Antimicrobial Resistance of *Acinetobacter baumannii*: Six Years of National Antimicrobial Resistance Surveillance Thailand (NARST) Surveillance

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Objective: *To determine the prevalence, clinical epidemiology, and antimicrobial susceptibilities of Acinetobacter baumannii in Thailand from 2000 to 2005.*
Material and Method: *Twenty-eight hospitals participated in the National Antimicrobial Resistance Surveillance Thailand program. All data were reviewed and analyzed for the prevalence, clinical epidemiology, and antimicrobial susceptibilities of the clinical isolates of A. baumannii from 2000 to 2005.*
Results: *The number of clinical isolates of Acinetobacter spp. increased from 8,699 isolates in 2000 to 14,071 isolates in 2005. The most common species, identified by biochemical and growth characteristics, was A. baumannii. More than 50% of all isolates were from the respiratory tract specimens. The percentage of resistance has been increasing, particularly multi-drug-resistant (MDR) or carbapenem-resistant phenotypes. Of carbapenem-resistant strains, the prevalence was 2.1% and 46.7% in 2000 and 2005, respectively. Most carbapenem-resistant strains were also MDR. The prevalence of MDR strains was highest in the Central region and Bangkok. Cefoperazone/sulbactam was the antimicrobial against largest proportion Acinetobacter spp., although the prevalence of resistance to this agent is on the upward trend.*
Conclusion*: A standardized technique to identify the organisms to the species level should be determined to be used in the surveillance system. Because the prevalence of Acinetobacter spp. resistant to multiple classes of antimicrobials including carbapenems and cefoperazone/sulbactam are increasing, there is an urgent need for a more active surveillance system, more stringent infection control efforts, and powerful antimicrobial stewardship programs in all healthcare sectors to minimize the further spread of this MDR strain.*

Keywords: *Acinetobacter baumannii, Anti-infective agents, Drug resistance, Bacterial, Microbial sensitivity tests, Population surveillance, Thailand*

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Acinetobacter spp. is strictly aerobic non-motile Gram-negative, catalase-positive, oxidase-negative bacilli, with 39% to 47% G-C content. According to the most recent review on the taxonomy of these bacteria, this genus contains 33 genomic species, 17 of which have a validated name and the rest are still designated as a number[1,2]. Twenty-five members of 33 genomic species of *Acinetobacter* that have been isolated from humans are *A. calcoaceticus* (DNA group 1), *A. baumannii* (DNA group 2) *A. haemolyticus* (DNA group 4), *A. junii* (DNA group 5), *A. johsonii* (DNA group 7) *A. lwoffii* (DNA groups 8 and 9), *A. radioresistens* (DNA group 12), *A. ursingii* (phenon 1) *A. schindleri* (phenon 2), *A. parvus* (phenon 4), *A. baylyi*, DNA group 3, 6, 10, 11, 13, 14, 15, 16, 17, 13 TU, 15 TU, "Close to 13TU", "Between 1 and 3", and

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"*A. septicus*[1-3]". Among these, groups 1, 2, 3, and 13 TU are closely related to each other, and many laboratories report the identification of these bacteria as *A. calcoaceticus-A. baumannii* complex (Acb complex)[4]. However, numerous clinical studies have suggested that *A. baumannii* is the most important species that causes many diseases in humans, largely among hospitalized patients[5-7]. As other Gram-negative nosocomial pathogens, the most common body site that the bacterium can be isolated is the lower respiratory tract. Other sites of infections include the bloodstream, skin and soft tissue, urinary tract, and central nervous system[8].

Although it is difficult to estimate the magnitude of the clinical role of *A. baumannii* in human health, this species is now generally accepted as a more and more important healthcare challenge since they are isolated more frequently than in the past, and in some instances, even at a higher percentages than the long known hospital pathogen *Pseudomonas aeruginosa*. From the National Antimicrobial Resistance Surveillance System (NARST) data[9], since 2000, it was recognized that *Acinetobacter* have increasingly been isolated from blood and sputum while the isolation rates of *P. aeruginosa* remained steady. Furthermore, this bacterial species can become quickly resistant to many antimicrobial agents, particularly carbapenems, which are one of the antibiotics with the broadest antibacterial activity[10]. Risks of having infections caused by *A. baumannii* include multiple and/or severe underlying illnesses, intensive care unit admission, older age, prolonged hospital stay, use of medical devices such as an endotracheal tube or a central venous catheter, and surgical or other invasive procedures. Infections with *A. baumannii*, particularly strains that are resistant to many antibiotics, have posed a major threat to a large number of patients and it is a difficult challenge for today's healthcare system[8].

The NARST (http://NARST.dmsc.moph.go.th), in collaboration with several medical schools, therefore, have conducted surveillance of the susceptibility of *A. baumannii* clinical isolates collected from 28 hospitals located in all regions of Thailand. The present study is the result of such surveillance performed from 2000 to 2005.

Material and Method

Isolates and participating hospitals

The NARST, Department of Medical Sciences, Ministry of Public Health (MOPH) Thailand, was organized in 1998, and it was supported by the World Health Organization (http://narst.dmsc.moph.go.th). Participating hospitals collected specimens from all body sites of patients and medical devices as indicated clinically, and performed the susceptibility tests on site. These hospitals include five in the North, six in the Northeast, five in the Center, four in the East, four in the South, and four in Bangkok. The size of hospitals varies from 310-bed to 500-bed general hospitals (eight hospitals), more than or equal 500 bed regional hospitals (16 hospitals), around the country, a university-affiliated medical school, and three private hospitals in Bangkok. Only susceptibility patterns of isolates that were identified as *A. baumannii* were analyzed.

