Penicillin vs. Erythromycin in the Treatment of Diphtheria

Rachel Kneen, Pham Ngoc Giao, Tom Solomon, Tran Thi My Van, Nguyen Thi Tuyet Hoa, Tran Buu Long, John Wain, Nicholas P. J. Day, Tran Tinh Hien, Christopher M. Parry, and Nicholas J. White

In an open-label, randomized trial, 44 Vietnamese children with diphtheria were given penicillin therapy (intramuscular benzylpenicillin, 50,000 U/[kg ⋅ d] for 5 days and then oral penicillin, 50 mg/[kg ⋅ d] for 5 days), and 42 were given erythromycin therapy (50 mg/[kg ⋅ d] orally for 10 days). There were no differences in times to membrane clearance or bacteriologic clearance, but median times to fever clearance were 27 hours (95% confidence interval [CI], 19–30; range, 0–124 hours) for penicillin recipients and 46 hours (95% CI, 34–54; range, 0–148 hours) for erythromycin recipients (P = .0004). In the penicillin group, acute treatment failed for one patient, and one patient relapsed. Three patients in the penicillin group developed diphtheritic myocarditis as evidenced by abnormal electrocardiograms. Erythromycin did not cause prolongation of the QT interval corrected for heart rate. Cultures of specimens from 15 patients (17.4%) were positive for toxigenic Corynebacterium diphtheriae. All isolates were susceptible to penicillin, but four isolates (27%), all of which were from patients who received penicillin treatment, were resistant to erythromycin (minimum inhibitory concentrations, >64 mg/L). Penicillin is recommended as first-line treatment for diphtheria in Vietnam.

Diphtheria remains an important public health problem in much of the developing world and has undergone a recent resurgence in eastern Europe and the former Soviet Union [1]. In southern Vietnam, >100 cases per year still occur, despite a vaccination coverage rate of >90% [2]. Infection with toxigenic Corynebacterium diphtheriae may result in widespread toxin-mediated damage, particularly to the heart (diphtheritic myocarditis), kidneys, and nervous system. The incidence of diphtheritic myocarditis following nasopharyngeal diphtheria is 10%–20%, and the associated mortality rate is ~50% [3]. Diphtheria is treated with both antitoxin and antibiotics. Antitoxin neutralizes unbound toxin, and antibiotics prevent further toxin production and spread of the bacterium.

C. diphtheriae is susceptible to a wide range of antibiotics [4], and currently both penicillin and erythromycin are recommended as treatment of diphtheria by the World Health Organization (WHO) [5]. However, erythromycin has recently been shown to be proarrhythmic, especially in patients with concurrent cardiac disease [6]. Whether drug-induced arrhythmias occur during erythromycin treatment of diphtheria is not known. The only clinical trial that set out to compare penicillin and erythromycin in the treatment of acute diphtheria was stopped early because of a high incidence of thrombophlebitis in patients receiving parenteral erythromycin [7]. To our knowledge, there have been no other comparisons of these antibiotics. In view of these uncertainties, we conducted a prospective, open-label, randomized trial of erythromycin and penicillin in the treatment of Vietnamese children with diphtheria.

Methods

This study was conducted between June 1995 and May 1996 on the diphtheria ward of the Centre for Tropical Diseases, Cho Quan Hospital, Ho Chi Minh City, Vietnam (a referral hospital for diphtheria patients from southern Vietnam). Children (younger than 16 years of age) for whom diphtheria was clinically diagnosed and whose parents or guardians gave informed consent to enrollment in the trial were studied.

Diphtheria was diagnosed if patients had an acute illness with a typical adherent membrane in the nasopharynx. The onset of the infection is nonspecific, although an abrupt onset with a high-grade fever and chills is unusual. The throat may not be sore. Often beginning on the tonsils, the appearance of the membrane is characteristic. It is initially cream colored and confluent (with a slightly wrinkled edge), enlarging to become gray and sometimes black in the center. The edge is clearly demarcated and surrounded by a narrow rim of erythema. In
cases of more extensive pharyngeal disease, there is always extensive swelling and congestion.

