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Susceptibility of Respiratory Tract Anaerobes to Orally Administered Penicillins and Cephalosporins

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Anaerobic bacteria recovered from airway-related infections were tested by agar dilution against selected penicillins and cephalosporins available for oral administration. Against 136 isolates, penicillins G and V showed comparable activity, particularly when pharmacological differences were considered. Although many isolates were exquisitely susceptible to the penicillins, only 55% of the *Bacteroides* species and 72% of all isolates were inhibited at 0.5 μg of penicillin G per ml. Results for penicillin V at 1 μg/ml were similar (59 and 73%). The two cephalosporins were more active at achievable levels, inhibiting 94 to 95% of *Bacteroides* and 95 to 96% of all isolates at 8 μg/ml. These levels represent approximately 50% of the reported peak serum levels after oral administration of 625 mg of the penicillins and 500 mg of the cephalosporins. Dicloxacillin and nafcillin were tested against 50 isolates. The two were comparably active on a weight basis; dicloxacillin was more active when pharmacological differences were considered, but did not match the other penicillins or the cephalosporins.

The anaerobic bacteria that populate the oropharyngeal secretions in concentrations of approximately 10^8/mm^3 (18) participate in anaerobic pleuropulmonary infections and infections following human bites as well as in a variety of dental infections, other local infections of the oral cavity, and infections of the paranasal sinuses, middle ear, and facial structures. They may also participate in brain abscesses. Penicillin G is considered the antimicrobial agent of choice for the treatment of most infections due to these organisms (2, 5, 7). Although penicillin may be administered intravenously as the initial therapy for seriously ill patients with pulmonary infections, the course of treatment is often continued by the oral route, particularly in patients requiring long-term antimicrobial therapy of lung abscesses. Some infections associated with the oropharyngeal anaerobes are treated initially by the oral route. In cases in which *Staphylococcus aureus* is suspected or implicated, an orally administered penicillinase-resistant penicillin or cephalosporin may be prescribed. Tetracycline, although occasionally used in these situations, has been shown to be relatively inactive against a number of strains of both *S. aureus* (12) and anaerobic gram-positive cocci (17). Because of potential toxicities, chloramphenicol and clindamycin, although effective against these organisms, should be reserved for life-threatening situations or for those in which an acceptable alternative antibiotic is not available.

Although the in vitro activity of penicillin G, carbenicillin, and the parenteral cephalosporins against anaerobic bacteria has been extensively investigated (21, 24), there is limited published information describing the anti-anaerobic activity of the oral agents penicillin V, cephalexin, and cephradine or of the penicillinase-resistant penicillins. In previous testing in this laboratory, penicillin V, dicloxacillin, and nafcillin were found to be distinctly less active than penicillin G against isolates of *Bacteroides melaninogenicus* and anaerobic gram-positive cocci (4, 6; S. M. Finegold, P. T. Sugihara, and A. B. Miller, Bacteriol. Proc., p. 96, 1967). In another study, Tally et al. showed cephalexin to be the least active of four cephalosporins and the cephamycin cefoxitin tested against 155 clinical strains of anaerobic bacteria (24). In none of these investigations were organisms recovered from airway sources evaluated separately from those recovered from other sources.

We have studied the in vitro activity of the antibiotics penicillin G, penicillin V, cephalexin, cephradine, dicloxacillin, and nafcillin against anaerobic bacteria recovered from patients with airway-related infections.

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MATERIALS AND METHODS

Bacteria. All strains tested were isolated between October 1974 and May 1976 from specimens collected from patients with airway-related infections. All patients were hospitalized at the Wadsworth Hospital Center, Veterans Administration, Los Angeles. Specimen sources included transtracheal aspirates (61 isolates), aspirates obtained through endotracheal or tracheostomy tubes or from bronchoscopy (23 isolates), pleural fluid aspirates (6 isolates), and aspirates of neck or oral wounds occurring in conjunction with major otolaryngological surgery or mandibular osteomyelitis (46 isolates). The isolates were identified by procedures described previously (23), using also criteria of the Virginia Polytechnic Institute and State University Anaerobe Laboratory (11).

The 64 *Bacteroides* species isolated included *B. melaninogenicus* (25 isolates). A total of 13 isolates were identified by the criteria used as *B. oralis* and 12 as *B. ruminicola*. Only two isolates of the *B. fragilis* group (one *B. fragilis* and one *B. thetaiotaomicron*) were recovered from airway-associated infections during this period. Both were isolated from a transtracheal aspirate from one patient. Other *Bacteroides* tested were *B. capillosus* (two isolates), *B. corrodens* (two isolates), *B. pneumosintes* (one isolate), and *Bacteroides* species (eight isolates).

