In Vitro Activities of Antibiotic Combinations Against Clinical Isolates of *Pseudomonas aeruginosa*

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Combination therapy has been recommended to treat *Pseudomonas aeruginosa* infections worldwide. The purpose of the present study was to determine the *in vitro* activities of piperacillin, cefepime, aztreonam, amikacin, and ciprofloxacin alone and in combination against 100 clinical isolates of *P. aeruginosa* from one medical center in southern Taiwan. The combination susceptibility assay was performed using the checkerboard technique. The percentage of resistance of *P. aeruginosa* to single agents in our study was relatively high for the Asia-Pacific area, except to aztreonam. Piperacillin plus amikacin exhibited the highest potential for synergy (59/100) in this study. Moreover, a high percentage of synergism was also noted with amikacin combined with cefepime (7/100) or aztreonam (16/100). The combination of two beta-lactams, such as cefepime with piperacillin, and aztreonam with cefepime or piperacillin, showed synergistic effects against some *P. aeruginosa* isolates. Although ciprofloxacin is a good anti-pseudomonal agent, a very low potential for synergy with other antibiotics was demonstrated in this study. No antagonism was exhibited by any combination in our study. Among piperacillin-resistant strains, there was synergy with a beta-lactam plus amikacin, including the combination of piperacillin and amikacin. However, the combination of two beta-lactams, such as piperacillin and cefepime or aztreonam, did not have any synergistic activity against these strains. In summary, the combinations of amikacin with the tested beta-lactams (piperacillin, aztreonam, cefepime) had a greater synergistic effect against *P. aeruginosa*, even piperacillin-resistant strains, than other combinations. Understanding the synergistic effect on clinical strains may help clinicians choose better empirical therapy in an area with high prevalence of multidrug-resistant *P. aeruginosa*.

Key Words: *Pseudomonas aeruginosa*, antimicrobial combination, *in vitro* susceptibility
(*Kaohsiung J Med Sci* 2004;20:261–7)

Pseudomonas aeruginosa, one of the leading pathogens of nosocomial infections around the world, has been one of the most difficult to treat [1,2]. It contributes to major infections in high-risk populations, particularly those who have cancer or are mechanically ventilated [3,4]. Despite the recent advances in antimicrobial therapy, *P. aeruginosa* infections cause high morbidity and mortality, especially among immunocompromised patients [5]. The development of antimicrobial resistance, a major challenge for physicians and hospitals worldwide, has been well documented with monotherapy [6]. Consequently, combination therapy has been generally recommended for *P. aeruginosa* infections, to prevent development of antimicrobial resistance and harness synergistic effects [7]. The combination of a beta-lactam and an aminoglycoside has been the standard empirical therapy

Received: February 3, 2004 Accepted: April 14, 2004
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for *P. aeruginosa* for years [8]. Fluoroquinolones, especially ciprofloxacin, have emerged recently as an alternative due to their lower toxicity [9].

However, in the microbiology laboratory, susceptibility is only tested with single antibiotics, which is often inadequate for multiresistant pathogens. Furthermore, the comparisons of *in vitro* synergism or antagonism among different combinations against *P. aeruginosa* have not been reported in Taiwan. Without this *in vitro* information, the choice of a combination regimen can often only be made empirically, which may result in a suboptimal treatment outcome.

In response to these challenges, we report here on the first analyses of *in vitro* activities of various combinations of several newly developed anti-pseudomonal agents on clinical *P. aeruginosa* isolates from a medical center in southern Taiwan.

Materials and Methods

Bacterial strains

A total of 100 consecutive, non-repetitive, clinical *P. aeruginosa* isolates were collected from the clinical bacteriology laboratory of Kaohsiung Medical University Hospital, a 1,200-bed medical center in southern Taiwan, between September 1 and 30, 2001. Forty isolates were from sputum specimens, 31 were from wounds, 16 were from urine samples, eight were from blood specimens, and five were from bile. Bacterial strains were stored at –70°C before testing.

Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined by both the agar dilution and disk diffusion tests, according to the National Committee for Clinical Laboratory Standards (NCCLS) [10,11]. For susceptibility testing by the agar dilution method, the following antimicrobial agents were obtained as standard reference powders of known potency for laboratory use: piperacillin (Lederle Laboratories, Pearl River, NY, USA), ciprofloxacin (Bayer Co, Leverkusen, Germany), and aztreonam, amikacin, and cefepime (Bristol-Myers Squibb Co, Princeton, NJ, USA). All drugs were incorporated into Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, MD, USA) in serial two-fold concentrations from 0.03 to 128 μg/mL. Three control strains, *Escherichia coli* ATCC 35218 and ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, were included in each test run. Inoculated plates were incubated in ambient air at 35°C for 16 to 18 hours. The minimal inhibitory concentration (MIC) of each antimicrobial agent was defined as the lowest concentration that inhibited visible growth of the organism on a plate.

