

## Diphtheria Carriers and the Effect of Erythromycin Therapy

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One hundred and fourteen *Corynebacterium diphtheriae*, toxigenic, gravis type, pharyngeal carriers were identified during a diphtheria epidemic in Elgin, Texas. All carriers were treated with erythromycin estolate, 1 g/day in divided doses for 6 days. Serial pharyngeal cultures were obtained in order to monitor the bacteriological response. Seventy-two carriers had positive cultures immediately prior to the start of therapy, and only these individuals were considered in the analysis of the effects of erythromycin. Forty-eight hours after institution of therapy, 96% of the carriers had become culture negative; all were negative by the 4th day of therapy, and all remained culture negative while taking the drug. Two days after cessation of therapy, all but one (99%) were culture negative. However, upon reculture 2 weeks later, 15 (21%) had relapsed to the carrier state. There were no significant differences in the serum diphtheria antitoxin levels, immunization status, age, sex, or socioeconomic status of those who relapsed and those who remained culture negative. This study demonstrates that erythromycin is effective in converting carriers to culture-negative status, but when given for only 6 days it is associated with large numbers of relapses. Because previous studies have not included follow-up cultures 2 weeks after therapy, it is suggested that all *C. diphtheriae* carriers be treated with either erythromycin or penicillin and that all be recultured at a minimum of 2 weeks after completion of therapy to assure eradication of the diphtheria organisms.

The antibiotic treatment of carriers of *Corynebacterium diphtheriae* is important in the control of diphtheria outbreaks. Currently the Committee on Infectious Diseases of the American Academy of Pediatrics recommends either intramuscular procaine penicillin or oral erythromycin for the treatment of diphtheria carriers. (1) However, a report of the Austin, Texas, diphtheria epidemic suggested that erythromycin was superior to penicillin (2). When a large number of *C. diphtheriae* carriers were identified in a diphtheria epidemic in Elgin, Texas, it was decided to treat carriers exclusively with oral erythromycin because of the Austin experience. Although this decision obviated comparison of drug efficacy, the outbreak did present an opportunity to study *C. diphtheriae* carriers and the effects of erythromycin therapy.

### MATERIALS AND METHODS

A carrier was defined as any asymptomatic individual with a positive throat culture for *C. diphtheriae* organisms. Carriers were found by several means: culture surveys in schools; investigations of contacts

of individuals infected with *C. diphtheriae*: or at special culture clinics held during the height of the epidemic.

Throat swabs obtained were processed either by incubating the swab overnight at 35 C on Loeffler medium and then streaking the swab onto Tinsdale medium or by incubating the swab overnight at 35 C on Pai medium and then streaking the swab onto Tinsdale and cystine tellurite medium for isolation. The two procedures gave very similar results. The former procedure was used to process all swabs taken during treatment and at 24 and 48 h after treatment. Methylene blue smears were made for morphological study, and biochemical and toxigenicity tests were performed (2). Antibiotic susceptibilities of the organisms were determined by the method described by McLaughlin et al. (7).

Carriers were given erythromycin estolate, 1 g/day, orally in four divided doses for 6 days. A 6-day course was chosen because of administrative problems in dispensing the medication. Repeat throat cultures were obtained just prior to the start and usually after the 2nd, 4th, and 6th day of therapy. In almost every case, follow-up cultures were obtained 24 h, 48 h, and 14 days after completion of the drug schedule.

Blood for serum diphtheria antitoxin measurement was taken from a group of students (ages 9 to 14 years)

at the time for their first culture. Antitoxin levels were determined by the Stavitsky hemagglutination method (11), as modified by Schubert and Cornell (9). Diphtheria immunization histories were also obtained on this group by review of medical records, when available or by interview; the immunization status was judged according to criteria established by the Center for Disease Control (8). Socioeconomic status was determined according to the method of Hollingshead and Redlich (5).

## RESULTS

A total of 115 carriers was identified during the Elgin epidemic. All carriers had at least one throat culture positive for toxin-producing *C. diphtheriae* gravis type. Antibiotic susceptibility studies revealed that the organisms were susceptible to 0.1 µg or less of penicillin per ml and less than 0.1 µg of erythromycin per ml.

Because of delays in isolating and reporting positive cultures, the interval between throat culture collection and the start of therapy varied from 1 to 7 days, with a mean of 5.5 days. Repeat cultures were taken on 101 carriers at the time therapy was initiated; 29 had become culture negative without therapy. Among the 72 carriers known to be positive at initiation of erythromycin, 69 (97%) were culture negative after 2 days of therapy, and they remained culture negative through their 6th day of erythromycin therapy (Table 1).

