Clinical Features and Predictors of Diphtheritic Cardiomyopathy in Vietnamese Children

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Background. Despite the availability of antitoxin and antibiotics, the mortality rate for diphtheria remains high, mostly because of cardiac complications.

Methods. During 1 year, 154 Vietnamese children with diphtheria admitted to a referral hospital were studied prospectively with clinical examination, including a simple pseudomembrane score, 12-lead and 24-hour electrocardiography, measurement of serum cardiac enzyme levels, and estimation of troponin T levels.

Results. Thirteen children had diphtheritic cardiomyopathy on admission, and 19 developed it subsequently. Twelve children (8%) died. The combination of pseudomembrane score of ≥1 and bull neck predicted the development of diphtheritic cardiomyopathy, with a positive predictive value of 83% and a negative predictive value of 93%. Administration of 24-hour electrocardiography on admission improved the ability to predict diphtheritic cardiomyopathy by 57%. Fatal outcome was best predicted by the combination of myocarditis on admission and a pseudomembrane score of ≥2. Of the cardiac enzyme levels measured, an elevated aspartate aminotransferase level was the best predictor. The presence of troponin T identified additional children with subclinical cardiac damage.

Conclusions. The development of diphtheritic cardiomyopathy can be predicted by means of simple measures.
with a diagnosis of diphtheria were admitted prospectively to the study during the period of April 1995 through March 1996. Diphtheria was diagnosed clinically either if the patient had a febrile illness with a characteristic adherent pseudomembrane visible in the nasopharynx or if the patient presented later (after pseudomembrane clearance) with a history of recent severe sore throat and signs of cardiomyopathy. We defined symptomatic diphtheritic cardiomyopathy in patients who developed symptoms of, and examination findings consistent with, heart failure (see Results) and abnormal findings on 12-lead electrocardiography. Children with no symptoms of heart failure, but with either clinically detected rhythm disturbances or abnormal findings on 12-lead electrocardiography, were defined as having asymptomatic diphtheritic cardiomyopathy. Patients were given a severity score defined as follows: “mild,” local symptoms only; “moderate,” patient is systemically unwell with a “toxic” facial appearance; “severe,” patient is bed-bound, is unable to drink, has difficulty breathing, or has alteration in mental status (table 1). We also prospectively devised a score that estimated the amount of pseudomembrane visible in the nasopharynx on admission to see whether this was a better predictor (table 1). Patients were examined daily and again 1 month after discharge.

Microbiological investigations. Four sterile swab specimens were taken on admission (1 from each tonsil and 1 from each nostril). An additional set of swab specimens was also obtained on days 2, 5, 12, 24, and at follow-up. Swabs were inoculated onto 5% sheep blood agar and Hoyles tellurite agar obtained on days 2, 5, 12, 24, and at follow-up. Swabs were each nostril). An additional set of swab specimens was also mens were taken on admission (1 from each tonsil and 1 from.

Clinical procedures. Blood was drawn on admission for determination of hematocrit, differential WBC count, platelet count, plasma biochemistry, and standard cardiac enzyme level estimation (creatinine phosphokinase, lactate dehydrogenase, and aspartate aminotransferase [AST] levels). Blood was also drawn for estimation of cardiac troponin T (cTnT) level at admission, weekly, at follow-up, and more frequently in severely ill patients. Samples for cardiac enzyme and cTnT level estimation were centrifuged immediately and were stored at −20°C until further analyses. cTnT levels were measured with the Enzymun-Test immunoassay (Boehringer Mannheim). The detection limit of the cTnT assay was 0.01–16.6 ng/mL [13]. The presence of any cTnT was considered to be abnormal [14]. Abnormal levels of cardiac enzymes were defined as follows: creatinine phosphokinase, >200 IU/L; lactate dehydrogenase, >250 IU/L; and AST, >47 IU/L.

Table 1. Severity and membrane scores at presentation for 154 children with diphtheria (32 with diphtheritic cardiomyopathy).