Anaerobic cocci tested included *Peptococcus* species (13 isolates), *Peptostreptococcus* species (14 isolates), and *Veillonella* species (13 isolates). There were 19 gram-positive bacilli: *Eubacterium* species (5 isolates), *Lactobacillus* species (6 isolates), *Propionibacterium* species (5 isolates), and *Actinomyces* species (3 isolates). Thirteen isolates of *Fusobacterium* species completed the total of 136 strains tested against penicillin G, penicillin V, cephalexin, and cephradine.

Fifty of the 136 isolates were also tested against dicloxacillin and nafcillin. These strains included *B. melaninogenicus* (nine isolates), *B. oralis* (eight isolates), *B. ruminicola* (four isolates), and *Bacteroides* species (three isolates). Also tested were *Peptococcus* species (five isolates), *Peptostreptococcus* species (five isolates), *Veillonella* species (five isolates), *Eubacterium* species (two isolates), *Lactobacillus* species (two isolates), *Propionibacterium* species (two isolates), and *Fusobacterium* species (five isolates).

Antibiotics. Laboratory standard powders of penicillin G, penicillin V, and cephalexin were supplied by Lilly Research Laboratories, Indianapolis, Ind. Cephradine was supplied by the Squibb Institute for Medical Research, Princeton, N.J.; sodium dicloxacillin by Ayerst Laboratories, New York, N.Y.; and sodium nafcillin by Wyeth Laboratories, Philadelphia, Pa. Antibiotic stock solutions (1,280 μg/ml) were prepared, using phosphate-buffered saline, pH 6.0, for the initial dilution of dicloxacillin and penicillin V and sterile distilled water for the other antibiotics. Solutions were either prepared on the day of inoculation or stored at −20°C for a maximum of 30 days prior to use. All antibiotics were tested in concentrations from 64 to 0.125 μg/ml.

Antimicrobial susceptibility tests. Minimal inhibitory concentrations were determined by the agar dilution method as previously described (23). Rapidly growing strains were incubated for 4 to 6 h, and slowly growing strains were incubated for 18 to 24 h prior to inoculation. All cultures were adjusted to one-half the turbidity of the number 1 McFarland standard to give an inoculum of 10^5 to 10^6 colony-forming units when the organisms were inoculated by means of a Steers replicator (20).

RESULTS

Against the 64 *Bacteroides* species tested (Fig. 1), penicillin G and penicillin V showed equivalent activity on a weight basis. Only at ≥16 μg of either agent per ml were over 90% of the strains inhibited. Cephalexin and cephradine likewise showed comparable activity although >90% inhibition was achieved at 4 μg of cephradine per ml and 8 μg of cephalexin per ml. Both isolates of *B. fragilis* tested were resistant to both the penicillins and cephalosporins. Additionally, approximately one-third of the isolates of *B. melaninogenicus* and *Bacteroides* species were resistant to levels of penicillin G or penicillin V achievable after oral administration of these agents. At concentrations below 16 μg/ml, the penicillinase-resistant penicillins were distinctly less active than either the cephpalosporins or penicillin G or V.

Against *Fusobacterium* species, penicillin G was slightly more active than penicillin V at concentrations ≤0.5 μg/ml, but the two antibiotics were equivalent at higher levels (Fig. 2). The cephalosporins both inhibited all 13 strains tested at ≤2 μg/ml. Nafcillin showed more activity on a weight basis than did dicloxacillin against the five *Fusobacterium* isolates tested with these two agents.

Although penicillins G and V were inhibitory to the gram-positive anaerobic bacilli examined (Fig. 3) at lower levels than were the cephalosporins, >90% of these organisms were inhibited by readily achievable blood levels of all four agents. On a weight basis, nafcillin appeared slightly more active than dicloxacillin against these organisms.

