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Short communication

Nationwide surveillance of antimicrobial resistance among non-fermentative Gram-negative bacteria in Intensive Care Units in Taiwan: SMART programme data 2005

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ABSTRACT

A nationwide surveillance of the antimicrobial susceptibilities of glucose non-fermentative Gram-negative bacteria isolates was conducted from 1 September 2005 to 30 November 2005 in Taiwan. A total of 456 isolates were recovered from patients hospitalised in the Intensive Care Units (ICUs) of ten major teaching hospitals. Rates of resistant pathogens, such as ciprofloxacin-resistant *Pseudomonas aeruginosa* (19%) and imipenem-resistant *Acinetobacter baumannii* (25%), were higher than those reported in 2000 (8% and 22%, respectively). Increased rates of isolates with resistant phenotypes correlated with prolonged length of ICU stay (48 h to ≤7 days vs. >7 days) for ceftazidime-non-susceptible *P. aeruginosa* (20.0% and 29.7%, respectively), imipenem-non-susceptible *P. aeruginosa* (4.0% and 13.5%, respectively) and imipenem-non-susceptible *A. baumannii* (15.4% and 29.8%, respectively), but not for ciprofloxacin-resistant *P. aeruginosa*. Alarming rates of emergence of extensively drug-resistant (XDR) *A. baumannii* (15%) and XDR *P. aeruginosa* (1.8%) were found, particularly among those isolates that were not susceptible to tigecycline and colistin. Interhospital dissemination of some clones of XDR *A. baumannii* in different ICUs was also noted. This study illustrates the crucial nature of continuous nationwide surveillance of resistant pathogens and implementation of effective strategies for ICU infection control and antibiotic restriction.

1. Introduction

Glucose non-fermentative Gram-negative bacteria (NFGNB), which usually cause severe nosocomial infections, are primarily considered opportunists, especially in immunocompromised and elderly hosts [1]. In a global study, NFGNB accounted for 11.5% of Gram-negative strains collected from clinical specimens [1]. Among the NFGNB strains, *Pseudomonas aeruginosa* and *Acinetobacter* spp. were responsible for >80% of clinical NFGNB infections [1]. Unfortunately, NFGNB are often intrinsically resistant to commonly prescribed important antimicrobials [2]. This antimicrobial resistance has resulted in great healthcare costs [2] that are predicted to impose an enormous impact on the management of patients in the Intensive Care Unit (ICU), including the establishment of treatment

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guidelines and the allocation of medical resources. As the increased burden of antimicrobial resistance in these notorious pathogens has become a global concern, a national programme is warranted to monitor regularly the evolving trends of antibiotic resistance and to compare the data with those of other countries.

The Surveillance for Multicenter Antimicrobial Resistance in Taiwan (SMART) programme, started in 2000, was designed to monitor longitudinally the in vitro antimicrobial susceptibility of clinically important pathogens. This report provides data regarding the in vitro susceptibilities of NFGNB isolates recovered from the ICUs of major teaching hospitals in Taiwan in 2005. Additionally, these data from 2005 are compared with those of a previous Taiwanese survey [2]. This study is part of the 2005 SMART programme.

2. Materials and methods

2.1. Bacterial isolates

This study analysed 456 non-duplicate isolates of important NFGNB collected from various specimens of patients hospitalised in ICUs of ten major teaching hospitals from 1 September 2005 to 30 November 2005. The isolates included *P. aeruginosa* (164 isolates), *Acinetobacter baumannii* (167 isolates), *Stenotrophomonas maltophilia* (85 isolates) and *Burkholderia cepacia* (40 isolates). The isolates were stored at −70 °C in trypticase soy broth (Difco Laboratories, Detroit, MI) supplemented with 15% glycerol before testing. The isolates were transported to the National Taiwan University Hospital for further identification by standard methods.

To investigate the relationship between the incidence of acquisition of drug-resistant NFGNB (*P. aeruginosa* and *A. baumannii*) and various durations of ICU hospitalisation, microorganisms were divided according to the timing of isolation as follows: within ≤48 h of hospitalisation; between 48 h and ≤7 days; and >7 days after hospitalisation.

