# BACTERIAL ANTIBIOTIC RESISTANCE BEFORE AND AFTER CLINICAL APPLICATION IN THE UNITED STATES*

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EXTENSIVE *in vitro* studies are normally performed before an antimicrobial agent is released for general clinical use. Such studies usually document a very low incidence of resistant strains among those species normally susceptible to the new agent. After release of these drugs, widespread use could affect the prevalence of preexisting resistant strains. Several years of widespread use may be required to influence selectively the incidence of resistance among strains within different institutions.

In 1976 our group began a series of collaborative studies designed to evaluate newer antimicrobial agents against large samples of commonly isolated, unselected bacterial pathogens. Between 1976 and 1985 several antimicrobial agents have been evaluated on two or three different occasions. Most of the newer $\beta$-lactam agents were tested before the United States Food and Drug Administration approved their release for clinical applications. Most drugs were then reevaluated three to five years after their release. In this report we review our records to determine whether the *in vitro* activity of these agents has been altered over the years. We accumulated data with 11 different antimicrobial agents including piperacillin, carbenicillin, ticarcillin, gentamicin, amikacin, cephalothin, cefamandole, cefotaxime, moxalactam, cefoperazone, and ceftazidime. Changes in the prevalence of resistance among six different species of Gram-negative bacilli was assessed.

## MATERIALS AND METHODS

*Study designs.* The Collaborative Antimicrobial Susceptibility Testing Group represents a group of clinical microbiologists who systematically evaluate the *in vitro* activity of the newer antimicrobial agents. Members of

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TABLE I. PARTICIPANTS IN *IN VITRO* STUDIES OF CLINICAL BACTERIAL ISOLATES FOR THE COLLABORATIVE ANTIMICROBIAL SUSCEPTIBILITY TESTING GROUP, 1976 to 1985

| *Laboratory director* | *Institution and location* |
|---|---|
| L. W. Ayers | The Ohio State University Medical Center, Columbus, Ohio |
| A. L. Barry | The University of California at Davis, Sacramento Medical Center, Sacramento, California |
| P. C. Fuchs | St. Vincent Hospital and Medical Center, Portland, Oregon |
| T. L. Gavan | The Cleveland Clinic Foundation, Cleveland, Ohio |
| E. H. Gerlach | St. Francis Hospital and Medical Center, Wichita, Kansas |
| R. N. Jones | Kaiser Permanente Regional Laboratory (Oregon Region), Clackamas, Oregon |
| H. M. Sommers | Northwestern Memorial Hospital, Chicago, Illinois |

the Group are all directors of clinical microbiology laboratories that routinely perform quantitative antimicrobial susceptibility tests by standardized broth microdilution or agar dilution methods. All facilities strictly adhere to procedures defined by the National Committee for Clinical Laboratory Standards.[1] Table I identifies the individuals and institutions that have participated in the studies that we review in this manuscript. Three primary teaching hospitals, two institutions with large outpatient work loads, and two private hospitals are represented. The study centers are located in Ohio, Illinois, Kansas, California, and Oregon.

One to three collaborative studies have been performed each year since 1976. For each study, four to six different medical centers participated. Over a 30-to-60-day period of time each laboratory tested all bacterial isolates normally selected for routine susceptibility tests. Each study involved quantitative tests with a study drug and two established comparison drugs. Standard quality control strains were tested at regular intervals while the data were being collected. A single study normally accumulated information with 5,000 to 10,000 bacterial isolates. This represents a good cross-section of the more common bacterial pathogens encountered in the study centers and at most other medical centers at the time of the drug evaluation.

*Data analysis. In vitro* tests with six different bacterial species were selected for analysis, i.e., *Escherichia coli, Citrobacter freundii, Enterobacter cloacae, Klebsiella pneumoniae, Serratia marcescens,* and *Pseudomonas aeruginosa.* These species were evaluated because of their high prevalence

in clinical material and because antibiotic-resistant strains belonging to these species have been reported to be endemic or epidemic in some institutions. Data with Gram-positive bacteria were not evaluated because of the lack of urgent clinical concerns about antibiotic resistance, with the exception of methicillin-resistant *Staphylococcus* sp. The drugs evaluated were limited to those that we have studied at least twice over a three-to-five-year period.