Patients for whom there was diagnostic uncertainty (i.e., those with acute pharyngitis but without clear membrane formation) were not included in this study. Moribund patients (those with shock or cyanosis) and patients who were known to be allergic to penicillin or erythromycin were also excluded from the study.

Treatment

As soon as the diagnosis of diphtheria was made clinically (i.e., at the time of admission), patients received an intramuscular injection of 20,000–60,000 IU of diphtheria antitoxin (Pasteur Institute, Nha Trang, Vietnam) in accordance with WHO guidelines [5]. Patients with severe swelling of the tonsils or pharynx were also given intravenous hydrocortisone (2–4 mg/[kg · d]) for 5–7 days. Patients were then randomized to receive either intramuscular benzylpenicillin (Helm Pharmaceuticals, Heidelberg, Germany; 50,000 U/[kg · d] for 5 days) followed by oral penicillin V (Oxacilline, Specia, Paris, France; 50 mg/[kg · d] for 5 days [the currently recommended treatment regimen at this center]) or oral erythromycin ethylsuccinate (Eryxine, Ciba Geigy, Rueil Malmaison, France; 50 mg/[kg · d] for 10 days). Treatment codes were contained in serially numbered sealed envelopes that were opened only after the patient was enrolled into the study.

Assessment of Patients

A detailed medical history was obtained and a clinical examination performed by a member of the study team at the time of admission. A history of previous treatment was obtained, although it was not possible to identify the antibiotics used with confidence. All details were recorded on standard forms. Axillary temperature and other vital signs were recorded every 6 hours. Patients were examined daily until discharge.

Serial 12-lead electrocardiograms were taken on alternate days during hospitalization from day 1 to day 10 and then weekly until discharge. Electrocardiography was performed more frequently for patients who developed clinical or electrocardiographic evidence of diphtheritic myocarditis. The QT interval corrected for heart rate (QTc) was calculated in chest lead 1, which was recorded at a rate of 50 mm/s, by means of Bazett’s formula (QTc = QT interval/√RR interval) [8]. From our previous experience with penicillin-treated patients at this center, we expected that the average time to membrane clearance would be 3 days. The study was therefore designed to detect an improvement in clearance time of 50%, with 95% confidence and 80% power.

Laboratory Procedures

At the time of admission, blood specimens were obtained for determination of hematocrit, differential WBC count, and platelet count, and for examination for malarial parasites. Four sterile swab specimens were obtained at admission: one swab specimen from each tonsil and one swab specimen from each nostril. In addition, a set of these four swab specimens was obtained on days 2, 5, 12, and 24, and 1 month after discharge.

Swabs were inoculated onto 5% sheep blood agar and Hoyle’s tellurite agar with 5% lysed sheep blood (Oxoid, Basingstoke, Hants, United Kingdom). Plates were incubated in room air at 37°C for 48 hours. Suspicious colonies were identified as *C. diphtheriae* on the basis of pyrazinamidase and cystinase tests [9], and identification was confirmed by using a commercial kit (API Coryne, Basingstoke). Toxigenicity was determined by means of the Elek immunoprecipitation test [9]. Antimicrobial susceptibilities were determined at the time of isolation by the modified Kirby-Bauer method with use of disks containing ampicillin (10 µg), chloramphenicol (30 µg), ceftriaxone (30 µg), erythromycin (15 µg), penicillin (10 IU), rifampin (5 µg), tetracycline (30 µg), and trimethoprim (5 µg). Isolates were saved in bacterial preservers (Prolab Diagnostics, Scunthorpe, United Kingdom) at −20°C. MICs were determined later by using an agar dilution method [10].

