CLINICAL MICROBIOLOGY REVIEWS, Apr. 1990, p. 171–196
0893-8512/90/020171-26$02.00/0

Vol. 3, No. 2

Pneumococcal Resistance to Antibiotics†

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INTRODUCTION

Bacteremic pneumococcal pneumonia carried a mortality of 77% in the preantibiotic era (258). The residual mortality of 28% for bacteremic pneumococcal disease in the 1950s and 1960s (14) is similar to that reported in the 1970s (197). This mortality is largely due to deaths in the elderly and in patients with underlying diseases such as renal and liver failure, chronic obstructive pulmonary disease, and diabetes mellitus (197). From the 1960s, when pneumococcal susceptibility to penicillin and tetracycline was considered invariable (75), to the 1970s, when resistant strains were occasional (197) and the possibility of worldwide spread of the resistant strains was considered extremely remote (77),

† I dedicate this review to Hendrick Koornhof of the University of the Witwatersrand, Johannesburg, South Africa, whose interest, enthusiasm, and knowledge have inspired me to pursue further the phenomenon of antibiotic resistance in pneumococci.

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physicians and microbiologists in the 1990s must face the increasing challenge of resistant pneumococci that became widespread in the 1980s.

HISTORICAL PERSPECTIVE

Optochin Resistance

The history of pneumococcal resistance to antimicrobial agents extends back to the use in the early part of the 20th century of optochin (ethylhydrocupreine) to treat pneumococcal infections. Optochin-resistant pneumococci were documented as early as 1912, following optochin therapy of experimentally infected mice (195). This may have been the first report of in vivo development of bacterial resistance to an antimicrobial agent (11). Acquired pneumococcal resistance to optochin during therapy of patients was documented in 1917 (192). Subsequent clinical use of optochin was limited by its severe side effects (4.5% of a series of patients with lobar pneumonia treated with optochin had loss of vision) (192).

Sulfonamide Resistance

Pneumococcal resistance to the then newly introduced sulfonamide 2-sulfanilylaminopyridene (sulfapyridene or M+B 693) was correlated in 1939 with the inability of the drug to cure experimental infection in mice, compared with the efficacy of the drug against susceptible strains (192). Serial passage of organisms through mice treated with sulfapyridene allowed the pneumococcus to become tolerant to the drug and reduced the required lethal dose of organisms (192). The development of resistance during therapy was documented that year in a human case of pneumococcal meningitis (227). Cultures taken 3 days apart, before and after the start of therapy with sulfapyridene, were compared. The second isolate showed tolerance to the drug, and the patient died despite a documented concentration of 33 mg of drug per liter in the cerebrospinal fluid (CSF). Sulfapyridine resistance was maintained in pneumococci despite 200 passages through normal mice (234).

Sulfadiazine resistance developing during therapy for pneumonia was reported in 1943 (79), and spread of the resistant strain to a second patient, unresponsive to sulfadiazine, was identified (79). The resistant strains could still be cultured from the patients' sputa 2 months after the onset of their illnesses (79).

NOTE ON NOMENCLATURE AND CRITERIA OF RESISTANCE

The original description of penicillin resistance was a penicillin MIC of 0.25 mg/liter (107), and the term penicillin resistant is most commonly applied in the literature to all strains resistant to ≥0.1 mg of penicillin per liter. Reservation of the term penicillin resistant for strains for which MICs are ≥2 mg/liter is likely to cause confusion with much existing data in the literature, including the first strain described as resistant (107). The clinical relevance of intermediate resistance to the management of meningitis and the potential importance of the distinction between intermediate and high-level resistance in the management of all pneumococcal infections demand the retention of the two subdivisions of penicillin-resistant strains. The terms intermediately resistant for pneumococci for which penicillin MICs are between 0.1 and 1.0 mg/liter inclusively and highly resistant for strains for which the MIC is ≥2 mg/liter may be desirable. The nomenclature of intermediate resistance is confused. Intermediate resistance is called, within only the confines of the titles in the literature cited for this paper, "partial resistance" (10; A. J. Parkinson, W. L. Heyward, R. R. Facklam, and M. J. Oxtoby, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 710, 1986), "penicillin insensitive" (3, 89, 149, 214), "relative resistance" (21, 121, 123, 125, 228; B. A. Lauer, L. B. Reller, H. A. Masters, Z. T. Johnson, and W. Kotasek, 25th ICAAC, abstr. no. 407, 1985), "increased resistance" (57, 211), "moderately resistant" (84), "relatively insensitive" (108), "reduced susceptibility" (137), "decreased susceptibility" (200), "decreased sensitivity" (199), and "intermediate resistance" (275). While the choice of a name is arbitrary, the terms intermediately and highly resistant fit the biochemical and genetic concepts of a stepwise increase in penicillin resistance (238, 259, 283) and accommodate the concept of low-level resistance, shown also to correlate with changes in affinity of penicillin-binding proteins (103; L. McDougal and C. Thornsberry, 29th ICAAC, abstr. no. 1289, 1989).

There is some diversity in the literature on criteria for resistance to other antibiotics (Tables 1, 2, 3, and 4). In the absence of data to determine the exact, clinically relevant criteria for resistance to these agents, the criterion for resistance to each antibiotic should be standardized to allow the comparison of data from different countries and documentation of the change of pneumococcal susceptibility over time in individual populations. Most studies (Table 1) use as the criterion for resistance the National Committee for Clinical Laboratory Standards (NCCLS) criterion for moderate susceptibility to erythromycin of ≥1.0 mg/liter (201). As there are <1% of strains for which the MIC is ≥1 mg/liter, in countries where resistance is rare (Table 1), this is likely to be both a sensitive and a specific criterion. The MIC criterion for resistance to trimethoprim-sulfamethoxazole (TMP-SMZ) is variable in published studies (Table 2). The NCCLS (201) suggests an interpretive standard of ≥4/76 mg/liter (MIC of trimethoprim/MIC of sulfamethoxazole) for resistance. They go on to say, however, that systemic infections should be treated with TMP-SMZ only when the MIC is ≤0.5/9.5 mg/liter. This suggests a criterion for resistance in studies with TMP-SMZ of ≥1/19 mg of TMP/SMZ per liter. As <1% of strains met this criterion in a large series (21) in which TMP-SMZ resistance was rare, this too appears to be a reasonable choice of standard. There is no reason not to accept the most often used criteria for tetracycline resistance (≥8 mg/liter) and for rifampin resistance (≥2 mg/liter). The criterion of ≥16 mg/liter is used for moderate susceptibility to chloramphenicol cited by NCCLS, although a greater number of studies have used the criterion of ≥8 mg/liter (cited by the NCCLS for resistance in treating *Haemophilus influenzae*), which cutoff is probably prudent for the use of chloramphenicol in the treatment of pneumococcal meningitis. Although the exact criteria for pneumococcal resistance to agents other than penicillin are somewhat arbitrary, suggested MIC criteria for the standardization of reporting antimicrobial resistance in pneumococci are as follows: penicillin (intermediate), ≥0.1; penicillin (high level), ≥2.0; erythromycin, ≥1.0; TMP-SMZ, ≥1/19; tetracycline ≥8.0; chloramphenicol, ≥8.0; and rifampin, ≥2.0 mg/liter. The range of MICs of other

TABLE 1. Erythromycin-resistant pneumococci

Country	Yr	No. resistant	No. tested	% Resistant	Criterion[a]	Type of isolates[b]	Reference
North America							
United States	1979–1981	5	80	6.3	≥1.0	Clinical	252
United States	1979–1984	27	3,400	0.8	≥1.0	Clinical	Oxtoby et al., 25th ICAAC
United States	1979–1987	17	5,479	0.3	≥8.0	Clinical	Spika et al., 29th ICAAC
Canada	1984–1986	2	468	0.4	≥1.0	Clinical	131
Australia/New Zealand							
New Zealand	1981–1986	1	233	0.4	≥1.0	Clinical	112
Europe							
Spain	1978–1981	5	200	2.5	≥1.0	Clinical	167
Spain	1984–1986	2	147	1.7	≥8.0	Blood	209
Spain	1984–1986	4	91	4.4	≥1.0	Clinical	205
Spain	1987	9	159	5.7	≥1.0	Carriers	215
Spain	1982–1989	36	456	7.9	≥8.0	Clinical	261
France	1970–1979	33	1,487	2.2	≥1.0	Clinical	1
France	1980–1986	186	1,266	14.7	≥1.0	Clinical	1
Italy	1980–1981	1	200	0.5	≥1.0	Mixed	74
Belgium	1980–1983	1	89	1.1	≥2.0	Clinical	267
Belgium	1988	6	47	12.8	≥2.0	Clinical	267
Switzerland	1984–1985	2	133	1.5	≥8.0	Clinical	280
Poland	1970	3	115	2.6	≥1.0	Mixed	50
Middle East							
Israel	1983	3	229	1.3	≥2.0	Clinical	187
Saudi Arabia	1985–1986	6	208	2.9	Stokes	Clinical	65
Asia							
Malaysia	1984–1985	2	248	0.8	NS	URT	41
Africa							
South Africa	1977	6	481	1.2	≥8.0	Carriers	152
South Africa	1977	124	227	54.6	>8.0	Hospital carriers	128
South Africa	1979–1982	19	2,355	0.8	≥1.0	Blood + CSF	142
South Africa	1983	241	829	29.1	≥1.0	Hospital carriers	204
South Africa	1983–1986	69	3,568	1.9	≥1.0	Blood + CSF	142
South Africa	1986	20	113	17.7	≥1.0	Carriers	145

[a] Stokes, Stokes disk diffusion method; NS, not stated.
[b] Carriers, Nasopharyngeal strains from children in the community; hospital carriers, nasopharyngeal strains from hospitalized children; mixed, nasopharyngeal and clinical strains; URT, strains from the upper respiratory tract.

agents used to treat pneumococcal infections are discussed later.

PREVALENCE AND DISTRIBUTION OF RESISTANT PNEUMOCOCCI

Penicillin Resistance

Laboratory mutants of pneumococci resistant to penicillin were selected as early as the 1940s (67, 184). It was 20 years, however, before the first clinical isolate with reduced susceptibility to penicillin was reported from Boston, Mass. (141). Two strains for which penicillin MICs were 0.1 and 0.2 mg/liter were identified among 200 clinical isolates, but the significance of the finding was missed by the authors and no clinical data were given, probably as the overall susceptibility data of the 200 strains were similar to previous data (141). The first penicillin-resistant strain reported as such was identified from a 25-year-old woman with hypogammaglobulinemia who had previously received penicillin, tetracycline, erythromycin, chloramphenicol, and sulfonamide therapy in Australia (107). This strain was intermediately resistant to penicillin (MIC, 0.6 mg/liter) and tetracycline (MIC, 5 mg/liter). Resistant strains were subsequently identified in New Guinea (109). In 1974, 12% of 518 New Guinean isolates were penicillin resistant (108), and by 1980 one-third of 57 strains were resistant to penicillin (89). The first case report of infection caused by penicillin-resistant pneumococci in the United States (MIC, 0.25 mg/liter) was of a patient with sickle cell disease who developed pneumococcal meningitis in 1974; the patient relapsed despite high-dose penicillin therapy (200).

From 1974 to 1984, the reported distribution of penicillin-resistant strains (MIC, ≥0.1 mg/liter) became worldwide (6). Foci with >10% of isolates resistant to penicillin were reported in New Guinea, Israel, Spain, Poland, and South Africa, as well as in New Mexico, Massachusetts, Oklahoma, Colorado, and Alaska in the United States (6). Comprehensive reviews covering penicillin resistance and the emergence of multiple resistance in South Africa appeared in 1980 (274) and 1981 (273), and a more recent review extends the documentation of penicillin resistance in studies up to 1984 (6). Published reports of penicillin resistance extending beyond 1984 are presented in Table 5, and these data as well as those mentioned in the text of this review and those reviewed previously (6) are illustrated in Fig. 1. Resistant isolates continue to be reported from Africa, Asia, Europe,

TABLE 2. TMP-SMZ-resistant pneumococci

Country	Yr	No. resistant	No. tested	% Resistant	Criterion[a]	Type of isolates[b]	Reference
North America							
United States	1978–1980	3	57	5.3	≥0.5/9.5	Carriers	113
United States	1979–1981	4	80	5.0	NS	Clinical	252
United States	1979–1984	32	3,400	0.9	≥1/19	Clinical	21
United States	1981–1985	13	113	11.5	≥0.5/9.5	Clinical	113
United States	1981–1985	60	153	39.2	≥0.5/9.5	Carriers	113
United States	1987–1988	22	487	4.5	≥4/76	Clinical	Jorgensen et al., 29th ICAAC
Australia/New Zealand							
New Zealand	1974	5	130	3.9	Stokes	Clinical	279
New Zealand	1981–1986	15	233	6.4	≥1/19	Clinical	112
Australia	1980–1981	25	230	10.9	≥1/19	Carriers	110
Europe							
Spain	1981–1983	72	191	37.7	≥2/38	Clinical	168
Spain	1984–1986	76	147	51.7	≥4/76	Blood	209
Spain	1984–1986	61	91	67.0	≥4/76	Clinical	205
Spain	1987	126	159	79.2	≥2/38	Carriers	215
Spain	1988	28	65	43.1	≥2/38	CSF	270
Italy	1980–1981	9	200	4.5	≥2/38	Mixed	74
Sweden	1981	3	180	1.7	≥1/19	Clinical	281
Switzerland	1984–1985	2	133	1.5	≥4/76	Clinical	280
Middle East							
Israel	1981–1982	20	229	8.7	≥2/38	Clinical	187
Saudi Arabia	1985–1986	135	208	64.9	Stokes	Clinical	65
Asia							
Pakistan	1989	26	79	32.9	≥4/76	Blood	Facklam et al., 29th ICAAC
Africa							
South Africa	1977	124	227	54.6	≥1/19	Hospital carriers	128
South Africa	1986	20	113	17.7	≥1/19	Carriers	145

[a] Stokes, Stokes disk diffusion method; NS, not stated.
[b] Carriers, Nasopharyngeal strains from children in the community; hospital carriers, nasopharyngeal strains from hospitalized children; mixed, nasopharyngeal and clinical strains.

