TICARCILLIN, CARBENICILLIN AND BL-P1908

IN VITRO COMPARISON OF THREE ANTI-PSEUDOMONAL SEMISYNTHETIC PENICILLINS

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Ticarcillin, carbenicillin and BL-P1908, a new anti-pseudomonal semisynthetic penicillin, were subjected to several *in vitro* comparisons—including minimal inhibitory and lethal concentrations (MIC and MLC), effects of inoculum size, effects of buffering the media and regression analyses of MIC and disc diffusion data. Whereas ticarcillin and carbenicillin showed comparable spectra of activity, with ticarcillin being more active against *Pseudomonas aeruginosa* and many *Enterobacteriaceae*, BL-P1908 exhibited a quite different spectrum, being much more active than either or the other two drugs against *P. aeruginosa* and *Streptococcus faecalis*, but virtually inactive against most of the *Enterobacteriaceae*. However, the MIC/MLC disparity against *P. aeruginosa* was much greater for BL-P1908 than for the other two drugs. The increase in MIC's resulting from increasing the inoculum sizes was comparable for the three drugs. The regression analyses showed good correlations between the disc diffusion and MIC data for all three drugs. Based on the regression analyses we conclude that for the 100-mcg carbenicillin disc the NCCLS recommended zone size breakpoints for *P. aeruginosa* should be utilized for all organisms, and that if a single disc should be selected as a representative for these two currently available antipseudomonal penicillins, the 75-mcg ticarcillin disc gave slightly better correlations with the MIC data of both drugs than the 100 mcg carbenicillin disc.

Anti-pseudomonal semisynthetic penicillins are playing an increasing role in modern antimicrobial chemotherapy. Carbenicillin, the first of such compounds to be clinically available, is now an important agent in the treatment of *Pseudomonas aeruginosa* infections[1] and anaerobic infections[2]. Ticarcillin, the most recent agent of this family to become available clinically, has been shown to be effective in the treatment of *Pseudomonas* infections[3~5] and *in vitro* appears to be more effective against *P. aerugi-*

nosa and some *Enterobacteriaceae* than carbenicillin[6~13]. A new compound in this category, BL-P1908 (patent pending) has been claimed to have even greater anti-pseudomonal activity (personal communication—Dr. K. PRICE, Bristol Laboratories). An *in vitro* comparison of these three drugs forms the substance of this report.

The studies reported herein were designed to: (1) determine the reproducibility of the disc diffusion and broth microdilution susceptibility tests for these three drugs by performing both tests on the same group of organisms at two different laboratories: (2) determine the effects of inoculum size on the minimal inhibitory concentration (MIC) of these antimicrobics; (3) determine the difference between the MIC's and minimal lethal concentrations (MLC) of these drugs; (4) determine the effect of buffering the MUELLER-HINTON media on the susceptibilities to these drugs; and (5) determine the regression curves by correlating disc diffusion data with MIC data for each drug.

Methods and Materials

Antibiotics.

Ticarcillin and carbenicillin were supplied in powdered form by Beecham Laboratories, Bristol, Tennessee. BL-P1908 was supplied in powdered form by Bristol Laboratories, Syracuse, New York.

Microorganisms.

The 392 organisms used in this study were clinical isolates contributed by the participating laboratories. These included 101 *Pseudomonas aeruginosa,* 6 *Pseudomonas cepacia,* 6 *Pseudomonas maltophilia,* 5 *Pseudomonas fluorescens,* 5 *Pseudomonas putida,* 5 *Pseudomonas stutzeri,* 25 *Acinetobacter,* 25 *Escherichia coli,* 25 *Klebsiella pneumoniae,* 25 *Proteus mirabilis,* 10 *Proteus morganii,* 9 *Proteus rettgeri,* 6 *Proteus vulgaris,* 11 *Enterobacter aerogenes,* 10 *Enterobacter cloacae,* 4 *Enterobacter agglomerans,* 37 *Haemophilus influenzae* (12 were ampicillin-resistant), 30 *Staphylococcus aureus* (10 were methicillin-resistant), 25 *Streptococcus faecalis,* 12 *Streptococcus pneumoniae* and 10 *Streptococcus pyogenes.*

Tests.