Checkerboard assay

The anti-pseudomonal properties of nine combinations of antimicrobial agents were determined using a two-dimensional checkerboard agar dilution method [12]. The nine combinations were: amikacin with ciprofloxacin, piperacillin, cefepime, or aztreonam; aztreonam with ciprofloxacin, cefepime, or piperacillin; and cefepime with ciprofloxacin or piperacillin. Serial dilutions of two different antimicrobial agents were mixed in Mueller-Hinton broth. Inocula were prepared from colonies grown on Mueller-Hinton agar plates after overnight culture. Bacterial suspensions with turbidities equivalent to that of a 0.5 McFarland standard were prepared to yield a final inoculum of 5×10^5 colony-forming units (CFU)/mL. After incubation at 35°C for 24 hours, MICs were determined as the lowest concentration at which there was no visible growth in broth. The fractional inhibitory concentration (FIC) (the ratio of the MIC of antibiotic A in the combination and the MIC of antibiotic A alone) was calculated for each antibiotic in each combination. The FIC for the combination was the sum of the FICs for the two antibiotics. Of the FIC indices calculated for all rows in the checkerboard, the minimum value was the FIC index for that isolate. Synergism was defined as when the FIC index was 0.5 or less, and antagonism was defined as when the FIC index was more than 4. No interaction was defined as an FIC index between 0.5 and 4. The definition of the effect of the combination of two antimicrobial agents was according to the latest reported criteria [13]. Quality control strains were the same as those described above.

Results

The percentages of non-susceptible isolates for various antimicrobial agents using the disk diffusion method were as follows: moxalactam (95%), ceftriaxone (66%), piperacillin (31%), ticarcillin/clavulanate (22%), gentamicin (17%), ceftazidime (12%), aztreonam (12%), ciprofloxacin (9%), piperacillin/tazobactam (9%), cefepime (9%), amikacin (7%), and imipenem (5%). The MICs for, and susceptibilities to, aztreonam, amikacin, ciprofloxacin, piperacillin, and cefepime using the broth microdilution method are shown in Table 1.

The distribution of FICs of nine combinations of two antimicrobial agents are shown in Table 2. Synergism was

Table 1. *In vitro* susceptibilities of 100 *Pseudomonas aeruginosa* isolates to five antimicrobial agents

Antibiotic	MIC (μg/mL)			Number of isolates		
	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Aztreonam	0.25–128	4	32	87	4	9
Amikacin	0.5–64	4	16	93	4	3
Ciprofloxacin	1–64	1	8	81	5	14
Piperacillin	1–128	8	128	78	–	22
Cefepime	0.5–128	4	16	86	6	8

MIC = minimum inhibitory concentration.

greatest with a combination of piperacillin and amikacin (59%), followed by aztreonam plus amikacin (16%), and cefepime with piperacillin (8%). No antagonism was seen with any of the nine combinations. All four amikacin-containing combinations had synergism in some isolates, especially when in combination with beta-lactams (piperacillin, cefepime, aztreonam).

Subgroup analysis for piperacillin-resistant isolates

Twenty-two *P. aeruginosa* isolates were resistant to piperacillin in our study. Of these, 9.1% were not susceptible to amikacin, 36.4% to ciprofloxacin, 36.4% to cefepime, and 40.9% to aztreonam. These non-susceptible rates are significantly higher than those among piperacillin-susceptible isolates (Fisher's exact test; $p = 0.039$, $p = 0.01$, $p < 0.001$, $p < 0.001$, respectively). The effects of combinations of two antimicrobial agents on the 22 piperacillin-resistant isolates are shown in Table 3. Amikacin showed synergy with piperacillin for five strains (22.7%), while piperacillin combined with cefepime or aztreonam did not reveal a synergistic effect. Amikacin also had a synergistic effect on some piperacillin-resistant isolates when combined with the other two beta-lactams (cefepime or aztreonam).

Discussion

Although combination therapy has been recommended for *P. aeruginosa* infections for years, to date, no *in vitro* data have been documented on its effect against clinical strains isolated in Taiwan.