At 24 and 48 h after the completion of therapy, only one individual had a positive culture, a treatment failure rate of only 1%. Approximately 2 weeks after therapy, a special culture survey of more than 500 Elgin residents, including all previously identified and treated carriers, was conducted. Nineteen *C. diphtheriae* pharyngeal carriers were found, 17 (89%) of whom were previously treated carriers known to be culture negative at the conclusion of their erythromycin therapy. Among these 17, 14 were in the treatment subgroup of 72 carriers with

positive cultures immediately prior to their erythromycin treatment (Table 1). The 17 carriers who had been previously treated were given a repeat 6-day regimen of oral erythromycin; all but one were throat culture negative on the 4th, 5th, and 12th days after retreatment. The patient who remained throat culture positive after the 2nd erythromycin treatment schedule was culture positive on post-treatment days 4, 5, and 12 and was then lost to follow-up.

Diphtheria antitoxin levels in serum obtained at the initial identification of the carrier state were available for 74 carriers who had repeat cultures prior to the start of therapy. The antitoxin levels of the carriers who became culture negative prior to therapy were significantly lower ( $P < 0.005$  by the Student's *t* test) than the levels of those who remained culture positive.

Of the 18 patients who had a positive throat culture any time after completion of the 6-day course of erythromycin, 15 had serum antitoxin levels determined at the time they were first identified as carriers. There was no significant difference in the serum diphtheria antitoxin levels between the therapy failures and therapy successes.

Immunization status was determined on 81 carriers; 79% were fully immunized and 21% inadequately immunized. There were no significant differences in immunization status of those who converted to negative culture and those who remained positive at the time of therapy. The immunization status of therapy failures was not significantly different from that of the therapy successes.

The age, sex, and socioeconomic status of the pretreatment converts and those who remained culture positive at the start of therapy were similar. Age, sex, and socioeconomic status were also similar in the treatment-success and treatment-failure groups.

TABLE 1. Culture status of diphtheria carriers after initial positive culture

Reculture status of carriers immediately prior to start of therapy <sup>a</sup>	No.	No. positive during therapy			No. positive after therapy			Total	% Positive after therapy
		Day			Day				
		2	4	6	1	2	14		
Reculture positive	72	3	0	0	1	1	14	15 <sup>b</sup>	21%
Reculture negative	29	0	0	0	0	0	1	1	3%
No reculture prior to therapy	13	0	0	0	0	0	2	2	15%
Total	114	3	0	0	1	1	17	18 <sup>b</sup>	16%

<sup>a</sup> All carriers had a positive culture, but because there was a delay in therapy, which varied from 1 to 7 days, repeat cultures were performed immediately prior to start of therapy.

<sup>b</sup> The cultures which were positive at 24 and 48 h were on the same patient.

No cutaneous diphtheria was observed at anytime during this study.

### DISCUSSION

The antibiotic treatment of diphtheria carriers has two important objectives. It helps protect the carrier from developing symptomatic disease, and it reduces the spread of *C. diphtheriae* organisms in the community. Among the antibiotics, erythromycin has been shown to be very effective against various strains of *C. diphtheriae* (4). Its usefulness in eradicating diphtheria from carriers was first demonstrated by Haight and Finland (3), and today erythromycin and procaine penicillin are the drugs recommended for treatment of diphtheria carriers (1).

In this epidemic, erythromycin was chosen over penicillin because of the Austin-Travis County Health Department's experience during a diphtheria epidemic from 1967 to 1969 (12). Organisms identified from carriers in Austin were all toxigenic, gravis strains. When the Austin carriers were treated with intramuscular procaine penicillin, 600,000 to 2,000,000 U/day intramuscularly, approximately 10% of the carriers remained culture positive at the conclusion of therapy. In each instance of penicillin failure, its replacement with erythromycin, 1 g orally per day in divided dose for 7 days, resulted in prompt eradication of the carrier state as determined by cultures on post-treatment days 1 and 2. In vitro antibiotic susceptibility studies on the specimens obtained from the Elgin outbreak showed that the diphtheria organisms isolated were susceptible to both erythromycin and penicillin. Because no treatment failures were demonstrated with erythromycin in the Austin experience, we felt obligated to use erythromycin exclusively in the Elgin outbreak.

During the interval from initial culture to initiation of antibiotic therapy, 29% of the carriers converted to culture-negative status. These spontaneous conversions could not be attributed to socioeconomic or immunization differences. The only difference noted was a significantly lower serum antitoxin level in the pretherapy converters, which may have represented a less intense infection in this group. Because quantitative culture techniques were not used, this conclusion cannot be verified. Differences in local immunoglobulins or pharyngeal-tonsillar anatomy may have been responsible for the differences, but these factors were not studied.