Strains were inoculated onto Columbia agar containing 5% horse blood, and plates were incubated at 37°C for 24 hours. A single colony of each isolate was subcultured into brain-heart infusion broth supplemented with yeast extract and Tween 80 (Remel, Lenexa, KS), and the suspensions were incubated for 18–20 hours at 37°C. A multipoint inoculator was used to apply 1-µL inocula (10⁶–10⁷ cfu) of each strain to the surface of Mueller-Hinton agar containing saponin-lysed sheep blood (5%), and serial twofold dilutions of each of the antibiotics were included.

Evaluation of Treatment Response

Time to bacteriologic clearance was defined as the time from the onset of treatment until all four swabs in a set were negative for *C. diphtheriae*. Time to membrane clearance was the time until the membrane cleared from the nasopharynx, and time to fever clearance was the time until the temperature fell to <37.5°C for at least 24 hours. The persistence of the membrane or isolation of *C. diphtheriae* from swabs at the end of treatment was considered an acute treatment failure. A relapse was defined as reappearance of the membrane or reisolation of *C. diphtheriae*. Patients were requested to return to the outpatient department 4 weeks after completion of treatment for further assessment.

Statistical Analysis

Normally distributed data for the two treatment groups were compared by using the Student’s *t*-test. Data that were not
Table 1. Clinical and laboratory features of 86 children with diphtheria who were treated with penicillin or erythromycin.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Penicillin recipients</th>
<th>Erythromycin recipients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in y (95% CI; range)</td>
<td>6 (4–8; 0.75–14)</td>
<td>4 (3–5; 0.75–13)</td>
<td>.06</td>
</tr>
<tr>
<td>Mean duration of illness before treatment ±</td>
<td>3.3 ± 1.3</td>
<td>3.2 ± 1.2</td>
<td>.89</td>
</tr>
<tr>
<td>SD in d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment with antibiotics</td>
<td>21 (48)</td>
<td>23 (55)</td>
<td>.51</td>
</tr>
<tr>
<td>Full primary immunization</td>
<td>21 (48)</td>
<td>26 (62)</td>
<td>.23</td>
</tr>
<tr>
<td>Bull neck</td>
<td>8 (18)</td>
<td>6 (14)</td>
<td>.62</td>
</tr>
<tr>
<td>Bleeding at membrane edge</td>
<td>3 (7)</td>
<td>1 (2.5)*</td>
<td>.33</td>
</tr>
<tr>
<td>Median temperature in ºC (95% CI; range)</td>
<td>38.2 (38–39; 37–40.8)</td>
<td>38.5 (38–38.8; 37–39.5)</td>
<td>.84</td>
</tr>
<tr>
<td>Median peripheral WBC count in ×10⁹/L (95% CI; range)</td>
<td>11.8 (11.9–16; 5.5–22)</td>
<td>13 (11–16.8; 6.2–26.3)</td>
<td>.46</td>
</tr>
<tr>
<td>Swab positive for Corynebacterium diphtheriae</td>
<td>11 (25)</td>
<td>4 (10)</td>
<td>.06</td>
</tr>
<tr>
<td>Hydrocortisone treatment required</td>
<td>11 (25)</td>
<td>7 (17)</td>
<td>.34</td>
</tr>
</tbody>
</table>

NOTE. Unless stated otherwise, data are no. (%) of patients.
* One patient also had petechiae on the palate.

normally distributed were compared by using the Mann-Whitney U test. Differences between proportions were tested by using the χ² test with Yates’ correction or Fisher’s exact test. Multiple regression analysis was used to investigate the influence of potential confounders on the main outcome variables.

Results

Demographic, clinical, and laboratory findings for the 86 children (44 randomized to penicillin therapy and 42 randomized to erythromycin therapy) who were enrolled in the trial are shown in table 1. Four children (age, 6–13 years), including a girl with an unrepaired cleft palate, were from one family. There were no significant differences between the two treatment groups in terms of characteristics at the time of admission. Overall, 49% of patients had a definite history of antibiotic therapy before admission to the hospital.

