Antibiotic Susceptibility Patterns of Recent Isolates of Corynebacterium diphtheriae

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A variety of factors which might affect zone sizes were studied with strains of Corynebacterium diphtheriae; a standard disc method for antimicrobial sensitivity testing was used. Moderate variations in inoculum size, inoculum preparation, and pH of Mueller Hinton agar (MHA) did not appreciably affect zone sizes. The addition of blood to MHA was necessary to insure the growth of all C. diphtheriae strains on all lots of MHA. Zone diameters on MHA with blood were consistently 4 to 9 mm smaller than on plain MHA; however, zone diameters were within the sensitive range for seven antibiotic discs used on both media. Minimal inhibitory concentration (MIC) values for penicillin, erythromycin, and rifampin were determined by a plate dilution method. The geographical source, toxigenicity, and type of the strains showed no significant correlation with MIC values or zone diameters for eight antibiotic discs. When MIC values were compared to obtainable blood levels, all of the strains appeared to be sensitive with MIC values of ≤ 0.5 µg/ml for penicillin and ≤ 0.01 µg/ml for erythromycin and rifampin. Strains from persons who failed to have C. diphtheriae eliminated by one course of treatment with penicillin or erythromycin were examined. The susceptibility of these strains did not vary significantly from that of the other strains studied.

From 1965 to 1969 the largest number of diphtheria cases reported in one year was 260 and that was in 1968 (21). Four-hundred and thirty cases were reported during 1970 (22). A large number of these cases were connected with outbreaks in various areas of the country. When outbreaks occur, efforts are made to insure the adequate immunization of the endangered population by prophylactic treatment with diphtheria toxoid (12, 20, 29). When carriers of Corynebacterium diphtheriae are detected, antimicrobials are usually given in an effort to eliminate the spread of the organism. Although antimicrobials have been reported to have little or no effect on the clinical course of the diphtheritic disease (4, 13, 24), antimicrobial therapy is usually recommended for a case to eliminate the carrier state and control secondary or associated infection.

The antimicrobials of choice most often mentioned for elimination of the carrier state are penicillin and erythromycin (3, 4, 7, 13, 23, 24). In vitro studies of the susceptibility of C. diphtheriae strains to these antimicrobials were performed by several groups. Florey (8) in 1952 and Welch (26) in 1959 reviewed these reports and found the minimal inhibitory concentration (MIC) values of penicillin to vary from 0.004 to 640 units/ml. Welch (25) also reviewed the reported MIC values for erythromycin which ranged from 0.003 to 3.12 µg/ml.

Failures to eliminate C. diphtheriae from cases and carriers treated with penicillin have been reported during the 1950's (8, 9, 11) and more recently by Zalma et al. (29). Erythromycin proved effective in the treatment of both cases of C. diphtheriae and carriers of C. diphtheriae (9, 11, 29) and has been especially useful when a course of penicillin treatment was ineffective (9, 11, 28, 29). Rifamycin SV was successfully used with 13 cases and seven carriers (19). Preliminary data in this laboratory showed C. diphtheriae strains to be extremely sensitive in vitro to rifampin, a derivative of rifamycin SV. Rifampin has been reported to be found in significant levels in saliva after oral treatment (5).

It is the purpose of this study to examine the antibiotic susceptibility patterns of C. diphtheriae strains to penicillin, erythromycin, and rifampin and to determine whether or not there are significant differences among these sensitivity patterns. Emphasis was placed on those strains isolated from cases or carriers associated with outbreaks during the last 2 years.
MIC values were determined with these three antibiotics, and these values were compared to inhibition zones around discs containing these antibiotics. Five additional antibiotics were included in the disc procedure only.

The disc-sensitivity-testing method of Bauer et al. (2) was employed. These authors recommended the addition of 5% blood to Mueller-Hinton agar (MHA) for organisms which failed to grow on this medium. They cautioned that their standards for interpretation of zone diameter were developed for rapidly growing pathogens and that more fastidious organisms had not been as completely studied. As part of this study, therefore, it was necessary to evaluate some of the factors which could affect zone sizes of C. diptheriae strains such as addition of blood to the medium, method of preparation of inoculum, size of inoculum, pH of the medium, and variation of lots of medium.