<table>
<thead>
<tr>
<th>Score</th>
<th>Children with fatal cases (n = 12)</th>
<th>Survivors (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0)</td>
<td>42 (0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0)</td>
<td>78 (7)</td>
</tr>
<tr>
<td>Severe</td>
<td>12 (12)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Membrane score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0*</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>29 (2)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>92 (7)</td>
</tr>
<tr>
<td>3</td>
<td>3 (3)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>4</td>
<td>9 (9)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

NOTE. Severity score: mild, local symptoms only; moderate, patient is systemically unwell with a “toxic” facial appearance; severe, patient is bed-bound, is unable to drink, has difficulty breathing, or has alteration in mental status. Membrane score: 0, membrane cleared before presentation; 1, nose only or incomplete/follicular coverage of tonsils; 2, confluent coverage of tonsils; 3, as above, plus palate and/or pharyngeal wall; 4, as above, plus nose and/or larynx.

* Two patients with diphtheritic cardiomyopathy presented after the membrane had cleared.

Twelve-lead electrocardiography was done at admission and as clinically indicated. Continuous electrocardiographic monitoring for 24 h was done with a Medilog 4000-II monitor (Oxford Instruments) on admission and at weekly intervals depending on the availability of the monitors. Twenty-four-hour electrocardiographic recordings were analyzed at a later date by a technician blind to the clinical details. Results were interpreted with the use of tables of normal values, and QT interval corrected for heart rate (QTc) was calculated by use of Bazett’s formula [15].

We used definitions of abnormalities used previously at our health care center when interpreting the 24-h electrocardiograms [5]. Because it was anticipated that 24-h electrocardiography might yield several abnormal findings, a 24-h electrocardiographic abnormality score was devised in which each different abnormality detected (excluding sinus tachycardia) counted as 1 point.

Treatment. At admission, patients were treated with 20–100,000 IU of equine diphtheria antitoxin (Pasteur Institute) administered intramuscularly in accordance with World Health Organization guidelines [16]. Patients with severe diphtheria were treated with benzyl penicillin at (100,000 IU/kg iv q.d. for 14 days). Patients with mild or moderate disease were included in a treatment trial [4] and received either intramuscular benzyl penicillin (50,000 IU/kg q.d. for 5 days), followed by oral penicillin V (50 mg/kg q.d. for 5 days), or oral erythromycin ethylsuccinate (50 mg/kg q.d. for 10 days). Severe tonsillar and
Table 2. Clinical features of 154 children with diphtheria.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Children with fatal cases (n = 12)</th>
<th>Survivors (n = 142)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>5 (42)</td>
<td>84 (59)</td>
<td>0.49 (0.13–1.84)</td>
<td>.24</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>7.5 (1.75–12)</td>
<td>5 (0.75–14)</td>
<td>NA</td>
<td>.08</td>
</tr>
<tr>
<td>Duration of illness, median days (range)</td>
<td>4.5 (3–12)</td>
<td>3 (1–20)</td>
<td>NA</td>
<td>.017</td>
</tr>
<tr>
<td>Rural residence</td>
<td>12 (100)</td>
<td>49 (35)</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12 (100)</td>
<td>126 (89)</td>
<td>NA</td>
<td>.25</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (42)</td>
<td>74 (52)</td>
<td>0.66 (0.17–2.45)</td>
<td>.16</td>
</tr>
<tr>
<td>Malaise</td>
<td>8 (67)</td>
<td>62 (44)</td>
<td>2.58 (0.66–10.75)</td>
<td>.22</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>5 (42)</td>
<td>44 (31)</td>
<td>1.59 (0.41–6)</td>
<td>.32</td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>10 (83)</td>
<td>38 (27)</td>
<td>13.68 (2.63–95.09)</td>
<td>.0001</td>
</tr>
<tr>
<td>Facial or neck swelling</td>
<td>11 (92)</td>
<td>27 (19)</td>
<td>46.85 (5.8–1012.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Full primary diphtheria toxoid immunization</td>
<td>0</td>
<td>35 (25)</td>
<td>NA</td>
<td>.04</td>
</tr>
<tr>
<td>Pretreatment with antibiotics</td>
<td>7 (58)</td>
<td>69 (49)</td>
<td>0.68 (0.18–2.52)</td>
<td>.7</td>
</tr>
<tr>
<td>Received antitoxin before day 3 of illness</td>
<td>0</td>
<td>35 (25)</td>
<td>NA</td>
<td>.04</td>
</tr>
<tr>
<td>Admission temperature, median °C (range)</td>
<td>37.5 (37–39.5)</td>
<td>38.2 (37–40.8)</td>
<td>NA</td>
<td>.01</td>
</tr>
<tr>
<td>Bull neck</td>
<td>12 (100)</td>
<td>22 (15)</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bleeding tendency</td>
<td>9 (75)</td>
<td>12 (8)</td>
<td>32.5 (6.7–178.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stridor requiring tracheotomy</td>
<td>6 (50)</td>
<td>6 (4)</td>
<td>22.67 (4.67–117.15)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diphtheritic cardiomyopathy at hospital admission</td>
<td>10 (83)</td>
<td>3 (2)</td>
<td>231.7 (27.8–2811.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><em>Clostridium diphtheriae</em> isolated</td>
<td>11 (92)</td>
<td>23 (16)</td>
<td>56.9 (16.9–1237.3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated. NA, not applicable.