The results were expressed as the percent of strains inhibited by MIC breakpoint concentrations defined by the National Committee for Clinical Laboratory Standards.[1] This permits assessment of strains in the intermediate or moderately susceptible category, separate from those in the resistant or susceptible categories. The percentage of strains susceptible to designated concentrations was calculated separately for each participating medical center, and the average of these percentages is presented. The spread of percentage values from different medical centers was examined. When the percent of susceptible strains in one medical center was more than 10% below that reported in other centers, it was assumed that the institution was encountering multiple isolates of a unique endemic antibiotic-resistant strain. Consequently, data from that institution were excluded and the average percentage of susceptible strains was recalculated: those data were presented parenthetically.

## RESULTS

*Ticarcillin.* Three separate studies in 1976, 1983, and 1985 involved tests with ticarcillin.[2-4] Table II summarizes the results of such tests with six different species of Gram-negative bacilli. Among *E. coli, C. freundii*, and *E. cloacae* isolates there was a slight decrease in the proportion of susceptible strains, but no substantial change was seen with the other species evaluated. One institution which did not participate in the initial 1976 study reported an unusually high incidence of resistance to ticarcillin, especially in the 1985 study. Presumably, that institution was encountering endemic $\beta$-lactamase-producing strains which skewed the overall efficacy figures for ticarcillin in 1985. When data from that medical center were excluded, the proportion of susceptible strains did not change substantially over the years. Ticarcillin remained effective against 87 to 90% of all *P. aeruginosa* isolates (MIC $\leq$ 64 $\mu$g/ml) and at 16 $\mu$g/ml approximately 80% of the *Enterobacteriaceae*, other than *K. pneumoniae*, were susceptible to ticarcillin.

*Piperacillin and carbenicillin.* Before its release, piperacillin was compared to carbenicillin,[5] and the same comparison was performed four years later.[6] Table III summarizes the results of those two studies. Piperacillin

TABLE II. TICARCILLIN SUSCEPTIBILITY IN 1976, 1983, AND 1985

| *Species* *Year tested* | *Total No. of isolates* | *%* Inhibited by (μg/ml)* ≤16 | ≤32 | ≤64 |
|---|---|---|---|---|
| *E. coli* | | | | |
| 1976 | 2,989 | 84 | 85 | 85 |
| 1983 | 1,872 | 77 | 78 | 78 |
| 1985 | 2,059 (1728)** | 77 (79)** | 77 (80) | NT† |
| *C. freundii* | | | | |
| 1976 | 110 | 79 | 81 | 85 |
| 1983 | 199 (135) | 75 (80) | 77 (81) | 85 (89) |
| 1985 | 130 (94) | 66 (72) | 77 (83) | NT |
| *E. cloacae* | | | | |
| 1976 | 209 | 86 | 89 | 89 |
| 1983 | 530 | 75 | 76 | 79 |
| 1985 | 345 (209) | 74 (80) | 76 (82) | NT |
| *K. pneumoniae* | | | | |
| 1976 | 810 | 4 | 10 | 24 |
| 1983 | 905 | 2 | 10 | 25 |
| 1985 | 514 | 6 | 11 | NT |
| *S. marcescens* | | | | |
| 1976 | 146 | 81 | 83 | 84 |
| 1983 | 309 | 81 | 83 | 85 |
| 1985 | 177 (137) | 83 (92) | 87 (93) | NT |
| *P. aeruginosa* | | | | |
| 1976 | 718 | 43 | 70 | 87 |
| 1983 | 1,337 (928) | 59 (64) | 76 (82) | 89 (90) |
| 1985 | 672 (554) | 45 (47) | 71 (75) | NT |

*Average of values calculated separately for each participating institution

**Numbers in parenthesis represent values calculated after excluding data from one institution with a unique endemic resistant strain. That institution did not participate in the 1976 study.

†Not tested at 64 μg/ml in the 1985 study

was initially effective against 82 to 98% of the *Enterobacteriaceae*, at 16 μg/ml, and 95% to 99% of *P. aeruginosa* isolates were susceptible to 64 μg/ml. Carbenicillin was much less active than piperacillin. Four years later there was a slight decrease in the proportion of strains susceptible to both penicillins. That was due to endemic strains reported in two medical centers. The overall efficacy of both drugs has not been seriously compromised during the four-year period between evaluations.