Antimicrobial susceptibility tests

A. baumannii were identified at the participating hospitals using conventional cultures and biochemical methods. *In vitro* susceptibility testing was determined by the disk diffusion method according to the guidelines of the Clinical Laboratory Standards Institute (CLSI) [formenly National committee for Clinical Laboratory Standards (NCCLS)][10], and the results of the test were reported to NARST. Antimicrobial agents that were tested against the bacterium were those listed in *Acinetobacter* panel of the CLSI. In addition, cefoperazone/sulbactam was also tested because it is a beta-lactam/beta-lactamase inhibitor combination commonly used (both empirically and specifically) in Thailand and some other countries except the United States for the treatment of infections caused by *A. baumannii*. Antibiotics that were tested in all hospitals against more than 40% of these bacteria included ceftazidime, imipenem, cefoperazone/sulbactam, ciprofloxacin, amikacin, gentamicin, and netilmicin. Some other antibiotics were tested against more than 40% of isolates from there own hospitals, but they were not tested consistently in others resulting in only a small portion of over all isolates of the whole country. These agents included ampicillin/sulbactam, cefepime, meropenem, and levofloxacin, and they will not be included in the data presented in this report.

Multi-drug-resistant (MDR) *A. baumannii* was defined as a strain resistant to at least three of antibiotic classes tested including a broad-spectrum beta-lactam (third-generation cephalosporins or carbapenems), an aminoglycoside, and a fluoroquinolone. *A. baumannii* ATCC (American Type Culture Collection) 49169 was used as the control organism.

The results of susceptibility testing were reported to NARST, and subsequently analyzed using the WHONET software program. Only the first isolates of the same species from the same patient were included.

Results

Identification of the organism

Overall, the number of clinical isolates of *Acinetobacter* spp. had increased over time, from 8,699 isolates in 2000 to 14,071 isolates in 2005 (Table 1). Of these, Acb complex (reported by hospitals as *A. baumannii*, *A. aniratus*, and *A. calcoaceticus*) was the most common species reported, *i.e.*, being 70-80% of all *Acinetobacter* spp. Among Acb complex, *A. baumannii* was the most common species. In the early phase of the program, the nomenclature of *Acinetobacter* spp. has not been standardized. Some hospital reported glucose-oxidizing, non-hemolytic *Acinetobacter* as *A. baumannii*, while others reported as *A. calcoaceticus* or *A. anitratus*, which are the old names of certain *Acinetobacter* spp. and some of them, were believed to be *A. baumannii* in the current nomenclature. The isolates that were reported as *A. baumannii* comprised 63% of *A. baumannii* complex in 2000 and increased to 71% in 2005 as a result of the regular training held by the Department of Medical Sciences, MOPH for laboratory personnel who work in the participating hospitals. However, a significant number (5.4%) of isolates was still labeled as *A. anitratus* in 2005. Because the majority of isolates were *A. baumannii*, the following results will mainly focus on this species.

A. baumannii was found most commonly from the respiratory tract (sputum, secretion obtained from the upper respiratory tract, tracheal aspirate, bronchoalveolar lavage, and lung tissue). The isolates from this site comprised 50% to 70% of all *A. baumannii* in this set of data. The next most common sites of isolation are pus from various body sites, urine, and blood. During the study period, around 4% to 6% of all *A. baumannii* was recovered from bloodstream or equivalent to 600 to 700 patients per year (Table 2).

Susceptibility patterns

Antimicrobial agents tested against *A. baumannii* in each participating hospital partly depended on the resources available both in the microbiology laboratory and for clinical use. Table 3 shows the percentages of resistance of the organism to antimicrobial agents that were tested regularly in all hospitals. From 2000 to 2005, the incidence of carbapenem resistance increased dramatically from 2.1% to 46.7% (Table 3). Although cefoperazone/sulbactam is usually active against *A. baumannii* in early clinical use, the resistance against this beta-lactam/beta-lactamase inhibitor combination has increased as well, *i.e.*, from 3.4% in 2000 to 12.1% in 2005, or 3.6-fold increased. The incidence of resistance to ceftazidime, gentamicin, amikacin, and ciprofloxacin were around 50% to 60% during the study period. For netilmicin, the incidence of resistance increased gradually (Table 2).

The data in Tables 3-8 show the resistance rates categorized by regions. There is a general trend of increasing resistance, which is more prominent in

Table 1. Number and percentage of *Acinetobacter* spp. isolates reported by 28 hospitals

Reported name	2000		2001		2002		2003		2004		2005	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. baumannii	5,458	62.7	7,107	69.2	7,708	67.4	7,715	57.8	8,792	65.4	9,941	70.6
A. anitratus	1,026	11.8	918	8.9	916	8.0	1,056	7.9	819	6.1	753	5.4
A. calcoaceticus	555	6.4	638	6.2	505	4.4	547	4.1	148	1.1	180	1.3
A. baumannii-A. calcoaceticus complex*	7,039	80.9	8,663	84.3	9,129	79.8	9,318	69.8	9,759	72.6	10,874	77.3
A. lwoffii	852	9.8	792	7.7	1,034	9.0	955	7.2	1,032	7.7	853	6.1
A. haemolyticus	58	0.7	86	0.8	6	0.1	2	0.0	4	0.0	10	0.1
A. junii	20	0.2	13	0.1	22	0.2	13	0.1	26	0.2	13	0.1
Acinetobacter sp.	730	8.4	723	7.0	1,249	10.9	3,053	22.9	2,621	19.5	2,321	16.5
Grand total	8,699		10,277		11,442		13,341		13,442		14,071	

