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In Vitro Activities of 12 Orally Administered Antimicrobial Agents against Four Species of Bacterial Respiratory Pathogens from U.S. Medical Centers in 1992 and 1993

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Clinical isolates of *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Moraxella catarrhalis* were gathered from 19 different clinical laboratories throughout the continental United States. The in vitro activities of 12 orally administered antimicrobial agents were compared by broth microdilution tests with 3,151 bacterial isolates. Among 890 *H. influenzae* isolates, 30% were capable of producing β-lactamase enzymes (12 to 41% in different medical centers). Most of the 619 β-lactamase-negative *H. influenzae* strains were susceptible to ampicillin (MIC, ≤1.0 μg/ml): 5 strains were intermediate in susceptibility (MIC, 2.0 μg/ml) and 1 strain was ampicillin resistant (MIC, 4.0 μg/ml). Ninety-two percent of 698 *M. catarrhalis* strains were β-lactamase positive. Of 799 *S. pneumoniae* isolates, 15% were intermediate in susceptibility to penicillin and 7% were resistant to penicillin. The prevalence of penicillin-susceptible pneumococci in different institutions ranged from 63 to 95%. Only 1% of 764 *S. pyogenes* isolates were resistant to the macrolides, but 5% of *S. pneumoniae* isolates were macrolide resistant. Only 71% of 58 penicillin-resistant *S. pneumoniae* isolates were erythromycin susceptible, whereas 97% of the 622 penicillin-susceptible strains were erythromycin susceptible. Penicillin-resistant pneumococci were also relatively resistant to the cephalosporins and amoxicillin. Penicillin-susceptible pneumococci were susceptible to amoxicillin-clavulanic acid (MIC for 90% of isolates tested [MIC_{90}], ≤0.12/0.06 μg/ml), cefixime (MIC_{90}, 0.25 μg/ml), cefuroxime axetil (MIC_{90}, ≤0.5 μg/ml), cefprozil (MIC_{90}, ≤0.5 μg/ml), cefaclor (MIC_{90}, 0.5 μg/ml), and loracarbef (MIC_{90}, 1.0 μg/ml). Most strains of the other species remained susceptible to the study drugs other than amoxicillin.

For chemotherapy of bacterial infections among outpatients, orally administered drugs are particularly advantageous. Urinary tract and respiratory tract infections account for the majority of infections that are encountered in adult outpatients. The bacterial pathogens that are most likely to be involved in community-acquired respiratory tract infections include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Moraxella catarrhalis* (12). Among those species, resistance to established antimicrobial agents has been reported (1, 6–8, 11, 15). In the study described in the current report we evaluated the antimicrobial susceptibilities of contemporary isolates of respiratory pathogens from different U.S. medical centers.

A national survey was designed to evaluate the in vitro potencies of 12 different orally administered antimicrobial agents that may be used in the treatment of community-acquired respiratory tract infections. Randomly sampled isolates of *H. influenzae*, *S. pneumoniae*, *S. pyogenes*, and *M. catarrhalis* were collected from 19 different microbiology laboratories throughout the continental United States. Broth microdilution tests compared cefixime, cefaclor, loracarbef, cefuroxime, cefprozil, ciprofloxacin, amoxicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, erythromycin, clarithromycin, and azithromycin against 3,151 bacterial isolates.

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MATERIALS AND METHODS

Source of bacterial isolates. Eighteen of the laboratories that contributed isolates for the present evaluation are located in large medical centers distributed throughout the United States. Each institution was asked to select the first 50 isolates of each of the four species: some fell short of that goal since these species are not always isolated in pure culture. The Clinical Microbiology Institute provided an additional set of 199 isolates that were being gathered from patients as they were enrolled into a concurrent clinical study involving 12 additional U.S. medical centers. For the purposes of the present study, the latter isolates were considered to represent a 19th medical center, although the strains were not collected from patients in the same geographic areas. The intent was to gather a random sample of contemporary isolates that is not affected by unusual strains that might be endemic in one geographic area. The isolates were recovered from the following types of respiratory tract specimens: sputum (47%), throat swabs (25%), trachael aspirates (8%), bronchial washings (3%), and unspecified specimens (17%). All strains were isolated from clinical specimens between July 1992 and June 1993 and were sent to a central laboratory for in vitro studies.