MATERIALS AND METHODS

Strains. Of the C. diptheriae strains submitted to the Center for Disease Control during 1969–1970 for confirmation, 136 were selected for this study. These strains were of the following types: 68 mitis, 37 gravis, 27 intermedius, and 4 mitis (Belfanti variety). The toxigenicity, source, and geographical area of distribution of these strains are shown in Table 1. Single colonies of the strains were picked to Pau medium. Methylen blue smears were made for morphological study, and biochemical and toxigenicity tests were performed (10). A Staphylococcus aureus strain of known susceptibility, Seattle 1945, was used as a standard control.

### Table 1. Number of C. diptheriae strains, by geographical origin, type, and toxigenicity

| Geographical origin | Mitis T | Gravis At | Intermedius T | Bel-fanti T |
|---------------------|---------|-----------|---------------|------------|
| Areas of U.S.       |         |           |               |            |
| Middle Atlantic     | 1       |           |               |            |
| East North-Central  | 3       | 2         | 5             |            |
| West North-Central  | 3       | 2         | 2             | 1          |
| South Atlantic      | 14      | 15        | 2             |            |
| East South-Central  | 3       |           |               |            |
| West South-Central  | 11      | 5         | 30            | 3          |
| Mountain             | 8       | 2         | 2             |            |
| Pacific              | 1       |           |               |            |
| Guam                 | 1       |           |               |            |
| Total                | 36      | 32        | 34            | 3          |

* T and At represent strains which were toxigenic and atoxigenic, respectively.

Antimicrobial testing. To determine the MIC, we incorporated various amounts of penicillin, erythromycin, or rifampin in 20 ml of MHA with and without 5% sheep blood. The agar was poured into plates (15 by 100 mm) and allowed to solidify. The under side of the agar part of each plate was marked off in pie-shaped sections. The inoculum was prepared from growth on an 18 hr Trypticase Soy agar (TSA) slant; the growth was suspended in Trypticase Soy broth (TSB) and standardized spectrophotometrically to a density equal to 0.5 MacFarland tube no. 1 (reference 17; MacFarland no. 1⁄2). The inoculum was streaked immediately with a 1-mm loop onto plates containing 0.025 to 0.5 μg of potassium penicillin (1,600 units per ml), 0.0025 to 0.025 μg of erythromycin per ml, and 0.001 to 0.01 μg of rifampin per ml. Plates were incubated for 18 to 24 hr at 35 to 37 C. The MIC was the lowest concentration of antibiotic which showed marked reduction of bacterial growth as compared to the confluent growth on a control plate containing only MHA or MHA with 5% sheep blood.

The method for disc-sensitivity studies was that described by Bauer et al. (2), with one exception. The inoculum was prepared by emulsifying the growth from an 18-hr TSA slant in TSB.

Antimicrobial agents. Penicillin dilutions were made from potassium penicillin containing 1,600 units/mg. Erythromycin dilutions were prepared from erythromycin ethyl succinate. Dilutions of both these antimicrobials were prepared in sterile distilled water. Rifampin (Mann Research Laboratories) was dissolved in N,N-dimethylformamide (27) and diluted with sterile distilled water. The discs employed were 10-unit penicillin (P), 15-μg erythromycin (E), 30-μg rifampin (R), 5-μg methicillin (Dp), 30-μg kanamycin (K), 10-μg streptomycin (S), 30-μg chloramphenicol (C), and 30-μg tetracycline (Te); all were from commercial sources.

RESULTS

MHA as recommended by Bauer et al. (2) was used in preliminary sensitivity testing of C. diptheriae strains. Since most of the intermedius strains and 18% of the mitis strains failed to grow on this medium, Oxoid Sensitivity Test agar (STA), a medium recommended by the manufacturer for the growth of fastidious organisms, was evaluated. Although growth of intermedius strains was slightly enhanced on STA, 13% of the mitis strains still failed to grow.

