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Susceptibilities of 177 Penicillin-Susceptible and -Resistant Pneumococci to FK 037, Cefpirome, Cefepime, Ceftriaxone, Cefotaxime, Ceftazidime, Imipenem, Biapenem, Meropenem, and Vancomycin

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MICs of six extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, FK 037, cefpirome, cefepime), three carbapenems (imipenem, meropenem, biapenem), and vancomycin for 49 penicillin-susceptible (S), 77 penicillin intermediate-resistant (I), and 51 penicillin-resistant (R) pneumococci were determined by agar dilution. Compared with ceftazidime (MICs for 90% of strains tested [MIC_{90}s] of 2.0, 16.0, and 16.0 μg/ml for S, I, and R strains, respectively), all other cephalosporins yielded lower MICs (MIC_{90}s of 0.06 to 0.125, 0.5 to 1.0, and 1.0 to 2.0 μg/ml against S, I, and R strains, respectively). All three carbapenems were very active, with MIC_{90}s, even for R strains, of ≤1.0 μg/ml. All strains were susceptible to vancomycin (MIC_{90} of 0.5 μg/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 being an important cause of otitis media and meningitis. The past two 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 (R) and other antimicrobial agents (1). In the United States, surveys performed before 1990 showed a prevalence of 4 to 5% (1). One report documented an incidence of 17.8% between 1990 and 1991 (24). It is not clear whether this increased incidence applies to the whole country or only applies to certain areas. In the absence of recent confirmatory multistate surveys, we do not know precisely the magnitude of this problem in the United States. Although nonmeningitic infections caused by R strain pneumococci may be treated under certain circumstances with high doses of penicillin and other β-lactams, treatment may not always be successful (17). By contrast, clinical failure of penicillin in treatment of meningitis caused by strains intermediately resistant to penicillin (I) approaches 80%, and no cases of meningitis caused by strains fully resistant to penicillin have responded to penicillin therapy (25).

There is an urgent need for antimicrobial agents which can be used for therapy of systemic infections (and especially meningitis) caused by R strain pneumococci. The aim of the current study was to examine the activity of six extended-spectrum cephalosporins (ceftazidime, cefotaxime, ceftriaxone, FK 037, cefpirome [HR 810], cefepime [BMY 28142]) (2, 3, 6, 10, 11, 14–16, 21, 25), three carbapenems (imipenem, meropenem, biapenem [LJC 10,627]) (13, 20, 25, 26), and vancomycin against 49 penicillin-susceptible (S), 77 I, and 51 R strains of *S. pneumoniae*.

A total of 177 isolates of *S. pneumoniae* isolated from blood, cerebrospinal fluid, ear, nasopharynx, or sputum were examined. S strains (MIC of <0.1 μg/ml) were isolated from various hospitals in the United States. R strains (MIC of ≥2.0 μg/ml) and most of the I strains (MICs of 0.1 to 1.0 μg/ml) were isolated in the United States, South Africa, France, Spain, or Hungary. Antimicrobial agents were supplied as laboratory powders of known potency, as follows. FK 037 was from the R. W. Johnson Research Institute, Raritan, N.J.; cefpirome and cefotaxime were from Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J.; cefepime was from Bristol-Myers Squibb Laboratories, Wallingford, Conn.; vancomycin and ceftazidime were from Lilly Laboratories, Indianapolis, Ind.; ceftriaxone was from Roche Laboratories, Nutley, N.J.; imipenem was from Merck Sharpe and Dohme Laboratories, Rahway, N.J.; biapenem was from Lederle Laboratories, Pearl River, N.Y.; and meropenem was from Zeneca Pharmaceuticals Group, Wilmington, Del.

MICs were determined by the agar dilution method recommended by the National Committee for Clinical Laboratory Standards, with Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 5% sheep blood (19). For MIC determinations, suspensions with a turbidity equivalent to that of a 0.5 McFarland standard were prepared by suspending growth from blood agar plates in 2 ml of Mueller-Hinton broth (BBL Microbiology Systems). 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 37°C. Standard quality control strains (19) were included in each run.

The results of susceptibility testing are presented in Table 1 as the cumulative percentage inhibited at a specific MIC. As can be seen, the susceptibility of all cephalosporins and carbapenems increased in line with the MIC of penicillin. Ceftazidime was the least active of the cephalosporins, with MICs for 90% of the S, I, and R strains tested of 2.0, 16.0, and 16.0 μg/ml, respectively. By contrast, all other cephalosporins showed greater activity, with MICs for 90% of the S, I, and R strains tested of 0.06 to 0.125, 0.5 to 1.0, and 1.0 to 2.0 μg/ml, respectively. MICs of FK 037, cefpirome, cefepime, cefotaxime, and ceftriaxone were very similar for all classes of pneumococcal strains. All three carbapenems were very active,

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TABLE 1. Susceptibility of pneumococci to antimicrobial agents