All patients had tonsillar diphtheria, 61 (71%) of whom had a membrane on both tonsils. In addition, seven children had a membrane on the pharyngeal wall and uvula. One of these patients had a nasal membrane and a shallow 5-mm ulcer on the philtrum of the upper lip. Treatment with antitoxin and antibiotics was started at the time of admission. All 15 isolates were susceptible to penicillin, ampicillin, ceftriaxone, and rifampin, but five (33%) were resistant to one or more antibiotics: 1 to tetracycline (MIC, 32 mg/L); 1 to

Complications

Three patients in the penicillin group developed clinical signs of myocarditis, all within the first week of illness. They complained of lassitude and weakness, and physical examination revealed quiet heart sounds and cardiac enlargement. All three patients had abnormal electrocardiograms. The first patient had a long QTc (0.45 second) on day 1 and developed left bundle-branch block on day 2; this heart block lasted 2 weeks and was associated with further QTc prolongation (up to 0.53 second). The second patient had multiple supraventricular ectopics and occasional ventricular ectopics from day 6 to day 13. The third patient had sinus tachycardia (heart rate, 125) and QTc prolongation (0.46 second) on days 6–8. This patient developed paralysis of the palate with nasal speech on day 22, which improved after 2 weeks.

Two other patients in the penicillin group and one patient in the erythromycin group, all of whom had no clinical signs of cardiac disease, developed prolonged QTc (>0.44 second) during treatment that resolved. The median QTc at the time of admission for erythromycin-treated patients was 0.40 second (range, 0.33–0.44 second), and that for penicillin-treated patients was 0.39 second (range, 0.33–0.45 second). The median increase in QTc during treatment was 0.03 second for the erythromycin group and 0.04 second for the penicillin group (P = .15). The QTc was longer for all patients during treatment and in the convalescent period than at the time of admission.

Microbiology

All 15 isolates were susceptible to penicillin, ampicillin, ceftriaxone, and rifampin, but five (33%) were resistant to one or more antibiotics: 1 to tetracycline (MIC, 32 mg/L); 1 to
erythromycin (MIC, >64 mg/L); 2 to both erythromycin (MIC, >64 mg/L) and tetracycline (MIC, 64 mg/L); and 1 to erythromycin (MIC, >64 mg/L), tetracycline (MIC, 64 mg/L), and chloramphenicol (MIC, 64 mg/L). All four children from whom erythromycin-resistant strains of \textit{C. diphtheriae} were isolated were randomized to the penicillin group.

### Discussion

Diphtheria is one of the oldest diseases known to humans. There are early descriptions of diphtheria in the writings of the ancient Hebrews. The 19th century French clinician-pathologist Bretonneau recognized the unique clinical features of the disease, including the characteristic leatherlike adherent membrane, after which he named the disease (Greek \textit{diphthera}: leather or hide). In 1888, Roux and Yersin demonstrated that the systemic complications of diphtheria were caused by a toxin and not direct bacterial invasion. With the development of antitoxin by von Behring and Kitasato in 1890, specific treatment for diphtheria became possible. In the 1930s, the sulfonamide antibiotics were used as treatment in addition to antitoxin, and in the 1940s, penicillin became the standard antimicrobial treatment for diphtheria [11].

Erythromycin, the prototype macrolide antibiotic, was discovered in 1952 [12]. Erythromycin has better in vitro activity against \textit{C. diphtheriae} than penicillin (MIC of erythromycin, 0.025–0.05 mg/L) [10, 13], and it is currently endorsed as a safe alternative to penicillin by the WHO [5]. It is considered by some investigators to be the treatment of choice. Cardiac side effects of erythromycin were first reported in the 1980s [14]. The drug has electrophysiological effects similar to those of class Ia and class III antiarrhythmic drugs, prolonging ventricular repolarization (QT interval) and occasionally leading to ventricular arrhythmias (including torsades de pointes) [6]. These effects are usually reported in association with high-dose intravenous infusions of erythromycin but have also occurred during oral therapy [15, 16]. Patients with underlying cardiac disease are more likely to suffer these cardiac adverse effects.