2.2. Susceptibility testing

Minimum inhibitory concentrations (MICs) of the isolates to antimicrobial agents were determined by the broth microdilution method in accordance with the guidelines provided by the Clinical and Laboratory Standards Institute (CLSI) [3]. Susceptibility results were interpreted using the CLSI breakpoints [4]. A total of 17 agents, including ampicillin/sulbactam (AMP/SUL) (only for *A. baumannii*), ceftazidime, cefepime, piperacillin/tazobactam (PIP/TAZ), cefoperazone/sulbactam (CFP/SUL), aztreonam, imipenem, meropenem, ertapenem, ciprofloxacin, levofloxacin, moxifloxacin, gentamicin, amikacin, isepamicin, tigecycline and colistin, were tested.

Escherichia coli ATCC 25922, *E. coli* ATCC 35218 (for β-lactam/β-lactamase inhibitor combinations) and *P. aeruginosa* ATCC 27853 were used as quality control strains for each run of MIC tests. MIC testing was repeated if the results for ATCC strains were outside the expected range recommended by the CLSI.

In this study, isolates intermediate-resistant or fully resistant to antimicrobial agents were classified as a resistant phenotype. Extensively drug-resistant *A. baumannii* (XDR-AB) and *P. aeruginosa* (XDR-PA) isolates were defined as isolates resistant to all agents tested, except colistin.

2.3. Molecular typing

Genotyping was determined using the pulsotypes generated by pulsed-field gel electrophoresis (PFGE). DNA extraction and purification were carried out as described previously [5]. DNA was digested by the restriction enzyme *Sma*I and the restriction fragments were separated in a CHEF-DRIII unit (Bio-Rad Laboratories, Hercules, CA) at 200 V for 27 h. Interpretation of the PFGE profiles followed the description of Tenover et al. [6]. PFGE profiles of the isolates were considered derived from a common ancestor (closely related isolates) if the number of fragment differences was three or less.

2.4. Statistical method

Statistical analysis was performed by means of the χ^2 test.

3. Results

3.1. Bacterial isolates

The majority of isolates (67.5%) were recovered from respiratory tract secretions, followed by sterile sites (16.5%). Fifteen percent of isolates were recovered from patients with bloodstream infections.

3.2. Antimicrobial susceptibilities, and differences in drug resistance prevalences for Pseudomonas aeruginosa and Acinetobacter baumannii between 2000 and 2005

Most of the β-lactams displayed moderate to good activity against ICU isolates of *P. aeruginosa* and *B. cepacia* (Table 1). However, CFP/SUL had significantly inferior in vitro activity against both of these bacterial strains (non-susceptibilities of 31% and 78% for *P. aeruginosa* and *B. cepacia*, respectively) among the β-lactams tested. In striking contrast, the β-lactams showed poor activity against *A. baumannii* and *S. maltophilia* isolates (especially the latter strains). Aztreonam exhibited moderate (44%) non-susceptibility against *P. aeruginosa* and very poor (<20%) susceptibilities for the other three NFGNB strains.

With the exception of ertapenem, the carbapenems (imipenem and meropenem) retained moderate to good activity against *P. aeruginosa* (susceptibilities of 90% for both) and *A. baumannii* (susceptibilities 75% and 72%, respectively). *Stenotrophomonas maltophilia* isolates were resistant to all carbapenems, but most (93%) of the ICU *B. cepacia* isolates were susceptible to meropenem.