North and South America, and Australia and New Zealand (Table 5).

In Africa, information about penicillin resistance outside of South Africa remains sparse. A single isolate from Nigeria of intermediate penicillin resistance was reported in 1977 (105), and although 10% of CSF isolates in Kenya were reported in 1981 to be resistant (272), most recently, only 2.6% of isolates from healthy childhood carriers in Zambia were resistant (78). More data are needed before the prevalence and trends of resistance in most of Africa can be determined. In South Africa, the prevalence of resistant strains among blood and CSF isolates has increased from 4.4% of 2,355 isolates between 1979 and 1982 to 7% of 3,568 isolates between 1983 and 1986 (142). However, at a pediatric hospital in Cape Town between 1983 and 1986, 19.6% of blood and CSF isolates were penicillin resistant (142). In a study of rural and urban children, 24.2% of pneumococci isolated from healthy childhood carriers were resistant to penicillin (147).

In Asia, among recent clinical isolates in Malaysia, 2% were reported to be penicillin resistant (41), including one isolate for which the MIC was 8 mg/liter. In Pakistan, 8.9% of blood isolates from children have recently been shown to be intermediately resistant to penicillin (R. Facklam, A. Ghafoor, C. Thornsberry, D. Granoff, and J. Spika, 29th ICAAC, abstr. no. 1288, 1989). More data are required from Asian countries, especially given the very high prevalence of resistant strains in New Guinea (89). Resistant strains increased from 0.9% in 1979 to 10.8% in 1982 in Jerusalem, Israel (4).

In Europe, Spain remains the focus of penicillin-resistant strains, both in childhood carriers (215) and in clinical isolates (209, 215). A recent report from Hungary (A. Marton, M. Guljas, and E. Meggyes, Abstr. 4th Eur. Congr. Clin. Microbiol., abstr. no. 548, 1989), however, revealed that >50% of pneumococcal isolates, including clinical strains, were resistant to penicillin. This high prevalence of resistance was attributed to the low cost and easy accessibility of antibiotics to the public in that country (Marton et al., Abstr. 4th Eur. Congr. Clin. Microbiol., 1989). Penicillin resistance remains at low levels in the rest of Europe, although no recent data are available from Poland, the site of a previous focus of resistant strains (50), or from other countries of Eastern Europe. In most of the United Kingdom, the trend of the prevalence is upward, with reports of 0.1% resistance in 1977 (119), 1.3% in 1981 (271), and 4% in 1987 (199). These studies, however, are based on different populations, and extrapolations may be inappropriate. Resistance appears to remain <1% in Northern Ireland (155).

The first published report on pneumococcal resistance in South America appeared in 1987 (142) and described clinical isolates from 1983 to 1985. Of 178 isolates, 39 (21.9%), were penicillin resistant; MICs were >1 mg/liter for 8 strains and 8 mg/liter for 2 strains. The prevalence of resistant pneumo-

TABLE 3. Tetracycline-resistant pneumococci

Country	Yr	No. resistant	No. tested	% Resistant	Criterion[a]	Type of isolates[b]	Reference
North America							
United States	1979–1984	131	3,400	3.9	≥8.0	Clinical	Oxtoby et al., 25th ICAAC
United States	1979–1987	157	5,479	2.9	≥16.0	Clinical	Spika et al., 29th ICAAC
United States	1987–1988	11	487	2.3	≥16.0	Clinical	Jorgensen et al., 29th ICAAC
Canada	1984–1986	8	468	1.7	≥8.0	Clinical	131
South America							
Chile	1983–1985	22	178	12.4	Disk	Clinical	135
Australia/New Zealand							
Australia	1963–1964	37	147	25.2	≥25.0	Hospital	106
Australia	1980–1981	2	291	0.7	≥8.0	Carriers	110
New Zealand	1974	9	130	6.9	Stokes	Clinical	279
New Zealand	1986–1987	9	233	3.9	≥8.0	Clinical	112
Europe							
Spain	1978–1981	144	200	72.0	≥8.0	Clinical	167
Spain	1984–1986	72	147	49.0	≥16.0	Blood	209
Spain	1984–1986	66	91	72.5	≥8.0	Clinical	205
Spain	1987	104	159	65.4	≥8.0	Carriers	215
England	1967–1968	29	161	18.0	≥25.0	Hospital	214
England	1967–1968	35	293	11.9	≥25/disk	Outpatients	214
Great Britain	1975	193	1,528	12.6	≥8.0	Clinical	2
Great Britain	1977	59	866	6.8	≥4.0	Clinical	119
N. Ireland	1986–1987	25	488	5.1	≥8.0	Clinical	155
France	1970–1979	499	1,487	33.6	≥4.0	Clinical	1
France	1980–1986	358	1,266	28.3	≥4.0	Clinical	1
Italy	1980–1981	70	200	35.0	≥4.0	Mixed	74
Switzerland	1984–1985	23	133	17.3	≥8.0	Clinical	280
Belgium	1987	61	379	16.1	Disk	Clinical	267
Federal Republic of Germany	1980–1986	15	124	12.1	≥2.0	Clinical	139
Sweden	1972	4	136	3.0	≥8.0	URT	136
Poland	1970	14	115	12.2	≥8.0	Mixed	50
Mixed East							
Saudi Arabia	1985–1986	52	208	25.0	Stokes	Clinical	65
Asia							
Hong Kong	1983	50	87	57.5	NS	NS	169
Malaysia	1984–1985	46	250	18.4	NS	URT	41
Pakistan	1989	66	79	83.5	≥16.0	Blood	Facklam et al., 29th ICAAC
Africa							
Nigeria	1978	10	50	20.0	≥50.0	Hospital carriers	105
South Africa	1977	8	481	1.7	≥16.0	Carriers	152
South Africa	1977	139	227	61.2	>12.0	Hospital carriers	128
South Africa	1979–1982	53	2,355	2.3	≥8.0	Blood, CSF	142
South Africa	1983	253	829	30.5	≥8.0	Hospital carriers	204
South Africa	1983–1986	100	3,568	2.8	≥8.0	Blood, CSF	142
South Africa	1986	20	113	17.7	≥8.0	Carriers	145

[a] Disk, Disk diffusion method; Stokes, Stokes disk diffusion method; NS, not stated.
[b] Carriers, Nasopharyngeal strains from children in the community; hospital carriers, nasopharyngeal stains from hospitalized carriers; mixed, nasopharyngeal and clinical strains; URT, strains from the upper respiratory tract; hospital, strains from hospitalized patients; outpatients, strains from hospital outpatients.

cocci in the rest of South America remains unknown and should be investigated promptly in light of the Chilean data.

Resistance in Canada remains low. The 3.7% resistance rate based on national surveillance in the United States during 1979 to 1984 increased to 5.1% when the data were extended to the end of 1987 (J. Spika, R. Facklam, M. Oxtoby, B. Plikaytis, and Pneumococcal Surveillance Working Group, 29th ICAAC, abstr. no. 1287, 1989). A separate study in 1987–1988 found 4.1% of pneumococci to be penicillin resistant (J. H. Jorgensen, L. A. Maher, A. W. Howell, J. S. Redding, and G. V. Doern, 29th ICAAC, abstr. no. 1286, 1989). Numerous foci of higher prevalence were reported up to 1984 (6). Within these areas, both an increase, in Denver, Colo., from 1% of blood isolates during 1975 to 1979 to 8% of blood or CSF isolates during 1981 (Lauer et al., 25th ICAAC), and a slight decrease, in Oklahoma City, Okla., from 15.5% resistance in 1977–1978 (228) to 12.2% resistance in 1984 (123), were reported. The only recent data published from an area of the United States of known high prevalence are from Alaska (10), where 5.3% of clinical isolates were resistant during 1980 to 1986, but a 1987

TABLE 4. Chloramphenicol-resistant pneumococci

Country	Yr	No. resistant	No. tested	% Resistant	Criterion[a]	Type of isolates[b]	Reference
North America							
United States	1979–1984	6	3,400	0.2	NS	Clinical	Oxtoby et al., 25th ICAAC
United States	1987–1988	6	487	1.2	≥32.0	Clinical	Jorgensen et al., 29th ICAAC
South America							
Chile	1983–1985	2	178	1.1	Disk	Clinical	135
Europe							
Spain	1978–1981	90	200	45.0	≥16.0	Clinical	167
Spain	1981–1983	56	166	33.7	≥16.0	Blood	209
Spain	1984–1986	55	147	37.4	≥16.0	Blood	209
Spain	1984–1986	43	91	47.3	≥16.0	Clinical	205
Spain	1987	68	159	42.8	≥16.0	Carriers	215
France	1970–1979	74	1,487	5.0	≥8.0	Clinical	1
France	1980–1986	58	1,266	4.6	≥8.0	Clinical	1
Italy	1980–1981	30	200	15.0	≥8.0	Mixed	74
Belgium	1987	6	379	1.6	Disk	Clinical	267
United Kingdom	1977	3	866	0.4	>8.0	Clinical	119
N. Ireland	1986–1987	24	488	4.9	≥8.0	Clinical	155
Sweden	1981	4	180	2.2	≥8.0	Clinical	281
Poland	1970	12	115	10.4	≥12.5	Mixed	50
Middle East							
Israel	1981–1982	2	229	0.9	≥8.0	Clinical	187
Saudi Arabia	1985–1986	6	208	2.9	Stokes	Clinical	65
Asia							
Pakistan	1989	29	79	36.7	≥8.0	Blood	Facklam et al., 29th ICAAC
Africa							
Nigeria	1978	7	50	14.0	≥10.0	Hospital carriers	105
South Africa	1977	13	481	2.7	≥16.0	Carriers	152
South Africa	1977	143	227	63.0	>25.0	Hospital carriers	128
South Africa	1979–1982	15	2,355	0.6	≥8.0	Blood + CSF	142
South Africa	1983	39	829	4.7	≥8.0	Hospital carriers	204
South Africa	1983–1986	27	3,568	0.8	≥8.0	Blood + CSF	142

[a] Disk, Disk diffusion method; Stokes, Stokes disk diffusion method; NS, not stated.
[b] Carriers, Nasopharyngeal strains from carriers in the community; hospital carriers, nasopharyngeal strains from hospitalized carriers; mixed, nasopharyngeal and clinical strains.

survey revealed 26% of 155 isolates from healthy carriers to be penicillin-resistant strains (10).

Erythromycin Resistance

Although six strains of pneumococci for which erythromycin MICs were ≥5 mg/liter were described as part of a report on the therapy of exacerbations of chronic bronchitis in 1964 (209), it was Dixon in Canada who brought the subject to the attention of the medical world in a letter to *The Lancet* 3 years later (56). Erythromycin resistance is linked to resistance to lincomycin and clindamycin in the vast majority of resistant strains. Sporadic case reports have documented erythromycin-resistant pneumococci in Australia (46) and the United States (40, 140, 185, 212). Erythromycin resistance has until recently remained at a low level in most parts of the world, and no erythromycin-resistant isolates were found among pneumococci isolated during studies in the 1970s and 1980s in the United Kingdom (119), Sweden (281), Hong Kong (169), Chile (135), Federal Republic of Germany (139), Northern Ireland (155), or Holland (66). The 6.3% resistance reported in the United States in 1979 to 1981 is likely to be an overestimate because of the bias towards penicillin-resistant strains in that sample (252), as there is a reported association between penicillin and erythromycin resistance in American strains of pneumococci (M. J. Oxtoby, G. A. Bolan, R. R. Facklam, B. D. Plikaytis, L. B. Rutledge, and C. V. Broome, 25th ICAAC, abstr. no. 408, 1985).