RESULTS

During the 1-year study, 154 children with a clinical diagnosis of diphtheria were admitted to the hospital. The median age was 5.5 years (range, 0.75–14 years). Eighty-nine (58%) were boys. Four children (ages 6–13 years) were from the same family, including a 13-year-old child with an unrepaired cleft palate. Thirteen children had diphtheritic cardiomyopathy at hospital admission, and 19 developed it subsequently. Twelve children (8%) died between 4 and 18 days (median, 10 days) after onset of the infection. Eight children (5%) developed diphtheritic neuropathy as a late complication. A description of their clinical courses will be the subject of a separate report.

Admission clinical features. Children typically presented with an acute febrile illness with a severe sore throat, cough, and malaise. A history of facial or neck swelling or hoarse voice was more frequent in patients who died (table 2). Those who received antitoxin early (before day 3 of symptoms) had a better outcome. All but 2 patients had pseudomembrane visible in the nasopharynx. Both of these patients presented late with a history of recent severe sore throat and had diphtheritic cardiomyopathy (on days 7 and 20 of the illness). Children with the following characteristics noted during initial examination were more likely to die: bull neck (figure 1); mucosal, skin, or nasal bleeding (figure 2); severe airway obstruction requiring a tracheotomy; a pseudomembrane score of >2; or an initial...
severity score of “severe” (tables 1 and 2). Forty-nine children (32%) had copious clear or blood-tinged nasal discharge, with pseudomembrane visible in the nares (figure 3). Twelve of 31 patients with a pseudomembrane score of >2 died, compared with none of those with a lower pseudomembrane score ($P < .0001$). In a multiple logistic regression model, the combination of the presence of diphtheritic cardiomyopathy at hospital admission and a pseudomembrane score of >2 proved the best predictor of fatal outcome, correctly identifying 10 of 12 fatal cases (sensitivity, 83%; specificity, 100%; PPV, 100%; NPV, 99%; OR, 232; 95% CI, 35–1150; $P < .0001$).

**Renal complications.** Oliguric renal failure developed in all patients who died. The serum creatinine level on admission (corrected for age and sex) was more likely to be elevated in fatal cases (16 nonfatal cases vs. 11 fatal cases; OR, 86.6; 95% CI, 10.3–1916.8; $P < .0001$) (table 3). Therefore, elevated serum creatinine levels at admission predicted fatal outcome with a sensitivity of 92%, a specificity of 89%, a PPV of 41%, and an NPV of 99%.