Levofloxacin, which showed similar in vitro activity against *P. aeruginosa* isolates as ciprofloxacin (susceptibilities of 77% and 81%, respectively), had significantly better in vitro susceptibility than ciprofloxacin against *S. maltophilia* isolates (73% vs. 6%). However, these two fluoroquinolones had poor in vitro activity against *A. baumannii* and *B. cepacia* isolates. The MIC for 90% of the isolates (MIC_{90}) of moxifloxacin was near to that of levofloxacin for the four NFGNB. Except for *P. aeruginosa* isolates, the aminoglycosides exhibited poor susceptibility against NFGNB isolates. The MIC_{90} values of tigecycline for *P. aeruginosa*, *A. baumannii*, *S. maltophilia* and *B. cepacia* isolates were 32, 4, 4, and 8 μg/mL, respectively.

With regard to differences in antibiotic resistance prevalences of two important NFGNB (*P. aeruginosa* and *A. baumannii*) in 2000 and 2005, constant percentages for ceftazidime-non-susceptible *P. aeruginosa* (22% vs. 20%; $P = 0.6345$) and imipenem-non-susceptible *A. baumannii* (22% vs. 25%; $P = 0.4980$) were found during this period. Notably, a markedly increased prevalence of ciprofloxacin-non-susceptible *P. aeruginosa* (from 8% to 19%; $P = 0.0057$) was noted.

3.3. Resistance rates and length of ICU stay

Information on the length of ICU stay before the acquisition of resistant bacteria was available for 162 isolates of *P. aeruginosa* and 161 isolates of *A. baumannii*. Fig. 1 illustrates the relationships between the percentages of various resistant phenotypes and the lengths of ICU stay for *P. aeruginosa* and *A. baumannii*

Table 1
Antimicrobial susceptibilities of 456 glucose non-fermentative Gram-negative bacterial isolates recovered from patients treated at Intensive Care Units of ten major teaching hospitals in Taiwan, 2005.