*Gentamicin and amikacin.* Table IV presents the results of separate studies performed in 1978, 1979, and 1983.[7-10] Both aminoglycosides remained highly effective against most *Enterobacteriaceae*. However, amikacin appeared to be superior to gentamicin against *S. marcescens* and *P. aeruginosa* isolates. When data from institutions with unique endemic strains were ex-

TABLE III. PIPERACILLIN AND CARBENICILLIN SUSCEPTIBILITY IN 1978 AND 1982

| Species Year tested | Total No. of isolates | | %* Inhibited by (μg/ml): Piperacillin ≤16 | | Piperacillin ≤64 | | Carbenicillin ≤16 | | Carbenicillin ≤32** | | Carbenicillin ≤128† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *E. coli* | | | | | | | | | | | | |
| 1978 | 3,461 | | 87 | | 94 | | 83 | | 84 | | 85 | |
| 1982 | 1,411 | | 82 | | 90 | | 73 | | 74 | | 75 | |
| *C. freundii* | | | | | | | | | | | | |
| 1978 | 140 | | 94 | | 98 | | 79 | | 83 | | 93 | |
| 1982 | 118 | (49)‡ | 75 | (82)‡ | 78 | (84) | 57 | (71) | 61 | (79) | 76 | (86) |
| *E. cloacae* | | | | | | | | | | | | |
| 1978 | 245 | | 93 | | 96 | | 84 | | 88 | | 97 | |
| 1982 | 278 | | 86 | | 90 | | 74 | | 78 | | 88 | |
| *K. pneumoniae* | | | | | | | | | | | | |
| 1978 | 1,313 | | 91 | | 96 | | 4 | | 9 | | 52 | |
| 1982 | 602 | | 92 | | 96 | | 4 | | 7 | | 43 | |
| *S. marcescens* | | | | | | | | | | | | |
| 1978 | 194 | | 98 | | 100 | | 90 | | 94 | | 97 | |
| 1982 | 161 | | 95 | | 97 | | 80 | | 84 | | 92 | |
| *P. aeruginosa* | | | | | | | | | | | | |
| 1978 | 1,582 | | 94 | | 99 | | 11 | | 48 | | 88 | |
| 1982 | 817 | (606) | 89 | (91) | 95 | (96) | 11 | (14) | 46 | (49) | 89 | (91) |

*Average of values calculated separately for each participating institution
**Susceptible or moderately susceptible for the *Enterobacteriaceae*
†Susceptible for *Pseudomonas* sp only
‡Numbers in parenthesis represent values calculated after excluding data from institutions with a unique endemic resistant strain.

cluded, the two aminoglycosides were nearly comparable and the proportion of susceptible strains did not change over time.

Table V presents a more detailed examination of gentamicin susceptibility data reported by six different study centers. All six centers participated in five different studies.[7,8,11-13] Species other than *S. marcescens* and *P. aeruginosa* were uniformly susceptible to gentamicin.

In the initial (1978) study, one medical center (laboratory E) reported that approximately one half of their *P. aeruginosa* isolates were resistant to gentamicin whereas 81% to 100% of the isolates were susceptible in the other study centers during the same period of time. In subsequent studies laboratory E reported 93% to 99% of their *P. aeruginosa* isolates susceptible to gentamicin. In the middle of 1979 laboratory D reported a sharp decline in the percentage of gentamicin-susceptible *P. aeruginosa* and in 1981 two other laboratories (A and F) reported a similar decline. Such endemic problems

TABLE IV. GENTAMICIN AND AMIKACIN SUSCEPTIBILITY IN 1978, 1979, AND 1983

| Species Year tested | %* Inhibited by (μg/ml): Gentamicin No. tested | ≤4 | ≤8 | Amikacin No. tested | ≤16 | ≤32 |
|---|---|---|---|---|---|---|
| *E. coli* | | | | | | |
| 1978 | 3,752 | 99 | 100 | 3,807 | 99 | 100 |
| 1979 | 3,654 | 99 | 99 | 3,632 | 99 | 100 |
| 1983 | 2,766 | 100 | 100 | 1,977 | 100 | NT** |
| *C. freundii* | | | | | | |
| 1978 | 179 | 90 | 90 | 183 | 99 | 99 |
| 1979 | 127 | 100 | 100 | 129 | 100 | 100 |
| 1983 | 86 | 96 | 96 | 61 | 98 | NT |
| *E. cloacae* | | | | | | |
| 1978 | 351 | 99 | 99 | 311 | 99 | 99 |
| 1979 | 406 | 96 | 97 | 405 | 100 | 100 |
| 1983 | 300 | 98 | 98 | 187 | 100 | NT |
| *K. pneumoniae* | | | | | | |
| 1978 | 1,148 | 98 | 98 | 863 | 100 | 100 |
| 1979 | 1,009 | 97 | 97 | 1,003 | 99 | 100 |
| 1983 | 764 | 99 | 100 | 419 | 100 | NT |
| *S. marcescens* | | | | | | |
| 1978 | 315 (224)† | 83 (93)† | 88 (96) | 333 | 98 | 99 |
| 1979 | 433 (330) | 85 (98) | 83 (99) | 431 | 96 | 99 |
| 1983 | 204 (159) | 89 (98) | 89 (98) | 189 | 98 | NT |
| *P. aeruginosa* | | | | | | |
| 1978 | 1,344 (1002) | 63 (72) | 81 (87) | 1,403 | 89 | 94 |
| 1979 | 880 (494) | 81 (85) | 93 (97) | 870 | 94 | 98 |
| 1983 | 723 | 82 | 93 | 565 | 98 | NT |