Microorganisms. Upon arrival, each isolate was subcultured onto appropriate agar medium, and selected screening tests were applied to confirm the viability and identity of each isolate. β-Lactamase production by all *H. influenzae* and *M. catarrhalis* isolates was documented by a nitrocefin-based filter paper spot test. Isolates of *S. pneumoniae* were confirmed to be bile soluble by a direct test with 10% desoxycholate. Each pneumococcus was screened by a 1-μg oxacillin disk test, and they were later tested against doubling dilutions of penicillin in cation-adjusted Mueller-Hinton broth with 2 to 3% lysed horse

TABLE 1. Overall Comparison of MICs in Mueller-Hinton broth with LHB with those observed in HTM broth

Antimicrobial agent and microorganism	No. of strains[a] with the following twofold differences in MICs:										
	Both MICs off scale[b]	LHB MICs > HTM MICs				MICs the same	HTM MICs > LHB MICs				
		≥4	3	2	1		1	2		3	≥4
Cefixime											
H. influenzae	51				6	13	7	2		0	1
S. pneumoniae	4			5	29	44	5	4		7	
M. catarrhalis	16				15	38	3				
S. pyogenes	7				20	25					
Cefaclor											
H. influenzae	21			2	8	30	14	3		2	
S. pneumoniae	5			6	41	33	13				
M. catarrhalis	0				10	50	12				
S. pyogenes	1			2	24	24	1				
Loracarbef											
H. influenzae	9	1	0	5	12	33	14	6			
S. pneumoniae	11			3	39	39	6				
M. catarrhalis	21				19	32					
S. pyogenes	51				1						
Cefuroxime											
H. influenzae	12			1	9	44	11	3			
S. pneumoniae	78			1	12	7					
M. catarrhalis	13				12	44	3				
S. pyogenes	52										
Cefprozil											
H. influenzae	9		2	1	14	30	18	4	2		
S. pneumoniae	77			3	10	7	1				
M. catarrhalis	16				9	41	6				
S. pyogenes	51				1						
Ciprofloxacin											
H. influenzae	79					1					
S. pneumoniae	0				9	54	22	3		8	2
M. catarrhalis	31					10	31				
S. pyogenes	1			1	14	34	2				
Amoxicillin											
H. influenzae	17			1	4	41	17				
S. pneumoniae	76			2	11	9					
M. catarrhalis	19				4	36	13				
S. pyogenes	51			1	0	0					
Amoxicillin-clavulanic acid[c]											
H. influenzae	2				3	48	27				
S. pneumoniae	77			3	9	9					
M. catarrhalis	46					24	2				
S. pyogenes	51			1							
Trimethoprim-sulfamethoxazole[d]											
H. influenzae	37				2	1	28	7		2	3
S. pneumoniae	9				4	23	34	19		9	
M. catarrhalis	1				1	5	27	36		2	
S. pyogenes	1	1	2	6	4	15	9	11		2	1
Erythromycin											
H. influenzae	0				2	42	32		2	1	1
S. pneumoniae	92			1	2	2	1				
M. catarrhalis	52				7	11	2				
S. pyogenes	51					1					
Clarithromycin											
H. influenzae	2			1	2	32	38	4		0	1
S. pneumoniae	92			1	4	1					
M. catarrhalis	71					0	1				
S. pyogenes	51					1					

Continued on following page

TABLE 1—*Continued*

Antimicrobial agent and microorganism	No. of strains[a] with the following twofold differences in MICs:								
	Both MICs off scale[b]	LHB MICs > HTM MICs				MICs the same	HTM MICs > LHB MICs			
		≥4	3	2	1		1	2	3	≥4
Azithromycin										
H. influenzae	7			1	3	14	40	13	2	
S. pneumoniae	93				3	1	1			
M. catarrhalis	72					0				
S. pyogenes	50				1	0	1			

[a] The 302 strains included 80 *H. influenzae* (42 ampicillin susceptible, 19 ampicillin resistant but β-lactamase negative, and 19 β-lactamase positive), 98 *S. pneumoniae* (36 penicillin intermediate or resistant), 72 *M. catarrhalis* (52 β-lactamase positive), and 52 *S. pyogenes*.

[b] Excludes MIC pairs that were off scale by both methods; when only one MIC was off scale, that MIC was assumed to be the lowest concentration tested or 1 doubling dilution greater than the highest concentration tested.