Strain/antimicrobial agent	MIC (μg/mL)			No. (%) of isolates		
	Range	MIC_{50}	MIC_{90}	S	I	R
Pseudomonas aeruginosa (*n* = 164)						
Ceftazidime	0.5 to >128	2	64	131 (80)	8 (5)	25 (15)
Cefepime	0.5 to >128	2	32	129 (79)	17 (10)	18 (11)
PIP/TAZ	2 to >128	8	128	135 (82)	0 (0)	29 (18)
CFP/SUL	2 to >64	16	64	112 (68)	17 (10)	35 (21)
Aztreonam	2 to >128	8	64	91 (55)	28 (17)	45 (27)
Imipenem	0.5 to >32	1	4	148 (90)	0 (0)	16 (10)
Meropenem	0.06 to >32	0.5	4	148 (90)	5 (3)	11 (7)
Ertapenem	1 to >32	8	>32	–	–	–
Ciprofloxacin	0.03–64	0.25	32	133 (81)	3 (2)	28 (17)
Levofloxacin	0.06 to >32	1	32	126 (77)	5 (3)	33 (20)
Moxifloxacin	1 to >32	2	32	–	–	–
Gentamicin	1 to >128	2	>128	127 (77)	8 (5)	29 (18)
Amikacin	1 to >128	4	16	154 (94)	4 (2)	6 (4)
Isepamicin	1 to >128	4	16	–	–	–
Tigecycline	2 to >32	32	32	–	–	–
Colistin	1–4	1	4	149 (91)	–	15 (9)
Acinetobacter baumannii (*n* = 167)						
AMP/SUL	2 to >128	16	128	55 (33)	29 (17)	83 (50)
Ceftazidime	2 to >128	128	>128	52 (31)	5 (3)	110 (66)
Cefepime	1 to >128	16	64	56 (34)	40 (24)	71 (43)
PIP/TAZ	0.03 to >128	128	>128	54 (32)	19 (11)	94 (56)
CFP/SUL	2 to >64	16	64	95 (57)	49 (29)	23 (14)
Aztreonam	16 to >128	64	128	0 (0)	5 (3)	162 (97)
Imipenem	0.12 to >32	2	16	125 (75)	22 (13)	20 (12)
Meropenem	0.12 to >32	1	32	121 (72)	5 (3)	41 (25)
Ertapenem	2 to >32	16	>32	–	–	–
Ciprofloxacin	0.06 to >128	64	128	51 (31)	2 (1)	114 (68)
Levofloxacin	0.06 to >32	8	16	55 (33)	0 (0)	112 (67)
Moxifloxacin	0.03 to >32	16	16	–	–	–
Gentamicin	0.25 to >128	>128	>128	46 (28)	2 (1)	119 (71)
Amikacin	0.25 to >128	>128	>128	62 (37)	3 (2)	102 (61)
Isepamicin	0.5 to >128	>128	>128	–	–	–
Tigecycline	0.12 to >16	2	4	–	–	–
Colistin	0.5–4	1	4	157 (94)	0 (0)	10 (6)
Stenotrophomonas maltophilia (*n* = 85)						
Ceftazidime	2 to >128	128	>128	11 (13)	6 (7)	68 (80)
Cefepime	16 to >128	64	128	0 (0)	7 (8)	78 (92)
PIP/TAZ	8 to >128	>128	>128	1 (1)	7 (8)	77 (91)
CFP/SUL	16 to >64	64	>64	8 (9)	18 (21)	59 (69)
Aztreonam	16 to >128	>128	>128	0 (0)	1 (1)	84 (99)
Imipenem	16 to >32	>32	>32	0 (0)	0 (0)	85 (100)
Meropenem	4 to >32	>32	>32	2 (2)	1 (1)	82 (96)
Ertapenem	16 to >32	>32	>32	–	–	–
Ciprofloxacin	1–64	4	16	5 (6)	24 (28)	56 (66)
Levofloxacin	0.5–32	2	8	62 (73)	12 (14)	11 (13)
Moxifloxacin	0.12–16	1	4	–	–	–
Gentamicin	0.5 to >128	64	>128	11 (13)	3 (4)	71 (84)
Amikacin	2 to >128	128	>128	15 (18)	10 (12)	60 (71)
Isepamicin	2 to >128	64	>128	–	–	–
Tigecycline	0.25–16	2	4	–	–	–
Colistin	2 to >128	64	>128	–	–	–
Burkholderia cepacia (*n* = 40)						
Ceftazidime	1 to >128	2	4	38 (95)	1 (3)	1 (3)
Cefepime	1 to >128	8	16	27 (68)	10 (25)	3 (8)
PIP/TAZ	0.03 to >128	4	8	37 (93)	2 (5)	1 (3)
CFP/SUL	4 to >64	32	64	9 (23)	15 (38)	16 (40)
Aztreonam	4 to >128	16	32	6 (15)	26 (65)	8 (20)
Imipenem	8 to >32	16	16	0 (0)	17 (43)	23 (58)
Meropenem	1 to >32	2	4	37 (93)	0 (0)	3 (8)
Ertapenem	4 to >32	16	16	–	–	–
Ciprofloxacin	0.5–64	4	4	6 (15)	10 (25)	24 (60)
Levofloxacin	1–32	4	4	9 (23)	27 (68)	4 (10)
Moxifloxacin	0.25–16	4	8	–	–	–
Gentamicin	4 to >128	>128	>128	1 (3)	1 (3)	38 (95)
Amikacin	8 to >128	128	>128	3 (8)	4 (10)	33 (83)
Isepamicin	4 to >128	>128	>128	–	–	–
Tigecycline	2–16	8	8	–	–	–
Colistin	>128	>128	>128	0 (0)	0 (0)	40 (100)

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC for 50% and 90% of the organisms, respectively; S, susceptible; I, intermediate; R, resistant; PIP/TAZ, piperacillin/tazobactam; CFP/SUL, cefoperazone/sulbactam; AMP/SUL, ampicillin/sulbactam; –, no MIC criteria provided by the Clinical and Laboratory Standards Institute [6].