*Average of values calculated separately for each participating institution

**Not tested, the intermediate concentration of 32μg amikacin per ml was not tested in 1983.

†Numbers in parenthesis represent values calculated after excluding data from institutions with a unique resistant strain.

resulted in marked differences in the incidence of gentamicin-resistant *P. aeruginosa* in different institutions or in one institution at different time intervals. If these endemic problems are excluded, the incidence of susceptibility remains quite constant.

*S. marcescens* isolates were generally susceptible to gentamicin. However, one laboratory found 60% to 63% of their *S. marcescens* resistant to gentamicin. This strain was found capable of producing several aminoglycoside-inactivating enzymes which made it resistant to all aminoglycosides other than amikacin. Multiple isolates of that single strain within one medical center influenced the combined test results throughout the study period (1978 to 1981). A similar strain appeared in laboratory D during 1978 and 1979, but

it was rarely encountered in 1981. In the absence of endemic spread of resistant strains within the four other institutions that contributed to these studies, gentamicin remained very active against *S. marcescens*.

*Cephalothin and cefamandole*. Data obtained with cephalothin[12,14,15] and with cefamandole[14,15,16] are summarized in Table VI. Over the four years between the first and the last test with both drugs, we found no important changes in the incidence of resistance to either drug. The apparent *in vitro* activity of cefamandole against *E. cloacae* had not changed substantially. However, when broth microdilution tests were used, only 67 to 70% of the *E. cloacae* were inhibited by cefamandole: 83-88% were considered susceptible when agar dilution methods were used. Only two laboratories participated in the 1976 study and both used broth microdilution procedures. Agar dilution tests were added in later studies. Because of the greater susceptibility reported by laboratories using agar dilution methods, one could be misled to conclude that resistance among *E. cloacae* isolates had actually decreased with time. No such change can be documented when methodological differences are considered.

*Third generation cephalosporins*. Prerelease studies were performed with cefotaxime,[11] moxalactam,[16] cefoperazone,[12] and ceftazidime.[13] With each drug two follow-up studies have been performed.[17,18] Postrelease studies with ceftazidime have not yet been done by our group, but a second prerelease study was performed four years after the first study. These data are presented in Tables VII and VIII. *C. freundii* and *E. cloacae* isolates appeared to decrease in their susceptibility to all four drugs during the years following the initial prerelease studies. However, we could clearly identify an endemic resistant strain within one of the participating institutions, and when that endemic situation was removed from our data base the efficacy of all four drugs remained essentially unchanged.

*P. aeruginosa* isolates were not as susceptible to cefotaxime, cefoperazone, or ceftazidime in 1984 as in the initial studies. This decrease in susceptibility could not be traced to a single endemic strain in any one of the participating institutions. Initially, 97% of *P. aeruginosa* isolates were susceptible to ceftazidime, but four years later only 89% were susceptible (8% decrease). In four institutions that participated in both studies, the percent of ceftazidime-susceptible strains of *P. aeruginosa* decreased by 3% to 15%. *P. aeruginosa* susceptibility to cefoperazone also diminished over the years (93% to 85%). Among the four institutions that contributed to both studies, the changes in susceptibility of *P. aeruginosa* to cefoperazone varied from a 2% decrease to a 14% decrease. One institution reported that *P. aeruginosa*