* *A. baumannii*, *A. anitratus*, and *A. calcoaceticus* altogether

Table 2. Type of specimens from which *Acinetobacter* spp. were reported by 28 hospitals from 2000 to 2005

Type of specimens	2000		2001		2002		2003		2004		2005	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Respiratory tract	4,446	52.0	5,101	53.3	6,449	60.3	7,259	65.3	7,512	63.4	7,447	64.4
Pus	1,992	23.3	2,019	21.1	2,024	18.9	1,729	15.6	1,768	14.9	1,505	13.0
Urine	1,108	13.0	1,221	12.7	983	9.2	953	8.6	1,156	9.8	1,238	10.7
Blood	339	4.0	535	5.6	535	5.0	569	5.1	708	6.0	654	5.7
Other	668	7.8	703	7.3	697	6.5	606	5.5	711	6.0	715	6.2
Total	8,553	100.0	9,579	100.0	10,688	100.0	11,116	100.0	11,855	100.0	11,559	100.0

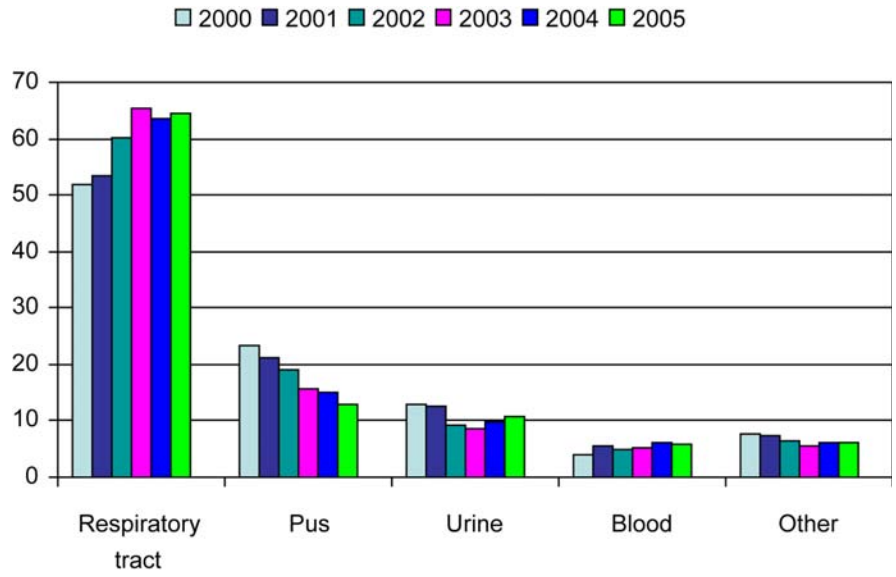

Fig. 1 Percentage of *Acinetobacter* spp. isolates of 28 hospitals by the type of specimens from 2000 to 2005

Bangkok and the Central region. The resistance to cefotaxime, ceftazidime, and ciprofloxacin, which has already been higher than 50%, has not significantly increased in the past six years. Isolates from the Northern region was the only group that showed an increase in the resistance rates while those from the Southern region were declining. Bangkok and the Central region were the areas where the resistance to amikacin have increased, but there were no such changes in all others. Of note, the carbapenem resistance has dramatically increased during the study period while a carbapenem was widely used. This change, again, was most clearly seen with the isolates from Bangkok and the Central region where imipenem-resistant isolates have increased from 0.6% and 3.1% in 2000 to 51.2% and 54.3% in 2005 for each area, respectively. Perhaps this trend has pressed microbiology laboratories and physicians in Bangkok area to search for other therapeutic options. Therefore, a sizable number of isolates in this particular area were tested against cefepime and piperacillin/tazobactam, which are the agents normally preserved for the treatment of infections caused by these problematic organisms in the hospitals. Unfortunately, the resistance to these two agents has also increased. In 2001, 38.6% of the isolates were resistant to cefepime, compared to 53.4% in 2005. For piperacillin/tazobactam, the rates of resistance were 42.1% in 2000 and 61.1% in 2005 (Table 3-4).

As in all other studies, the isolates obtained from the patients admitted to the intensive care units (ICUs) are usually more resistant to antimicrobial agents

Table 3. Percentage of resistance of *Acinetobacter baumannii* to commonly tested antimicrobial agents

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Ceftazidime	4,654	59.1	6,542	59.1	6,831	57.9	6,911	60.5	8,248	59.9	9,359	64.0
Imipenem	3,629	2.1	5,033	5.5	5,345	19.4	5,560	27.5	7,065	38.1	8,507	46.7
Cefoperazone/sulbactam	4,168	3.4	4,180	3.8	4,849	3.7	5,272	6.9	6,167	7.1	7,874	12.1
Gentamicin	5,157	62.0	6,894	61.5	7,088	59.8	7,011	59.8	8,405	60.1	9,364	61.2
Amikacin	5,012	47.8	6,710	51.9	6,989	52.7	6,919	52.8	8,335	50.7	9,405	49.5
Netilmicin	3,552	28.0	4,772	39.4	4,296	39.0	3,669	35.1	5,011	34.3	6,117	36.8
Ciprofloxacin	4,715	50.6	6,401	53.7	6,513	55.4	6,614	57.5	7,982	57.1	9,161	61.7