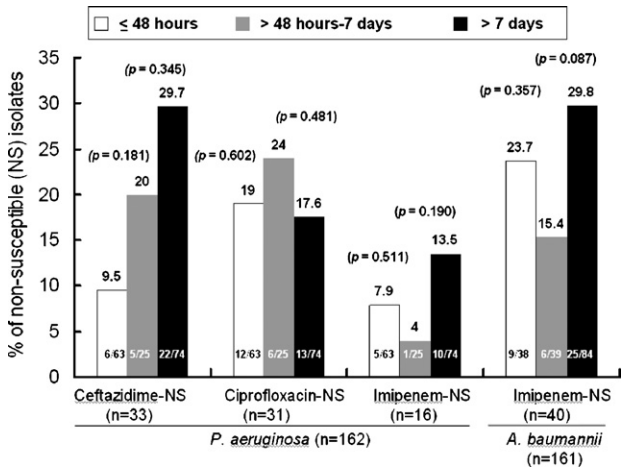

Fig. 1. Relationship between several resistant phenotypes of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and length of stay in the Intensive Care Unit (ICU).

isolates. Increased incidences of patients acquiring ceftazidime- and imipenem-non-susceptible *P. aeruginosa* and imipenem-non-susceptible *A. baumannii* were correlated with longer ICU stay. In contrast, the incidence of ciprofloxacin-non-susceptible *P. aeruginosa* isolates for patients with ICU hospitalisation between 48 h and 7 days was higher than for those with longer ICU stay. However, the differences between length of ICU stay and rates of various resistant phenotypes were not statistically significant (Fig. 1).

3.4. Prevalence of XDR isolates

XDR-AB and XDR-PA isolates accounted for 15% (25/167 isolates) and 1.8% (3/164 isolates) of ICU isolates, respectively. Most of the XDR isolates were clustered in the northern part of Taiwan (76% of XDR-AB and all XDR-PA isolates). Among the 25 XDR-AB isolates, 10 (40%) had tigecycline MICs of ≤1 μg/mL, 5 (20%) had tigecycline MICs of 2 μg/mL and the remaining 10 (40%) had tigecycline MICs of 4–16 μg/mL. Ten (40%) of the XDR-AB and all of the XDR-PA isolates were also resistant to colistin, and all colistin-resistant XDR-AB were also resistant to tigecycline.

3.5. PFGE analysis of XDR-AB isolates

A total of six pulsotypes (A–F) and 22 pulsosubtypes (A1–A3, B1–B6, C1–C4, D1–D4, E1–2 and F1–3) were identified among the 25 XDR-AB isolates. The same pulsotypes were found in different ICUs of the Taiwanese hospitals included in this study: pulsotype B isolates in ICUs at hospitals N1 and N3; pulsotype B and C isolates in ICUs at N1, N2 and N3; pulsotype D isolates in ICUs at M1 and M2; pulsotype E isolates in ICUs at S1 and S2; and pulsotype F isolates in ICUs at N3 and N5 (where N, M and S represented the hospitals located in the northern, middle and southern part of Taiwan, respectively) (Fig. 2).

4. Discussion

This nationwide ICU surveillance of the antimicrobial susceptibilities of NFGNB isolates disclosed four important points. First, a significantly increasing prevalence of ciprofloxacin-non-