TABLE V. GENTAMICIN SUSCEPTIBILITY AMONG *P. AERUGINOSA* AND *S. MARCESCENS* ISOLATES IN SIX DIFFERENT MEDICAL CENTERS* FROM 1978 TO 1981

| *Species* / *Year tested*** | *% Inhibited by 8.0 μg gentamicin per ml* | | | | | |
|---|---|---|---|---|---|---|
| | *Lab A* | *Lab B* | *Lab C* | *Lab D* | *Lab E* | *Lab F* |
| *P. aeruginosa* | | | | | | |
| 1978 | 81 | 82 | 92 | 81 | 49 | 100 |
| 1979-1 | 75 | 98 | 96 | 97 | 93 | 100 |
| 1979-2 | 85 | 97 | 96 | 75 | 97 | 95 |
| 1979-3 | 99 | 87 | 89 | 78 | 99 | 97 |
| 1981 | 81 | 92 | 79 | 95 | 95 | 71 |
| *S. marcescens* | | | | | | |
| 1978 | 100 | 92 | 75 | 67 | 80 | 100 |
| 1979-1 | 98 | 100 | 32 | 100 | 100 | 100 |
| 1979-2 | 98 | 100 | 40 | 73 | 97 | 100 |
| 1979-3 | 98 | 92 | 45 | 77 | 100 | 100 |
| 1981 | 99 | 100 | 53 | 96 | 100 | 100 |

*Laboratories A, B, and C utilized microdilution methods, laboratories D, E, and F used an agar dilution method.

**All six laboratories participated in three separate studies in 1979.

susceptibility to cefoperazone decreased from 97% to 83%. The following year that institution found that 95% of their *P. aeruginosa* isolates were susceptible to cefoperazone (based on tests with 779 isolates compared to 87 isolates sampled in 1984). Also, such a decline in susceptibility to cefoperazone was not observed when a much larger nationwide data base was reviewed by Jones.[19]

## Discussion

The *in vitro* data included in this report were obtained with well standardized, carefully controlled testing procedures. Most surveys of this nature utilize data collected from routine susceptibility tests of unknown reliability.[20] We have made every effort to minimize technical variables which might have resulted in artificial fluctuations in the incidence of resistant strains in different institutions or during different periods of time. We have also attempted to identify uniquely resistant strains that might be endemic in one or more of the institutions sampled.

We have evaluated the *in vitro* activity of 11 antimicrobial agents against six different species of commonly isolated Gram-negative bacilli. Studies performed over a three-to-five-year period of time were compared to determine whether the incidence of antibiotic resistance has changed with time. With some drugs we were able to document the prevalence of resistant strains be-

TABLE VI. CEPHALOTHIN AND CEFAMANDOLE SUSCEPTIBILITY IN 1976, 1979, AND 1980

| Species Year tested | Cephalothin | | Cefamadole | |
|---|---|---|---|---|
| | *No. of isolates* | *% Inhibited by ≤8.0 μg/ml* | *No. of isolates* | *% Inhibited by ≤8.0 μg/ml* |
| *E. coli* | | | | |
| 1976 | 1,595 | 83 | 1,595 | 98 |
| 1979 | 2,742 | 82 | 2,560 | 96 |
| 1980 | 2,700 | 86 | 2,700 | 98 |
| *C. freundii* | | | | |
| 1976 | 68 | 0 | 29 | 90 |
| 1979 | 102 | 16 | 109 | 74 |
| 1980 | 87 | 7 | 87 | 82 |
| *E. cloacae* | | | | |
| 1976 | 40 | 0 | 40 | 68* |
| 1979 | 299 | 4 | 201 | 78** |
| 1980 | 259 | 5 | 259 | 77† |
| *K. pneumoniae* | | | | |
| 1976 | 203 | 95 | 203 | 98 |
| 1979 | 794 | 88 | 570 | 94 |
| 1980 | 590 | 91 | 590 | 96 |
| *S. marcescens* | | | | |
| 1976 | 7 | 0 | 7 | 29 |
| 1979 | 181 | 5 | 226 | 10 |
| 1980 | 115 | 0 | 115 | 1 |

*All tests done by broth dilution methods.
**70% susceptible by broth dilution methods, 88% susceptible by agar dilution.
†67% susceptible by broth dilution methods, 83% susceptible by agar dilution.

fore the drug was released and then three to five years later. Our data failed to confirm the common assumption that the incidence of resistant strains would markedly increase after limited or widespread use of the antibiotic within a patient population. Actual antibiotic utilization records from the seven participating institutions are not available to us. However, these newer agents were widely utilized as they were released for clinical application. It is possible that continued use of the newer β-lactams might eventually select resistant populations of bacteria in some institutions. Although we could find no substantial widespread change over the 10-year period, endemic resistant strains did occur sporadically in some institutions.