Table 4. Resistance rates of *Acinetobacter baumannii* in Bangkok

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	351	61.8	312	59.3	373	61.4	337	65.0	500	52.6	529	55.6
Ceftazidime	337	54.3	403	52.4	517	56.5	454	63.7	635	55.0	728	59.3
Cefepime			332	38.6	411	59.1	387	56.6	575	53.2	714	53.4
Imipenem	356	0.6	403	13.2	603	31.0	460	41.3	661	44.0	734	51.2
Ampicillin/sulbactam	50	8.0	112	25.0	209	14.8	223	25.6	619	32.8	628	41.7
Cefoperazone/sulbactam	354	3.1	333	3.6	597	5.7	458	9.6	652	14.6	684	21.1
Piperacillin/tazobactam	335	42.1	377	37.4	441	58.0	347	64.8	375	66.4	579	61.1
Gentamicin	358	58.1	401	55.6	597	51.8	455	54.7	652	53.8	718	57.5
Amikacin	346	48.0	405	51.4	601	51.4	438	58.9	655	52.4	732	57.0
Netilmicin	350	31.7	374	40.1	594	40.1	422	35.1	653	34.0	730	39.3
Ciprofloxacin	333	54.1	368	53.0	552	58.3	450	57.3	642	55.1	719	62.0

Table 5. Resistance rates of *Acinetobacter baumannii* in the Central region

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	77	48.1	163	62.6	105	57.1	178	61.2	179	71.5	217	58.5
Ceftazidime	689	59.1	922	61.4	783	61.7	1,118	61.0	1,211	64.3	1,485	66.4
Cefepime					65	53.8					480	70.0
Imipenem	619	3.1	800	6.1	670	21.8	925	29.1	1,049	45.1	1,301	54.3
Ampicillin/sulbactam	360	24.2	289	25.6	336	20.2	391	17.4	422	17.8	467	33.4
Cefoperazone/sulbactam	603	7.1	795	4.2	693	3.9	942	8.9	1,055	8.9	1,339	17.1
Piperacillin/tazobactam			107	43.0			293	62.5	136	57.4	415	68.0
Gentamicin	695	64.0	926	64.5	784	60.3	1,124	52.8	1,239	65.8	1,485	63.4
Amikacin	702	49.6	925	56.6	791	49.9	1,127	49.6	1,244	60.1	1,493	55.0
Netilmicin	619	25.5	814	38.9	585	44.3	657	38.1	592	36.3	636	39.8
Ciprofloxacin	671	60.5	898	57.2	727	58.5	1,122	58.4	1,236	63.8	1,488	64.7

Table 6. Resistance rates of *Acinetobacter baumannii* in the Northern region

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	631	52.9	470	54.7	349	41.3	317	51.4	501	64.9	421	61.8
Ceftazidime	1,405	51.0	1,715	54.8	1,263	44.7	1,271	54.7	1,399	62.7	1,712	63.6
Cefepime	19	47.4			47	21.3	15	40.0	177	61.6	32	71.9
Imipenem	1,220	0.5	1,571	1.2	1,261	3.6	1,190	20.1	1,104	42.1	1,693	44.1
Ampicillin/sulbactam												
Cefoperazone/sulbactam	1,516	3.1	1,504	1.8	1,264	2.5	1,172	6.7	1,394	3.7	1,451	6.5
Piperacillin/tazobactam	115	44.3	4	50.0	49	10.2	85	24.7	12	66.7	372	50.8
Gentamicin	1,567	56.4	1,714	56.5	1,262	47.0	1,259	55.9	1,390	60.6	1,706	55.9
Amikacin	1,568	41.0	1,712	47.0	1,265	41.3	1,274	48.1	1,401	44.0	1,708	43.4
Netilmicin	953	28.3	1,125	38.5	666	36.5	583	33.8	680	24.9	1,055	28.3
Ciprofloxacin	1,336	42.7	1,676	47.9	1,201	42.3	1,205	53.1	1,354	62.2	1,693	62.8

Table 7. Resistance rates of *Acinetobacter baumannii* in the Northeastern region

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	557	72.4	1,148	69.9	1,810	67.3	1,146	69.8	1,185	69.8	1,391	71.8
Ceftazidime	1,291	66.8	1,644	63.8	2,604	64.6	2,233	66	2,410	65.6	2,653	67.9
Cefepime			65	66.2	447	69.6	770	63.9	763	62.0	948	65.0
Imipenem	530	2.6	449	17.6	1,304	44.5	1,336	53.7	1,847	53.0	2,202	60.2
Cefoperazone/sulbactam	868	3.2	800	4.9	1,283	4.8	1,038	8.9	860	12.7	1,580	19.4
Piperacillin/tazobactam					62	67.7	14	85.7	149	47.0	1,888	65.3
Gentamicin	1,318	68.9	1,734	71.6	2,635	71.8	2,224	71.1	2,439	66.9	2,650	68.9
Amikacin	1,310	56.4	1,673	57.9	2,610	60.0	2,243	57.9	2,436	55.2	2,624	56.3
Netilmicin	1,048	30.2	1,346	42.7	1,596	36.9	1,296	32.3	1,764	43.0	2,411	45.3
Ciprofloxacin	1,284	46.3	1,563	57.5	2,553	60.7	2,218	63.6	2,430	60.7	2,658	64.9

than those from other areas of the hospital. Table 8 shows the comparisons of such differences for commonly tested antibiotics. It should be noted that only 50% and 36% of *A. baumannii* isolates from patients hospitalized in non-ICU and ICU areas, respectively, were still susceptible to imipenem.