To insure the growth of all C. diptheriae strains, we added 5% sheep blood to MHA. No significant difference in zone diameters was observed when various lots of blood were compared. In Table 2, the average zone sizes obtained with strains (grouped by type) grown on plain MHA and on MHA with 5% sheep blood are compared. Zone diameters of C. diptheriae on MHA with blood were consistently 4 to 9 mm smaller than those on plain MHA. The S.
TABLE 2. Average zone sizes on plain Mueller-Hinton agar (MHA) and MHA with 5% sheep blood

| Antimicrobial agents | MHA | MHA with blood | MHA | MHA with blood | MHA | MHA with blood | MHA | MHA with blood |
|----------------------|-----|----------------|-----|----------------|-----|----------------|-----|----------------|
| Methicillin (DP)     | 19.8| 14.5           | 21.8| 16.8           | 14.3| 21.5           | 15.2| 16.5           |
| Kanamycin (K)        | 30.7| 25.2           | 31.4| 27.0           | 21.6| 34.2           | 28.5| 24.7           |
| Streptomycin (S)     | 22.9| 18.3           | 23.2| 20.3           | 17.1| 26.0           | 21.7| 19.7           |
| Chloramphenicol (C)  | 37.0| 32.5           | 37.5| 33.8           | 28.6| 39.0           | 34.7| 22.7           |
| Tetracycline (Te)    | 32.6| 27.9           | 32.7| 29.0           | 24.3| 34.2           | 31.0| 24.7           |
| Penicillin G (P)     | 36.7| 30.8           | 38.7| 30.8           | 29.8| 39.5           | 34.2| 32.2           |
| Erythromycin (E)     | 42.2| 34.7           | 42.5| 34.7           | 30.4| 42.0           | 37.7| 27.2           |
| Rifampin (R)         | 44.9| 36.5           | 45.5| 35.9           | 32.2| 48.0           | 40.5| 32.7           |

* Number of strains tested.
* No growth.

TABLE 3. Zone sizes and viability counts for three methods of inocula preparation on Mueller-Hinton with 5% sheep blood

| Strains | Zone size around antibiotic disc on various inocula* | Viability counts |
|---------|----------------------------------------------------|------------------|
|         | Penicillin | Erythromycin | Rifampin |
|         | TSA | TSB (18 hr) | TSB (5 hr) | TSA | TSB (18 hr) | TSB (5 hr) | TSA | TSB (18 hr) | TSB (5 hr) |
| Mitis   | 33  | 35         | 34         | 37  | 38         | 40         | 41  | 41         | 40         |
| Gravis  | 30  | 35         | 34         | 33  | 36         | 36         | 35  | 40         | 37         |
| Intermedius | 28  | 31         | 28         | 32  | 35         | 30         | 33  | 40         | 32         |
| Staphylococci | 33  | 36         | 32         | 27  | 30         | 25         | 32  | 36         | 31         |

* TSA, Trypticase Soy agar; TSB, Trypticase Soy broth.

* aureus control strain tested in the same manner showed only ≤2.5 mm difference in zone sizes.

Other factors that might influence zone sizes were also studied. First, three methods of inocula preparation were tested. Inocula from 5-hr TSB, 18-hr TSB, and 18-hr TSA were standardized spectrophotometrically to an optical density equal to a MacFarland ½. In Table 3, zone sizes around penicillin, erythromycin, and rifampin discs are listed for the three methods of inocula preparation; the viability counts for three of the strains tested are also given.

Next, the necessity of standardizing all cultures to a MacFarland ½ was evaluated. Strains grown on TSA were suspended in TSB, and two-fold dilutions of the suspension were prepared equal to a MacFarland 1, ½, ¼, ⅛, ¼₈, ⅛₈. The same strains grown in TSB for 5 hr were diluted to MacFarland ½, ¼, ⅛, ¼₈, ⅛₈ because growth never reached a MacFarland 1. With the eight antibiotics discussed, zone sizes of the three *C. diphtheriae* type strains varied only 0 to 5 mm for dilutions of MacFarland 1, ½, ¼, ⅛, ¼₈, ⅛₈. At the ⅛₈ dilution, growth was not always confluent. The standard deviations (SD) calculated for dilutions of MacFarland ½, ¼, ⅛, ¼₈ for *C. diphtheriae* and *S. aureus* control strains are in Table 4. These values ranged from 0.4 to 1.9 mm.