The highest prevalence of erythromycin-resistant strains was, until recently, found among strains showing multiple resistance, identified from carriers in hospitals in South Africa (128, 204). Erythromycin-resistant isolates from blood or CSF comprised 8.3% of strains identified from these sites at one hospital in 1983 (204), and although the overall prevalence in blood or CSF strains from South African hospitals is less (142), this prevalence is increasing (142) (Table 1). During the late 1980s, the identification in South Africa of a high prevalence of erythromycin-resistant strains associated with multiple resistance in pneumococci isolated from healthy children in the community (145, 146) led to the concern that resistance may increase in countries where the drug is widely used (143). The use of erythromycin in adults for therapy of community-acquired pneumonia is also increasing, not only because of its indication in penicillin-

TABLE 5. Penicillin-resistant pneumococci since 1984[a]

Country	Yr	No. resistant	No. tested	% Resistant	Criterion	Type of isolates[b]	Reference
North America							
Alaska	1980–1986	15	284	5.3	≥0.1	Clinical	10
Alaska	1987	40	155	26.0	Oxacillin disk	Hospital carriers	10
United States	1979–1987	280	5,479	5.1	≥0.1	Clinical	Spika et al., 29th ICAAC
United States	1987–1988	20	487	4.1	≥0.1	Clinical	Jorgensen et al., 29th ICAAC
Canada	1984–1986	6	468	1.3	≥0.1	Clinical	131
South America							
Chile	1983–1985	39	178	21.9	≥0.1	Clinical	135
Australia/New Zealand							
New Zealand	1981–1986	3	233	1.3	≥0.1	Clinical	112
Europe							
Spain	1984–1986	21	147	14.3	≥0.1	Blood	209
Spain	1984–1986	48	91	52.7	≥0.1	Clinical	205
Spain	1987	57	159	35.9	≥0.1	Carriers	215
France	1980–1986	4	1,266	0.3	≥0.1	Clinical	1
England	1987	4	100	4.0	≥0.1	Clinical	199
N. Ireland	1986–1987	4	488	0.8	≥0.1	Clinical	155
Switzerland	1984–1985	3	133	2.3	≥0.1	Clinical	280
Asia							
Malaysia	1984–1985	5	249	2.0	≥0.1	Clinical	41
Pakistan	1989	7	79	8.9	≥0.1	Blood	Facklam et al., 29th ICAAC
Africa							
Zambia	1986	1	39	2.6	≥0.1	Carriers	78
South Africa	1983–1986	249	3,568	7.0	≥0.1	Blood + CSF	142
South Africa	1986	73	302	24.2	≥0.1	Carriers	147

[a] Table includes studies that commenced prior to 1984, but concluded in 1985 or later.
[b] Carriers, Nasopharyngeal strains from carriers in the community; hospital carriers, nasopharyngeal strains and strains fron nonsterile sites in hospitalized patients.

allergic patients, but also because of an increased awareness of *Legionella pneumophila* infection (175). In a report published in 1988 on antimicrobial susceptibilities of the pneumococcus over 17 years at two Paris hospitals, erythromycin resistance had increased dramatically from 0% before 1976, with a mean of 2.2% during the 1970s (1) (Table 1), to a peak of 26% of clinical isolates in 1985 (1). Similarly, erythromycin-resistant pneumococci have increased from 1 to 6% during the 1980s in Belgium (286) and comprise 7.9% of clinical pneumococcal isolates in San Sebastian, Spain (261); also, four of nine pneumococcal blood isolates during 5 months of 1988 at St. Thomas' Hospital, London, England, were resistant to erythromycin (69).

All of the erythromycin-resistant strains isolated from childhood carriers in South Africa were multiply resistant (128, 145, 204). In South Africa, 91% of 69 erythromycin-resistant blood and CSF isolates from 1983 to 1986 also showed resistance to other agents, and of these multiply resistant strains, 44% were not penicillin resistant (142). Similarly, in France, 75.2% of 125 erythromcyin-resistant clinical strains isolated from 1983 to 1986 were multiply resistant and, of these, 97.9% were not penicillin resistant (1). Although, as mentioned above, an association exists between erythromycin resistance and relative penicillin resistance in the United States (Oxtoby et al., 25th ICAAC), this association is less clear in Spain (261). In addition, the absence of erythromycin resistance in strains from urban and rural South African childhood carriers, despite the 24.2% carriage of penicillin-resistant pneumococci in that group (147), suggests that penicillin and erythromycin resistance may have evolved in response to differing antibiotic pressures on the communities in these countries. This potential correlation between the prevalence of resistance and use of antibiotics remains, however, to be confirmed in an area where specific data on antibiotic use are available.

TMP-SMZ Resistance

TMP-SMZ resistance was identified in 1972 when an organism resistant to both drugs, alone and in combination, was found in the sputum of a 58-year-old woman with an acute exacerbation of chronic bronchitis (120). Sinusitis due to a resistant strain has been reported following TMP-SMZ prophylaxis (178), and both bacteremic pneumonia (146) and exacerbation of chronic bronchitis (191) caused by resistant strains have followed TMP-SMZ therapy. TMP-SMZ-resistant pneumococci are associated with multiply resistant strains isolated from both childhood carriers in hospitals (128) and healthy children in the community (145). Carriage rates in an American community increased from 5.3% in 1978 to 1980 to 39.2% in 1981 to 1985 (113).

TMP-SMZ-resistant strains in healthy carriers in Australia (110), South Africa (145), and Spain (215) comprised 10.9, 17.7, and 79.2%, respectively, of isolated pneumococci (Table 2). In Spain, an area of high endemic prevalence of penicillin-resistant pneumococci, 26% of the TMP-SMZ-resistant strains from clinical specimens and 45% from carriers were associated with penicillin resistance (215). In the similar situation of high-level prevalence of penicillin-resistant strains among childhood carriers in South Africa,

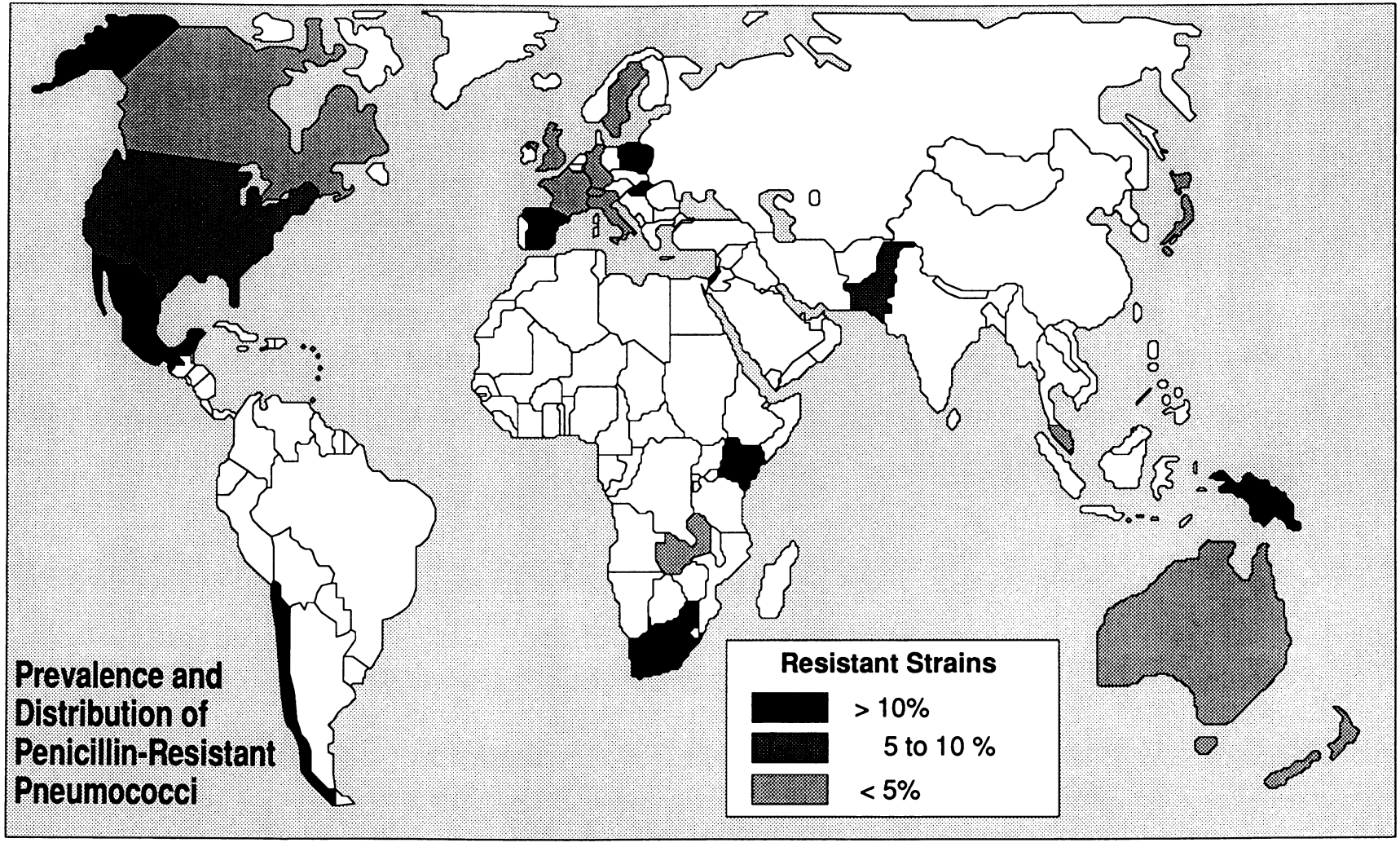

FIG. 1. Countries from which reports of penicillin-resistant pneumococci (MIC, ≥0.1 mg/liter) have been reviewed in the text, Table 1, and reference 6: Unshaded areas represent those countries from which data were not found. It is probable that foci of high prevalence of resistance exist within these areas. Less than 5% of strains are reported to be penicillin resistant in Canada, Switzerland, France, Federal Republic of Germany, Great Britain, Sweden, Italy, Zambia, Malaysia, Japan, Australia, and New Zealand; 5 to 10% in Pakistan and the United States, with foci >10% in Alaska and (not shown) in Colorado, Massachusetts, New Mexico, and Oklahoma; and foci >10% in Mexico, Chile, Spain, Hungary, Poland, South Africa, Kenya, Israel, and New Guinea.

42.5% of 40 penicillin-resistant strains were also resistant to TMP-SMZ (147).

Rates of TMP-SMZ resistance are higher in carriers than they are in clinical isolates, and the drug should not be used in areas of high prevalence of resistance (Table 2). Microbiologists should screen for TMP-SMZ resistance in all countries where the drug is widely used.

Tetracycline Resistance

The emergence in the 1960s of tetracycline resistance in pneumococci parallels the widespread use of this drug for the management of acute exacerbations of chronic bronchitis. At that time, it was thought that pneumococcal susceptibility to tetracycline was invariable (77). The first case of tetracycline resistance had already been reported from Australia, however, in February 1963 (68). The isolate (MIC, 11 mg/liter) was from the CSF of a 10-month-old child. The same year, tetracycline-resistant pneumococci were isolated from the sputa of four elderly patients with chronic bronchitis in the United Kingdom (222) and an outbreak of tetracycline-resistant pneumococci was detected in two general wards in Liverpool, United Kingdom (264). Five of the ten patients had received tetracycline prior to the isolation of the resistant strain, all failed to respond to tetracycline or relapsed after initial improvement, and one had a profuse growth of tetracycline-resistant pneumococci in the sputum 4 months after discharge from hospital (264). The first report from the United States emanated from the Rockefeller University in New York, N.Y., in 1964 (232), followed by a case report from Nashville, Tenn., in 1966 (233). A hospital outbreak involved 37 patients in Australia (106), and, in 1969, the further association of antecedent tetracycline therapy with tetracycline-resistant pneumococcal infection was made (19). The increasing resistance in pneumococci to tetracycline during the 1960s was noted by Percival et al., who found 23% of pneumococci isolated during 1969 at the Liverpool Royal Infirmary to be tetracycline resistant (214). The importance of this report was not only the increasing numbers of resistant isolates, but also the isolation of commuity-acquired strains.

It appears that pneumococcal resistance to tetracycline in Great Britain declined after that time (Table 3). This fall may reflect a reduction in the use of tetracycline in that country as tetracycline prescriptions in the United Kingdom dropped from 14.5 million in 1969 to 10.1 million in 1976 (119). While tetracycline resistance is found in <5% of clinical isolates from the United States, Canada, Australia, New Zealand, South Africa, and Sweden, there appears to be widespread resistance (≥±20% of pneumococci isolated from clinical isolates) in southern Europe as well as in Asia and the Middle East and in hospitalized carriers in Africa (Table 3).

Chloramphenicol Resistance

Chloramphenicol-resistant pneumococci were first identified in Poland in 1970 (50). Virtually all reported strains showing chloramphenicol resistance are resistant to other agents, usually including tetracycline and often including penicillin. To date, resistance to chloramphenicol has been reported only rarely outside of Europe (Table 4), and the drug therefore remains a useful agent for the treatment of pneumococcal meningitis in most parts of the world. Within Europe, Spain is the focus of resistance, where approximately 40% of pneumococcal strains are resistant to chloramphenicol. This percentage has remained constant since 1978 (Table 4). In South Africa, the percentage of pneumococci resistant to chloramphenicol among strains from hospitalized carriers has decreased from 63 to 4.7% (Table 4) and chloramphenicol resistance is rare in clinical isolates (142). The unpredicted and very high prevalence (36.7%) of chloramphenicol resistance recently found in pneumococcal blood isolates from children in Pakistan (Facklam et al., 29th ICAAC) highlights the necessity for individual countries to determine the pneumococcal susceptibility of clinical strains within their hospitals.