[c] Amoxicillin plus clavulanic acid at a 2:1 ratio.

[d] Trimethoprim plus sulfamethoxazole at a 1:19 ratio.

blood. They were then categorized as being penicillin susceptible, intermediate, or resistant (MICs, ≤0.06, 0.12 to 1.0, and ≥2.0 μg/ml, respectively). In the same way, β-lactamase-negative strains of *H. influenzae* were tested against ampicillin diluted in Haemophilus Test Medium (HTM) (10). They were then categorized as being ampicillin susceptible (MIC, ≤0.5 μg/ml), intermediate in susceptibility (MIC, 1.0 μg/ml), or ampicillin resistant (MIC, ≥2.0 μg/ml). Only one ampicillin-resistant, β-lactamase-negative strain was detected.

Broth microdilution tests. The broth microdilution test procedures described by the National Committee for Clinical Laboratory Standards (NCCLS) (14) were followed as closely as possible. The inocula were adjusted to deliver approximately 3×10^5 to 5×10^5 CFU/ml to each well, as confirmed by periodic colony counts. Trays were incubated for approximately 20 to 24 h in ambient air when testing *H. influenzae* isolates or 16 to 18 h when testing the other species.

In order to study four different species, the use of a single broth medium is very desirable. HTM has been recommended for testing *H. influenzae* (10) and *S. pneumoniae* (9). Mueller-Hinton broth with 2 to 5% lysed horse blood (LHB) is currently recommended by NCCLS (14) for testing pneumococci and other streptococci. Preliminary studies comparing the MICs obtained with these two broth media have been reported previously (5). In the present study we extended our earlier observations by testing a total of 302 isolates in both media. Those 302 isolates included 80 *H. influenzae*, 98 *S. pneumoniae*, 52 *S. pyogenes*, and 72 *M. catarrhalis* strains. Both types of enriched media were prepared by supplementing the same lot of cation-adjusted Mueller-Hinton broth.

RESULTS

Susceptibility testing medium. A direct comparison of the MICs recorded with two different broth media (HTM and LHB) is summarized in Table 1. On-scale MICs for all species combined differed by no more than 1 doubling dilution for >90% of the tests with 10 of the 12 drugs. For each of the individual species, on-scale MICs were also essentially identical (±1 dilution step). Trimethoprim-sulfamethoxazole was one of the two exceptions; i.e., MICs tended to be 1 or 2 dilutions lower in LHB than in HTM. Presumably, the thymidine phosphorylase added to our HTM broth was not sufficient to completely inactivate the trimethoprim or sulfonamide antagonists in the medium. The other exception involved the macrolides tested against *H. influenzae* strains. Those MICs tended to be about 1 dilution step higher in LHB and lower in HTM. Similar medium-related differences with clarithromycin and erythromycin have been reported (2). For the other species, the majority of MICs were off scale (MIC, ≤0.25 μg/ml) in both media, and consequently, medium-related differences could not be documented. For each of the four species and 12 antimicrobial agents, MICs for 50 and 90% of isolates tested (MIC_{50}s and MIC_{90}s, respectively) generated in the two media were the same or differed by only one twofold concentration (data not shown).

More than 3,000 clinical isolates have subsequently been tested in microdilution trays that were prepared with HTM broth. Approximately 5% of those strains initially failed to grow in HTM, but the majority grew satisfactorily when they were retested in the same medium. Fifteen of 3,166 strains grew only in trays containing LHB (five *H. influenzae*, three *S. pneumoniae*, four *S. pyogenes*, and three *M. catarrhalis*). We concluded that the initial growth failures were due to technical problems other than nutritive deficiencies in the HTM broth. Because HTM is a clear medium, the endpoints were believed to be easier to identify, and for that reason we elected to dilute all 12 study drugs in HTM broth for the present comparative study. This report describes only data for the 3,151 isolates that grew in the HTM broth.