The pH of the medium had little effect on the zone sizes of *C. diphtheriae* strains. The same lot of MHA was adjusted to pH values of 7.05, 7.3, 7.4, 7.6, and 8.04, and strains were tested in duplicate. Nonlinear variations of ≤5 mm occurred with seven of the eight antimicrobials. However, the zone sizes of *C. diphtheriae* around the tetracycline disc decreased 10 mm as the pH increased from 7.05 to 8.04.

Seven lots of MHA from two manufacturers were compared for their possible effect on zone size. If necessary, the pH of these lots was adjusted to 7.4 ± 0.1. Without blood, one lot
failed to support the growth of any of the strains; on three other lots of MHA, one or more of the *C. diphtheriae* types failed to grow. When growth was supported, zone diameters were neither consistently high nor low on any particular lot of medium. With the addition of 5% sheep blood, all of the lots supported growth of all *C. diphtheriae* strains. The differences between zone sizes obtained on different lots of media varied depending upon the antibiotic disc used. The SD in zone sizes for the *C. diphtheriae* and *S. aureus* strains on the seven lots of MHA are given in Table 4. These are compared with the SD in zone sizes obtained on one lot of MHA tested eight times. Also included in this table are the day-to-day SD and average zone sizes of the *C. diphtheriae* and *S. aureus* control strains as tested throughout this study.

In Fig. 1, the penicillin MIC values of 136 strains of *C. diphtheriae* are compared with zone sizes around 10-unit penicillin discs. The data for both procedures are from a single determination made with each test on MHA with blood. Zone sizes ranged from 24 to 36 mm with MIC values of 0.025 to 0.5 μg/ml for penicillin. The erythromycin values for the same 136 strains are compared with zone sizes around 15-μg erythromycin discs in Fig. 2. The zone sizes ranged from 25 to 40 mm with MIC values of 0.0025 to 0.01 μg/ml. Rifampin sensitivity results for these strains are shown in Fig. 3. The zone sizes around 30-μg rifampin discs ranged from 28 to 45 mm for MIC values of 0.001 to 0.01 μg/ml.

Zone sizes for the 136 strains of *C. diphtheriae* were: 10 to 25 mm around 5-μg methicillin discs, 20 to 38 mm around 30-μg kanamycin discs, 15 to 28 mm around 10-μg streptomycin discs, 23 to 43 mm around 30-μg chloramphenicol discs, and 21 to 36 mm around 30-μg tetracycline discs.

Nineteen strains were tested from 12 persons who were reported to be still carrying *C. diphtheriae* after one series of treatments with either penicillin or erythromycin. The MIC values and zone sizes for these strains were not different from results obtained with other strains.

When plain MHA supported growth of *C. diphtheriae* strains, MIC values and zone sizes were determined on both MHA alone and MHA with 5% sheep blood. Erythromycin and rifampin MIC values for *C. diphtheriae* strains on both media were comparable. However, penicillin MIC values for the same strains were frequently one dilution higher on the blood containing MHA. There were no significant differences in MIC values with strains from all four *C. diphtheriae* types.

The rifampin solvent, *N*,*N*-dimethylformamide, was diluted to the concentrations used in the test, and no inhibition of growth was demonstrated for eight test strains of *C. diphtheriae*.

**DISCUSSION**

Bauer (1) and Petersdorf and Sherris (18), in their work with rapidly growing organisms, found that zone sizes were not appreciably affected by
**FIG. 1.** Relationship between plate dilution sensitivity to penicillin and inhibition zone around 10-unit penicillin disc on Mueller-Hinton medium with 5% sheep blood.

**FIG. 2.** Relationship between plate dilution sensitivity to erythromycin and inhibition zone around 15-µg erythromycin disc on Mueller-Hinton medium with 5% sheep blood.
moderate variations in inoculum size, inoculum preparation (5- or 18-hr growth in TSB), pH of MHA, or addition of blood to MHA. As Bauer et al. (2) suggested for more slowly growing organisms, we added 5% sheep blood to MHA to insure growth of all C. diphteriae strains on all lots of MHA. We found that moderate variations in inoculum size, inoculum preparation (5- or 18-hr growth in TSB, or 18-hr TSA), and pH of the medium did not significantly affect zone diameters of C. diphteriae strains. Zone sizes were consistently 4 to 9 mm smaller for C. diphteriae on MHA with blood than they were on plain MHA. Interpretations of zone sizes for strains on both media with seven antimicrobial agents were sensitive when we used the updated interpretative chart of Sherris (16). Since no strains were encountered that gave zone sizes in the resistant or intermediate ranges, a comparison of MIC values for such strains was not possible.