The *Peptococcus* species and *Peptostreptococcus* species studied (Fig. 4) were again considerably more susceptible to penicillins G and V at low levels than to the cephalosporins at the same concentrations. In addition, the cephalosporins had minimal inhibitory concentrations of ≥32 μg/ml against three strains (one *Peptococcus variabilis*, one *P. asaccharolyticus*,

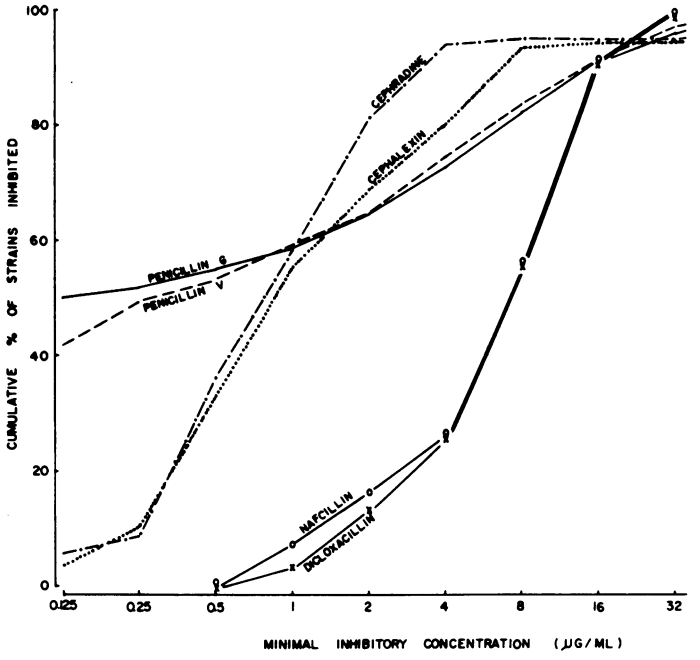

FIG. 1. *Antibiotic susceptibility patterns of Bacteroides species from airway-related infections (64 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 24 strains tested against dicloxacillin and nafcillin).*

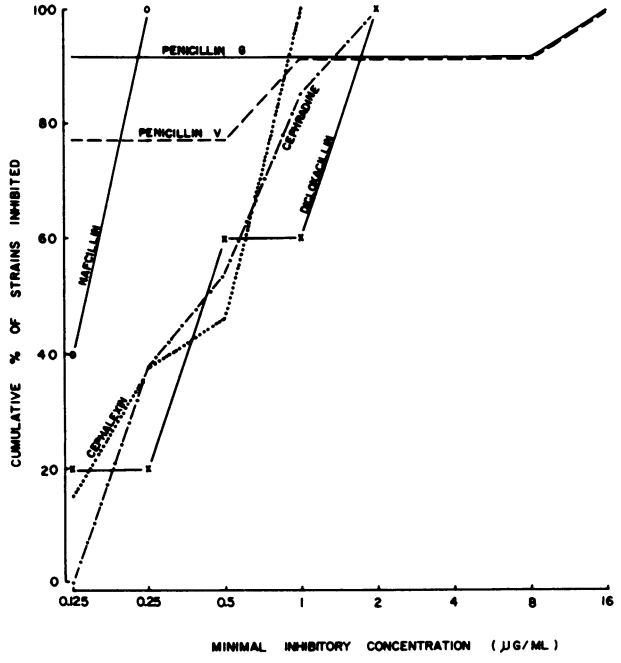

FIG. 2. *Antibiotic susceptibility patterns of Fusobacterium species from airway-related infections (13 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 5 strains tested against dicloxacillin and nafcillin).*

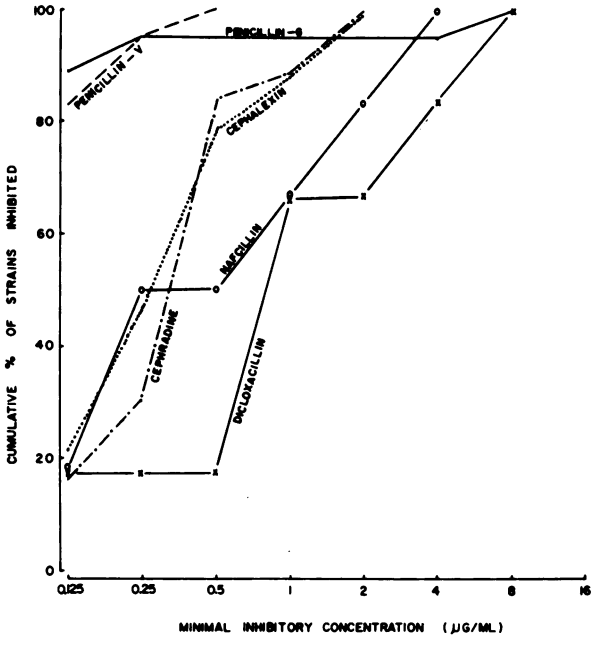

FIG. 3. *Antibiotic susceptibility patterns of anaerobic gram-positive bacilli from airway-related infections (19 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 6 strains tested against dicloxacillin and nafcillin).*

and one *Peptostreptococcus micros*). In testing against 10 of the anaerobic gram-positive cocci, the penicillinase-resistant penicillins demonstrated activity equivalent to or slightly better than that of the cephalosporins.