Bacterial isolates. The microorganisms that were contributed by the 19 study sites are described in Table 2. β-Lactamase production was documented for 30% of 890 *H. influenzae* isolates (13 to 41% in different medical centers). Among the 619 β-lactamase-negative *H. influenzae* isolates, 613 were susceptible to ampicillin, 5 strains were intermediate in susceptibility, and 1 strain was resistant to ampicillin (MIC, 4.0 μg/ml). The six β-lactamase-negative strains that were not susceptible to ampicillin were obtained from five different institutions. Among the 698 isolates of *M. catarrhalis*, 8% failed to produce β-lactamase: all but one institution contributed at least one such strain. Among the 799 *S. pneumoniae* isolates, 622 (78%) were penicillin susceptible (MIC, ≤0.06 μg/ml), 119 (15%) were intermediate in susceptibility (MIC, 0.12 to 1.0 μg/ml), and 58 (7%) were resistant (MIC, ≥2.0 μg/ml). Fourteen of 19 medical centers each contributed one or more penicillin-resistant strains, but they were particularly prevalent (15 of 46 isolates) among pneumococci from one medical center in New York City. The supplementary strains provided by the Clinical Microbiology Institute did not contain outliers that could skew the statistics, and thus, those strains were included in the analysis.

TABLE 2. Description of respiratory tract isolates contributed for evaluation

City and state	No. of isolates contributed by each medical center							
	H. influenzae[a]		*S. pneumoniae*[b]			*M. catarrhalis*[a]		*S. pyogenes*
	β-LacNeg	β-LacPos	PenS	PenI	PenR	β-LacNeg	β-LacPos	
Ann Arbor, Mich.	32[c]	15	43	8	1	2	50	50
Chicago, Ill.	33	5	23	9	0	2	48	49
Decatur, Ga.	29	21	41	9	6	0	30	59
Durham, N.C.	35[d]	15	26	7	6	2	33	50
Jacksonville, Fla.	32	16	33	15	1	2	28	48
Los Angeles, Calif.	34[e]	14	19	3	5	3	27	50
Memphis, Tenn.	38	17	35	12	3	2	48	32
Nashville, Tenn.	29	6	5	7	2	2	6	35
New Haven, Conn.	35	17	47	4	0	8	42	50
New York, N.Y.	31	12	29	2	15	9	42	43
Philadelphia, Pa.	40	10	29	5	0	3	38	50
Phoenix, Ariz.	39[e]	16	39	6	4	4	50	46
Portland, Oreg.	36	19	21	1	0	2	32	17
Salt Lake City, Utah	15	2	0	0	0	0	0	50
San Antonio, Tex.	34	12	34	10	4	1	28	49
Seattle, Wash.	33[e]	16	40	7	3	1	23	11
Wichita, Kans.	34	16	33	2	1	6	44	17
Worcester, Mass.	27	19	49	2	2	2	35	49
U.S. clinical study sites[f]	33	23	76	10	5	2	41	9
All laboratories	619	271	622	119	58	53	645	764

[a] β-LacNeg and β-LacPos, β-lactamase negative and positive, respectively, by a nitrocefin spot test.
[b] PenS, PenI, and PenR, penicillin susceptible, intermediate, or resistant respectively; MICs were ≤0.06, 0.12 to 1.0, μ and ≥2.0 μg/ml, respectively, as determined in Mueller-Hinton broth with LHB.
[c] Includes one strain resistant to ampicillin (MIC, 2.0 μg/ml when tested in HTM broth).
[d] Includes two strains with intermediate susceptibilities to ampicillin (MIC, 1.0 μg/ml when tested in HTM broth).
[e] Includes one strain with intermediate susceptibility to ampicillin (MIC, 1.0 μg/ml when tested in HTM broth).
[f] Selected isolates obtained from 12 additional institutions within the United States.

Relative potencies of 12 agents. Table 3 summarizes the in vitro studies by listing MIC_{50}s and MIC_{90}s for isolates within each subgroup. Cefixime and ciprofloxacin were particularly potent against isolates of *H. influenzae*, irrespective of β-lactamase production. Cefaclor, loracarbef, and cefprozil were less potent against *H. influenzae*. For penicillin-resistant *S. pneumoniae*, the MICs of all five cephem drugs were elevated. Some, but not all, strains with intermediate susceptibilities also showed decreased susceptibilities to the cephalosporins, i.e., MIC_{90}s were elevated but MIC_{50}s were essentially the same as those for penicillin-susceptible strains. Cefuroxime, cefprozil, and cefixime were particularly active against penicillin-susceptible pneumococci. Trimethoprim-sulfamethoxazole was also quite active, but resistant strains did occur, especially among penicillin-resistant *S. pneumoniae*. Resistance to the macrolides and azalide occurred in 1% of *S. pyogenes* strains but was more common among penicillin-resistant *S. pneumoniae* (MIC_{90}, ≥16 μg/ml versus ≤0.25 μg/ml for penicillin-susceptible strains). Ciprofloxacin was very potent against *H. influenzae* and *M. catarrhalis* isolates, but it had relatively poor activity against the two *Streptococcus* species.