The following procedures were carried out at both Sacramento Medical Center (SMC) and the Center for Disease Control (CDC) in accordance with previously described principles[14].

Minimal inhibitory concentrations (MIC's) were determined by the broth microdilution method. The antimicrobics were prepared in MUELLER-HINTON broth (MHB) in serial twofold concentrations ranging from 256 mcg/ml to 0.06 mcg/ml. These were commercially dispensed in 0.1 ml aliquots in the wells of plastic trays (Micro-Media Systems, Campbell, California) and stored at $-60°C$ for up to 8 weeks with no evidence of deterioration, as determined by no change in endpoint determinations of appropriate quality control organisms. After thawing at room temperature, the trays were inoculated with plastic disposable inoculators delivering 5 mcl to each well and incubated at 35°C for 18 hours. The MIC was read as the lowest concentration with no visible growth.

The inocula were standardized by diluting logarithmic phase broth cultures to match the turbidity of a MACFARLAND 0.5 standard. This was further diluted 1: 50 in sterile water with 0.02% Tween 80 and then inoculated with the disposable inoculator. The final inoculum concentration thus achieved was approximately 10^5 colony forming units (CFU) per ml.

The inoculum for *S. pneumoniae* and *S. pyogenes* was prepared in MHB with 5% lysed rabbit blood and 0.1 ml of the standardized inoculum was added to each well, giving a final concentration of approximately 10^5 CFU/ml. Because the volume of the inoculum equalled that of the antibiotic-containing broth, the concentration of antibiotic was halved in each well and the MIC's were read accordingly. The inoculum for *Haemophilus influenzae* was prepared by suspending colonies directly in MHB with 10% peptic digest and 2% Isovitalex and then diluting to match the turbidity of a MACFARLAND 0.5 standard. This was further diluted to approximately 10^4 CFU/ml and 0.1 ml was added to each well. The trays were incubated under increased CO_2 for both *Streptococci* and *H. influenzae.*

Tests were performed in MHB (pH 7.3) and in buffered MHB (BMHB), which was prepared by adding one part phosphate buffer (pH 7.2) to nine parts MHB to give a final pH of 7.3.

The effect of varying the inoculum size was studied with 98 isolates. The cell suspensions were adjusted to give final inocula of 10^3, 10^5 and 10^7 CFU/ml.

The bactericidal activity was determined by subculturing approximately 5 mcl from each well of a MIC tray (previously inoculated and incubated) to 15 cm petri plates containing MUELLER-HINTON agar (SMC) or trypticase soy agar with 4% rabbit blood (CDC) with a disposable inoculator. After 24 hours incubation at 35°C the MLC was read as the lowest concentration which yielded no more than 0.1% survivors (99.9% kill).

Agar diffusion susceptibility testing was carried out as previously discribed by BAUER, *et al.*[15] and modified by the NCCLS Subcommittee for Antimicrobial Susceptibility Tests[16]. The MIC/zone size regression data were computer analyzed at CDC. Discs contained 75 mcg of ticarcillin, 100 mcg of carbenicillin or 20 mcg of BL-P1908.

Results

The MIC results at SMC and CDC laboratories against the same organisms were the same ± 1 dilution for ticarcillin (94%), carbenicillin (96%) and BL-P1908 (95%). The agar diffusion zone sizes obtained on the same organisms at CDC and SMC were the same ± 7 mm in 96%, 98% and 97% of instances for ticarcillin, carbenicillin and BL-P1908 respectively. The zone sizes at SMC averaged 2 mm greater than at CDC. A $3 \sim 4$ mm change in zone size corresponds to a single doubling dilution interval in MIC values (Fig. 1). A variation of ± 1 dilution interval in MIC values would correspond to a range of $6 \sim 8$ mm in zone diameter.