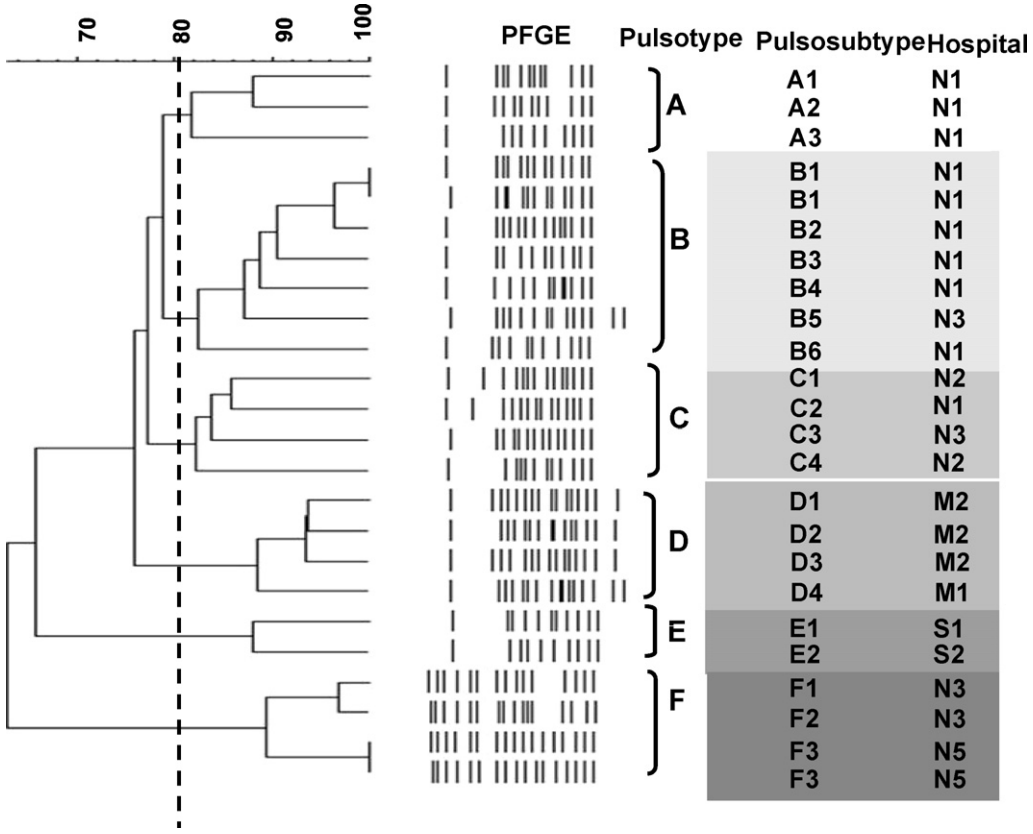

Fig. 2. Dendrogram illustrating the genetic relatedness of the extensively drug-resistant *Acinetobacter baumannii* (XDR-AB) isolates. Results were obtained by pulsed-field gel electrophoresis (PFGE) after digestion with *Sma*I for 24 isolates of XDR-AB from eight Intensive Care Units (N1–N3, N5, M1, M2, S1 and S2) of teaching hospitals in Taiwan. Six pulsotypes (A–F) and 22 pulsosubtypes (A1–A3, B1–B6, C1–C4, D1–D4, E1–2 and F1–3) were identified.

susceptible *P. aeruginosa* and a persistently high prevalence of imipenem-non-susceptible *A. baumannii* were noted in comparison with the data from Taiwanese ICUs in 2000. Second, rates of resistant phenotypes among patients did not always correlate well with length of ICU stay (ciprofloxacin-non-susceptible *P. aeruginosa*), indicating that antibiotic selective pressure varied among ICUs (data not shown). Third, the emergence of XDR-AB and XDR-PA isolates is alarming, particularly those also resistant to tigecycline and colistin. Finally, the finding of interhospital dissemination of some clones of XDR-AB in different ICUs suggests that implementation of an effective national strategy of infection and antibiotic control is mandatory.

In this ICU investigation, susceptibility data for *P. aeruginosa* were similar to those reported from Japan [7]. Although multidrug resistance mechanisms were reported to exist concurrently in a *P. aeruginosa* strain [8], after exclusion of aztreonam the other antipseudomonal compounds had an average 82% eradication rate for *P. aeruginosa* pathogens. Notably, the in vitro susceptibility of CFP/SUL was much lower than that of PIP/TAZ for *P. aeruginosa* isolates. Fass et al. [9] have demonstrated a persistently poor in vitro enhancement effect of adding sulbactam ($\leq$8 μg/mL) to cefoperazone for *P. aeruginosa* strains, which is consistent with the finding of the present survey.