Equal concentrations of penicillin G, cephalexin, and cephradine showed similar activity against 13 isolates of *Veillonella* species (Fig. 5). Penicillin V was somewhat less active against these organisms. The five isolates tested against dicloxacillin and nafcillin were distinctly resistant to these antibiotics.

The pattern of activity of the six antibiotics tested against the entire panel of organisms (Fig. 6) indicates the general equivalence of penicillin G with penicillin V, of cephalexin with cephradine, and of nafcillin with dicloxacillin (when considered on a weight basis).

DISCUSSION

An interpretation of antimicrobial susceptibility test results requires comparison of the minimal inhibitory and/or minimal bactericidal concentrations achieved by an antimicrobial agent with the pharmacological characteristics of the drug. Break points for susceptibility are generally defined in relation to achievable serum levels of the agent tested. Although organisms inhibited by ≤ 0.25 μg of penicillin G per ml have been considered susceptible for purposes of oral therapy of mild infections (3), similar criteria have not been proposed for penicillin V, the orally administered cephalosporins, or penicillinase-resistant penicillins. Table 1 shows the inhibition of the anaerobes tested in this study by penicillins G and V and the oral cephalosporins at approximately 50 and 100% of the reported peak serum levels achieved after a 625-mg oral dose of the penicillins (14) or a 500-mg oral dose of the cephalosporins (10). At these levels, penicillin G was slightly more active than penicillin V against *Veillonella* species, but the two were otherwise equivalent. Even at peak levels, only 58 to 64% of all *Bacteroides* tested were inhibited by these antibiotics. In contrast, the cephalosporins inhibited 95% of the *Bacteroides* strains and all isolates of *Veillonella* at peak levels and were comparably active at 50% of the peak levels. At 16 μg/ml, the only isolates not inhibited by the cephalosporins were the two *B. fragilis* strains, one *B. oralis*, one *P. variabilis*, one *P. asaccharolyticus*, and one *P. micros*. The two cephalosporins showed no important differences in activity. Both were more active against the airway-associated anaerobes examined in this study than was cephalexin in testing against a panel of anaerobes isolated from all clinical sources by Tally et al. (24). This may be explained in part by the small numbers of *B.*

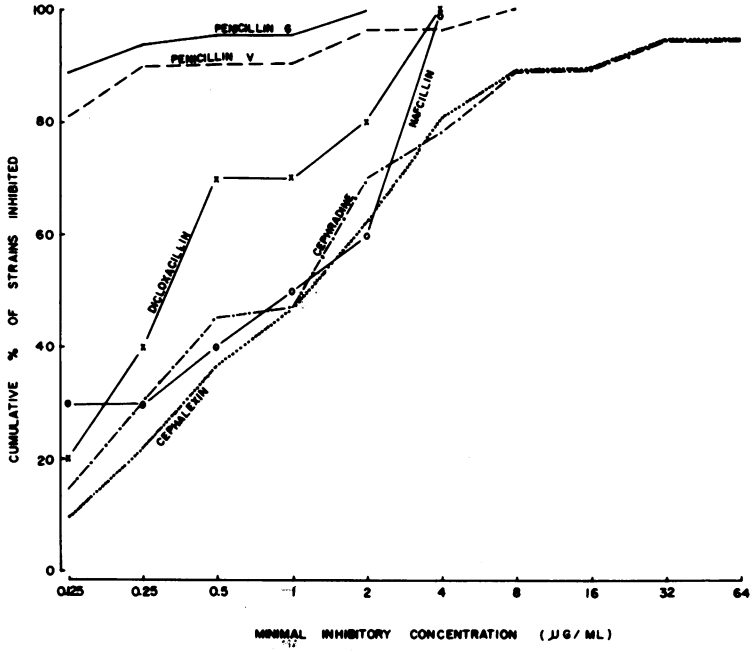

FIG. 4. *Antibiotic susceptibility patterns of anaerobic gram-positive cocci from airway-related infections (27 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 10 strains tested against dicloxacillin and nafcillin).*