Minimal Inhibitory Concentrations

The MIC's of the three drugs against the 392 strains are summarized in Table 1. Ticarcillin and carbenicillin exhibited comparable spectra against gram-negative organisms, with ticarcillin tending to show slightly greater activity against several species of the *Enterobacteriaceae* and a more pronounced activity against *P. aeruginosa*. BL-P1908, on the other hand, showed very poor activity against the *Enterobacteriaceae* (except for *P. mirabilis*), but had the best activity of the three drugs against *P. aeruginosa*, with a modal MIC of 1 mcg/ml (compared to 16 mcg/ml for ticarcillin and 64 mcg/ml for carbenicillin). Against gram-positive strains ticarcillin and carbenicillin were generally comparable. BL-P1908, on the other hand, showed generally poorer activity against staphylococci, but greater activity than the other two drugs against streptococci, especially *S. faecalis* against which it had a modal MIC of 4 mcg/ml *vs* 64 mcg/ml for the other two drugs. Ampicillin-resistant *H. influenzae* and methicillin-resistant *S. aureus* exhibited significantly greater resistance to the three study drugs than did their susceptible counterparts, with virtually no overlapping of the MIC ranges.

Inoculum Size Effects

The effects of varying inoculum size is summarized in Table 2. The change from 10^3 to 10^5 CFU/ml had relatively little effect on MIC's since over 90% of tested strains showed no MIC change or the MIC's were increased by only one concentration. A more pronounced effect occurred with increasing the inoculum size from 10^5 to 10^7 CFU/ml, where an increase in MIC of 4 or more doubling concentrations was necessary to include 90% of the strains tested.

Minimal Lethal Concentration

Bactericidal concentrations of the three study drugs for 98 strains are tabulated in Table 3. Assuming a drug is bactericidal if the MLC is no more than 2 doubling concentrations higher than the MIC,

Table 1. Range of MIC's of ticarcillin, carbenicillin and BL-P1908 against 392 bacterial strains

Organism	Number tested	MIC's (mcg/ml): Range (mode) for:		
		Ticarcillin	Carbenicillin	BL-P1908
S. aureus (meth-sens)	20	1~64 (8)	≤0.5~64 (8)	1~>64 (16)
S. aureus (meth-res.)	10	64~128 (64)	64~256 (128)	>64
S. faecalis	25	16~128 (64)	8~64 (64)	4~16 (4)
S. pneumoniae	12	0.5~1 (0.5)	≤0.25~0.5 (≤0.25)	≤0.06~0.12 (≤0.06)
S. pyogenes	10	≤0.25~0.5 (0.5)	≤0.25	0.12
H. influenzae (amp-sens)	25	≤0.25~1 (≤0.25)	≤0.25~2 (≤0.25)	≤0.06~0.12 (≤0.06)
H. influenzae (amp-res.)	12	2~128 (128)	2~>128 (64)	2~>32 (>32)
E. coli	25	≤0.5~>256 (2)	1~>256 (4)	8~>64 (16)
K. pneumoniae	25	32~>256 (256)	64~>256 (>256)	>64
P. mirabilis	25	≤0.5~1 (≤0.5)	≤0.5~1 (≤0.5)	0.5~2 (1)
P. morganii	10	≤0.5~64 (1)	0.5~8 (1)	>64
P. rettgeri	9	≤0.5~>256 (>256)	≤0.5~>256 (>256)	4~>64 (>64)
P. vulgaris	6	≤0.5~>256 (24)	≤0.5~>256 (4)	4~>64 (>64)
E. aerogenes	11	1~>256 (1)	1~>256 (4)	64~>64 (>64)
E. cloacae	10	2~>256 (2)	2~>256 (4)	64~>64 (>64)
E. agglomerans	4	8~>256 (>256)	16~>256 (>256)	64~>64 (>64)
P. aeruginosa	101	≤0.5~>256 (16)	1~>256 (64)	0.25~>64 (1)
P. fluorescens	5	256~>256 (>256)	>256	1~4 (2)
P. cepacia	6	256~>256 (>256)	>256	>64
P. maltophilia	6	8~256 (8)	8~128 (32)	4~>64 (4)
P. putida	5	128~>256 (256)	>256	4~16 (4)
P. stutzeri	5	2~8 (4)	4~32 (4)	0.25~2 (1)
Acinetobacter	25	≤0.5~16 (16)	0.5~32 (8)	0.25~>64 (>64)