Prevalence of susceptibility. The percentage of strains susceptible to each of the study drugs is described in Table 4. For these calculations we used the MIC breakpoints that have been approved by NCCLS (14), except that ampicillin breakpoints were used for amoxicillin tests because there are no interpretive criteria for the latter. Appropriate MIC breakpoints for orally administered cephalosporins versus *S. pneumoniae* have yet to be established, and consequently, data for *S. pneumoniae* are not included in Table 4. The orally administered cephalosporins, amoxicillin, and amoxicillin-clavulanic acid all displayed decreased levels of activity against penicillin-resistant pneumococci (Table 3). Some investigators believe that all penicillin-intermediate and -resistant pneumococci should be considered resistant to all other β-lactams, and thus, only penicillin needs to be tested routinely. For similar reasons, the NCCLS documents now offer no interpretive criteria for tests of *M. catarrhalis* since a β-lactamase test is all that is needed in the clinical laboratory. For different reasons, specific criteria for interpreting the MICs for *S. pyogenes* isolates have yet to be defined. To summarize the data obtained for the latter two species, we elected to apply the MIC breakpoints listed for species that can be tested in cation-adjusted Mueller-Hinton broth without additional supplements. We are unaware of any reason to believe that those breakpoints should not be used to interpret tests with those two species, and that should be true regardless of how the broth medium was supplemented to enable growth of *M. catarrhalis* and *S. pyogenes* isolates.

DISCUSSION

Among those antimicrobial agents that are candidates for empiric therapy for community-acquired respiratory infections, the physician must select from a broad range of useful compounds. The ideal agent is one to which no known strains are resistant. Unfortunately, there is no perfect agent that fulfills such a criterion. A great deal of attention has been paid to the emergence of antibiotic-resistant strains among different species. Throughout the world, the prevalence of β-lactamase-producing *H. influenzae* is now great enough to rule out the empiric use of drugs that are susceptible to inactivation by these enzymes. Among the 12 drugs that we studied, only amoxicillin would be ruled out because of its β-lactamase susceptibility. The activities of cefaclor, loracarbef, and cefpro-

TABLE 3. In vitro activities of 12 orally administered antimicrobial agents against bacterial pathogens from U.S. medical centers isolated during 1992 and 1993

MIC group and antimicrobial agent	MIC (μg/ml) for strains within each subgroup[a]							
	H. influenzae[b]		*S. pneumoniae*[c]			*M. catarrhalis*[b]		*S. pyogenes* (764)
	β-LacNeg (619)[d]	β-LacPos (271)	PenS (622)	PenI (119)	PenR (58)	β-LacNeg (53)	β-LacPos (645)	
MIC_{50}								
Cefixime	≤0.06	≤0.06	0.12	0.5	8.0	≤0.06	0.25	≤0.06
Cefaclor	2.0	4.0	0.5	1.0	>8.0	0.25	2.0	≤0.06
Loracarbef	2.0	2.0	1.0	2.0	64	≤0.5	4.0	≤0.5
Cefuroxime	1.0	1.0	≤0.5	≤0.5	4.0	≤0.5	2.0	≤0.5
Cefprozil	2.0	4.0	≤0.5	≤0.5	8.0	≤0.5	4.0	≤0.5
Ciprofloxacin	≤0.03	≤0.03	1.0	0.5	0.5	≤0.03	≤0.03	0.5
Amoxicillin	0.5	>16	≤0.12	≤0.12	1.0	≤0.12	16	≤0.12
Amoxicillin-clavulanic acid[e]	0.5	1.0	≤0.12	≤0.12	1.0	≤0.12	0.25	≤0.12
Trimethoprim-sulfamethoxazole[f]	≤0.12	≤0.12	0.5	2.0	>4.0	0.5	1.0	0.25
Erythromycin	4.0	4.0	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25
Clarithromycin	8.0	8.0	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25
Azithromycin	1.0	1.0	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25
MIC_{90}								
Cefixime	≤0.06	≤0.06	0.25	8.0	>8.0	0.12	0.5	0.12
Cefaclor	8.0	>8.0	0.5	8.0	>8.0	1.0	4.0	0.12
Loracarbef	4.0	32	1.0	32	>64	1.0	16	≤0.5
Cefuroxime	2.0	2.0	≤0.5	2.0	16	1.0	4.0	≤0.5
Cefprozil	8.0	32	≤0.5	2.0	16	1.0	8.0	≤0.5
Ciprofloxacin	≤0.03	≤0.03	2.0	2.0	2.0	0.06	0.06	1.0
Amoxicillin	1.0	>16	≤0.12	0.5	4.0	0.25	>16	≤0.12
Amoxicillin-clavulanic acid[e]	1.0	2.0	≤0.12	0.5	4.0	0.25	0.5	≤0.12
Trimethoprim-sulfamethoxazol[f]	0.25	2.0	2.0	>4.0	>4.0	1.0	1.0	1.0
Erythromycin	16	8.0	≤0.25	4.0	32	0.5	0.5	≤0.25
Clarithromycin	16	16	≤0.25	2.0	16	0.5	≤0.25	≤0.25
Azithromycin	2.0	2.0	≤0.25	8.0	>32	≤0.25	≤0.25	≤0.25

