

Susceptibilities of 200 Penicillin-Susceptible and -Resistant Pneumococci to Piperacillin, Piperacillin-Tazobactam, Ticarcillin, Ticarcillin-Clavulanate, Ampicillin, Ampicillin-Sulbactam, Ceftazidime, and Ceftriaxone

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MICs of eight β -lactams (piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanate, ampicillin, ampicillin-sulbactam, ceftazidime, and ceftriaxone) were determined by agar dilution against 64 penicillin-susceptible, 70 intermediately penicillin-resistant, and 66 fully penicillin-resistant pneumococci. The MICs of piperacillin with and without tazobactam for 90% of the susceptible, intermediately resistant, and resistant strains tested (MIC₉₀s) were ≤ 0.064 , 2.0, and 4.0 $\mu\text{g/ml}$, respectively. By comparison, those of ampicillin with and without sulbactam were 0.125, 2.0, and 4.0 $\mu\text{g/ml}$ and those of ceftriaxone were ≤ 0.064 , 1.0, and 2.0 $\mu\text{g/ml}$, respectively. Strains were less susceptible to ticarcillin with and without clavulanate (MIC₉₀s, 2.0, 64.0, and 128.0 $\mu\text{g/ml}$) and ceftazidime (MIC₉₀s, 1.0, 8.0, and 32.0 $\mu\text{g/ml}$).

Streptococcus pneumoniae continues to be a significant cause of morbidity and mortality in humans and is the leading cause of bacterial pneumonia, as well as an important cause of otitis media and meningitis. The past 2 decades, and in particular the past 5 years, have witnessed a dramatic increase in the incidence of pneumococcal strains which are resistant to penicillin G and other antimicrobial agents (1, 2, 5-7, 9). In the United States, recent surveys show a countrywide prevalence of 4 to 5% (1). McDougal and coworkers have recently documented the dissemination in the United States of a multiresistant type 23F clone which is related to multiresistant isolates from Spain and South Africa (12), emphasizing the tendency of these strains to spread from country to country and even from continent to continent. The problem has recently been exacerbated by the appearance of pneumococci with high-level resistance to cefotaxime and ceftriaxone (3, 4, 14). Although nonmeningitic infections caused by pneumococci with intermediate penicillin resistance (I strains) may be treated, under certain circumstances, with large doses of penicillin and other β -lactams, treatment may not always be successful (2, 5, 7, 9-11, 16). By contrast, clinical failure of penicillin in the treatment of meningitis caused by I strains approaches 80% and very few cases of meningitis caused by strains fully resistant to penicillin (R strains) have responded to penicillin therapy (2, 5, 7, 9-11, 16).

There is an urgent need for antimicrobial agents which can be used for parenteral therapy of systemic infections caused by penicillin-resistant pneumococci. Ward and Moellering, in 1981, described low MICs of piperacillin for penicillin-susceptible strains (S strains), I strains, and R strains of pneumococci (17). Subsequently, Tweardy and coworkers, in 1983 (16), described similarly improved activity of piperacillin compared with ticarcillin and ceftazidime against the same groups of organisms. The aim of the current study was to confirm and extend these findings by examining the activity of eight β -lac-

tams (piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanate, ampicillin, ampicillin-sulbactam, ceftazidime, and ceftriaxone) against 64 S, 70 I, and 66 R strains of *S. pneumoniae*.

Blood, cerebrospinal fluid, ear, nasopharynx, and sputum isolates of pneumococcal strains collected over the past 10 years were examined. S strains (MIC, $<0.1 \mu\text{g/ml}$) were isolated from various U.S. hospitals. R isolates (MIC, $\geq 2.0 \mu\text{g/ml}$) and most of the I strains tested (MIC, 0.1 to 1.0 $\mu\text{g/ml}$) were isolated in the United States, South Africa, France, Spain, or Hungary. Organisms were frozen at -70°C in double-strength skim milk (Difco Laboratories, Detroit, Mich.) prior to use and plated onto Trypticase soy agar plates (BBL Microbiology Systems, Cockeysville, Md.) containing 5% sheep blood after thawing. Purity was confirmed throughout the study by Gram stain and colony morphology. Antimicrobial agents were supplied as laboratory powders of known potency, as follows: piperacillin and tazobactam, Lederle Laboratories, Pearl River, N.Y.; ampicillin, Sigma Chemical Co., St. Louis, Mo.; sulbactam, Pfizer, Inc., New York, N.Y.; ticarcillin and clavulanate, SmithKline Beecham Laboratories, King of Prussia, Pa.; ceftazidime, Lilly Laboratories, Indianapolis, Ind.; ceftriaxone, Roche Laboratories, Nutley, N.J.