Rifampin Resistance

Rifampin has been used to treat chronic purulent bronchitis, though its use is not recommended because of the rapid emergence of resistant bacteria (42). It may have a role in the eradication from the nasopharynx of pneumococci resistant to other agents (128), although despite its use in combination with fusidic acid or erythromycin in an attempt to prevent the emergence of resistance, rifampin-resistant strains were detected (128). A single rifampin-resistant strain was identified in a series of 468 clinical isolates in Canada (131). In South Africa, however, where the pediatric population is widely exposed to the agent during therapy for tuberculosis, 90 blood or CSF isolates resistant to rifampin have been reported (142). Rifampin resistance is increasing in that population (142, 143), but the worldwide prevalence of rifampin resistance in pneumococci is unknown.

Multiple Resistance

Resistance to at least three different classes of antibiotics is defined as multiple resistance (128, 186). The emergence of multiple resistance in South Africa (128) might have been expected following the description of organisms resistant to penicillin and chloramphenicol in Durban in 1977 (7). The first multiply resistant strain was isolated from the purulent sputum of a child who, in July 1977, at Baragwanath Hospital, Johannesburg (8, 128), developed pneumonia following previous therapy with penicillin and cephalothin. The strain was resistant to penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol, and TMP-SMZ. At six hospitals in Johannesburg, 56.5% of 315 pneumococci isolated from carriers were multiply drug resistant, as were 15.5% of 180 strains from carriers at three hospitals in Durban, South Africa (152). The isolation of multiply resistant pneumococci received widespread editorial and leading article comment (76, 127; editorial, Lancet **ii**:803–804, 1977; editorial, S. Afr. Med. J. **55**:313–314, 1979). Although the prevalence of multiple drug resistance in pneumococcal isolates from hospitalized carriers in South Africa remains high (28.2% of 829 strains at Baragwanath Hospital, Johannesburg, in 1983 [259]), infections caused by these strains are rare (1.1% of 2,355 blood or CSF isolates from 1979 to 1982 and 2.0% of 3,568 isolates from 1983 to 1986 [142]).

Following the emergence of multiply resistant pneumococci in South Africa, the potential for spread of these strains was suggested by the isolation of a multiply resistant strain from a person in Britain, following a vacation in Spain (186). Spain was subsequently identified as an area with a high prevalence of antimicrobial agent-resistant pneumococci (80). Strains resistant to penicillin, tetracycline, and chloramphenicol were isolated from two patients in Britain late in 1981 (276); multiply resistant pneumococci, including erythromycin and TMP-SMZ resistance, were found in a carrier (86) and have more recently been isolated from the

eye of a neonate in Great Britain (213). A serogroup 23 penicillin-, tetracycline-, and chloramphenicol-resistant pneumococcus was recovered in 1988 from six hospitalized patients in Newcastle (88) and four patients in Bristol (191), United Kingdom, and multiply resistant strains have been reported to the Central Public Health Laboratory from 14 of 15 health regions in England and Wales and from Scotland and Ireland (85). While resistance in the United Kingdom to any one of the drugs penicillin, tetracycline, chloramphenicol, or erythromycin has increased from 5.1% of 681 strains in 1984 to 12.3% of 638 strains in October 1987, the number of strains reported resistant to three or more antibiotics has increased from 2 in 1984 to 40 in 1987 (85).

In Italy, 4 of 200 strains were resistant to three different classes of antibiotics in 1982 (74). In view of the occurrence of multiply resistant strains in Spain, Britain, and Italy, it is not surprising that multiply resistant pneumococci have also been found in France (1, 30, 62) and Belgium (267). Recently presented but unpublished data from Hungary are that of penicillin-resistant strains from that country (Marton et al., Abstr. 4th Eur. Congr. Clin. Microbiol.), >50% are also resistant to tetracycline, erythromycin, and TMP-SMZ, with one-third of these strains resistant to chloramphenicol. In Pakistan, 16.4% of pneumococcal blood isolates from children were resistant to chloramphenicol, tetracycline, and TMP-SMZ (Facklam et al., 29th ICAAC).

The epidemiology of multiply resistant pneumococci in South Africa and Spain was initially similar, i.e., associated with hospitalized children receiving antibiotics. Disease caused by resistant pneumococci in hospitalized adults, however, is now a significant problem in Spain (208), and the predominant group in which multiply resistant pneumococcal strains are found in Great Britain are elderly hospitalized patients exposed to multiple antibiotics for exacerbations of chronic bronchitis (88, 191).

The first community-acquired infection caused by multiply resistant pneumococci was documented in Denver, Colo., during 1981 (219). Strains were identified in Ohio (203) and Vermont (221) the following year. The first Canadian isolate was reported in 1983 (160). More recently, a cluster of serotype 19A multiply resistant pneumococci were found among adults in New York (241). Community-acquired disease in adults due to multiply resistant strains has now emerged in South Africa (72, 229) and Spain (208, 270).

Multiply resistant pneumococci, susceptible to penicillin, yet resistant to tetracycline, erythromycin, clindamycin, and TMP-SMZ, were isolated from 8% of 254 children attending day-care centers in Johannesburg, South Africa, and represented 18% of the pneumococcal strains isolated (145). These strains were not found in neighboring pediatric populations exposed to beta-lactams rather than to erythromycin or TMP-SMZ (147). Pneumococci with this pattern of resistance have caused bacteremia and meningitis (146, 147) and have been found in Italy (74), France (1), and Belgium (267).

Resistance to Other Agents

The MICs of various β-lactam antibiotics for penicillin-resistant strains are summarized in Table 6. Of currently available β-lactam agents, cefotaxime (21, 147, 159, 205, 265, 275), ceftriaxone (21, 147, 265), and imipenem (147, 159, 205, 265, 275) are the most active in vitro against penicillin-resistant strains. Penicillin-resistant strains (147) and multiply resistant strains, resistant (128) or susceptible (145) to penicillin, may show high-level resistance (MICs, ≥500 mg/liter) to streptomycin.

TABLE 6. MIC_{90} of β-lactam antibiotics against penicillin-resistant pneumococci

Antimicrobial agent	MIC_{90} (mg/liter)		Reference(s)
	Intermediately penicillin-resistant strains	High penicillin-resistant strains	
Ampicillin	0.5	8	125, 265
Oxacillin	4.0	31	275
Methicillin	NR[a]	64	159
Carbenicillin	32.0	64	265
Cefaclor	4.0–16.0	16	21, 125, 205
Cephalothin	1.0	8–31	205, 265, 275
Cefonicid	16.0	16	205
Cefoxitin	4.0–8.0	32–125	159, 265, 275
Cefoperazone	1.0–2.0	2–16	159, 265, 275
Cefamandole	0.5–2.0	8–31	21, 125, 159, 265, 275
Cefuroxime	0.25–0.44	NR	21, 125, 147
Cefpodoxime	2.0	2.0	9
Cefotaxime	0.125–1.0	1–4	21, 125, 147, 159, 205, 265, 275
Ceftriaxone	0.12–0.5	1	21, 125, 147, 265
Ceftazidime	3.2–32.0	64	21, 147, 265
Ticarcillin	64.0	128	265
Piperacillin	1.0	8–16	159, 265, 275
Mezlocillin	1.0–2.0	8–15	159, 265, 275
Azlocillin	1.0	16	275
Moxalactam	2.0–4.0	128	21, 159, 265
Imipenem	0.06–1.0	1–2	125, 147, 159, 205, 265, 275

[a] NR, Not recorded in the given references.

The quinolones norfloxacin, enoxacin, ofloxacin, and ciprofloxacin have MICs of 1 to 8 mg/liter against susceptible pneumococci (9,218) and MICs of 1 to 16 mg/liter for 90% (MIC_{90}) of highly penicillin-resistant strains (9, 87). For all of these agents, laboratory mutants having twice the initial MIC could be selected at a frequency of 1.02×10^{-7} cell divisions (218). Higher (four- and sixfold) increases in MIC could be obtained against norfloxacin (218). Even with twofold increases in MICs, the activity of these agents is likely to be marginal in terms of their achievable tissue concentrations, and they are unlikely to be useful against resistant pneumococci. The development of pneumococcal resistance during therapy with pefloxacin has been documented (176), associated with an increase in the modal MIC from 4 to 16 mg/liter.

There is little optimism for the use of the presently available quinolone agents as first-line agents for the management of pneumococcal pulmonary infections (52; R. Kuschner, F. Briones, B. E. Scully, and H. C. Neu, 29th ICAAC, abstr. no. 547, 1989; Y. Mouton, C. Beuscart, O. Leroy, B. Sivery, and Multicentric Group, 29th ICAAC, abstr. no. 550, 1989). Newer quinolone agents with enhanced activity against the pneumococcus have been synthesized. These include temafloxacin (MIC_{90}, 0.5 to 1 mg/liter) (E. Loza, J. Martinez-Beltran, F. Almaraz, R. Canton, A. Leon, and F. Baquero, 29th ICAAC, abstr. no. 106, 1989; P. Weber, G. Leturnier, A. Fremaux, P. Geslin, and Y. Boussougant, 29th ICAAC, abstr. no. 102, 1989) and tosufloxacin (MIC_{90}, 0.25 mg/liter) (Weber et al., 29th ICAAC). Temafloxacin was more effective than ciprofloxacin or ofloxacin in

the treatment of pneumococcal pneumonia in an experimental mouse model (E. Azoulay-Dupuis, J. P. Bedos, and J. J. Pocidalo, 29th ICAAC, abstr. no. 309, 1989), but the clinical use of these agents for pneumococcal infections in humans remains to be determined. The lipopeptide antibiotic daptomycin is active against susceptible and highly penicillin-resistant pneumococcal strains (MIC_{90}, 0.125 mg/liter), but the penetration of this drug into inflamed meninges has not yet been reported (9). The MIC_{90} of the spectinomycin analog trospectinomycin is 4 mg/liter for both susceptible and highly penicillin-resistant strains (9). No pneumococcal strains resistant to vancomycin or to teicoplanin have been reported to date.

FACTORS ASSOCIATED WITH CARRIAGE OF AND INFECTION WITH DRUG-RESISTANT PNEUMOCOCCI

Serogroups and Serotypes

Pneumococci may be serotyped by the Quellung reaction of the capsular polysaccharide (224). According to the Danish nomenclature, the serotyping system is based on the reactions to 48 antisera. Some antisera recognize a specific serotype, e.g., serotype 1, while other antisera recognize multiple serotypes within a serogroup, e.g., serogroup 6 antiserum which identifies both serotype 6A and 6B pneumococci.

High-level resistance to penicillin and multiple drug resistance. High-level penicillin resistance (MIC, ≥2.0 mg/liter) and multiple resistance traits are recognized worldwide among only a few pneumococcal serogroups. These same serogroups dominate the intermediately resistant strains, although a much larger range of serogroups is implicated in intermediate penicillin resistance.

High-level penicillin resistance and multiple resistance were first recognized only among serotype 6A and 19A pneumococci in hospitalized children in South Africa (134). Six years later, in the same hospital, multiply resistant strains were limited to serotypes 6A, 6B, and 19A (204). The outbreak in adults of multiply resistant pneumococci, also associated with penicillin MICs of ≥2 mg/liter in Brooklyn, N.Y., was similarly restricted to serotype 19A (241). The Denver, Colo., focus of multiply resistant strains in children at a day-care center were all serotype 6B (219). Multiple resistance in the absence of penicillin resistance, associated with day-care centers in South Africa, was restricted to serotypes 6B, 19F, and 14 (145). In a study of hospitalized children in Durban, South Africa, all resistant strains were of serogroup 6 or 19 (226). These groups together with serotype 14 accounted for 58% of isolates susceptible to penicillin in that pediatric hospitalized population (226). Together, serogroups 6 and 19 and serotype 14 account for 28 to 67% of pneumococcal bacteremias in children (17, 22, 27, 90, 92, 130, 240), but only 1 to 16% of pneumococcal bacteremias in adults (12, 197; S. W. Hayden-Smith, M.Sc. thesis, University of the Witwatersrand, Johannesburg, South Africa, 1981).

In Spain, highly resistant strains are found predominantly in serogroup 23, although resistant serogroups 6 and 15 and untyped strains have been found in Barcelona (218). Multiply resistant strains, including penicillin resistance, are predominantly serogroups 23 and 6 and serotype 14, although isolates of serotypes or groups 1, 5, 15, and 35 are reported (215). In France, the serogroups and serotypes most frequently associated with multiple resistance from 1970 to 1986 were serogroups 19 and 6 and serotype 14, with serogroup 23 a problem since 1978 (30). In England, the hospital outbreak of multiply resistant strains in Newcastle reported in 1987 was due to a serogroup 23 strain (88). The similar outbreak that year in Bristol was also due to a serogroup 23 strain (191), and a multiply resistant serogroup 6 strain has also been reported from Bristol (213).

In Israel, of 17 strains for which penicillin MICs were ≥1.0 mg/liter, 14 belonged to serotypes 6B, 14, and 19F (187). Of the remaining three strains, two were serotype 3 and one was serogroup 15. Strains for which the MIC was 1 mg/liter, usually defined as having intermediate resistance, were included with highly resistant strains in this study, and it is unclear whether the serotype 3 and serogroup 15 strains fell into that category. As the serotype 3 pneumococcus has been associated with increased virulence (55% mortality versus 22% mortality for all other serogroups combined [14]), a penicillin MIC of 1 mg/liter is of concern, regardless of the category to which it is assigned. Recently, a serotype 3 multiply resistant pneumococcus, susceptible to penicillin, was associated with a rapidly fatal infection in a 17-year-old schoolboy in South Africa (162). In contrast to the predominance of serogroup 6, 19, and 23 and serotype 14 multiply resistant pneumococci, serotype 31 strains, resistant to chloramphenicol, tetracycline, and TMP-SMZ, have recently been described from Pakistan (Facklam et al., 29th ICAAC).