Because of the spontaneous conversions to culture-negative status, it became obvious that in order to assess the efficacy of the antibiotic

treatment of carriers, we would need a control group or information on the natural history of the untreated carrier state. Because ethical considerations precluded a control group in our study, data from studies on the duration of the diphtheria carrier state in the preantibiotic era were used for comparison. Weaver (11) observed a group of 52 *C. diphtheriae* carriers in the period 1918 to 1920 and found that 17 (32.7%) became culture negative within 5 days of their original culture identification. This was not significantly different from the findings in the present study (29%) (Fig. 1).

In an attempt to evaluate how long a carrier remained infectious while taking erythromycin, throat cultures were obtained throughout the course of therapy. Of the 72 carriers known to be positive at the start of therapy, only 3 (4%) were culture positive on the 2nd day of therapy, and all were culture negative for the remainder of the therapy schedule (Fig. 1). In the group of untreated carriers observed by Weaver (11), 50% were still positive after a similar period of time. When it became apparent that very few people had positive cultures after the start of therapy, carriers were allowed to return to normal activity after completing 2 days of therapy if we were assured that they would continue the medication for the prescribed 6 days.

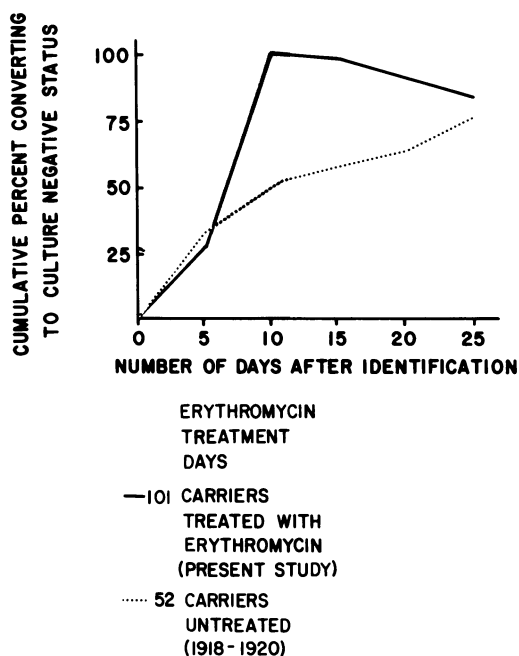


FIG. 1. Conversion of carriers to culture-negative status.

Fifteen days after identification, Weaver (11) found that 40% of untreated carriers remained culture positive. After a similar period of time in the Elgin outbreak, 2% of erythromycin-treated carriers were culture positive. McCloskey found in the San Antonio diphtheria epidemic that intramuscular benzathine penicillin resulted in an 11% culture positive rate after a similar interval (6).

In the present study, 2 weeks after therapy had been discontinued (approximately 25 days after initial identification) a culture survey serendipitously identified 19 carriers, 17 of whom were previously treated with erythromycin and were found to have negative throat cultures 1 and 2 days after therapy. Because only two new carriers were found in this survey and because no cases had occurred in Elgin in the interim, we concluded that 17 of these individuals represented relapses and not new infections.

The 17 patients who relapsed and the one drug failure identified immediately after therapy were similar in all respects, including antitoxin levels, to those who remained culture negative. Because studies to verify drug compliance were not undertaken, it is possible that these 18 individuals did not complete the prescribed course of erythromycin. Although this explanation cannot be ruled out, we had no information about these individuals, which made us suspect non-compliance. Because the object of carrier treatment is eradication of the organism, the 17 relapses were considered treatment failures.

Weaver (11) found 23% of carriers were culture positive 25 days after identification. The 17 relapses discovered in our study approximately 25 days after identification represented 15% of the original 114 carriers. This difference in proportion positive is not significant by the chi-square test of independence. Thus, this study demonstrates that erythromycin is very effective in converting diphtheria carriers to culture negative status, but when given for only 6 days, it is associated with a high relapse rate within 2 weeks of treatment. Because previous studies on the treatment of *C. diphtheriae* carriers have not included follow-up cultures 2 weeks after completion of therapy, both penicil-

lin and erythromycin in the usual 7-to-10-day courses also may have high relapse rates. We are, therefore, unable to make any statement concerning the relative efficacies of erythromycin and penicillin in eradicating the carrier state. We suggest that *C. diphtheriae* carriers be treated with either penicillin or erythromycin and that cultures be taken at the conclusion of therapy and 2 weeks post-therapy in order to assure eradication of the carrier state.

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