Table 2. Effect of inoculum size on MIC's of ticarcillin, carbenicillin and BL-P1908 against 96 isolates[a]

Antimicrobic	Inoculum increase	No.[b]	Increase in MIC's—in number of doubling concentrations							
			0	1	2	3	4	5	6	7
Ticarcillin	$10^3 \rightarrow 10^5$	69	58[c]	33	6		3			
	$10^5 \rightarrow 10^7$	58	16	16	26	19	12	10	2	
Carbenicillin	$10^3 \rightarrow 10^5$	70	51	37	6	3	3			
	$10^5 \rightarrow 10^7$	61	10	26	28	16	13	3	2	2
BL-P1908	$10^3 \rightarrow 10^5$	69	51	42	4	1	1			
	$10^5 \rightarrow 10^7$	48	17	35	23	15	4	4	2	

a Organisms tested include 10 *E. coli*, 10 *K. pneumoniae*, 10 *Enterobacter* spp., 10 *P. mirabilis*, 10 indole-positive *Proteus* spp., 23 *P. aeruginosa*, 10 *Pseudomonas* spp., 10 *Acinetobacter* spp. and 5 *S. aureus*.

b Number tallied include only "on scale" endpoints at both concentrations tested.

c Numbers represent the % in each category.

then ticarcillin, carbenicillin and BL-P1908 were bactericidal for 80%, 86% and 78% of the strains tested. *Pseudomonas* accounted for virtually all organisms that escaped the bactericidal activity of these drugs.

Prolonged Incubation

Table 4 summarizes the effect of prolonged (additional 24 hours) incubation on the MIC endpoints. Ninety-eight percent or more of the strains tested produced visible growth in no more than two doubling

Table 3. Bactericidal activity of ticarcillin, carbenicillin and BL-P1908

Organism	Number tested	MLC: Expressed as No. twofold concentrations greater than MIC for:											
		Ticarcillin				Carbenicillin				BL-P1908			
		0	1	2	≥3	0	1	2	≥3	0	1	2	≥3
E. coli	10	8	1			7	3			7	3		
K. pneumoniae	10	4	5	1		4	4						
Enterobacter spp.	10	6	2	1	1	8		2					
P. mirabilis	10					2				3	4	2	1
Proteus (Indole-pos.)	7	1	2	1	3		3	2	1	1	1	1	
P. aeruginosa	23	6	5	3	8	8	7	1	6	4	1	5	13
Pseudomonas spp.	10	2	3		3		1		4	2	2	1	3
Acinetobacter spp.	8	1	4			5	2	1		4	2		
S. aureus	10	9			1	6	4			8	1		1
Total	98	37	22	6	16	40	24	6	11	29	14	9	18

* Tests with MIC or MLC outside the range tested were excluded from the tally.

Table 4. Effect of additional 24 hours incubation on MIC's[a]

Antimicrobic	Medium	No. of strains[b]	Dilution increase in MIC at 42 *vs* 18 hrs[c]				
			0 dil.	1 dil.	2 dil.	3 dil.	> 3 dil.
Ticarcillin	MHB	365	72	23	4	1	0.3
	BMHB	389	70	24	4	1	1
Carbenicillin	MHB	360	71	24	4	1	0
	BMHB	358	67	26	5	1	0.3
BL-P1908	MHB	336	56	34	7	1	1
	BMHB	357	49	38	7	3	2

a Done at SMC

b 447 strains were tested; the tally excludes strains with endpoints that were off scale, *i.e.*, with MIC's 〈or〉 the lowest and highest concentrations tested, respectively.

c Numbers represent % of strains with 0, 1, 2, 3 or >3 doubling concentrations increase in MIC values after 40~42 hours at 35°C *vs* 16~18 hours.