In this SMART programme data, PFGE results for *A. baumannii* revealed that one or more of the six XDR-AB clones were present in all of the different major Taiwanese hospitals surveyed. This finding is similar to the results reported in previous studies of outbreaks [10], supporting the endemic propensity of *A. baumannii*. Collectively, the carbapenem susceptibilities in this survey were significantly lower than those from Japan [7] as well as a recent global investigation [11]. In addition, all of the other evaluated antimicrobials showed markedly high in vitro non-susceptible rates. For multidrug-resistant *Acinetobacter* spp., sulbactam had been suggested as a synergistic antibacterial when combined with some penicillins or cephalosporins [9]. However, the prominently higher MIC_{90} values (for both AMP/SUL and CFP/SUL) of *A. baumannii* isolates from this Taiwanese study suggest that recommendations based on data from other countries may no longer be appropriate. This survey indicates that monotherapy with sulbactam is not suitable for management of serious *Acinetobacter* spp. infections in Taiwan. The tigecycline MIC_{90} value (4 μg/mL) for our *A. baumannii* strains is consistent with the data from Europe and the USA [12], in which the vast majority (85.1%) of *A. baumannii* strains were susceptible to tigecycline if the MIC interpretative criterion of resistance was set at >4 μg/mL.

Few studies have reported the in vitro profile of *S. maltophilia*. As previously noted by Fass et al. [9], the addition of sulbactam remarkably improved the susceptibility of *S. maltophilia* isolates to cefoperazone. These findings contrasted with the results of the present survey. However, newer fluoroquinolones (gatifloxacin and levofloxacin) showed good susceptibilities (both 86%) in a global survey [11], which is similar to our findings. Combined with the consideration of broad-spectrum activity against many nosocomial pathogens by tigecycline, the above findings suggest that levofloxacin and tigecycline will continue to be important agents for many types of severe ICU infections in Taiwan.

In our survey, *B. cepacia*, occasionally reported as the aetiology of nosocomial pneumonia, displayed lower MIC_{90} levels than those reported by Traczewski and Brown in the USA [13]. Unlike the present survey, they found that doripenem and levofloxacin were the two most effective antimicrobials in vitro against *B. cepacia* [13].

Our review of the literature revealed that gradual decreases in the susceptibilities of ceftazidime (from 90.8% in 1998 to 88.7% in 2000) and ciprofloxacin (from 81.7% in 1998 to 75.0% in 2001) for ICU *P. aeruginosa* isolates were noted in the USA [14]. A similar ciprofloxacin resistance trend (1996–2000) was also found in another survey [8], which is consistent with our SMART 2005 data. Additionally, the higher resistance epidemiologies of ceftazidime-non-susceptible *P. aeruginosa* and imipenem-non-susceptible *A. baumannii* in Taiwanese ICUs compared with those of the USA alert us to choose appropriate antimicrobials more cautiously. Although the increased consumption of ciprofloxacin has been verified to result in co-resistance to other antimicrobials (including ceftazidime, imipenem and amikacin) among many Gram-negative bacteria (*P. aeruginosa*, *Enterobacter* spp. and *Klebsiella pneumoniae*) [15], the incidence of ciprofloxacin-non-susceptible *P. aeruginosa* in this study did not linearly increase with prolonged ICU hospitalisation, and we did not have sufficient data to confirm that this association existed in our study.

In conclusion, this study of SMART programme 2005 data from Taiwan found that most antipseudomonal drugs exhibited acceptable (>75% susceptibilities) activities against ICU *P. aeruginosa* isolates. In contrast, significantly high in vitro non-susceptible rates to routinely tested antimicrobials were clearly demonstrated and were worrisome for the *A. baumannii* isolates, particularly for CFP/SUL, carbapenems and AMP/SUL. Levofloxacin displayed fair in vitro activity against *S. maltophilia* strains. Meropenem, ceftazidime and PIP/TAZ showed good in vitro activities against *B. cepacia* isolates. Continuous surveillance of in vitro susceptibilities for ICU NFGNB isolates is essential to track the trends of resistant pathogens and to provide optimal guidelines for empirical antimicrobial therapy in ICU patients.

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