Antimicrobial agent and strain	Cumulative % of strains inhibited at MIC (μg/ml) of:									
	≤0.015	0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0
Penicillin G										
S	49.0	68.7	98.0	100						
I	0	0	3.8	18.0	40.0	66.0	100			
R	0	2.0	2.0	4.0	6.0	8.0	10.2	71.4	96.0	100
FK 037										
S	35.0	72.5	82.4	98.0	100					
I	10.4	27.3	37.7	61.0	81.8	98.7	100			
R	0	8.2	10.2	14.3	28.6	55.1	100			
Cefpirome										
S	45.1	80.4	88.2	94.1	98.0	100				
I	6.5	24.5	37.7	50.6	84.4	97.4	100			
R	0	6.1	12.5	14.3	32.7	40.3	97.9	100		
Cefepime										
S	17.6	41.2	72.6	94.1	98.0	100				
I	2.6	10.2	28.6	49.4	52.0	93.5	100			
R	2.0	2.0	6.1	16.3	24.5	46.9	73.5	97.9	100	
Ceftriaxone										
S	23.5	50.9	92.2	98.0	100					
I	6.5	23.4	35.1	45.5	72.7	94.8	100			
R	0	6.1	6.1	12.3	26.5	51.0	69.4	95.9	100	
Cefotaxime										
S	33.3	68.6	80.4	90.2	98.0	100				
I	0	14.3	29.9	48.1	58.4	80.5	100			
R	0	10.2	14.3	22.5	34.7	59.2	95.9	100		
Ceftazidime										
S	2.0	3.9	3.9	13.7	33.3	44.0	49.4	88.2	90.2	96.1
I	0	0	1.3	2.6	9.1	15.6	37.7	57.1	71.4	83.1
R	0	0	0	2.0	4.1	10.2	16.3	26.5	30.6	40.8
Imipenem										
S	96.1	96.1	98.0	100						
I	53.3	83.1	96.1	98.7	100					
R	18.4	32.7	51.0	93.9	100					
Meropenem										
S	78.4	90.2	96.0	100						
I	36.4	45.5	68.8	92.2	97.4	100				
R	4.1	24.5	33.3	53.1	77.8	95.6	100			
Biapenem										
S	94.1	100								
I	33.8	46.8	81.8	98.7	100					
R	2.0	2.0	10.2	98.0	100					
Vancomycin[a]			4.0	14.1	45.2	100				

[a] Identical results were obtained with S, I, and R strains (dilution range between 0.06 and 2.0 μg/ml only).

with all strains susceptible at MICs of ≤1.0 μg/ml. All strains were susceptible to vancomycin at MICs of ≤0.5 μg/ml.

High MICs of ceftazidime, in contrast to the lower MICs of both cefotaxime and ceftriaxone for I and R pneumococcal strains, have been described before (16, 25). FK 037, cefpirome, and cefepime are all new extended-spectrum cephalosporins with broad-spectrum antimicrobial activity against gram-positive and gram-negative organisms equal or superior to that of existing broad-spectrum cephalosporins (2, 3, 6, 10, 11, 14–16, 21). Geslin and coworkers (6) and Liñares and coworkers (16) have documented good in vitro activity of cefpirome against S, I, and R pneumococci (MICs for 90% of the strains tested of ≤0.03, 0.5, and 1.0 μg/ml, respectively). Our results confirm the latter findings and extend them to FK 037 and cefepime. Low imipenem MICs for all groups of pneumococci have been described before (16, 25). The current study documents comparably low MICs for these organisms of meropenem (13) and biapenem, a new broad-spectrum carbapenem which is also stable in response to human renal dehydropeptidase (20, 26). Although MICs of carbapenems increased with the penicillin MIC, all strains were susceptible at MICs of ≤1.0 μg/ml. The uniform susceptibility of all pneumococcal strains to vancomycin has been amply documented (16, 25).

Although a few cases of systemic infections caused by pneumococci with cefotaxime and ceftriaxone MICs greater

than those of penicillin G have been described (4, 5, 22), most I and R strains which are encountered in clinical practice require MICs of the latter two drugs (and also of FK 037, cefpirome, and cefepime) of ≤2.0 μg/ml. It is not known how rapidly cefotaxime- and ceftriaxone-resistant pneumococci will spread. The susceptibility breakpoints currently recommended by the National Committee for Clinical Laboratory Standards for ceftriaxone, cefotaxime, and cefepime against other species (19) have been lowered to ≤0.25 μg/ml (susceptible), 0.5 to 1.0 μg/ml (intermediate), and ≥2.0 μg/ml (resistant) for pneumococci, with the proviso that cerebrospinal fluid isolates that yield MICs in the intermediate range be considered resistant (19). At the present time, cefotaxime and ceftriaxone are the treatment modalities of choice for systemic nonmeningitic infections caused by I strains of pneumococci (7–9, 12, 28). However, they are not recommended for treatment of meningitis caused by these strains. Treatment failures in meningitis caused by I and R strains have been found with vancomycin and chloramphenicol (9, 27), and the epileptogenic properties of imipenem make it less attractive for meningitis therapy, despite the low MICs obtained with this drug (7). There is thus an urgent need for additional compounds which are effective in treatment of infections caused by R strain pneumococci. Meropenem does not seem to have the central nervous system side effects of imipenem (18), besides being very active against these organisms. The effects of biapenem on the central nervous system are unknown at the present time, but preliminary evidence in experimental animals points to no untoward central nervous system side effects (23). Clinical studies are required to determine the role of FK 037, cefpirome, cefepime, meropenem, and biapenem in the treatment of systemic infections caused by R strain pneumococci.

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