Table 5. Mathematical analysis of susceptibility data

Antimicrobic	Organism	Number tested	Zone sizes: mean±1SD	Regression coefficient	% of variation 2° to regression	Intercept*	Correlation coefficient
Ticarcillin	*P. aeruginosa*	101	17.8±6.6	−0.27	85.6	12.0	0.92
	All organisms	392	21.9±10.5	−0.27	70.8	11.5	0.84
Carbenicillin	*P. aeruginosa*	101	16.2±6.2	−0.24	89.7	12.3	0.85
	All organisms	392	21.7±10.6	−0.29	78.2	12.3	0.88
BL-P1908	*P. aeruginosa*	101	20.3±6.8	−0.36	90.7	13.9	0.95
	All organisms	392	16.6±10.2	−0.35	91.4	13.6	0.96

* Expressed in $\log_2$ scale.

concentrations above the 18 hours MIC. No good correlations were seen between these results and MLC's.

Buffered Mueller-Hinton Medium

The effect of buffering MHB was studied with the 392 strains. With ticarcillin and carbenicillin 95% of the MIC endpoints in BMHB were the same ±1 dilution as in MHB. By contrast, only

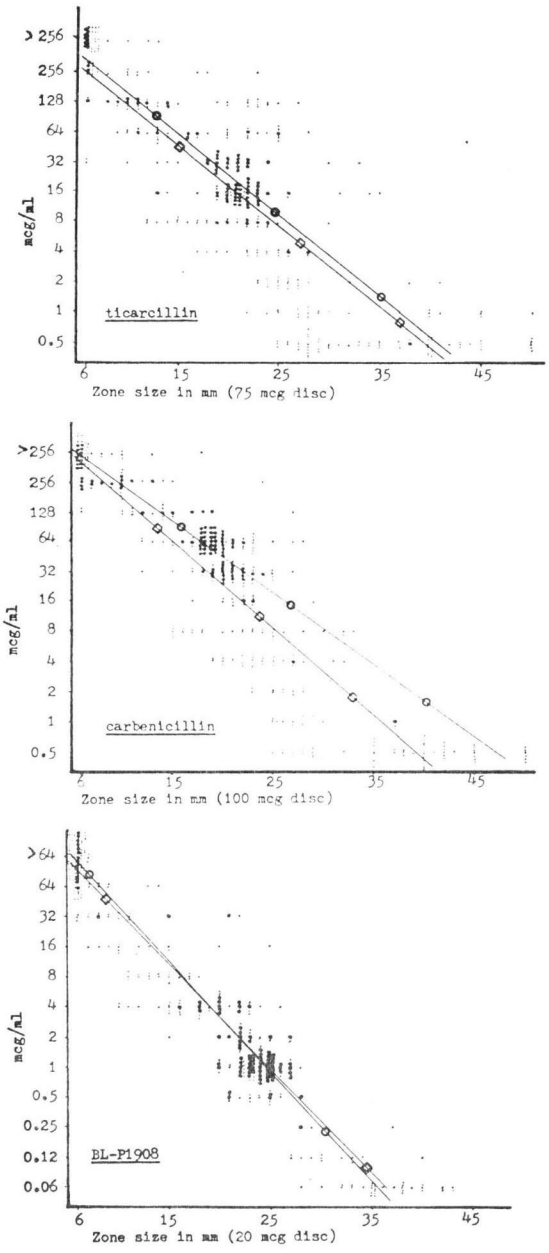
76% of tests showed such agreement with BL-P1908. Buffering of MUELLER-HINTON agar for disc tests had no appreciable effect on zone sizes. The zone sizes were the same ±2 mm in 94%, 98% and 98% of comparisons for ticarcillin, carbenicillin and BL-P1908, respectively.

Broth Microdilution/Disc Diffusion Comparison

Fig. 1 depicts regression analyses for 101 *P. aeruginosa* strains and 392 total organisms against ticarcillin, carbenicillin and BL-P1908. Table 5 shows the results of the mathematical analyses of these data. The correlation coefficients varied from 0.84 for ticarcillin against all organisms to 0.96 for BL-P1908 against all organisms. Only the slopes for ticarcillin were identical for both *P. aeruginosa* and all other organisms. With BL-P1908 the regression lines for the two groups of organisms were very close.