[a] The number of isolates in each subgroup is designated in parentheses.
[b] β-LacNeg and β-LacPos, β-lactamase negative and positive, respectively.
[c] PenS, PenI, and PenR, penicillin susceptible, intermediate, and resistant, respectively.
[d] Includes 613 ampicillin-susceptible strains, 5 ampicillin-intermediate strains (MIC, 1.0 μg/ml), and 1 ampicillin-resistant stain (MIC, 2.0 μg/ml).
[e] Amoxicillin plus clavulanic acid at a 2:1 ratio; results are expressed as the concentration of amoxicillin in the combination.
[f] Trimethoprim plus sulfamethoxazole at a 1:19 ratio; results are expressed as the concentration of trimethoprim in the combination.

zil appear to be somewhat compromised against β-lactamase-producing strains of *H. influenzae*; the clinical relevance of that observation is unknown. Cefixime was the most potent cephem studied against *H. influenzae* (MIC_{90}, ≤0.06 μg/ml, versus 2.0 to 32 μg/ml for other cephems). That observation is consistent with previously published data (4). Ampicillin-resistant, β-lactamase-negative strains of *H. influenzae* are occasionally seen in the United States (6–8, 11, 15); they are usually considered resistant to amoxicillin-clavulanic acid and all other β-lactams, including the cephem compounds that we studied (3).

S. pneumoniae strains with altered penicillin-binding proteins and a subsequent decrease in their susceptibilities to penicillin G have become a worldwide problem (1). Penicillin-resistant or relatively resistant (intermediate) strains also tend to be relatively resistant to other β-lactams (13). There is a continuum of increasing penicillin MICs, and the breakpoints separating the susceptible, intermediate, and resistant categories are entirely arbitrary. Furthermore, cross-resistance to other β-lactams also presents a continuum of increasing MICs. It is difficult to determine how much the MICs can increase before one can expect clinical failures when treating respiratory tract infections. Penicillin-resistant *S. pneumoniae* probably should be assumed to be resistant to the cephalosporins and other β-lactam drugs. Strains with intermediate susceptibilities to penicillin do not show such predictable cross-resistance. The oxacillin disk test is a simple screening test that is widely used in most clinical laboratories. It does not distinguish between resistant and relatively resistant (intermediate) strains. Furthermore, some of our penicillin-susceptible strains were categorized as being resistant by this screening procedure. Approximately 25% of our pneumococci were resistant by the oxacillin disk test (8 to 39% in different medical centers). However, 11% of those strains were actually susceptible to penicillin (MIC, ≤0.06 μg/ml), and 60% of the oxacillin-resistant strains were only relatively resistant to penicillin (MIC, 0.12 to 1.0 μg/ml). Strains that are resistant by the oxacillin disk test are not necessarily resistant to the cephalosporins.

Because of cross-resistance to different β-lactams, other classes of drugs could have a significant advantage in that they might be active against β-lactamase-producing *H. influenzae* and penicillin-resistant *S. pneumoniae*. The fluoroquinolone included in the present study (ciprofloxacin) was very potent against *H. influenzae* and *M. catarrhalis* isolates but showed relatively poor activity against the gram-positive species. For *S. pneumoniae* and *S. pyogenes*, the MICs of ciprofloxacin were often near the breakpoints, and a significant number of strains fell into the intermediate category. High-level resistance seems to be very uncommon; i.e., MICs of >4.0 μg/ml occurred for only two *S. pneumoniae* and two *S. pyogenes* isolates.