**Diphtheritic cardiomyopathy.** Thirty-two children (21%) developed either symptomatic or asymptomatic diphtheritic cardiomyopathy; 13 (41%) had evidence of diphtheritic cardiomyopathy at hospital admission, and 19 (59%) developed diphtheritic cardiomyopathy subsequently. Twenty-eight patients with diphtheritic cardiomyopathy were symptomatic, but 4 remained asymptomatic (with cardiac rhythm abnormalities as the only manifestation). Twelve children (37.5%) with diphtheritic cardiomyopathy died. The median time from onset of the infection to the manifestations of diphtheritic cardiomyopathy was shorter in fatal cases (5 days [range, 3–12 days] vs. 8 days [range, 2–20 days]; $P = .03$). In fatal cases, the median time to death from the onset of the illness was 10 days (range, 4–24 days). For the 19 children who developed diphtheritic cardiomyopathy after admission, the examination findings that predicted its development were similar to those that predicted fatal outcome (table 4). In a multiple logistic regression model, the combination of bull neck and pseudomembrane admission score of >2 gave the best predictor of the development of diphtheritic cardiomyopathy, correctly identifying 10 of 19 patients who developed it and 120 of 122 patients who did not (sensitivity, 53%; specificity, 98%; PPV, 83%; NPV, 93%; OR, 31.6; 95% CI, 5.9–306; $P < .0001$). Among the 20 survivors of diphtheritic cardiomyopathy, symptoms or abnormal clinical cardiac findings remained present for median of 10 days (range, 3–35 days).

The 28 children with symptomatic diphtheritic cardiomyopathy typically were tired and listless, looked pale and clammy, and had decreased appetite or vomiting. Frequent findings of physical examinations included tachypnea, hepatomegaly, quiet heart sounds, signs of cardiac enlargement, tachycardia, pal-pable ectopic beats, irregularly irregular heart beat, gallop rhythm, new murmurs, poor peripheral perfusion, widening of pulse pressure, and in severe cases, hypotension. Patients with...
severe cases developed signs and chest radiographic abnormalities consistent with pulmonary edema.

**Admission 12-lead electrocardiography findings.** Abnormalities of heart rate or rhythm occurred in all 32 children with diphtheritic cardiomyopathy. Initial 12-lead electrocardiographic abnormalities associated with a fatal outcome were complete heart block ($P<.05$) and ischemic changes ($P<.01$), whereas sinus tachycardia was associated with a good outcome ($P<.01$) (table 5).

**Fatal cases.** All patients with fatal cases died of diphtheritic cardiomyopathy. They all developed worsening heart failure and died during a cardiac arrest. Two children developed persistent ventricular tachycardia 2 and 4 h before death. The development of complete heart block occurred in 9 cases; all were fatal. In 4 patients, complete heart block developed suddenly and was the first electrocardiographic abnormality, but in 5, complete heart block followed other electrocardiographic abnormalities and was an agonal finding. Four patients (3 with fatal cases) had a temporary cardiac pacemaker inserted (between days 7 and 11) as part of a prospective trial [10].

**Twenty-four-hour electrocardiography results.** A total of 125 continuous 24-h electrocardiographic recordings were made for 79 patients. Seventy children (89%) had abnormalities detected on their first 24-h electrocardiograph. At the time of their first 24-h electrocardiographic recording, 13 children had diphtheritic cardiomyopathy (symptomatic or asymptomatic), and all had abnormalities detected. Among the remaining 66 children, results of 24-h electrocardiography at admission were normal for 47 (71%), if sinus tachycardia is accepted as a variant of normal, and 1 of these children subsequently developed diphtheritic cardiomyopathy. Nineteen children had abnormal 24-h electrocardiographic results at admission, and 11 of these subsequently developed diphtheritic cardiomyopathy (OR, 63.3; 95% CI, 6.6–1507.2; $P<.0001$). Thus, the presence of an abnormality other than sinus tachycardia on a 24-h electrocardiograph at admission predicted the development of diphtheritic cardiomyopathy with a sensitivity of 92%, a specificity of 85%, a PPV of 58%, and an NPV of 98%. Only 7 of these children were already predicted to develop diphtheritic cardiomyopathy by clinical predictors. Thus, 24-h electrocardiography improved our ability to predict diphtheritic cardiomyopathy by 57%.