Table 6 shows the predictability of MIC's of carbenicillin and ticarcillin by the disc diffusion method with 100-mcg carbenicillin discs utilizing the NCCLS recommended breakpoints[16] and 75-mcg ticarcillin discs utilizing the breakpoints recommended by PARRY and NEU[12]. In general, the ticarcillin disc gave slightly better correlation with the MIC's of both drugs than did the carbenicillin disc.

Fig. 1. Regression curves for ticarcillin, carbenicillin and BL-P1908
Line with open circles: *P. aeruginosa* (larger dots) and other organisms (smaller dots).
Line with open squares: All organisms.



Discussion

The *in vitro* susceptibility test results showing greater activity of ticarcillin than carbenicillin against *P. aeruginosa* and to a lesser extent against many species of *Enterobacteriaceae* support the findings of previous studies[6~13]. BL-P1908, while showing little activity against most of the *Enterobacteriaceae*, exhibited striking activity against *P. aeruginosa* and *S. faecalis*, having a modal MIC 1/16 of that of ticarcillin against these two organisms. Since the achievable blood levels and other pharmacological properties of BL-P1908 are not available to us at this time, the significance of this increased activity by weight remains speculative.

There were relatively minor differences among the three antimicrobics with respect to the effect of inoculum size (Table 2), the effect of prolonged incubation (Table 4) and the comparison of MIC

Table 6. Comparison of ticarcillin and carbenicillin disc zone sizes with their MIC's

Organism	Anti-microbic	Zone size (Category)	No.	Ticarcillin MIC's					Carbenicillin MIC's				
				≥256	128	64	32	≤16	≥256	128	64	32	≤16
P. aeruginosa	Ticarcillin (75 mcg disc)	≤11 mm (R)[a]	23	15	7	1			23				
		12~14 mm (I)	6		3	2		1	5	1			
		≥15 mm (S)	72			4	21	47		5	41	22	4
	Carbenicillin (100 mcg disc)	≤13 mm (R)[b]	30	15	10	4		1	28	2			
		14~16 mm (I)	2			1	1			1	1		
		≥17 mm (S)	69			2	20	47		3	40	22	4
Other gram-negative bacilli	Ticarcillin (75 mcg disc)	≤11 mm (R)[a]	46	39	4	1	2		42	2		2	
		12~14 mm (I)	14	2	3	3	2	4	4	4	1	2	3
		≥15 mm (S)	115	1	1	3	1	109	1	1	3	5	105
	Carbenicillin (100 mcg disc)	≤13 mm (R)[b]	50	42	5	2	1		46	3		1	
		14~16 mm (I)	8		2	2	2	2		4	1	1	2
		≥17 mm (S)	117	1		3	2	111	1		3	7	106
		≤17 mm (R)	62[c]	42	7	5	4	4	46	7	3	3	3
		18~22 mm (I)	23	1		1	1	20	1		1	5	16
		≥23 mm (S)	90			1		89				1	89

a Ticarcillin zone size breakpoints recommended by PARRY and NEU[12]; MIC correlates: ≥128 mcg/ml for resistant and ≤64 mcg/ml for susceptible.

b Carbenicillin zone size breakpoints recommended for *Pseudomonas* by NCCLS[11]; MIC correlates: ≥256 mcg/ml for resistant and ≤128 mcg/ml for susceptible.

c Carbenicillin zone size breakpoints recommended for non-*Pseudomonas* by NCCLS[11]; MIC correlates: ≥32 mcg/ml for resistant and ≤16 mcg/ml for susceptible.

and MLC (Table 3). BL-P1908 generally was least affected by inoculum size, but was most affected by prolonged incubation and showed the greatest MIC/MLC disparity, especially with *P. aeruginosa*. This renders suspect the apparent advantage of the lower MIC of BL-P1908 against *P. aeruginosa*.