Ciprofloxacin- and ceftazidime-resistant blood isolates were also on the upward trend. The resistance rates of the two agents were 29.9% and 31% in 2000, respectively; these figures were 50% for both agents in 2005. The remarkably increased resistance rates were also observed among the isolates obtained from the respiratory tract, particularly the emerging resistance to imipenem, the carbapenem most commonly tested in this study. Resistance to imipenem increased from 2% in 2000 to 51% in 2005 among the respiratory tract isolates while the resistance rate among the blood isolates was 35% in 2005 (data not shown). The agents that seem to best cover *A. baumannii* were netilmicin and cefoperazone/sulbactam as the resistance rates to each agents were 12.4% and 35.3%, respectively. However, the urinary tract isolates showed the most prominent resistance to ceftazidime, cefoperazone/sulbactam, and gentamicin, to which 75% of isolates were resistant.

MDR A. baumannii (MDR-AB)

A. baumannii has a propensity to be resistant to multiple antimicrobials simultaneously. In this study, high percentages of the organisms were resistant to

Table 8. Resistance rates of *A. baumannii* in the Eastern region

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	376	67.0	593	63.7	529	62.4	830	67.2	857	63.5	1,159	71.4
Ceftazidime	624	63.9	1,156	62.7	1,085	60.8	1,262	64.5	1,229	62.1	1,450	71.1
Cefepime	35	91.4	65	66.2			438	45.9	188	29.8	303	53.5
Imipenem	589	2.7	1,115	4.0	894	7.5	1,065	12.9	1,060	29.2	1,192	44.0
Ampicillin/sulbactam	73	12.3	23	13.0			166	21.7	422	17.5	820	20.4
Cefoperazone/sulbactam	549	1.3	620	5.3	636	2.5	1,056	4.9	1,173	4.6	1,455	9.7
Piperacillin/tazobactam	145	46.2	247	61.9	426	52.8	894	48.1	815	54.6	1,241	63.7
Gentamicin	890	65.3	1,429	58.8	1,232	59.3	1,382	59.8	1,361	58.5	1,582	64.6
Amikacin	759	50.2	1,283	53.3	1,131	57.8	1,261	59.8	1,230	56.0	1,452	53.0
Netilmicin	257	29.2	410	56.1	349	60.7	214	70.6			39	38.5
Ciprofloxacin	766	60.3	1,215	55.8	1,119	56.9	1,144	58.1	1,075	56.4	1,257	68.0

Table 9. Resistance rates of *Acinetobacter baumannii* in Southern region

	2000		2001		2002		2003		2004		2005	
	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%	No. tested	%
Cefotaxime	384	64.6	687	57.8	626	54.3	602	43.5	652	41.9	656	48.0
Ceftazidime	378	59.0	704	53.6	706	49.3	753	44.5	1,366	43.9	1,450	49.9
Cefepime	19	31.6	98	42.9	465	38.9	160	52.5	611	41.1	1,410	45.6
Imipenem	383	5.5	697	4.9	703	3.8	751	3.1	1,345	13.0	1,506	23.5
Ampicillin/sulbactam	1	0					70	11.4	199	6.0	264	14.0
Cefoperazone/sulbactam	349	2.9	130	11.5	471	2.8	609	2.3	1,036	3.4	1,485	3.5
Piperacillin/tazobactam			60	61.7	318	29.6	55	12.7	209	16.7	332	32.2
Gentamicin	397	53.9	690	53.5	705	46.2	743	45.9	1,324	47.0	1,343	48.9
Amikacin	396	38.6	713	41.2	706	41.6	757	34.7	1,369	36.1	1,515	32.5
Netilmicin	395	21.0	703	24.5	600	28.5	666	27.2	1,323	27.5	1,366	25.5
Ciprofloxacin	390	52.6	682	50.9	478	48.7	651	42.9	1,246	40.1	1,457	45.4

ceftazidime, amikacin, and ciprofloxacin; these isolates were considered to be MDR. In 2000, 46% of all *A. baumannii* were MDR and this number rose to 56% in 2005. The Central region had the highest prevalence of MDR isolates, followed by the Northeastern and Eastern regions (Table 10).

Carbapenem-resistant A. baumannii (CRAB)

As mentioned earlier, the most stunning increased resistance rates were observed with carbapenem. Therefore, this section will now focus on this phenomenon. Over all, around 2% of *A. baumannii* clinical isolates were resistant to imipenem; this figure was 46.7% in 2005. The Northeastern region was affected most, having as high as 60% resistance rate in 2005. A sudden increase in the resistance rate was first noted in Bangkok and the Northeastern region in 2001 (Tables 3-6). While the rates of resistance have continuously increased exponentially in these two regions, the Central region was the next to see the epidemic in 2002, followed by the Northern and Eastern regions in 2003. The Southern region was the last area affected by CRAB in 2004 epidemic when the resistance rates have increased from 3.1% in the previous year to 13% in 2004. Not only more proportion of these clinical isolates was the CRAB isolates, but the number has also increased. In 2000, there were 109 imipenem-resistant isolates identified.