TABLE 4. Effectiveness of 12 different orally administered antimicrobial agents as the proportion of strains susceptible to breakpoint concentrations[a]

Antimicrobial agent, MIC breakpoint (μg/ml)	% Strains susceptible to designated concentrations				
	H. influenzae[b]		*M. catarrhalis*[b]		*S. pyogenes* (764)
	β-LacNeg (619)[c]	β-LacPos (271)	β-LacNeg (53)	β-LacPos (645)	
Cefixime, ≤1.0	>99	100	100	>99	>99
Cefaclor, ≤8.0	97	79	100	>99	100
Loracarbef, ≤8.0	97	81	100	87	100
Cefuroxime, ≤4.0	98	98	93	97	100
Cefprozil, ≤8.0	95	75	100	91	100
Ciprofloxacin, ≤1.0	100	100	100	>99	92
Amoxicillin, ≤0.12[d]	95	<1	91	<1	100
Amoxicillin-clavulanic acid, ≤8.0/4.0[e]	>99	98	100	100	100
Trimethoprim-sulfamethoxazole, ≤2.0/38[f]	96	89	96	>99	97
Erythromycin, ≤0.5	2	<1	91	97	97
Clarithromycin, ≤2.0[g]	82	73	91	>99	99
Azithromycin, ≤2.0[g]	>99	>99	92	>99	97

[a] Data for *S. pneumoniae* are not included because specific MIC breakpoints for testing *S. pneumoniae* have not yet been established for most of the drugs listed.
[b] β-LacNeg and β-LacPos, β-lactamase negative and positive, respectively.
[c] The number of isolates in each subgroup is designated in parentheses.
[d] Amoxicillin breakpoints are those defined for ampicillin, i.e., ≤1.0 μg/ml for *H. influenzae*, ≤0.25 %g/ml for *M. catarrahlis*, and ≤0.12 μg/ml for *S. pyogenes*.
[e] Amoxicillin plus clavulanic acid at a 2:1 ratio; for testing *H. influenzae* the breakpoint was ≤4.0/2.0 μg/ml.
[f] Trimethoprim plus sulfamethoxazole at a 1:19 ratio; for testing *H. influenzae* the breakpoint was ≤0.5/4.5 μg/ml.
[g] When testing *H. influenza*, breakpoints are ≤8.0 μg/ml for clarithromycin and ≤4.0 μg/ml for azithromycin.

Trimethoprim-sulfamethoxazole is another option that must be considered. Unfortunately, only 21 to 60% of pneumococci from different centers were susceptible to trimethoprim-sulfamethoxazole. That drug combination might have appeared more effective if we had elected to use a broth medium with LHB rather than HTM broth (Table 1). The true prevalence of trimethoprim-sulfamethoxazole resistance in different centers is difficult to define on the basis of our in vitro data, but it is reasonable to assume that there will be a considerable amount of variation between medical centers.

The macrolide and azalide drugs present another option. For *H. influenzae* erythromycin and clarithromycin MICs were very similar, but the azalide azithromycin was two to eight times more active. Both clarithromycin and azithromycin have been approved for use in the United States in the treatment of selected respiratory tract infections caused by *H. influenzae*. Unfortunately, erythromycin-resistant gram-positive cocci are also resistant to clarithromycin and azithromycin. Among the *S. pneumoniae* isolates, the prevalence of erythromycin resistance was a disconcerting 5%. For *S. pyogenes* and *M. catarrhalis*, that figure was only 1%. Since both drugs are effective only against erythromycin-susceptible strains, the prevalence of erythromycin-resistant pneumococci (5%) is a matter of concern.

All of the orally administered antimicrobial agents that we studied are potentially useful for the empiric therapy of community-acquired respiratory tract infections. However, they all have deficiencies in their spectra of activity. The magnitudes of these deficiencies can be assessed by the type of survey described here. The prevalence of resistance can vary from time to time and from one institution to another. For that reason, well-controlled periodic surveys involving multiple institutions and uniform methodologies are needed in order to monitor changes that may take place over long periods of time.

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