The effect of pH changes in the *in vitro* system on the MIC of ticarcillin and carbenicillin has been previously shown.[17] The activity of both drugs was found to be less at pH 6.4 than at 7.2. An attempt to evaluate the possible effect of pH changes occurring in the test system was made by comparing MIC's and zone size data in standard MUELLER-HINTON media with MUELLER-HINTON media buffered at pH 7.3. There were virtually no differences in endpoints between the two media with ticarcillin and carbenicillin. With BL-P1908, 14% of BMHB endpoints were ≥2 dilution steps lower than MIC endpoints in MHB and 7% of the tests in BMHB were higher than those in MHB. For the two currently available drugs, ticarcillin and carbenicillin, it appears safe to say that buffering the MUELLER-HINTON media offers no advantage over the standard *in vitro* susceptibility testing to these drugs.

The regression analyses (Tables 5 and 6, Fig. 1) reveal good correlations between the zone sizes and MIC's for all three drugs. Since serum levels of BL-P1908 are not available to us, no attempt was made to determine optimal zone size breakpoints for susceptible, intermediate and resistant organisms.

Difficulties in interpreting agar diffusion disc zone sizes for carbenicillin and ticarcillin can be appreciated from Table 6. The NCCLS[16] recommended carbenicillin breakpoints for resistance are 13 mm and 17 mm for *Pseudomonas* and non-*Pseudomonas* microbes respectively. The respective susceptible breakpoints are 17 and 23 mm. This double standard is not only confusing, but also unnecessary. We agree with PARRY and NEU[12] that the recommended carbenicillin breakpoints for *Pseudomonas* are quite adequate for the *Enterobacteriaceae*. In our series only one of 117 non-*Pseudomonas* gram-negative strain with a zone of 17 mm or greater had a MIC of more than 64 mcg/ml. Likewise only one of 50 such strains with zone sizes of 13 mm or less had a MIC of 64 mcg/ml or less. The

NCCLS[16] MIC correlates of $\leq$16 and $\geq$32 mcg/ml for susceptible and resistant among the *Enterobacteriaceae* appear to be unrealistically low. We feel that corresponding correlates of $\leq$64 and $\geq$128 mcg/ml are more in line with levels achieved in current dosage schedules. Furthermore, over 90% of non-Pseudomonal gram-negative rods with carbenicillin zone sizes of $\geq$17 mm actually have MIC's of 16 mcg/ml or less.

With respect to the 75-mcg ticarcillin disc, we find the breakpoints recommended by PARRY and NEU[12] to quite satisfactorily discriminate between susceptible and resistant isolates if MIC corresponding correlates of $\leq$64 mcg/ml and $\geq$128 mcg/ml respectively are used. These MIC correlates for ticarcillin, being half those for carbenicillin, are more appropriate since the current recommended dosage (Hospital Formulary Information, Beecham Laboratories, Bristol, Tennessee) and hence the serum levels achieved are nearly half those of carbenicillin. As in the case of carbenicillin, our data support the position of having a single set of zone size criteria for all organisms rather than having two sets of criteria—one for *Pseudomonas* and one for *Enterobacteriaceae*.

A method of evaluating the effectiveness of agar diffusion zone size criteria is to determine the frequency of so-called "major errors" and "very major errors". Major errors are defined as susceptible organisms by MIC interpreted as resistant by zone size criteria; very major errors are resistant organisms by MIC interpreted as susceptible by zone size criteria. By these definitions the data in Table 6 yield the following results for very major and major errors respectively: ticarcillin 75-mcg disc *vs* ticarcillin MIC—2(0.7%) and 4(1.4%); ticarcillin 75-mcg disc *vs* carbenicillin MIC—4(1.4%) and 1 (0.4%); carbenicillin 100-mcg disc *vs* carbenicillin MIC—6(2.2 %) and 1 (0.4%), and carbenicillin 100-mcg disc *vs* ticarcillin MIC—1(0.4%) and 8(2.9%). These would appear to be within acceptable limits. If a single disc should be required as a representative for both drugs, the ticarcillin 75-mcg disc gave fewer major and very major errors for both drugs than did the carbenicillin disc, and hence would be slightly preferable.

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