Intermediate resistance to penicillin. Although the same limited number of serogroups that dominate multiple resistance and high-level penicillin resistance also are the commonest serogroups associated with intermediately penicillin-resistant strains, the spectrum of intermediate penicillin resistance has expanded to the extent that virtually all serogroups commonly isolated have now been found to manifest intermediate resistance to penicillin. The following serogroups (and serotypes in parentheses when they have been specified) have been recorded: 1, 2, 3, 4, 6 (A, B), 7 (F), 8, 9 (N), 10 (F), 11 (F, A), 13, 14, 15 (F, B, C), 16, 17 (F), 18 (F, C), 19 (F, A), 21, 22 (F), 23 (F, A), 24 (F), 33, 34, and 35 (F) (36, 57, 108, 123, 128, 137, 142, 161, 167, 187, 205, 257, 270, 273; Parkinson et al., 26th ICAAC). It should be emphasized, however, that despite this wide diversity of serogroups, only a few serogroups dominate a large percentage of all intermediately resistant strains, with some geographic differences in the exact percentages of those strains. For example, of 240 strains for which MICs of penicillin were ≥0.1 mg/liter in South Africa, isolated from 1979 to 1986, 97.6% belonged to serogroup 6 or 19 or to serotype 14, with only 6 strains identified in serotypes 1 and 4 or in serogroups 15 and 23 (142). In the United States, 27% of 132 serotype 19A strains received by the Centers for Disease Control were penicillin resistant, as were 9.4% of 553 serotype 14 strains, compared with 3.7% resistance in all serogroups combined (Oxtoby et al., 25th ICAAC).

Resistance to other antimicrobial agents. Resistance to erythromycin and to chloramphenicol tend to be restricted to the same serogroups associated with multiple resistance, including those antibiotics (30, 142, 215). Limited available data suggest that TMP-SMZ resistance (215) and rifampin resistance (142) are more widespread in their serogroup distributions (215). Resistance to tetracycline has been recognized among more than 20 serogroups (25).

Acquisition and Carriage of Pneumococci

The number and variety of pneumococcal strains identified from the nasopharynx of a given individual are enhanced

by using more than one method of pharyngeal culture (13). Carrier rates based only on culture with selective blood agar media will therefore yield rates that should be considered as minima (13).

Pneumococci may be carried as early as the first day of life (97), and >95% of children are colonized at some time during the first 2 years of life (91, 97). The mean age of first detection is 6 months (93), and this first detection of pneumococci is associated with the longest duration of carriage, with duration of carriage decreasing with age and sequential acquisition of new strains (91). First acquisition is earlier in larger families, and children in large families tend to carry more strains (90). Finally, first acquisition is associated with an increased risk of clinical disease (91).

Serogroups 6, 19, and 23, together with serotype 14, in addition to being the predominant serogroups of pneumococci manifesting antimicrobial resistance, account for two-thirds of all pneumococci isolated during the first 2 years of life (91). They are the dominant types reidentified following antibiotic therapy (91) and are carried for a longer period of time (mean of 4.2 months versus 2.7 months for all other serogroups combined; $P < 0.01$). As mentioned previously, they are the commonest causes of bacteremia (17, 22, 27, 90, 92, 130, 240) and also of otitis media (15, 90, 138) in children, but are less common in adults (12, 197; Hayden-Smith, M.Sc. thesis). Pneumococci of these three serogroups and single serotype are poorly immunogenic in young children and infants (58, 154, 164).

Prolonged carriage and rapid reacquisition provide an increased chance of exposure to antibiotics and thus may be important selective factors in predisposing these particular serogroups to antibiotic resistance in a hospital setting. The stability of the chromosomally determined resistance, lack of evidence to suggest decreased virulence or decreased ability of resistant strains to colonize, and the advantage of these strains in the face of antibiotic pressure eventually lead to the widespread communal distribution of these strains. The carriage of infective strains is correlated with the level of disease caused by those strains in a given community (115). A high prevalence of drug-resistant isolates from patients is now apparent in those parts of the world with the highest prevalence of carriage of resistant pneumococcal strains.

Age

Infection with and carriage of resistant pneumococci have mostly been associated with young children (3, 4, 6, 10, 128, 145, 153, 204, 219, 273). Bacteremias with resistant pneumococci occur in younger children (mean age, 13.1 months) than do those due to susceptible strains (mean age, 31.6 months; $P < 0.01$) (204). The median age of carriers of resistant strains in a study in another hospital was 1.4 years, compared with 2.4 years for carriers of susceptible strains (226). In the United States, clinical isolates of intermediately resistant pneumococci are more than twice as common in children <5 years of age than in older persons (Oxtoby et al., 25th ICAAC). The carriage of resistant pneumococci by very young children and infection of children by these resistant strains are compatible with the overwhelming representation of resistance in serogroups common in very young children.

In adults, infections with resistant pneumococci are usually caused by these "childhood" strains (72, 208, 229, 270). Data from areas where resistant strains are isolated from a high percentage of adults with pneumococcal disease (94) suggest that, in those areas, the selective advantage of resistant strains is changing the distribution of serotypes in adults to one with an increasing percentage of childhood types.

While only sporadic infections have been caused by resistant strains in adults in many countries (35, 47, 107, 216, 229), foci of infection in adults have been reported from South Africa (95), the United States (241), and Great Britain (88, 191), and infection caused by resistant pneumococci in adults is common in Spain (94, 208, 270). Of 39 clinical isolates of penicillin-resistant pneumococci in Chile, 11 were recovered from adults (142). In a recent study from Oklahoma City, the highest rates of resistant pneumococcal invasive disease were both in children <4 years of age and in adults ≥70 years old, who as a group had increased numbers of previous hospital admissions compared with those of younger adults (123). Very few recent studies have examined the prevalence of resistant strains in adult carriers. One resistant strain was identified among seven pneumococcal isolates (14.3%) from 51 staff members at six day-care centers where 18% of pneumococci isolated from children were drug resistant (145). The carriage rate of pneumococci in the children was, however, 44%, compared with 14% in the adults, so that while the percentages of resistant isolates were similar in the adults and children, the great preponderance of resistant strains was carried by the children. In Alice Springs, Australia, 34% of adults were found to be carrying pneumococci, of which 14% were resistant to one or more antimicrobial agents (111).

Tetracycline resistance alone is usually associated with isolates from adults with chronic lung disease (2, 106); thus, a significant association of tetracycline resistance with age of ≥50 years has been made (2). Tetracycline resistance as part of multiple resistance occurs in adults (88, 191, 208, 270), but also in children (128, 145, 146), because the other agents more commonly prescribed for children (penicillin, erythromycin, or TMP-SMZ) favor the selection of these strains.

Hospitalization

In both children and adults, infection with resistant pneumococci has been associated with hospitalization. For inpatients, the acquisition of resistant strains has been correlated with duration of hospitalization. Other patients presenting with resistant pneumococcal infection have had recent exposure to hospitalization. In children, both multiple drug resistance and resistance to penicillin at a level of ≥2 mg/liter first emerged in hospitalized children (7, 128). Resistant pneumococci were isolated from 29% of 543 pediatric patients versus only 2% of hospital staff (128). At a nearby isolation hospital, 75 of 80 patients in a measles ward were carrying resistant strains versus none of 71 staff, and 9 of the 75 children apparently acquired the resistant strain within 4 days of hospitalization (128). Ninety percent of new admissions were colonized with drug-resistant strains within 1 week in a setting of 80% prevalence of resistant strains in hospitalized carriers, compared with 15% acquisition of resistant strains in 1 week in a setting of 33% prevalence of resistant strains in hospitalized carriers (273). Duration of hospitalization has been correlated with acquisition of penicillin-resistant strains, with patients colonized by susceptible strains having been hospitalized a median of <1 day and patients carrying resistant strains having been hospitalized a median of 5.5 days (226).

In adults, infection with tetracycline-resistant pneumococci has been associated with hospitalization (2), and spread of tetracycline-resistant strains within hospitals is

well documented (106, 214, 264). A patient was identified with bronchopneumonia caused by tetracycline-resistant pneumococci, and within 5 days three patients, all on tetracycline, had been infected with the same strain (214). Spread of a tetracycline-resistant serogroup 9 strain to four other patients also on tetracycline therapy was also described (214). Hospital infection outbreaks caused by multiply resistant strains, with apparent transmission of the strains within the hospital, have occurred (88, 191). In a study of bacteremic pneumonia in adults caused by penicillin-resistant pneumococci, 58% of 24 patients infected with penicillin-resistant pneumococci had been hospitalized in the previous 3 months, compared with 21% of 48 control patients infected with penicillin-susceptible pneumococci ($P = 0.0038$) (208). Similarly, nosocomial pneumonia was caused by penicillin-resistant strains in 37% of patients, in comparison with 6% of nosocomial infections caused by penicillin-susceptible strains in controls ($P = 0.0032$) (208).

Community Carriage of Resistant Strains

In contrast to nosocomial infections caused by drug-resistant pneumococci in hospitals, recent reports from South Africa (73, 146, 229), the United States (241), and Spain (270) have emphasized a new phenomenon of infections caused by resistant pneumococci, community-acquired infections. A reservoir of resistant strains outside the hospital environment appears likely. Such a reservoir was previously found in healthy carriers in the early 1970s in New Guinea (104, 108, 109). The first resistant strains in New Guinea were isolated from healthy carriers participating in a trial of monthly procaine penicillin therapy designed to reduce the incidence of pneumococcal carriage with invasive serotypes (59). In the previous 10 years, the 507 people in the remote villages where pneumococcal resistance developed had been exposed to 1,357 courses of penicillin for various ailments, including 532 episodes of acute lower-respiratory-tract infection (59).

Two studies in South Africa in 1986 demonstrated that 8 to 19% of children in day-care centers were carrying drug-resistant pneumococci (19 to 31% of pneumococci isolated were resistant) (145, 147). Recently published studies in the United States (113) and Spain (215) have also documented high levels of carriage of resistant pneumococci by children in day-care centers. In North Carolina, between 1978 and 1985, 30% of isolates from children at day-care centers were resistant to TMP-SMZ, with an increase from 5.4% before 1981 to 39% from 1981 to 1985. Isolates resistant to penicillin comprised 11.9% of all pneumococci isolated (113). In Spain, 35.9% of 159 isolates in children at play schools in Barcelona were resistant to penicillin; 42.8%, to chloramphenicol; 65.4%, to tetracycline; and 79.2%, to TMP-SMZ; and numerous patterns of multiple resistance were found (215). In Mexico, penicillin MICs were $\geq$0.156 mg/liter for 74.5% of strains isolated from healthy carriers (96). Finally, among aborigines in Alice Springs, Australia, 29% of isolates from children were resistant to one or more antimicrobial agents compared with 22% from adolescents and 14% from adults (111). The burden of resistant strains among children is further emphasized by the pneumococcal carriage rates of 89% in children, 39% in adolescents, and 34% in adults (111).

During the epidemiological investigation of the first case of a community-acquired multiply resistant pneumococcus in Denver, Colo. (219), 27% of children in the same room as the index case were carrying the strain, compared with 11% of older children and staff. Five of 15 family contacts of colonized children acquired the resistant strain, compared with none of 19 household contacts of children not carrying the resistant strain (219). A survey of the day-care center and of the households of the carriers 2 months later revealed that 7 of 14 carriers remained colonized by the resistant strain, and 5 new carriers were identified (219).

Prior Exposure to Antibiotics

A growing body of evidence suggests that exposure to antibiotics to which the pneumococcus is resistant may predispose to infection with resistant rather than susceptible strains, especially in communities in which resistant strains are common. Prior exposure to antibiotics may also contribute to carriage of resistant strains, thus potentially increasing the dissemination of resistant strains. Jackson and co-workers (125) found that 56% of patients with penicillin-resistant pneumococcal infections had had prior β-lactam therapy, while only 14% of patients with susceptible pneumococcal infection gave such a history ($P = 0.009$). Pallares and co-workers (208) have produced similar data from their studies of bacteremic pneumonias due to resistant pneumococci in adults. They show that 65% of patients infected with resistant pneumococci gave a history of having received antibiotics in the previous 3 months, compared with 17% of controls with susceptible pneumococcal infections (208). As the patients with infections caused by resistant strains were more likely to have nosocomial pneumonia and to have had previous hospital admissions in that study, it is possible that exposure to the hospital microflora per se contributed to the acquisition and subsequent infection with resistant strains. Duration of hospitalization was also not considered in the Jackson study (125). Saah and co-workers were unable to find an association with previous antibiotic therapy in 16 patients of whom only 4 were definitely infected with the resistant strain (228). However, in a study by Robins-Browne and co-workers, acquisition of penicillin-resistant strains by hospitalized children was significantly related to exposure to β-lactams even after controlling for duration of hospitalization and young age (226). In their case control study, Amitai and co-workers also matched their control group by age and found equal numbers of patients in each group with nosocomial and community-acquired infection (4). They found, however, that the duration of exposure to β-lactams was greater (13.3 days) in those infected with penicillin-resistant strains than in those infected with susceptible strains (4.2 days; $P < 0.02$). Most of the antibiotics were administered during hospitalization (4). In hospitalized patients, numerous studies have related previous tetracycline exposure to infection with tetracycline-resistant strains (2, 19, 106, 214, 264).