Table 10. Percentage of resistance of *Acinetobacter baumannii* isolates in intensive care unit (ICU) and non-ICU populations

Antibiotic	Ward	2000	2001	2002	2003	2004	2005
Ceftazidime	ICU	61.6	63.9	65.8	72.1	71.2	74.4
	non-ICU	54.6	57.2	52.4	59.4	61.6	65.8
Cefepime	ICU	44.4	23.3	63.4	65.4	61.7	72.5
	non-ICU	57.3	50.6	48.3	54.0	53.3	65.6
Imipenem	ICU	2.6	3.9	20.0	37.9	52.0	64.1
	non-ICU	1.0	4.6	11.1	24.5	36.4	48.4
Meropenem	ICU	0	4.3	34.8	48.4	53.2	65.0
	non-ICU	1.2	4.6	14.1	35.4	39.5	50.4
Cefoperazone/sulbactam	ICU	3.4	1.9	4.9	8.6	3.5	8.1
	non-ICU	1.5	2.8	3.1	5.7	4.1	10.0
Piperacillin/tazobactam	ICU			45.1	14.8	41.3	71.5
	non-ICU	47.3	61.8	43.2	40.9	48.1	59.6
Gentamicin	ICU	62.4	68.8	65.4	72.3	73.9	72.9
	non-ICU	54.3	56.5	51.8	59.3	60.0	61.3
Amikacin	ICU	50.3	55.1	59.8	62.3	55.0	55.7
	non-ICU	39.4	48.3	46.7	54.5	48.9	49.2
Netilmicin	ICU	34.5	31.4	33.3	32.9	35.9	50.2
	non-ICU	27.2	37.6	36.6	38.4	30.3	40.6
Ciprofloxacin	ICU	53.3	56.8	64.4	65.6	65.1	69.7
	non-ICU	49.0	51.8	51.1	56.1	59.9	63.7

In contrast, 4484 isolates in 2005 were imipenem-resistant, equivalent to 44-fold increase for the whole country. The largest proportion of CRAB in 2005 was from the Northeastern region, comprising the one-third of all CRAB isolated, followed by the Northern, Southern, Central, Eastern regions, and Bangkok, respectively (Fig. 2). Although the Northeast started out in 2000 with 15 isolates in 2000, the number of CRAB dramatically increased to 1493 isolates, which is out of proportion, compared to other regions.

Being resistant to carbapenem would not be problematic if other antimicrobial agents are still active and available. Unfortunately, CRAB isolates tend to be resistant to other agents in many groups at the same

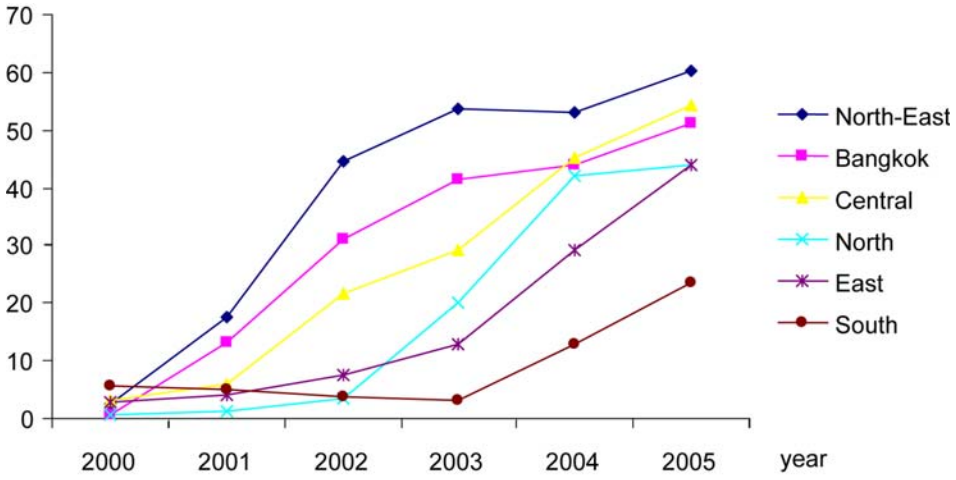

Fig. 2 Prevalence of imipenem-resistant *Acinetobacter baumannii* by regions including Bangkok

time. Not uncommonly, these isolates are resistant to all available antibiotics in clinical use, thus they are pandrug-resistant organisms that can cause difficult-to-treat infections and usually result in a fatal outcome. Imipenem-resistant isolates were almost always resistant to cefotaxime, cefepime, ceftazidime, pipera-cillin/tazobactam, ciprofloxacin, gentamicin, and trime-thoprim/sulfamethoxazole (Table 11). Considering the rates of resistance to these agents and the criteria for MDR, CRAB would have been classified as MDR in approximately at least 62%. The agent that seemed to be able to cover more isolates was cefoperazone/sulbactam since the resistance rates were between 19% and 23%. The next agent that may be useful is netilmicin, to which the resistance rates were between 39% and 51%.