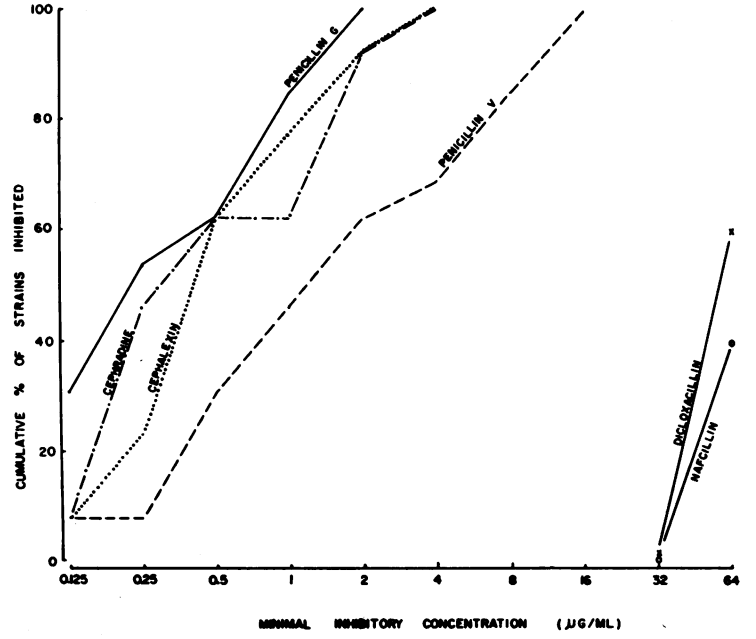

FIG. 5. *Antibiotic susceptibility patterns of Veillonella species from airway-related infections (13 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 5 strains tested against dicloxacillin and nafcillin).*

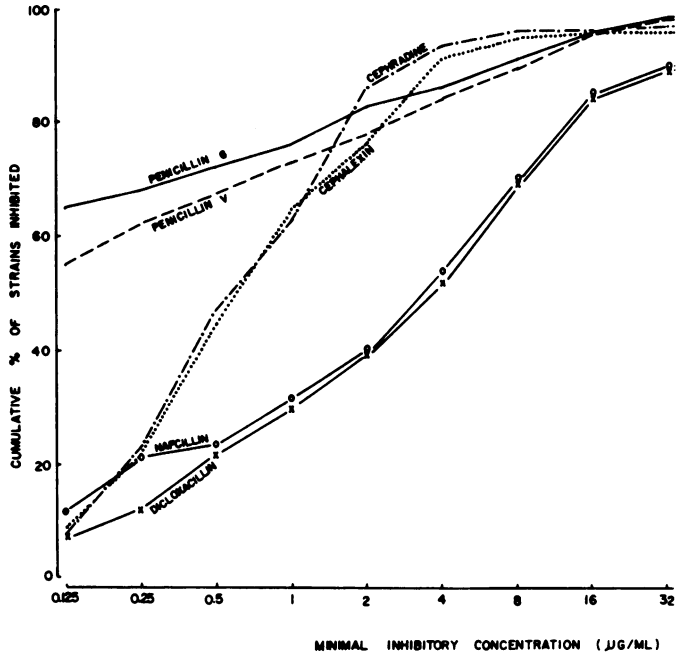

FIG. 6. *Composite antibiotic susceptibility patterns of anaerobic bacteria recovered from airway-related infections (136 strains tested against penicillin G, penicillin V, cephalexin, and cephradine; 50 strains tested against dicloxacillin and nafcillin).*

TABLE 1. *Antibiotic susceptibility of 136 anaerobic bacteria from airway-related infections to penicillins and cephalosporins at approximately 50 and 100% of the peak serum concentrations achieved after a 500-mg oral dose of cephalosporin or a 625-mg oral dose of penicillin given every 6 h (10, 14)*

Antibiotic	Peak serum level (μg/ml)	Level tested (μg/ml)	% of peak level	% Susceptible					
				Bacteroides species (64 strains)	*Fusobacterium* species (13 strains)	Anaerobic gram-positive bacilli (19 strains)	Anaerobic gram-positive cocci (27 strains)	*Veillonella* species (13 strains)	All organisms (136 strains)
Penicillin G	0.81	0.5	62	55	92	95	96	62	72
		1	123	58	92	95	96	85	76
Penicillin V	1.56	1	64	59	92	100	89	46	73
		2	128	64	92	100	96	62	78
Cephalexin	19.8	8	40	94	100	100	89	100	95
		16	81	95	100	100	89	100	96
Cephradine	19.2	8	42	95	100	100	89	100	96
		16	83	95	100	100	89	100	96

fragilis and the absence of *Clostridium* species in the present study. The possibility that strains of anaerobic species isolated from airway sources may be more susceptible to certain antibiotics than their counterparts at other sites has not been evaluated.