Diphtheritic myocarditis occurs in 10%–20% of patients with diphtheria and is the usual cause of death. Manifestations of diphtheritic myocarditis include toxic dilated cardiomyopathy and conduction disturbances leading to complete heart block [17]. Cardiac complications usually develop during the first 2 weeks of illness. The risk of complications is proportional to the extent of the initial infection; most patients with severe diphtheritic pharyngitis will develop cardiac complications. In the current study, which excluded very severe cases, three patients (3.5%) developed clinical signs of cardiac disease, and a further three patients (3.5%) had electrocardiographic features only. In five of these patients, the complication developed after treatment began, but only one was randomized to erythromycin therapy. Treatment with erythromycin did not
cause a significant prolongation of QTc when compared with penicillin.

In Vietnam, as in many tropical countries, antibiotics are available freely without prescription, and pretreatment before hospital admission is very common. This fact may limit disease progression and also contributes to the low rate of positive cultures.

Penicillin and erythromycin have been compared once previously in an open-label trial during an outbreak of diphtheria in Texas [7]. Adults and children were randomized to penicillin therapy (intramuscularly for 3 days and then orally for 4 days) or erythromycin therapy (intravenously for 3 days and then orally for 4 days). However, the trial was stopped after 26 patients had received erythromycin treatment because of a high incidence of thrombophlebitis. The efficacy of erythromycin and penicillin in the eradication of carriage has also been assessed in several studies. Although erythromycin may be slightly better in clearing C. diphtheriae from the nasopharynx, both drugs are recommended for treatment of diphtheria [18–20].

In this study, the time to fever clearance was considerably shorter for patients treated with penicillin than for those treated with erythromycin, although no differences were demonstrated in times to bacteriologic or membrane clearance. The shorter time to fever clearance may be related to the mechanism of action of the drugs; penicillin is bactericidal against C. diphtheriae, whereas in conventional doses erythromycin is bacteriostatic [12]. Penicillin may also be more effective against secondary infection associated with tissue damage in the oropharynx. Although penicillin was initially given parenterally and erythromycin was initially given by mouth, erythromycin is well absorbed orally, and since there is no reason to suspect malabsorption in our patients, pharmacokinetic factors are not likely to explain the difference between the two drugs. Compliance with oral erythromycin was also ensured because the drugs were administered by nurses and all patients were in the hospital throughout the study. Although initial hydrocortisone treatment may have attenuated fever, it did not account for the difference in times to fever clearance between the two treatment groups.

Four (27%) of 15 isolates were erythromycin-resistant, and three of these isolates were also resistant to other antibiotics. Fortunately, patients from whom these isolates were recovered were randomized to the penicillin group. Erythromycin-resistant C. diphtheriae have been described before, and resistance was found to be plasmid-mediated [21]. The emergence of multidrug-resistant C. diphtheriae is probably related to the widespread availability of antibiotics in Vietnam. One-half the patients in this study had received antibiotic therapy before admission. Studies on a larger number of C. diphtheriae isolates from Vietnam showed that tetracycline and trimethoprim are also not predictably active against these bacteria (C. M. Parry, unpublished observations). The efficacy of alternative antibiotics may need to be evaluated if the incidence of resistance to erythromycin increases.

This study showed that penicillin and erythromycin are both effective for the treatment of diphtheria. No clinically important cardiotoxic effects of erythromycin were demonstrated. However, because of the slower fever clearance and higher incidence of gastrointestinal side effects associated with erythromycin therapy and, most importantly, the high incidence of resistance, penicillin is recommended as the drug of choice for treatment of patients with diphtheria in Vietnam. Erythromycin should be reserved for treatment of penicillin-allergic patients.

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