Table 11. Percentage of multidrug-resistant *Acinetobacter baumannii* isolates tested in five regions of Thailand from 2000 to 2005

Region	2000	2001	2002	2003	2004	2005
Northeast	52	50	56	59	57	60
North	36	46	38	49	55	57
Central*	53	56	55	56	59	64
East	43	47	54	57	55	60
South	43	44	40	38	36	32
All	46	49	51	54	54	56

Multidrug-resistance: resistant to ceftazidime, amikacin, and ciprofloxacin
* Central region included Bangkok

Discussion

The present data reveal many existing challenges that have evolved over the past 6 years, which seem to be continuously creating more therapeutic dilemma. These issues include the proficiency of microbiology laboratories country-wide, including laboratory reporting standards, surveillance systems, infection control needs and practices, and appropriate national and hospital-specific antibiotic policy.

As pointed out earlier, the accurate identification of *Acinetobacter* to the species level is sometimes not always straightforward. The gene sequencing is needed in order to accurately identify *A. baumannii*. Such a technique is costly and not feasible in routine microbiology laboratory services. Even laboratories with advanced technology may occasionally be confused with the identification. Moreover, since the taxonomic delineation of the genus and species is somewhat uncertain, the nomenclature of the bacterium is therefore not consistent among different laboratories. The present data showed that most *Acinetobacter* isolates obtained from clinical specimens were physiologically identified as *A. baumannii*. This is in concordance with other published reports worldwide indicating that this species has the greatest impact in human infections. The accurate identification is very important in clinical and (molecular) microbiological epidemiology. Therefore, microbiology laboratory personnel should be updated and well trained in this regard so that they will be able to more precisely identify the organisms and to report the results in the same manner. In

Table 12. Antibiogram of imipenem-resistant *Acinetobacter baumannii*

Antibiotic	2003 (1738 isolates)				2004 (2864 isolates)				2005 (4484 isolates)			
	Number	%R	%I	%S	Number	%R	%I	%S	Number	%R	%I	%S
Cefotaxime	585	95	5	0	1,116	97	3	0	1,917	97	3	0
Ceftazidime	1,720	92	1	7	2,514	94	1	5	4,428	94	1	5
Cefepime	654	89	9	2	804	93	5	2	1,820	93	5	2
Cefoperazone/sulbactam	1,058	19	39	42	1,612	15	41	44	3,627	23	52	25
Piperacillin/tazobactam	440	99	0	0	649	98	2	1	2,402	97	1	1
Gentamicin	1,718	89	2	9	2,515	91	3	6	4,372	90	5	5
Amikacin	1,725	79	5	16	2,521	77	10	13	4,462	72	11	17
Netilmicin	1,234	39	4	57	1,686	50	4	46	3,046	51	3	46
Ciprofloxacin	1,699	88	6	7	2,480	91	3	5	4,396	93	3	5
Trimethoprim/ sulfamethoxazole	1,025	92	2	7	1,632	92	2	6	3,510	90	2	7

addition, the antimicrobial agents that should be tested against the organisms should be standardized, and each agent in the surveillance should be made available to all participating hospitals. Since all hospital laboratories in Thailand identify *Acinetobacter* by traditional biochemical tests, it is not possible to identify and report *Acinetobacter* to the species (gemomic species) level with high degree of accuracy. For this reason, the authors recommend that non-hemolytic, glucose oxidizing, *Acinetobacter* which grow at 41°C would be reported as *A. calcoaceticus-A. baumannii* complex as suggested in a recent study[4].

By following the resistance rates of *A. baumannii* over the past 6 years, the authors obviously observe the continuously increased occurrence of MDR AB and CRAB. This phenomenon is still ongoing such that most large hospitals in the country have become endemic areas where all control efforts are more difficult to implement with satisfactory success. The data from the early period of the present study indicated that the most drastic resistance trait, CRAB, has firstly emerged in tertiary care hospitals in the Central and Northeastern regions and spread out to others year by year from 2001. The resistance rates have exponentially increased in the following years in all regions. This probably correlates with the increased use of carbapenems in the country. Imipenem/cilastatin was the first to be registered in 1996, followed by meropenem and ertapenem in 2000 and 2003, respectively. The available data showed that the amount of carbapenems imported into the country has also exponentially increased from 2000. Approximately 192,000 gram entered the nation, subsequently in 2005; almost 600,000 gram were imported (the Food and Drug Administration, MOPH, personal communication). It is generally accepted that the use of antibiotics will give rise to the selective advantage for the isolates carrying the resistance genes to that particular agent and other antibiotics belonging to the same class. Even worse, the co-resistance among different classes of antimicrobial agents could occur due the presence of genetic elements such as the integron that can facilitate cross resistance between them. Studies conducted in a research institute clearly showed that many of CRAB isolates carry novel carbapenemases, which emerge as a result of the pressure use of carbapenems. All information mentioned in our study indicates that our surveillance system is not sensitive enough to detect the problems that will arise in the future. The authors hope our observation will be a nation-wide background of the resistance problems in the country. The present surveillance needs to be strengthen further towards a more sensitive and effective system that alerts all others in the healthcare system sooner than what have been done recently so that it will not let a small outbreak turn out to be a country-wide endemic. Any emerging resistance among key hospital or community pathogens should arouse attention of laboratory personnel and physicians who provide care for patients as well.