To obtain a valid estimate of the true prevalence of resistant strains within our participating institutions, data gathered from four to six different centers were combined for each study period. On several occasions we noted the

TABLE VII. CEFOTAXIME AND MOXALACTAM SUSCEPTIBILITY IN 1979, 1980, AND 1984

| | *Cefotaxime* | | | | *Moxalactam* | | | |
|---|---|---|---|---|---|---|---|---|
| *Species* | *No. of* | *%* Inhibited by:* | | | *No. of* | *%* Inhibited by:* | | |
| *Year tested* | *isolates* | *≤8* | | *≤32* | *isolates* | *≤8* | | *≤32* |
| *E. coli* | | | | | | | | |
| 1979 | 2,805 | 99 | | 99 | 2,572 | 99 | | 100 |
| 1980 | 1,882 | 99 | | 100 | 1,833 | 99 | | 99 |
| 1984** | 2,049 | 99 | | 99 | 1,402 | 99 | | NT† |
| *C. freundii* | | | | | | | | |
| 1979 | 167 | 97 | | 99 | 110 | 99 | | 100 |
| 1980 | 67 | 96 | | 97 | 67 | 99 | | 100 |
| 1984 | 83 | 91 | | 96 | 240 | 97 | | NT |
| *E. cloacae* | | | | | | | | |
| 1979 | 433 | 95 | | 98 | 201 | 91 | | 98 |
| 1980 | 209 | 92 | | 95 | 206 | 94 | | 100 |
| 1984 | 223 (124)‡ | 76 | (90) | 86 (91) | 302 (206) | 87 | (94) | NT |
| *K. pneumoniae* | | | | | | | | |
| 1979 | 997 | 99 | | 100 | 570 | 98 | | 99 |
| 1980 | 472 | 100 | | 100 | 460 | 99 | | 99 |
| 1984 | 498 | 98 | | 99 | 488 | 99 | | NT |
| *S. marcescens* | | | | | | | | |
| 1979 | 264 | 96 | | 98 | 227 | 93 | | 99 |
| 1980 | 67 | 93 | | 97 | 60 | 98 | | 100 |
| 1984 | 109 | 93 | | 98 | 212 | 98 | | NT |
| *P. aeruginosa* | | | | | | | | |
| 1979 | 820 | 33 | | 88 | 638 | 28 | | 78 |
| 1980 | 289 | 36 | | 85 | 277 | 25 | | 79 |
| 1984 | 677 | 19 | | 76 | 730 | 26 | | NT |

*Average of values calculated separately for each participating institution.

**Two separate studies in 1984: one included cefotaxime, the other included moxalactam.

† Not tested at 32 μg/ml in the 1984 study.

‡Numbers in parenthesis represent values calculated after excluding data from institutions with a unique resistant strain.

sporadic appearance of unusually resistant strains within some institutions, but not within others, during the same study period. Within one institution multiple isolates of the same resistant strain can and has greatly influenced the apparent *in vitro* effectiveness of an antimicrobial agent. By averaging values separately calculated for each institution, we minimized but did not eliminate the skewing effect produced by such endemic or epidemic strains. In our experience, problems associated with antibiotic-resistant strains that occur within an institution appear to be sporadic events that come and go in an unpredictable manner. The problems associated with gentamicin-

TABLE VIII. CEFOPERAZONE AND CEFTAZIDIME SUSCEPTIBILITY IN 1979, 1980, AND 1984

| Species Year tested | *Cefoperazone* No. of isolates | *Cefoperazone* %* Inhibited by ≤16 μg/ml | *Ceftazidime* No. of isolates | *Ceftazidime* %* Inhibited by ≤8.0 μg/ml |
|---|---|---|---|---|
| *E. coli* | | | | |
| 1979-80** | 2,772 | 98 | 4,149 | 99 |
| 1984† | 2,903 | 98 | 4,582 | 99 |
| *C. freundii* | | | | |
| 1979-80 | 98 (84)‡ | 91 (94) | 224 | 91 |
| 1984 | 161 (95) | 88 (91) | 220 (172) | 84 (88) |
| *E. cloacae* | | | | |
| 1979-80 | 300 | 92 | 497 | 90 |
| 1984 | 374 | 87 (91) | 560 | 83 (88) |
| *K. pneumoniae* | | | | |
| 1979-80 | 786 | 98 | 1,057 | 99 |
| 1984 | 819 | 97 | 1,100 | 99 |
| *S. marcescens* | | | | |
| 1979-80 | 231 (184) | 82 (92) | 332 | 98 |
| 1984 | 350 (326) | 88 (91) | 394 | 98 |
| *P. aeruginosa* | | | | |
| 1979-80 | 717 | 93 | 1,153 | 97 |
| 1984 | 1,135 (730) | 83 (85) | 1,367 | 89 |