Community carriage of multiply resistant strains was related by Radetsky and co-workers to exposure to antibiotics in the previous 2 months in 7 of 18 carriers of multiply resistant pneumococci, but in only 2 of 25 carriers of susceptible strains ($P = 0.019$) (219). In a recent study, Henderson and co-workers (113) found that of 48 children at day-care centers who had received TMP-SMZ, 29 at some stage carried TMP-SMZ-resistant strains. Seventeen of the 29 patients, however, received the drug after colonization, and 12 of 24 children who had never received the drug were similarly colonized. Although this study demonstrates that community acquisition of resistant strains is often independent of direct antibiotic selective pressure, it does not address the question of the relative likelihood of children exposed to TMP-SMZ acquiring susceptible rather than resistant strains.

The 8 to 19% carriage of resistant strains in the community, e.g., in South Africa, supports the idea that resistant strains have become part of the resident microflora of large numbers of children; since carriage of resistant pneumococci was common even in rural areas, where exposure to antibiotics would be less likely (147), these resistant strains probably colonize children in direct competition with susceptible strains even in the absence of antibiotic pressure (144). The use of antibiotics would, however, give these strains a selective advantage and may increase the prevalence of resistant strains in communities in which those antibiotics are administered. In South Africa, pneumococci resistant to erythromycin and TMP-SMZ were found only in more affluent communities in which these drugs were commonly prescribed. In contrast, β-lactam-resistant pneumococci were found in 14 to 19% of children in less affluent communities, who were less likely to receive erythromycin or TMP-SMZ than a β-lactam such as penicillin or ampicillin (145, 147). Similarly, penicillin resistance was part of the pattern of resistance in 66 to 89% of resistant strains in hospitals catering to poor communities, compared with 28% in more affluent community hospitals (142).

Immunodeficiency and Underlying Disease

A review of 64 hospitalized patients infected with penicillin-resistant (MIC, ≥2.0 mg/liter) pneumococcal infections revealed that 33 had measles, 21 were malnourished, 12 had gastroenteritis, 3 had tuberculosis, and 1 had congenital immunodeficiency (293). Data of this type and numerous case reports of resistant pneumococcal infections in patients with nutritional deficits (7) or immune deficiency (3, 107, 174, 200, 207) led to a hypothesis that cell wall changes in resistant pneumococci may alter their ability to stimulate the alternate complement pathway and give these strains a selective advantage in immunodeficient individuals (207). There is, however, no current evidence to support this hypothesis. Controlled studies have failed to associate immune deficiency or underlying disease with either infection caused by resistant strains (4, 125) or acquisition of these strains (244). Although previous episodes of pneumonia and an initial critical condition have been associated with infection caused by resistant strains (208), these patients also had increased exposure to the hospital environment and increased exposure to antibiotics prior to the onset of infection caused by the resistant strains (226). The distribution of patients with infection caused by drug-resistant pneumococci in pediatric wards in the third world mainly reflects patients with the underlying diseases mentioned above (273). A recent controlled comparison at such a hospital, where 50% of infections caused by drug-resistant pneumococci were community acquired (204), failed to find different underlying conditions between bacteremic patients infected with resistant versus susceptible strains, except for a possible ($P = 0.07$) association with malnutrition (204). No relation between underlying disease conditions and resistant pneumococcal infection was found by Saah and co-workers (228), but as previously mentioned, in that study only 4 of 16 patients with resistant pneumococci had definite infections with the resistant strains. Amitai and co-workers also failed to find an association between underlying disease and resistant pneumococcal infection in their case control study in Israel (4), and a recent study of predominantly community-acquired meningitis in adults found the same underlying conditions in patients infected with resistant or susceptible pneumococci (270).

It therefore appears that, although underlying conditions are common in patients with resistant pneumococcal infections, this association is secondary to the association of these conditions with hospitalization and antibiotic administration. Few data suggest direct selection by underlying condition of infection caused by resistant rather than susceptible strains.

THERAPEUTIC CHOICES AND IMPACT OF RESISTANCE ON CLINICAL OUTCOME

Pneumonia and Bacteremia

The mortality rate of 5% for 35 South African children with mainly community-acquired pneumococcal bacteremias caused by susceptible strains was less ($P = 0.002$) than that of children with mainly hospital-acquired bacteremias due to strains for which penicillin MICs were ≥0.1 mg/liter (47% of 15 patients) and also less ($P = 0.003$) than that due to strains for which penicillin MICs were ≥2.0 mg/liter (50% of 10 patients) (151). The severity of underlying disease, however, probably accounts for much of the excess mortality in the hospitalized children (151). A comparison of the 50% mortality (5 of 10) of hospitalized patients with penicillin-resistant pneumococcal bacteremias treated with β-lactam antibiotics with that of similar patients treated with other appropriate agents (25% mortality, 7 of 28 patients) revealed no significant difference, although the numbers are small (151). Larger studies are required to assess the role of resistance in the outcomes of therapy of pneumococcal bacteremias with β-lactam antibiotics. The data mentioned above are similar to those of Pallares and co-workers (208), who found 54% mortality (13 of 24) in hospitalized adults infected with penicillin-resistant pneumococci compared with 25% mortality (12 of 48) in patients infected with susceptible strains. They too, however, attributed the excess mortality to an initial critical condition and not to the resistance itself (208).

Even fewer data are available on the therapy of bacteremias caused by strains for which MICs are ≥4 mg/liter. Pallares and co-workers noted that the two patients with infections caused by strains with penicillin MICs of ≥4 mg/liter had a poor response to β-lactam therapy (208). Failure of ampicillin and cefazolin (53) and cefazolin and gentamicin (229) in the therapy of resistant pneumococcal pneumonia have been reported. The underlying conditions of these patients (53, 208, 229), however, may have contributed to their poor response to β-lactam therapy. Nonbacteremic bronchopneumonia caused by a strain for which the MIC was 8 mg/liter responded to ampicillin (41), and in an exacerbation of chronic bronchitis caused by resistant pneumococci, a patient unresponsive to a standard dose of amoxicillin responded to 2 g administered three times daily (47).

Penicillin therapy alone is probably sufficient for treating bacteremic or nonbacteremic pneumonia caused by intermediately penicillin-resistant pneumococcal strains (216, 257), although prudence may lead the physician to consider alternative management of pneumonia caused by highly resistant strains, especially in the neutropenic or otherwise immunocompromised patient.

Tetracycline-resistant strains respond poorly to tetracycline (106, 214). In case reports of pneumonia caused by TMP-SMZ-resistant (168) and erythromycin-resistant (56) strains, the patients responded poorly to these drugs and were cured with penicillin (168) and ampicillin (56), respec-

tively. The clinical relevance of TMP-SMZ or erythromycin resistance in the management of systemic pneumococcal infections, however, has not been further addressed.

Meningitis

Numerous studies and case reports have documented the poor response to penicillin therapy of patients with meningitis caused by intermediately penicillin-resistant pneumococci (3, 7, 44, 84, 121, 125, 200, 211, 219, 228), although some patients have responded to increased doses of penicillin (135, 174, 200). A review of the reported cases to 1980 (273) showed that 2 of 12 patients with meningitis caused by relatively resistant strains responded to penicillin, compared with none of 9 responses to penicillin in patients infected with strains for which penicillin MICs were ≥2.0 mg/liter. A bias almost certainly exists towards the reporting of failures of therapy, as penicillin MICs may more likely be determined in cases with a poor response to penicillin therapy (3). These reports, however, are consistent with data from experimental pneumococcal meningitis showing that the concentration of penicillin in CSF is well below 10- to 30-fold the MBC of intermediately resistant strains which is required for maximal killing of pneumococci by β-lactam antibiotics (253–255). In a rabbit model of experimental pneumococcal meningitis, penicillin or chloramphenicol failed to stop the growth of resistant strains for which penicillin MICs were 3.1 to 6.25 mg/liter or chloramphenicol MICs were 12.5 to 25 mg/liter, a finding that correlated with achievable CSF concentrations of each drug below the MICs for the two organisms (16).

Imipenem, cefotaxime, ceftriaxone, and vancomycin are among the agents most active against penicillin-resistant pneumococci (147, 265). Although the MICs of broad-spectrum cephalosporins are increased against penicillin-resistant strains when compared with those of susceptible strains, these MICs fall below the achievable CSF levels for cefotaxime, ceftriaxone (231), and imipenem, at least in the presence of the dipeptidase inhibitor cilastin, included with the last (189). Imipenem, ceftriaxone, and vancomycin have been evaluated with success in models of experimental meningitis with resistant strains (16, 183). Ceftriaxone was more active than penicillin against an intermediately resistant strain, sterilizing the CSF after a 9-h infusion in four rabbits (183). A single dose of either penicillin or ceftriaxone failed to reduce bacterial counts of a strain for which the penicillin MIC was 4 mg/liter, while vancomycin or imipenem were effective and sterilized the CSF after a 9-h infusion of antibiotic (183). The very limited clinical experiences with cefotaxime (44, 270) and vancomycin (31, 125, 290) in treating meningitis caused by intermediately penicillin-resistant strains have been successful, while imipenem is not currently recommended for the therapy of meningitis, because of a possible predisposition to seizures in these patients (34).

A consensus report on the management of bacterial meningitis, including consideration of penicillin-resistant pneumococcal strains (182), recommends cefotaxime, ceftriaxone, or vancomycin. Chloramphenicol is useful when the strain is susceptible (182, 204, 270), and the addition of rifampin has been suggested (73, 204). On the basis of experimental (183) and limited clinical (270) experience, meningitis due to strains for which MICS are ≥2 mg/liter should probably be treated with vancomycin. Rifampin should be added (204) when the strain is susceptible. An initial report from Spain of vancomycin (7.5 to 15 mg/kg every 6 h) as first-line therapy for adult pneumococcal meningitis is disappointing. Only 6 of 11 patients were treated successfully without increased vancomycin dosage (one patient) or change to β-lactam therapy (three patients) (P. F. Viladrich, F. Gudiol, J. Linares, R. Pallares, I. Sabate, G. Rufi, and J. Ariza, 29th ICAAC, abstr. no. 1116, 1989). These authors suggest that the treatment failures were associated with poor levels of vancomycin in the CSF and recommend reserving the drug for proven penicillin-resistant pneumococcal meningitis only.

Other Infections

There have been no studies of the effect of drug resistance on the management of pneumococcal otitis media and sinusitis. Anecdotal reports suggest the failure of TMP-SMZ for the management of otitis media (256) or sinusitis (178) caused by pneumococci resistant to TMP-SMZ.

TREATMENT OF THE CARRIER STATE AND OTHER CONTROL MEASURES

Surveillance for resistant pneumococci should be instituted in all countries at this time, with increased attention being paid to limiting unnecessary use of antibiotics. Isolation of patients may be indicated in hospital outbreaks or localized community outbreaks (e.g., a day-care center) in all countries in which resistant pneumococci are not widespread in the hospital or community. Most of the work on eradication of the carrier state was carried out during the emergence of multiple resistance in South Africa (128, 153). The treatment of carriers was based on the susceptibility of the strain they carried (153). All patients were treated for 7 days, and success of the therapy was based on three nasopharyngeal swabs negative for resistant pneumococci in the week following therapy (153). Erythromycin alone (45 mg/kg per day) was less successful (42%) against penicillin-resistant, but erythromycin-susceptible, strains than minocycline (84%) or erythromycin plus rifampin (20 mg/kg per day) (96% success) (153). The eradication of multiply resistant strains was more difficult, and the most widely tested regimen of rifampin plus fusidic acid (30 mg/kg per day) was only 63% successful. There were 43 carriers of multiply resistant strains that failed initial therapy, and most of these strains had acquired rifampin resistance during their attempt at eradication with rifampin. Finally, vancomycin (45 mg/kg per day) was given for up to 5 days with 74% success (153). The use of mupirocin to eradicate carriage of resistant pneumococci has recently been suggested (210).

The control measures outlined above may have reduced the number of infections caused by multiply resistant strains during a year of follow-up (153). The multiply resistant variants of strains 19A and 6A have remained at a level of <1% of blood and CSF pneumococcal isolates in South Africa from 1979 to 1986 (142), despite yearly increases in other strains resistant to penicillin alone and strains resistant to multiple antibiotics not including penicillin (145). The direct contribution of the control measures to the long-term control of multiply resistant serotype 6A and 19A strains is, however, difficult to evaluate because they remain rare even at centers in which no control measures were instituted (142, 266). There is at present no rationale for the treatment of carriers in endemic resistance situations, and the benefit of carrier treatment in outbreak situations remains, in light of the data above, unproven. The difficulty of documenting the true status of pneumococcal carriage by using standard

methods of culture on agar plates (13) hampers the interpretation of data on the eradication of the carrier state.