Data from 50 isolates tested against dicloxacillin and nafcillin (Table 2) show inferior activity of the latter antibiotic. Although nafcillin was generally as active as dicloxacillin on a weight basis, the lower peak levels reportedly achieved by orally administered nafcillin (even when given with probenecid) (8, 9) resulted in the lower activity of nafcillin recorded in this table. Dicloxacillin was less active than the cephalosporins against *Bacteroides* species and was inactive against *Veillonella* species.

The susceptibility to penicillin G of the *Bacteroides* species tested in this study is similar to that recorded by Staneck and Washington in 1974 (19). These strains are, however, more resistant than those tested by Finegold and

TABLE 2. *Antibiotic susceptibility of 50 anaerobic isolates from airway-related infections to dicloxacillin and nafcillin at approximately 50 and 100% of the peak serum concentrations achieved after a 500-mg oral dose given every 6 h (8, 9)*

Antibiotic	Peak serum level (μg/ml)	Serum level (μg/ml)	% of peak level	% Susceptible					
				Bacteroides species (24 strains)	*Fusobacterium* species (5 strains)	Anaerobic gram-positive bacilli (6 strains)	Anaerobic gram-positive cocci (10 strains)	*Veillonella* species (5 strains)	All organisms (50 strains)
Dicloxacillin	17	8	47	58	100	100	100	0	70
		16	94	92	100	100	100	0	86
Nafcillin[a]	0.8	0.5	62	0	100	50	40	0	24
		1.0	125	8	100	67	50	0	32

[a] Given with probenecid.

Sutter in 1972 (6); in that study, only 2 of 44 isolates of *B. melaninogenicus* and *B. oralis* were not inhibited by ≤0.8 μg of penicillin G per ml. As 92% of the 64 *Bacteroides* strains tested in the present study were inhibited by penicillin G at 16 μg/ml and only two strains were resistant at 32 μg/ml, this resistance should be considered relative; these levels can be effectively achieved in serum with the use of intermittently administered intravenous penicillin. Ampicillin, amoxicillin, and carbenicillin, although not tested in this study, have been shown to have activity generally comparable on a weight basis to that of penicillin G against anaerobic bacteria in general and *Bacteroides* species in particular (22). After the oral administration of 500 mg, the following approximate peak serum levels may be achieved: ampicillin, 4.5 μg/ml (16); amoxicillin, 9.3 μg/ml (16); and indanyl carbenicillin, 6 μg/ml (13). These are all levels considerably higher than those achieved by penicillins G or V after oral administration.

Penicillin G is currently the antibiotic of choice for pulmonary infections involving anaerobic bacteria. To date, this drug has been effective in the treatment of a limited number of anaerobic pulmonary infections, even when *B. fragilis* was isolated as part of a mixed flora (2). This organism, although not normally resident in the upper airway, has been recovered in 15 to 20% of the anaerobic pleuropulmonary infections in two series (1, 15) and is generally resistant to penicillin G. The importance of the increasingly resistant strains of other *Bacteroides* species in airway-associated infections has not yet been established. The presence of these organisms should be considered in patients not responding to low-dose parenteral or oral penicillin therapy given for anaerobic pleuropulmonary infections or other anaerobic infections associated with oropharyngeal flora. Other orally administered penicillins such as ampicillin, amoxicillin, or carbenicillin may be useful in these circumstances because of the higher serum levels achieved by these agents; however, there is at present little or no recorded clinical experience in treating anaerobic infections with amoxicillin or oral carbenicillin. The oral cephalosporins may provide another alternative to the institution of high-dose intravenous penicillin therapy or the use of a potentially more toxic antibiotic such as clindamycin or chloramphenicol. The cephalosporins may also be satisfactory agents for the therapy of certain mixed aerobic and anaerobic infections involving the oropharyngeal flora and, for example, *S. aureus*. They may also be considered in the initial treatment of these infections in selected penicillin-allergic patients.

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