MICs were determined by the agar dilution method recommended by the National Committee for Clinical Laboratory Standards (13) with Mueller-Hinton agar (BBL Microbiology Systems) supplemented with 5% sheep blood. Tazobactam was added to piperacillin at a fixed concentration of 4.0 $\mu\text{g/ml}$, and clavulanate was added to ticarcillin at a fixed concentration of 2.0 $\mu\text{g/ml}$. Sulbactam was combined with ampicillin at a 1:2 ratio. For MIC determinations, suspensions with a turbidity equivalent to a 0.5 McFarland standard were prepared by suspending growth from blood agar plates in 2 ml of Mueller-Hinton broth (BBL). Suspensions were further diluted 1:10 to obtain a final inoculum of 10^4 CFU per spot. Plates were inoculated with a Steers replicator and incubated overnight in ambient air at 35°C . Standard quality control strains, including *S. pneumoniae* ATCC 49619 (13), were included in each run.

Results of susceptibility testing are presented in Table 1. As

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TABLE 1. Susceptibility of pneumococci to antimicrobial agents

Drug tested and penicillin resistance group	Cumulative % of strains inhibited at conc (µg/ml) of:												MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)
	≤0.064 ^a	0.125	0.25	0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	>64.0		
Penicillin G														
S	100.0												0.015	0.032
I		35.7	58.6	78.6	100.0								0.25	1.0
R						80.3	95.5	100.0					2.0	4.0
Piperacillin														
S	90.6	95.3	98.4	100.0									≤0.064	≤0.064
I		10.0	41.4	65.7	75.7	95.7	100.0						0.5	2.0
R						10.6	93.9	97.0	100.0				4.0	4.0
Piperacillin-tazobactam														
S	95.3	96.9	98.4	100.0									≤0.064	≤0.064
I	4.3	18.6	48.5	71.4	77.1	97.1	100.0						0.5	2.0
R						10.6	93.9	97.0	100.0				4.0	4.0
Ticarcillin														
S		3.1	4.6	31.2	78.1	96.9	100.0						1.0	2.0
I					1.4	5.7	32.8	57.1	74.3	87.1	100.0		8.0	64.0
R										3.0	77.3	100.0	64.0	128.0
Ticarcillin-clavulanate														
S	3.1	3.1	26.5	65.6	87.5	100.0							0.5	2.0
I	1.4	1.4	1.4	1.4	7.1	18.6	40.0	55.7	75.7	87.1	100.0		8.0	64.0
R										3.0	71.2	100.0	64.0	128.0
Ampicillin														
S	87.5	98.4	100.0										0.032	0.125
I	21.4	50.0	67.1	72.9	78.6	95.7	100.0						0.125	2.0
R					3.0	21.2	92.4	95.5	100.0				4.0	4.0
Ampicillin-sulbactam														
S	89.1	98.4	100.0										0.032	0.125
I	22.9	51.4	67.1	72.9	78.6	98.6	100.0						0.125	2.0
R					3.0	31.8	93.9	95.5	100.0				4.0	4.0
Ceftazidime														
S	7.8	28.1	65.6	68.7	93.8	96.9	100.0						0.25	1.0
I		1.4	2.8	25.7	51.4	60.0	72.9	92.9	98.6	100.0			1.0	8.0
R							3.0	63.6	87.9	100.0			8.0	32.0
Ceftriaxone														
S	93.8	98.4	100.0										≤0.064	≤0.064
I	41.4	57.1	72.9	85.7	97.1	97.1	100.0						0.125	1.0
R				4.5	87.9	98.5	100.0						1.0	2.0

^a The lowest concentration of all of the compounds tested was 0.015 µg/ml, except for piperacillin with and without tazobactam and for ceftriaxone, whose lowest concentration was 0.064 µg/ml.