During the past decade, the increasing prevalence of antimicrobial resistance among clinical isolates of *P. aeruginosa* has been a critical issue in hospitals worldwide [14–16]. Compared with the results of the worldwide SENTRY antimicrobial surveillance program published in 2002 [17], the prevalence of non-susceptible clinical isolates in our study was relatively high for the Asia-Pacific area, except for aztreonam (our study vs Asia-Pacific area in SENTRY, 13% vs 19.1%), cefepime (14% vs 6.5%), piperacillin (22% vs 14.5%), amikacin (7% vs 4.8%), and ciprofloxacin (19% vs 11.6%) (Table 1). The high resistance rate to piperacillin in our single-agent susceptibility study might

Table 2. Fractional inhibitory concentrations (FICs) of combinations of two antimicrobial agents for 100 clinical *Pseudomonas aeruginosa* isolates

	FIC				Number of isolates			
	Range	Median	Mean	SD	FIC ≤ 0.5	0.5 < FIC ≤ 2	2 < FIC ≤ 4	FIC > 4
Amk-Cip	0.31–1.25	1.03	1.01	0.13	2	98	0	0
Amk-Pip	0.03–2.25	0.375	0.55	0.4	59	39	2	0
Amk-Fep	0.25–1.5	1	0.91	0.29	7	93	0	0
Fep-Pip	0.28–2	1.25	1.09	0.38	8	92	0	0
Fep-Cip	0.06–1.5	1.03	1.05	0.14	1	99	0	0
Atm-Amk	0.16–2	1.03	0.91	0.35	16	84	0	0
Atm-Cip	0.63–1.5	1.02	1.02	0.08	0	100	0	0
Atm-Fep	0.38–1.5	1.06	1.10	0.21	2	98	0	0
Atm-Pip	0.31–2.5	1.06	1.08	0.44	1	97	2	0

SD = standard deviation; Amk = amikacin; Cip = ciprofloxacin; Pip = piperacillin; Fep = cefepime; Atm = aztreonam.

Table 3. Fractional inhibitory concentrations (FICs) of combinations of two antimicrobial agents for 22 piperacillin-resistant *Pseudomonas aeruginosa* isolates

	FIC				Number of isolates			
	Range	Median	Mean	SD	FIC ≤ 0.5	0.5 < FIC ≤ 2	2 < FIC ≤ 4	FIC > 4
Amk-Cip	0.51–1.25	1.0	0.99	0.15	0	22	0	0
Amk-Pip	0.04–1.06	0.625	0.679	0.32	5	17	0	0
Amk-Fep	0.25–1.25	0.75	0.82	0.26	3	19	0	0
Fep-Pip	1.03–1.5	1.25	1.16	0.12	0	22	0	0
Fep-Cip	0.52–1.02	1.00	0.97	0.12	0	22	0	0
Atm-Amk	0.16–1.06	0.75	0.74	0.28	4	18	0	0
Atm-Cip	0.63–1.13	1.0	0.93	0.14	0	22	0	0
Atm-Fep	0.38–1.5	1.0	1.06	0.22	1	21	0	0
Atm-Pip	0.56–1.5	1.09	1.16	0.25	0	22	0	0

SD = standard deviation; Amk = amikacin; Cip = ciprofloxacin; Pip = piperacillin; Fep = cefepime; Atm = aztreonam.

be attributable to the extended use of piperacillin plus an aminoglycoside as the initial empirical combination therapy against nosocomial infections (Annual Report of Infection Control Committee, Kaohsiung Medical University Hospital, unpublished data), mainly because piperacillin has been the only first-line antimicrobial agent available among the tested anti-pseudomonal agents in the reimbursement system of the National Health Insurance. The lower resistance rate to aztreonam might be attributed to the lower consumption in our hospital, compared to other antimicrobial agents (Annual Report of Infection Control Committee, Kaohsiung Medical University Hospital, unpublished data).

Against *P. aeruginosa*, the combination of a beta-lactam and an aminoglycoside has been reported to have a relatively high rate of synergy [18,19]. The combination of an aminoglycoside (amikacin) and a beta-lactam (cefepime, piperacillin, or aztreonam) exhibited synergy in a high percentage of isolates in the present study (Table 2), especially the combination of amikacin plus piperacillin.

Synergistic effects were found with combinations of two beta-lactams, such as aztreonam plus cefepime or piperacillin, in some *P. aeruginosa* isolates, although all beta-lactams work through the inhibition of bacterial cell wall synthesis. Although several animal models have demonstrated antagonism against *P. aeruginosa* with beta-lactam/beta-lactam combinations [20], Lister et al [21] and Sader et al [22] have reported that aztreonam enhances the antibacterial activity of cefepime, especially against derepressed strains of *P. aeruginosa*. The synergism might be partially attributed to the protection provided by aztreonam to other beta-lactams in the extracellular environment from extracellular beta-lactamase inactivation, such as Bush group 1 chromosomal cephalosporinase [21]. With the diminished level of extracellular inactivation of cefepime, more active cefepime would gain access to the periplasmic space where aztreonam could provide protection as well. However, this synergy between cefepime and aztreonam has not been consistently exhibited in other studies [23,24].

Combination therapy is more important for infections with piperacillin-resistant strains, which had a higher percentage of multidrug resistance in the present study. Therefore, we studied the synergistic potential of combination therapy against these resistant strains. The combination of piperacillin and amikacin showed synergism in five of the 22 piperacillin-resistant isolates. However, no synergy was found with the combinations of piperacillin with cefepime or aztreonam.