MIC values for penicillin, erythromycin, and rifampin were determined by a plate dilution method on plain MHA and MHA with 5% blood. The MIC values on both media were the same for most strains tested with erythromycin and rifampin; however, 68% of the strains had MIC values one dilution higher with penicillin on MHA with blood than on plain MHA. MIC values for the three antimicrobial agents indicated that all strains were susceptible if the criterion for comparison was the antimicrobial level obtainable in blood (7, 15). This interpretation would be in agreement with the interpretation used in the disc method. We conclude that C. diphteriae strains with zone diameters of ≥24 mm around a 10-unit penicillin disc, ≥25 mm around a 15-µg erythromycin disc, and ≥29 mm around a 30-µg rifampin disc are sensitive on the basis of comparison to MIC values. Zone sizes could not be used in a regression curve to interpolate the actual MIC value.

The geographical source, toxigenicity, and type of the strains showed no significant correlation with MIC values or zone sizes on the eight discs tested.

Long in 1946 (14) stressed the importance of attaining high concentrations of penicillin in the saliva of persons harboring C. diphteriae. Since this organism is most commonly found in the nose, nasopharynx, and throat of both cases and carriers, a more accurate parameter for comparison of MIC values might be saliva rather than blood levels obtained after treatment.

We could find no definition of precise saliva
levels after penicillin treatment in the literature. Saliva levels after treatment have been reported to be 0.0037 to 0.12 µg/ml for erythromycin (6) and ≥0.125 µg/ml for rifampin (5). MIC values for 80% of the C. diphtheriae strains tested were within one dilution of the lowest saliva level reported for erythromycin. The remaining 20% of the strains had MIC values of 0.01 µg/ml. All of the strains tested had MIC values for rifampin of ≤0.01 µg/ml which were below the levels obtained in saliva by Devine et al. (5).

During the 1950’s several workers (8, 9, 11) reported that penicillin failed to eradicate C. diphtheriae from cases or carriers; however, the treatment doses and schedules were not always the same. Long (14) suggested that not less than 500,000 units a day be given. Recently penicillin has been reported (29) to fail to eliminate the organism in 9.9% of carriers who receive procaine penicillin (intramuscularly), 600,000 to 2,000,000 units a day for seven to ten days. These carriers are then successfully treated with erythromycin (1 g/day in divided doses for seven days). Erythromycin also has been reported to be ineffective in eliminating C. diphtheriae from one of 38 carriers when cultures were taken on the second day after completion of a 7-day series of treatment with 250 mg four times a day (Richard V. McCloskey, personal communication). In another study, 15 (13%) of 115 carriers of C. diphtheriae were reported to carry the organism after a similar 6-day course of erythromycin treatment. In this case, a second course of treatment with erythromycin eliminated the organism in 14 carriers (J. L. Olden, L. W. Miller, James Drake, and Sherwood Zimmerman, personal communication). For their in vitro susceptibility, we studied strains taken from four patients prior to treatment (29), one strain taken after treatment (McCloskey, personal communication), and 14 strains isolated from seven carriers prior to and after treatment (Older, personal communication). The MIC values of these strains were the same (± one dilution) whether the culture had been taken before or after the patient was treated. These MIC values were no different than MIC values for strains isolated from individuals from whom the C. diphtheriae strain was eliminated by similar treatment.

Razzi (19) reported that rifamycin SV could be used to eradicate C. diphtheriae from cases and carriers. Our in vitro susceptibility results indicate that strains of C. diphtheriae isolated during 1969 and 1970 were sensitive to rifampin, a derivative of rifamycin SV which is effective by oral administration. Since rifampin is found in blood and saliva in levels exceeding the MIC values for C. diphtheriae strains studied, these results would suggest that rifampin might be effective for the elimination of C. diphtheriae. Treatment with rifampin should be used only if careful attention is given to the possible emergence of rifampin-resistant organisms as have been encountered with other bacteria after its use (5, 7).

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