can be seen, susceptibility to all β-lactams increased in line with the MIC of penicillin. The MICs of piperacillin with and without tazobactam against 90% of the S, I, and R strains tested (MIC₉₀s) were ≤0.064, 2.0, and 4.0 µg/ml, respectively. By comparison, those for ampicillin with and without sulbactam were 0.125, 2.0, and 4.0 µg/ml and those for ceftriaxone were ≤0.064, 1.0, and 2.0 µg/ml. Strains were less susceptible to ticarcillin with and without clavulanate (MIC₉₀s, 2.0, 64.0, and 128.0 µg/ml) and ceftazidime (MIC₉₀s, 1.0, 8.0, and 32.0 µg/ml).

Tweardy and coworkers (16), in a study of 25 S, 18 I, and 27 R pneumococci (all of the I and R pneumococci were isolated in South Africa), reported piperacillin MIC₉₀s of 0.125, 1.0, and 8.0 µg/ml, compared with ticarcillin MIC₉₀s of 1.0, 64.0, and 128.0 µg/ml, respectively. The same workers reported ceftazidime MIC₉₀s of 0.25, 32, and 64.0 µg/ml and ampicillin MIC₉₀s of 0.015, 0.5, and 8.0 µg/ml, respectively. Similarly,

Ward and Moellering reported piperacillin MIC₉₀s against S, I, and R strains of 0.03, 1.0, and 16.0 µg/ml, respectively (17). Our findings with a larger group of pneumococci, with I and R strains isolated from several different countries, are similar to these reports. High MICs of ceftazidime, in contrast to lower MICs of ceftriaxone against I and R pneumococcal strains, have been described before (10, 11). Because the mechanism of β-lactam resistance in pneumococci is mediated by changes in penicillin-binding proteins (8), the activity of β-lactam-β-lactamase inhibitor combinations against I and R pneumococci is due solely to the β-lactam component. Sörgel and Kinzig (15) have reported human pharmacokinetic data for piperacillin with and without tazobactam. After a 5-min intravenous infusion of piperacillin alone, the maximum concentration of the drug in serum was 380.0 (4-g dose) or 178 (2-g dose) µg/ml. When 4 g of piperacillin was given as a 30-min infusion, the mean maximum level in plasma was 284 µg/ml, about 75% of

the 5-min infusion value. The half-life of piperacillin was not significantly altered with increasing doses in these studies. With the currently recommended piperacillin-tazobactam doses of 3.0 and 0.375 g, respectively, every 6 h (infusion time, 6 to 30 min), the maximum concentration of the drugs in serum on day 1 was $247 \pm 20 \mu\text{g/ml}$ and the area under the concentration-time curve was $253.0 \pm 15.0 \mu\text{g/h/ml}$. In view of these findings, serum piperacillin levels well above the MIC can be achieved for even the most resistant pneumococci. With the exception of the two highly penicillin-resistant pneumococci, both with penicillin MICs of $8.0 \mu\text{g/ml}$ (MIC of piperacillin with or without tazobactam, $16.0 \mu\text{g/ml}$), the highest MIC of piperacillin with or without tazobactam for R strains was $8.0 \mu\text{g/ml}$. It should be noted that R pneumococci with MICs of $>4.0 \mu\text{g/ml}$ have been described only in Eastern Europe and are not known to be present in the United States. Most R pneumococci isolated in the United States are of the I variety (1, 9).

There are currently no breakpoints for pneumococci recommended by the National Committee for Clinical Laboratory Standards for the β -lactams tested in this study other than ceftriaxone (13). In view of the rapid worldwide spread of I and R strains, this deficiency requires urgent rectification. MICs for piperacillin with and without tazobactam against R pneumococci are clearly lower than the levels achievable in serum and tissue. This is particularly true for I strains, which account for $>90\%$ of the penicillin-resistant pneumococci isolated in the United States (1). Additionally, in view of the above-mentioned pharmacokinetic data, serum piperacillin levels sufficient to inhibit I and R organisms may be achievable in humans. Clinical studies are necessary to ascertain whether piperacillin with and without tazobactam may represent an alternative to cefotaxime or ceftriaxone for therapy of systemic nonmeningeal infections caused by I and R pneumococci.

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