P-value	**0.041**	**0.042**	0.189	0.014	**0.013**	**0.018**
Gentamicin	*r*	+0.81	+0.58	+0.04	-0.45	-0.47	-0.43
	P-value	0.094	0.307	0.946	0.444	0.421	0.465
Ciprofloxacin	*r*	-0.56	-0.16	-0.41	+0.55	+0.55	+0.57
	P-value	0.325	0.799	0.494	0.333	0.335	0.311
Antipseudomonal carbapenems	*r*	-0.65	-0.57	-0.01	+0.36	+0.38	+0.34
	P-value	0.237	0.319	0.986	0.556	0.523	0.574

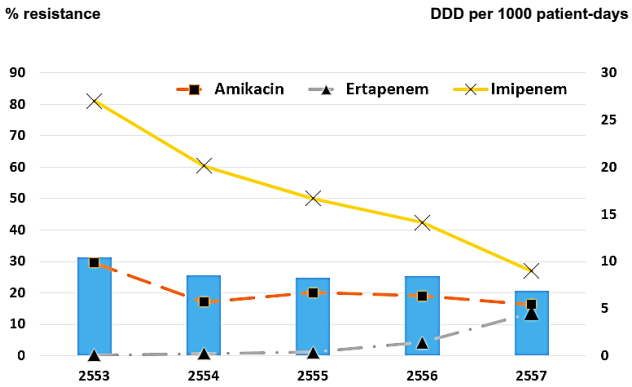

Figure 1 Association between DDD per 1000 patient-days of amikacin, ertapenem and imipenem and rates of multi-drug resistant strains of *P. aeruginosa*. Note: 2553 – 2557 BE = 2010 – 2014 AD.

Discussions and Conclusion

Our study found that DDD per 1000 patient-days of carbapenem group had increased from 2010 to 2014; while those of aminoglycosides had decreased. In comparison with results from a medical school hospital, its DDD per 1000 patient-days of imipenem in 2010 and 2011 were 3.21 and 3.90 doses respectively, which were lower than what we found in our study, 27.02 and 20.14, respectively. In constrast, in 2010, DDD per 1000 patient-days of meropenem in our study (13.54 doses) were comparable to that in the medical school hospital (13.56 doses).[13]

In terms of antipseudomonal carbapenem (imipenem + meropenem), in 2011, DDD per 1000 patient-days in our study was 48.23 doses which was higher than 20.28 doses found in the medical school hospital in the same year.[13] In contrast to antipseudomonal carbapenem, non-antipseudomonal carbapenem (ertapenem) in our study in 2010 and 2011 were 0.08 and 0.26 doses, respectively, which were lower than those in the medical school hospital in the same years, 7.39 and 13.57 doses, respectively.[13] This suggests that medical school hospital might be more likely to order non-antipseudomonal carbapenem, since medical schools have more infectious specialists[14] and/or have more effective infectious control measures.[15]

Another important finding was that the decrease in imipenem use and the increase in ertapenem use both were significantly associated with the decrease of the multi-drug resistant strains of *P. aeruginosa*. This was consistent with the study of Sausa et al. which found that the increase in ertapenem use and the decrease in imipenem use resulted in a decrease in resistance of *P. aeruginosa* towards imipenem.[16] With these results, it is recommended that for any bacterial infections, other than *P. aeruginosa* or *A. baumannii*, which are susceptible to carbapenem group, ertapenem should be the first option.[17]

The decreasing trend of amikacin use found in our study was associated with increasing trend of imipenem non-susceptible strains, meropenem non-susceptible strains, and multi-drug resistant strains of *A. baumannii*. This could be attributable to an increased use of antibiotics other than amikacin lately. More of the other antibiotics that were used, the higher rates of resistance towards these antibiotics, other than amikacin, were seen.[18]

For ceftazidime and ciprofloxacin, the use of these two antibiotics was not associated with rate of resistance in our study. However, previous studies found that the increasing use of ceftazidime[19] and ciprofloxacin[20,21] was associated with a rising rate of resistance in the hospital.

Despite critical findings, this study was not free from limitations. Its retrospective design with the use of electronic medical records made it impossible to retrieve complete information of cases, not recorded or recorded with incomplete data. In the study period of 2010 to 2014, a low use rate of ertapenem in 2010 could be attributable to its first introduction to this hospital in 2010. Interpretation on the ertapenem use in the first year should be done with caution.

Results from our study suggested that the use of carbapenem antibiotics should be controlled by means of rational measures, including the hospital infectious control. This recommendation was proper, even though not all of our findings on DDD per 1000 patient-days of and on resistance

towards carbapenem drugs were significant. In addition, it was cautioned that the use of carbapenem drugs in our hospital, which was higher than that in medical school hospital, did not always mean the inappropriate antibiotics use. It could mean that the hospital might already have a high rate of resistance which inevitably required the use of carbapenems. We recommend drug use evaluation in addition to the analysis on antibiotic use rate.

Conclusion

In 2010 to 2014, the use of carbapenem antibiotics in Hua-Hin hospital was high. A decreased use of amikacin and imepenem was significantly associated with the decrease in the rates of multi-drug resistant strains of *P. aeruginosa* over time. To encourage a hospital rational drug use, it is highly critical to have in place parallel measures, such as, the hospital infectious control and drug use evaluation (DUE).

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Editorial note

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