The rationale for vaccination of persons of ≥65 years of age (122) may be further strengthened by the increasing prevalence of resistant pneumococci in the elderly (71), although resistance per se has not been shown as yet (albeit in limited studies) to increase the risk of death in this patient group. In addition, hospitalized patients at risk of bacteremia with resistant pneumococci are precisely those patients with acquired immunodeficiency (208) who respond poorly to the existing vaccine (20; editorial, Ann. Intern. Med. **108**:757–759, 1988). The serogroups associated with resistance are not immunogenic in children <2 years old (58, 154, 164), although it is possible that protein conjugates of these capsular polysaccharides may be useful in the future (5, 166, 235).

MECHANISMS OF RESISTANCE

Penicillin Resistance

No β-lactamase activity has been detected in pneumococci (225). Penicillin resistance is mediated by changes in the affinity or rate of acylation of enzymes known as penicillin-binding proteins (PBPs). These proteins are believed to be enzymes that catalyze the terminal stages of murein synthesis (259) and are inhibited by covalent bonding with penicillin at their active site. Six PBPs are found in susceptible strains, with only rare exceptions to this pattern: PBP 1a (92 to 100 kilodaltons [kDa]), PBP 1b (89 to 95 kDa), PBP 2x (85 kDa), PBP 2a (80 to 81 kDa), PBP 2b (77 to 78 kDa), and PBP 3 (43 to 52 kDa) (64, 177). The factors affecting the resolution and visualization of these bands by sodium dodecyl sulfate-polyacrylamide gel electrophoresis have recently been reviewed (23, 98). PBP 3 has been purified and shown to have DD-carboxypeptidase activity (99), to have high affinity for penicillin (102), and not to change its penicillin affinity in resistant strains. The specificity of β-lactam interaction with pneumococcal PBPs is partially specified by the R1 side chain of the β-lactam antibiotic, such that β-lactams with different structures but with common R1 side chains bind to the same PBP; e.g., the monobactam azthreonam and the cephalosporin ceftazidime share the same 2-methyl propionic acid side chain and both bind preferentially to PBP 3 (100). These, and other β-lactams that do not bind to PBP 2b, do not cause bacterial lysis, suggesting that binding to PBP 2b is essential for the lytic activity of β-lactams on pneumococci (100). PBP 2b may be the lethal target of penicillin in *Streptococcus pneumoniae* (100). This protein may also play a critical role in peptidoglycan synthesis, because, in the presence of penicillin, the amount of PBP 2b not saturated by penicillin is correlated with the amount of peptidoglycan synthesized, at least in an autolysis-defective pneumococcal mutant (277).

Penicillin bound to pneumococcal PBPs is degraded, both by hydrolysis of the penicillin-PBP ester linkage (deacylation) to produce penicillinoic acid and by fragmentation of the penicillin to produce phenylacetylglycine and *N*-formylpenicillamine (64). No change in the rate of deacylation has been detected in resistant compared with susceptible strains (102). PBPs have affinity for penicillin, and, in contrast, affinity for their natural peptide substrates used in the biosynthesis of murein. While the affinity for penicillin of PBPs from resistant strains is lessened, the PBPs must retain affinity for their natural substrates or other alternate substrates that can be used for murein synthesis. There is recent evidence that PBPs from resistant strains alter their affinity for their endogenous disaccharide peptide substrates. In contrast to susceptible strains which use mainly linear stem peptides for wall synthesis, resistant strains have a preference for branched peptides which contain dialanyl or alanylserine substituents on the epsilon amino groups of the stem peptide lysine residues (83).

Multiple rounds of transformation with DNA from progressively more resistant mutants produce high-level β-lactam resistance in vitro, using the susceptible pneumococcal strain R6 as the recipient (103, 238, 282, 283), and the increase in resistance is associated with a stepwise change in affinity of PBPs 1a, 2a (102), and 2b (283). Associated also with the increased resistance is a decrease in the apparent molecular weight of the PBP 1a protein in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (187). This lower-molecular-weight (92,000) PBP 1a found in resistant strains has been called PBP 1c (102). In contrast, however, to the stable pattern of changing affinities seen in laboratory transformants of strain R6, transformation of other strains allows the rapid selection of high-level resistant mutants (38). Furthermore, multiple different patterns of PBPs may be associated with transformants of these strains (38) and with wild-type resistant strains (39, 157, 177), suggesting that pneumococci are able to remodel their PBPs in more than one way to achieve lower penicillin affinity. Implicit in this suggestion is the idea that penicillin resistance may have emerged more than once, producing different "families" of PBP types (124). A quantitative relationship between PBP penicillin affinity and the MIC is unclear, probably because the penicillin affinity does not measure the change in the enzymatic activity of PBPs from resistant strains on their natural substrates (157). The major change in the carboxy-terminal sequence of PBP 2b, hypothesized to be associated with the decreased penicillin affinity of the resistant strain, is the substitution of seven consecutive amino acids (61) in an area analogous to the loop downstream of the active-site serine at the penicillin-binding site of β-lactamases and some PBPs (55, 114, 134). Alterations within this domain have been found in the PBPs of chromosomally penicillin-resistant *Neisseria gonorrhoeae* (245) and cephalexin-resistant *Escherichia coli* (214, 215). Partial sequencing of the genes encoding pneumococcal PBPs has revealed extensive homology with some of the PBPs of *E. coli* (T. Briese, G. Laible, C. Martin, C. Schueter, and R. Hakenbeck, 29th ICAAC, abstr. no. 1126, 1989): PBP 1a to *E. coli* PBP 1a/1b, PBP 2x to *E. coli* PCP 3, and PBP 3 to *E. coli* PBP 5 (Briese et al., 29th ICAAC).

Penicillin Tolerance

Pneumococci that fail to lyse and are more slowly killed following exposure to concentrations of penicillin above the MIC are termed tolerant. Eagle and Musselman showed in 1948 (63) that some pneumococcal strains exhibit a "paradoxical" effect in that there is an optimum penicillin concentration above the MIC for bacterial lysis. Higher concentrations of penicillin caused a paradoxical lack of lysis. Laboratory mutants have been described more recently in which autolytic enzymes are detectable in the bacteria, but they do not lyse at 32°C (171). At 37°C, they do lyse, but show the paradoxical effect (171). The mechanism of this effect is unknown.

Pneumococci produce at least two autolytic enzymes, an amidase (20; editorial, Ann. Intern. Med.) and a glucosaminidase (82). The amidase gene has been cloned and

sequenced (81), and amidase autolytic activity is inhibited by lipotechoic acid and choline (24, 116). Tolerance cannot, however, be correlated with specific autolysin activity (173). The mechanism by which penicillin induces the activity of the autolytic enzymes (or fails to do so in tolerant strains) and the role of this lysis in the bactericidal effect of penicillin are incompletely understood. Although mutants in which the amidase gene has been insertionally inactivated (Lyt^-) have a greatly reduced lytic response to penicillin, these mutants are still rapidly killed, at a rate of only 1 log/h less than that of Lyt^+ strains (193). Transformation of a rapidly killed strain (4 to 5 logs/h) by one that is slowly killed (1 log/h) has led to the discovery of a gene in the rapidly killed strain, called *cid* (from the word bactericidal) (193). The *cid* gene is absent in slowly killed strains (Cid^-). Although the *cid* gene may encode a product that regulates the action of autolytic enzyme, the mechanism of its function remains speculative (193).

The majority of penicillin-resistant pneumococci manifest defective autolysis in concentrations of penicillin exceeding the MIC (170, 194). The traits of resistance and defective lysis are separable in transformation experiments (170), suggesting that in resistant strains there may be an alteration in control of the autolysis mechanism (170). While high levels of penicillin (20-fold MIC achieved at peak levels during penicillin therapy) may select tolerant survivors for which the MIC is unchanged, trough levels just above the MIC may then select resistant strains for which MICs are increased from among these tolerant survivors (194). Failure of bacteria to lyse appears to delay the leukocytic response to infection in experimental meningitis in rabbits (263). The role of defective lysis in relapse or persistent disease in immunocompromised humans has been suggested in a few patients, but remains to be confirmed in a larger series (263). Immunocompetent patients with pneumococcal bacteremia (263) caused by strains with defective ability to lyse did not appear to have a more severe clinical course than patients whose disease was caused by lytic strains. The role of amidase production in the virulence of pneumococci for mice is controversial. Mutant strains with insertional inactivation of the major autolysin (amidase) gene have been shown to be less virulent (18) or, after serial passage in mice, equally virulent (260) to their parent strains with intact amidase genes.

Resistance to Other Agents and Multiple Resistance

Although plasmids were described in pneumococci in 1979 (242), their relation to drug resistance in pneumococci has not been established. Linkage between the genes encoding erythromycin and tetracycline resistance (28) and tetracycline and chloramphenicol resistance (239) was a prelude to the demonstration, in 1980, that multiple resistance could be transferred by conjugation in pneumococci (29) and to the identification in 1986 of chromosomal conjugative elements that transfer multiple resistance (48, 268, 269). Transposon Tn*1545* confers resistance to chloramphenicol, erythromycin, kanamycin, and tetracycline. The erythromycin resistance is due to the gene *ermAM*, the kanamycin resistance is due to *aphA-3*, and the tetracycline resistance is due to *tetM* (48, 49). The location of these genes within the transposon has been elucidated (32), and two proteins involved in the excision system of Tn*1545* are similar to proteins involved in the excision of lambdoid phages (C. Poyart-Salmeron, P. Trieu-Cuot, C. Carlier, and P. Courvalin, 29th ICAAC, abstr. no. 150, 1989). A transposon containing *tetM* (45) is present in the Minnesota strain of multiply resistant pneumococcus identified in 1977 (37). The conjugative element BM6001 in pneumococcal strain DP1322 has also been mapped and contains genes encoding chloramphenicol and tetracycline (*tetM*) resistance (268).

The mechanisms of bacterial resistance to aminoglycosides, optochin, sulfonamides, trimethoprim, tetracycline, macrolides, chloramphenicol, and rifampin are briefly reviewed here, with specific reference to resistance mechanisms established for the pneumococcus.

The affinity of the ribosome for streptomycin has been shown to determine the level of resistance of pneumococci to streptomycin, and mutations in the locus *str* alter the affinity of this binding (248). Kanamycin resistance, on the other hand, is due to a 3′ aminoglycoside phosphotransferase type III enzyme (43, 49). This aminoglycoside-modifying enzyme phosphorylates the hydroxyl group in the 3′ position of aminohexose I of kanamycin. The type III enzyme is distinguished from types I and II (found in gram-negative bacteria) by differences in its aminoglycoside substrate range in vitro (262). The gene encoding the phosphotransferase, *aphA-3*, is found not only in the pneumococcus on transposon Tn*1545*, but also on plasmids in streptococci, staphylococci, and *Campylobacter coli* (33, 262). Although the structural genes of *aphA-3* are identical in Tn*1545* of *S. pneumoniae* and plasmids pJH1 and pIP1433 of *Enterococcus faecalis* and *C. coli*, respectively, there are differences in their promoter regions, with the streptococcal promoters representing deletion mutants of the *C. coli* promoter (33).

Optochin acts by inhibition of a pneumococcal diaphorase (235). Optochin-resistant diaphorases show increased resistance to heat inactivation as well as to inhibition by optochin, and show greater diaphorase activity per milligram of proteins (235).

Pneumococci were thought to mutate to sulfonamide resistance by means of a change in the enzyme dihydropteroate synthase, such that it would preferentially bind *para*-aminobenzoic acid rather than the sulfonamide and not block folate synthesis (278). However, a mutated gene, *sulD*, identified following prolonged selection with sulfanilamide (118), cloned into a plasmid (246), sequenced to reveal an insert of 6 base pairs in the dihydropteroate synthase enzyme gene (172), and finally expressed in *E. coli*, failed to produce sulfonamide resistance, suggesting that resistance to sulfonamides may be due to mutation of another, as yet unidentified enzyme in the pneumococcal folate synthesis pathway (172). Bacterial resistance to trimethoprim may be mediated by production of an altered dihydrofolate reductase enzyme with decreased affinity for trimethoprim (202), but the details of trimethoprim resistance in pneumococci have not been delineated.

The *tetM* gene encoding tetracycline resistance in pneumococci as part of the conjugative shuttle transposon Tn*1545* has been cloned and sequenced (180, 181). The *tetM* gene is found in the chromosome of several drug-resistant streptococcal species (243) and until recently was thought to be restricted to gram-positive cocci (165). The gene has now been found in resistant *Mycoplasma*, *Ureaplasma*, and *Gardnerella* species (163), in *Neisseria* species including *N. gonorrhoeae* (163, 196; C. Poyart-Salmeron, P. Trieu-Cuot, C. Carlier, and P. Courvalin, 29th ICAAC, abstr. no. 149, 1989) and *N. meningitidis* (148), and in *Kingella denitrificans*, *Eikenella corrodens* (148), and numerous gram-positive and gram-negative anaerobic bacteria of the oral microflora (223). The gene, *tetM*, encodes a soluble protein of 7.25 kDa (180) thought to bind to the ribosome, preventing the

inhibitory action of tetracycline on protein synthesis (26, 180). In contrast, *tetA*, *tetB*, and *tetC* genes of gram-negative bacilli code for hydropathic membrane-bound proteins that mediate tetracycline efflux from resistant bacteria (165, 180). The TetM protein has recently been shown to share N-terminal homology with five translational elongation factors, strengthening the assertion that its mode of action involves ribosomal binding (230).