There are many mechanisms for the emergence and establishment of drug-resistant organisms in healthcare facilities. These mechanisms basically involve the import of such organisms into the hospital, the pressure from the use of antimicrobial agents, and the spreading via different routes. There is no single strategy to overcome such a situation. It has to be the multidisciplinary approach. The strategies include good infection control practices and antimicrobial stewardship programs. However, in a resource-limited setting, it is probably not feasible to implement a good isolation system in general hospitals where many patients stay in a common room, being cared for by the limited number of nurses, paramedic, and physicians, and inadequate number of medical devices to be used separately for a single patient. It is now the time to re-think about the investment for prevention of these problematic pathogens in terms of cost and benefit of establishing and adhering to good infection control practices versus the health and economic burden arising from these organisms. It has been shown in literature that adequate infection control can, at least, slow down the rates of increasing resistance or even terminate many outbreaks within the institute. It has also been shown in many studies, including the one that was carried out in a tertiary care university hospital in Thailand that an antimicrobial stewardship program can change the patterns of antimicrobial use, which led to reduction in the incidence of some drug-resistant organisms[12].

The present study has many limitations. Since only the susceptibility data were reported to NARST without some essential clinical information, such as whether the isolates were community- or hospital-acquired pathogens, they were ICU or non-ICU isolates, or they were colonizers or the real infecting organisms. The sources where the organisms were isolated were called differently among participating hospitals. Therefore, it is difficult to interpret these data in more detail. However, the presented data has provided the nation-wide antimicrobial susceptibility of *Acinetobacter* spp. to be used as a rough guide for the selection of empirical antimicrobial agents in each region.

Beyond the surveillance system is that how do we integrate all available resources to cope with the situation. The policy and practices that are appropriate for developing countries such as Thailand, where resources are limited, are still lacking. There is a lot more work to accomplish, including the present study to evaluate existing recommendations for the control of antimicrobial resistance in healthcare systems used in developed countries, clinical and perhaps molecular microbiological epidemiology to better understand the epidemic, as well as treatment options that better suit the studied population. These tasks certainly are a real challenge requiring multi-disciplinary approaches with good coordination. Without such co-operation, it can be predicted that we will lose the war against these microbes.

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การดื้อยาต้านจุลชีพของเชื้อ Acinetobacter baumannii: ข้อมูล 6 ปี การเฝ้าระวังเชื้อดื้อยาต้านจุลชีพ

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***จุดประสงค์**: ศึกษาอุบัติการณ์ ระบาดวิทยา และความไวของเชื้อ Acinetobacter baumannii ต่อยาต้านจุลชีพในประเทศระหว่าง พ.ศ. 2543-2548*

***วัสดุและวิธีการ**: รวบรวมข้อมูลการทดสอบความไวของเชื้อต่อยาจากโปรแกรม WHONET ที่ส่งจากโรงพยาบาลในเครือข่ายเฝ้าระวังเชื้อดื้อยาต้านจุลชีพแห่งชาติ (NARST) 28 แห่ง และทำการวิเคราะห์อุบัติการณ์, ระบาดวิทยาทางคลินิก และผลการทดสอบความไวของเชื้อ Acinetobacter baumannii ต่อยา ในช่วงปี พ.ศ. 2543-2548*

***ผลการศึกษา**: จำนวนเชื้อ Acinetobacter spp. ที่พบในผู้ป่วยเพิ่มจาก 8,699 สายพันธุ์ ในปี พ.ศ. 2543 เป็น 14,071 ในปี พ.ศ. 2548 ในการแยกชนิดโดยวิธีศึกษาคุณลักษณะการเจริญเติบโตและวิธีทางชีวเคมี พบว่าเป็น A. baumannii มากที่สุด โดยมากกว่า ร้อยละ 50ของเชื้อที่ตรวจทั้งหมด แยกได้จากตัวอย่างระบบทางเดินหายใจ อัตราการดื้อยาสูงขึ้นทุกปี โดยเฉพาะเชื้อ ที่ดื้อยาหลายชนิดพร้อมกันและเชื้อที่ดื้อยากลุ่ม carbapenem พบว่าเชื้อที่ดื้อยากลุ่ม carbapenem เพิ่มจาก 2.1%ในปี พ.ศ. 2543 เป็น 46.7% ในปี พ.ศ. 2548 เชื้อที่ดื้อ carbapenem มักเป็นเชื้อที่ดื้อยาหลายชนิดพร้อมกันด้วย ภาคกลางและกรุงเทพเป็นพื้นที่ที่พบเชื้อดื้อยาหลายชนิดพร้อมกันมากที่สุด ถึงแม้ว่าจะพบแนวโน้มการดื้อยา cefoperazone/sulbactam เพิ่มขึ้นแต่ยาดังกล่าวเป็นยาที่ไวที่สุดต่อ Acinetobacter spp.*

***สรุป**: โรงพยาบาลควรใช้เทคนิคที่มาตรฐานสำหรับการเฝ้าระวังในการแยกชนิดเชื้อใน genus Acinetobacter และเนื่องจากพบว่า Acinetobacter spp.มีแนวโน้มการดื้อยาหลายชนิดพร้อมกันเพิ่มขึ้น พร้อมทั้งมีแนวโน้มการดื้อยา carbapenem และ cefoperazone/sulbactam เพิ่มขึ้นทุกปีเช่นกัน จึงมีความจำเป็นอย่างยิ่งที่จะต้องทำการเฝ้าระวังอย่างเต็มที่ รวมทั้งให้มีการควบคุมการติดเชื้อดังกล่าวอย่างเข้มงวด พร้อมกับมีโครงการกำกับการใช้ยาในสถานพยาบาลเพื่อลดอัตราการแพร่เชื้อดื้อยาต่อไป*