*Average of values calculated separately for each participating institution.

**Prerelease studies with cefoperazone were done in 1979, ceftazidime was tested in 1980 and again in 1984 (both before the drug's release for clinical use).

†Two separate studies were done in 1984, data from both studies combined.

‡Numbers in parenthesis represent values calculated after excluding data from institutions with a unique endemic resistant strain.

resistant *P. aeruginosa* and *S. marcescens* strains in six of our study centers are examples of sporadic events that influenced our survey data. If those centers were the only institutions involved, gentamicin would have appeared to be of little value against *P. aeruginosa* or *S. marcescens*, and that is clearly not true for the vast majority of medical centers.

Emergence of resistant strains during therapy with cefamandole have been documented, especially when treating infections due to *Enterobacter* sp.[21] One could question whether current *in vitro* testing methods adequately detect a potential for clinical resistance among *Enterobacter* sp. and certain other genera with inducible β-lactamase enzymes. In that respect, broth microdilution tests were more effective than agar dilution tests, presumably because of differences in the inoculum densities achieved with the two methods.[22] Stably derepressed enzyme-producing strains were readily detected by all

test methods. We can only observe that the apparent *in vitro* susceptibility of *E. cloacae* and *C. freundii* isolates to cefamandole has not changed between 1979 and 1981.

Among *E. cloacae* and *C. freundii* isolates, resistance to the third generation cephalosporins and to the broad spectrum penicillins has increased slightly over the last few years because of sporadically occurring endemic strains. These endemic resistant strains might have been selected by widespread utilization of cefamandole or cefoxitin rather than by use of the broad spectrum β-lactams. It is only speculative to guess whether *Enterobacter* sp. with decreased susceptibility to the broad spectrum β-lactams will continue to be selected out in some medical centers. The apparent decrease in the susceptibility of *P. aeruginosa* to cefoperazone and ceftazidime also deserves careful observation along with such structurally related β-lactams as aztreonam.[23]

Since the prevalence of resistant strains seems to vary from time to time and from institution to institution, each medical center should monitor susceptibility data obtained with isolates from their own patient populations. Knowledge of the current incidence of susceptibility to different antimicrobial agents should be considered when selecting antimicrobial agents to be included in the institution's formulary or when selecting drugs to be used for empiric therapy. Care must be taken to minimize skewing of such data by repeated tests of an endemic strain from different patients, by repeated tests of a uniquely resistant strain from multiple culture sites from the same patient, or from epidemiologically related patients.

Except for the sporadic appearance of antibiotic-resistant strains periodically endemic in some institutions, we can document no substantial changes in the proportion of resistant strains among isolates of the six species that we have evaluated. Three to five years after release of the newer β-lactams that we have studied, their spectrum of activity is essentially the same as that which was documented in prerelease studies. Current utilization rates of these broad spectrum antibiotics has not significantly altered their usefulness or their spectrum relationships to each other.

## SUMMARY

Results of collaborative *in vitro* susceptibility testing studies performed between 1976 and 1985 were reviewed to determine whether the incidence of resistance to antimicrobial agents has changed over the years. Piperacillin, ticarcillin, cefamandole, cefotaxime, moxalactam, and cefoperazone were

evaluated before their release and then three to five years later. No substantial change in the incidence of resistant strains could be documented, but sporadically occurring resistant strains seemed to be endemic in some hospitals, but not others. Similar studies with carbenicillin, gentamicin, amikacin, ceftazidime, and cephalothin also failed to demonstrate a substantial shift in the prevalence of resistant strains, but there were significant fluctuations in the incidence of resistant strains in different institutions or in one institution over different periods of time. Ceftazidime and cefoperazone demonstrated a slight (8%) reduction in spectrum against *Pseudomonas aeruginosa* over a four-to-five-year period of time.

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