In pneumococci, the gene encoding resistance to erythromycin has also been identified on transposon Tn*1545* as *ermAM*, where it confers resistance to macrolides, lincosamide, and streptogramin-B (so-called MLS resistance) (49). The *ermAM* gene has been shown to hybridize to chromosomal DNA of highly erythromycin-resistant *E. coli* and a strain of resistant *Klebsiella* sp. (262). Resistance to erythromycin in *Staphylococcus aureus* is associated with dimethylation of adenine in 23S rRNA (156) and reduced affinity of the ribosome for erythromycin. The gene product of the staphylococcal gene *ermC* is such an RNA methylase (237), and extensive homology exists between the nucleotide sequence of *ermC* and the *ermAM* gene found in streptococci (198). Upstream of *ermAM* in *Streptococcus sanguis* is a region of numerous inverted repeat sequences thought to encode a 36-amino-acid control peptide (117). The peptide may control the production of the *ermAM* gene product posttranscriptionally. This sequence is missing from the *Enterococcus faecalis* plasmid pAMβ1 containing *ermAM* (179), the *Bacillus subtilis* plasmid pIM13 containing *ermC* (190), and the *Staphylococcus epidermidis* plasmid pNE131 containing *ermAM* (158). Erythromycin resistance is constitutively expressed by these strains containing these plasmids, and the lack of the control peptide is thought to allow this constitutive expression (158, 179, 190). The control of *ermAM* expression and the gene product in the pneumococcus may be inferred to be similar to the above but remains to be reported.

Chloramphenicol resistance in pneumococci is due to the production by resistant strains of inducible chloramphenicol acetyltransferase (188, 225). Rifampin resistance may be based on an altered DNA-dependent RNA polymerase, as a result of a single amino acid substitution, and as this mutation may be present in low numbers in many populations of bacteria, use of rifampin alone rapidly selects resistant strains (202). No specific details of rifampin resistance in pneumococci have been reported to date.

MOLECULAR EVOLUTION OF PENICILLIN RESISTANCE

Examination of resistant strains from around the world shows that the pattern of PBPs of two highly resistant South African strains differs from that of not only resistant strains from other countries (177), but also other resistant strains in South Africa (39, 177). These findings have led to the conclusion that resistance has developed in a number of different clones of pneumococci worldwide (124). The idea of a diversity of resistant clones is supported by the carboxy-terminal sequence data of PBP 2b from a resistant South African strain compared with three susceptible strains, which show multiple coding substitutions, not only in the putative penicillin-binding domain (thought to mediate the decreased affinity for penicillin) of the resistant strain, but also in other areas of the molecule, where a large number of substitutions have occurred. These substitutions suggest the separate clonal identity of the resistant strain (61). The three susceptible strains have virtually identical PBP 2b nucleotide sequences despite the fact that two of them were isolated in Brighton, England, in 1986 (61) while the third strain, R6, was derived from R36 and in turn from D39, originally isolated from a patient with pneumonia in New York in 1916 (122).

A recent study of the sequences of pneumococcal PBP 2b transpeptidase domains from 14 resistant strains from around the world found that these strains fell into two classes (A and B) (60). Although the evolutionary history of penicillin resistance is speculative, one suggestion, based on these data, is that homologous transformation of large blocks of sequences from a resistant donor (possibly another streptococcal species) created the two classes, with subsequent recombination events with susceptible strains dividing the resistant sequences into smaller blocks separated by sequences virtually identical to those of susceptible strains. An alternative hypothesis requires multiple separate introductions of the same gene (60). Using the hypothesis of a single introductory event followed by secondary modification, the class A resistant genes probably arose in New Guinea as early as the 1950s and are now found in Europe, the United States, and Africa. The class B strains are all of serogroup 23, are resistant to tetracycline and chloramphenicol, and to date have been found only in the United Kingdom and Spain, suggesting an origin probably in Spain in the 1970s (60). The extension of this type of analysis to the other PBPs may reveal more information on the evolution of penicillin resistance in the pneumococcus.

IDENTIFICATION OF RESISTANT PNEUMOCOCCI

Optochin Resistance

Resistant pneumococci are identified as pneumococci by using routine methods (70), including colonial morphology, capsular typing, and optochin resistance. Recent reports of optochin resistance in pneumococci (150, 217) stress the importance of potential misidentification of optochin-resistant strains as viridans streptococci, although both reports point out that the resistant colonies growing up to the optochin disk were a subpopulation of optochin-susceptible strains. Incubation in CO_2 may also interfere with the ability to recognize optochin susceptibility as zone sizes are smaller after incubation in 5% CO_2 than after incubation in room air (220). In view of this phenomenon, a zone size of >13 mm should be used as the cutoff for presumptive pneumococcal identification (70).

Disk Susceptibility Testing

The recommended NCCLS method incorporating Mueller-Hinton medium (201) is widely used to identify resistant pneumococci, and its general use in research would have the advantage of providing ready comparability, although little data exist to suggest the superiority of that medium for testing susceptibility of pneumococci or the superiority of NCCLS testing over the Stokes method (247).

Penicillin resistance as defined by MICs is not reliably identified by disk susceptibility testing with a 10-U penicillin disk, leading to the suggestion that a 35-mm-zone size cutoff for resistance be used as opposed to 29 mm (250). The use of 0.03-U penicillin disks was also proposed (126, 149), and current recommendations (201) include either the use of 5-μg methicillin disks (which should be used with a 25-mm cutoff [132]) or 1-μg oxacillin disks with a 20-mm cutoff. However, for disk diffusion susceptibility testing of pneumococcal

resistance to penicillin, use of 1-μg oxacillin disks is the preferred method based on a longer shelf life of the disks (201) and the advantage of having an international standard (249). The 1-μg oxacillin disk is also the preferred disk to use with the Stokes method (199). The use of the NCCLS standard of 20 rather than 25 mm for methicillin (201) reduced the correct identification of resistant strains to 38% compared with 91% with a 1-μg oxacillin disk at a zone size cutoff of 20 mm (206). Penicillin 10-U disks gave a 14% success rate in that study (206).

Less than 15% of College of American Pathologists participating laboratories could identify intermediate penicillin resistance in 1981 (132), although this percentage apparently increased to 78% in 1983 (133). However, a survey in 1985 of 77 acute-care hospitals in Tennessee revealed only 21 hospitals (27%) testing pneumococci for resistance with established standards (54). Local laboratories in New York failed to recognize the multiply resistant strains, which were found there only because of surveillance of participants as part of a trial of pneumococcal vaccination (241).

A study in the United Kingdom in 1987 revealed that 20% of laboratories failed to detect a pneumococcus for which the MIC was 0.25 mg/liter as resistant, while 4% of laboratories failed to recognize the resistance of a strain for which the MIC was 1 mg/liter (244). Common laboratory errors such as failure to standardize the inoculum, use of a loop instead of a swab to inoculate the plate, failure to use controls, or failure to measure the zone size if it was less than control or doubtful contributed to failure to detect resistant strains (244). Only 21 of 330 laboratories used oxacillin, methicillin, or cloxacillin to assess penicillin resistance, and these laboratories made fewer errors (3.17%) compared with laboratories that used penicillin disks (9.1% errors). Laboratories using 1-U penicillin disks made fewer errors (3.74%) compared with those using >1-U disks (15.7% errors) (244). As the strains used in this quality control exercise showed multiple resistance, the ability of laboratories to determine erythromycin, tetracycline, and chloramphenicol resistance could also be assessed. Fewer errors were made with 1-, 2-, or 5-μg erythromycin disks than with 10- or 15-μg disks; with 1-, 5-, or 10-μg tetracycline disks than with 25-, 35-, or 50-μg disks; and with 2-, 5-, or 10-μg chloramphenicol disks than with 25-, 30-, or 50-μg disks (244). Although NCCLS standards include 15-μg erythromycin disks and 30-μg tetracycline and chloramphenicol disks (201), these data, based on errors in either direction and using divergent laboratory methods, cannot be used as a basis for changing the recommended disk concentrations for susceptibility testing of pneumococci against these agents, but suggest that this potential problem be addressed by laboratories that use the Stokes method, as these problems were not encountered with the NCCLS method (129).

MICs

MICs may be determined by using either an agar dilution method or broth microdilution (201). Broth microdilution has been shown to be equivalent to agar dilution for pneumococcal susceptibility testing (251). The recommendation that broth microdilution be carried out in cation-supplemented Mueller-Hinton broth plus 5% lysed and centrifuged horse blood (201) may pose a problem for laboratories that use commercial microdilution systems. Dilution of the inoculum into 10% defibrinated sheep blood and adding to an equal volume of double-strength cation-supplemented Mueller-Hinton broth gave >94% agreement with the standard method and identified all resistant strains (51). One unmodified commercial microdilution system has been shown to give falsely penicillin-susceptible results for resistant strains (236). Media with a high thymidine or *para*-aminobenzoate content will give false resistance data for sulfonamide and trimethoprim susceptibility testing (101). The addition of lysed horse blood to cation-supplemented Mueller-Hinton broth obviates this problem, although other media such as Iso-Sensitest agar are preferred by some for this reason (101).

CONCLUSIONS

The distribution of penicillin-resistant pneumococci is now worldwide. Comparative data are available from only a few localities, but in these localities there is, with little exception, an upward trend in prevalence of resistant strains. There are now numerous foci of high prevalence of penicillin-resistant strains. Erythromycin resistance is increasing in parts of Europe, notably, France, and in populations elsewhere exposed to the drug. Most erythromycin-resistant strains are resistant to other antibiotics, in addition to erythromycin. TMP-SMZ resistance is widespread, and more data are required on the worldwide distribution of such resistant strains. While tetracycline resistance is common in southern Europe, Asia, and the Middle East, it is rare elsewhere and the prevalence in Britain has fallen. Clinical isolates of pneumococci in Spain, Hungary, and Pakistan have a high prevalence of chloramphenicol resistance. Rifampin resistance is found in low prevalence in South Africa, but is increasing. Although multiple resistance remains common in hospitalized carriers in South Africa, these strains are, in clinical isolates, often found in Spain and appear to be increasing in prevalence in other parts of Europe. Community-acquired disease caused by drug-resistant pneumococci has appeared in numerous locales, including community carriage of multiply resistant strains, susceptible to penicillin, in South Africa.

Pneumococcal serogroups 6, 19, and 23 and serotype 14 represent the overwhelming majority of resistant pneumococci isolated worldwide to date. These strains are the first strains acquired by children, are poorly immunogenic in children, and are carried for the longest time, allowing the greatest chance for selection of resistant strains. Infection of hospitalized patients ≤2 years old remains the common presentation of infections with resistant pneumococci, but community-acquired disease and disease in adults are now increasingly recognized.

Duration of hospitalization and exposure to antibiotics to which the strain is resistant are both risk factors for resistant pneumococcal infection and, in some studies, carriage of resistant strains. Immunodeficiency and underlying disease have not been shown independently to predict infection with resistant strains.

No clear-cut recommendations on the management of resistant pneumococcal infections can be made on the basis of prospective studies, controlled for the risk factors of immunodeficiency and underlying disease as well as for the severity of disease on presentation. On the basis of existing data, the following recommendations may be made. Bacteremia and meningitis caused by highly resistant strains and meningitis due to intermediately resistant strains should be treated with agents other than penicillin. Therapy of these infections may include chloramphenicol (if susceptible) or cefotaxime, ceftriaxone, or vancomycin, possibly with the addition of rifampin, depending on the patient's response

and factors such as the serum bactericidal activity. Pneumonia caused by intermediately resistant strains may be treated in most cases with high-dose penicillin alone. Tetracycline, erythromycin, and TMP-SMZ should not be used for the management of systemic infections by strains resistant to these agents.

In an isolated outbreak of resistant pneumococcal disease, investigation of the prevalence of resistant strains in carriers, isolation of patients, perhaps treatment of carriers, and limitation of the use of antibiotics to which the strain is resistant may be appropriate interventions. Pneumococcal vaccination of high-risk patients may, in areas of high endemic prevalence of resistant strains, reduce the number of infections caused by resistant strains in those high-risk patients.

The mechanisms of penicillin resistance are being further elucidated, and the cloning and sequencing of the genes encoding the PBPs hold promise of further insights into the molecular mechanisms and evolution of penicillin resistance. A molecular approach to multiple resistance in pneumococci is also revealing the likely mechanisms of resistance to agents other than penicillin.

The recognition of appropriate methods for the detection of penicillin-resistant pneumococci by clinical laboratories appears to be increasing, and, with that, more useful information may be forthcoming from areas in which the prevalence of resistance is unknown.

ACKNOWLEDGMENTS

I acknowledge the helpful discussions and constructive suggestions of Robert Austrian, University of Pennsylvania, Philadelphia; Alexander Tomasz, Emil Gotschlich, and Elaine Tuomanen, Rockefeller University, New York, N.Y.; Peter Appelbaum, Hershey Medical Center, Hershey, Pa.; and Michael Jacobs, Case Western Reserve University, Cleveland, Ohio.

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