Recently, fluoroquinolones have become important in the treatment of *P. aeruginosa* infections. Various antimicrobial interactions have been documented in combination therapy including a fluoroquinolone. Synergism, indifference, or antagonism of fluoroquinolones have been reported when combined with beta-lactams in different studies [25–27]. In our study, a very low potential of synergy was found with the combinations of ciprofloxacin and cefepime (1/100) or aztreonam (0/100). Furthermore, ciprofloxacin plus amikacin exhibited synergism in only two of 100 strains. Among piperacillin-resistant strains, we also found no synergistic effect with amikacin plus ciprofloxacin. Some newly developed fluoroquinolones, such as trovafloxacin and gatifloxacin, may exhibit synergy with a beta-lactam in *P. aeruginosa* [27,28].

To date, there have been different criteria upon which to interpret the antagonism of antimicrobial combinations

using the checkerboard method. Originally, synergism was defined as an FIC index of 0.5 or less, and antagonism as an FIC index of at least 2.0 [12]. However, several recent publications recommend a stricter criterion to redefine antagonism as an FIC index of more than 4.0 [13,29]. Using this strict criterion, no antagonism was found in any combination tested in our study, although with amikacin plus piperacillin, two strains had FIC indices between 2.0 and 4.0, and with aztreonam plus piperacillin, two strains had an FIC index between 2.0 and 4.0.

Several methods are used to evaluate *in vitro* antimicrobial combination effects, including the checkerboard and time-kill methods [12]. The checkerboard method is the best known and simplest. Although it is not able to provide a more dynamic description of antimicrobial effect over time, its results can easily be compared with most published data. However, the results generated from these two methods do not correlate well [30,31]. Burgess et al, using the time-kill method, demonstrated synergy more frequently when a beta-lactam was combined with an aminoglycoside than with a fluoroquinolone for *P. aeruginosa* [32].

In conclusion, combination therapy has been recommended for *P. aeruginosa* infections, especially as there is a high prevalence of drug resistance in Taiwan. Amikacin plus piperacillin was the antibiotic combination with a synergistic effect for most clinical *P. aeruginosa* isolates. According to the greatest potential for synergy in our study, amikacin plus cefepime and amikacin plus aztreonam were also favorable combination therapies for most *P. aeruginosa* infections, even those caused by piperacillin-resistant strains. Combinations of two beta-lactams also exhibited synergy for some *P. aeruginosa* isolates. Compared with other combinations, combinations with ciprofloxacin provide no further synergistic effect. Although there was no concomitant investigation on clinical efficacy in our study, these *in vitro* results might provide practical information for the optimal choice of empirical combination therapy against *P. aeruginosa*.

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台灣綠膿桿菌臨床菌株對不同抗生素組合的感受性之研究

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綠膿桿菌是全世界院內感染常見之菌種，且其抗藥性也是目前之重要課題。目前臨床上對於此感染，一般建議採用兩種以上之抗生素合併療法，但台灣地區尚無相關之體外感受性報告。本研究是針對台灣一醫學中心於 2001 年所收集之 100 株臨床菌株進行數種抗生素單獨及合併使用之體外藥物感受性試驗。在單一藥物感受性試驗方面，本研究之綠膿桿菌除對 aztreonam 之不敏感性較低外，其他藥物之不敏感性都較亞洲地區之平均值高，顯示台灣地區之綠膿桿菌抗藥性的嚴重。在藥物組合中，以 piperacillin 合併 amikacin 表現出最高程度之加乘效果 (59/100)，而 amikacin 合併其他 beta-lactam 類藥物 (cefepime 或 aztreonam) 也有不錯之加乘效果 (7/100 或 16/100)。此外，合併兩種 beta-lactam 類之藥物於本研究中亦可見其加乘效果。近來， ciprofloxacin 已成為治療綠膿桿菌感染相當重要之藥物，但本研究發現其和其他類藥物合併使用並沒有產生相當明顯之加乘作用。關於具 piperacillin 抗藥性之綠膿桿菌，合併 amikacin 及 beta-lactam (含 piperacillin) 仍具有相當程度之加乘作用，但兩種 beta-lactam 類藥物之合併則無加乘作用。本研究並未發現任何藥物組合對綠膿桿菌具有互相拮抗之作用。整體而言，以 amikacin 合併 beta-lactam 類藥物對綠膿桿菌表現出最好之加乘效果；而這些結果可進一步提供高抗藥地區之臨床醫師用藥的重要參考資料。

關鍵詞：綠膿桿菌，合併療法，藥物感受性試驗

（高雄醫誌 2004;20:261－7）

收文日期：93 年 2 月 3 日
接受刊載：93 年 4 月 14 日
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