Serial 24-h electrocardiography was performed for 39 patients (32 had 2 recordings and 7 had 3 recordings). For 13

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**Table 3.** Results of laboratory studies performed at the time of hospital admission for 154 children with diphtheria.

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Survivors ($n = 142$)</th>
<th>Children with fatal cases ($n = 12$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.65 (0.28–1.42)</td>
<td>1.35 (0.9–2.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>WBC count, $\times 10^7$ cells/L</td>
<td>16.1 (6.4–34)</td>
<td>12 (12–26.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Platelet count, $\times 10^9$ platelets/L</td>
<td>170 (108–200)</td>
<td>180 (102–290)</td>
<td>.6</td>
</tr>
<tr>
<td>Creatinine phosphokinase, IU/L</td>
<td>81.5 (23–2196)</td>
<td>292 (99–3934)</td>
<td>.0001</td>
</tr>
<tr>
<td>Lactate dehydrogenase, IU/L</td>
<td>278 (74–1303)</td>
<td>386 (253–802)</td>
<td>.01</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>37 (12–286)</td>
<td>119 (47–370)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cardiac troponin T, ng/mL</td>
<td>0 (0–0.07)</td>
<td>0.09 (0–0.2)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (range).

**Table 4.** Predictors for the development of diphtheritic cardiomyopathy after hospital admission among 141 children with diphtheria.

<table>
<thead>
<tr>
<th>Examination finding</th>
<th>Children who developed diphtheritic cardiomyopathy ($n = 19$)</th>
<th>Children who did not develop diphtheritic cardiomyopathy ($n = 122$)</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classified as “severe” case</td>
<td>12 (63)</td>
<td>9 (7)</td>
<td>21.5 (6–81.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Membrane score of &gt;2</td>
<td>13 (68)</td>
<td>8 (7)</td>
<td>30.9 (8.1–126)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bull neck</td>
<td>13 (68)</td>
<td>11 (9)</td>
<td>21.9 (6.1–82.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bleeding tendency</td>
<td>7 (37)</td>
<td>5 (4)</td>
<td>13.7 (3.2–60.6)</td>
<td>.0001</td>
</tr>
<tr>
<td>Stridor (requiring tracheotomy)</td>
<td>3 (16)</td>
<td>4 (3)</td>
<td>5.5 (0.9–33.4)</td>
<td>.05</td>
</tr>
<tr>
<td>Clostridium diphtheriae isolated</td>
<td>12 (63)</td>
<td>13 (11)</td>
<td>14.4 (4.3–50.1)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients. Thirteen children with diphtheritic cardiomyopathy at presentation are excluded.
patients, diphtheritic cardiomyopathy either was present at the
time of admission or developed after admission. All had more
significant findings on their second recording. In 2 children, a
third 24-h electrocardiograph was recorded after symptoms and
signs of diphtheritic cardiomyopathy had resolved (days 30 and
37 of the illness), and abnormalities were still present on these
recordings.

Ischemic findings (ST depression or elevation) on the
admission 24-h electrocardiograph were more frequent in those
who died (8 of 8 patients with fatal cases vs. 5 of 71 of those
with nonfatal cases; \( P < .0001 \)). The median electrocardio-
graphic abnormality score for admission electrocardiographs
was higher for those who died (3.5 [range, 2–8] vs. 0 [range,
0–6]; \( P < .0001 \)).

**Laboratory investigation results.** Levels of cardiac en-
zymes (creatine phosphokinase, lactate dehydrogenase, and
AST) were higher at the time of hospital admission for patients
who died (table 3). Of the cardiac enzymes, an elevated AST
level (\( \geq 47 \text{IU/L} \)) was the best predictor of fatal outcome, with
a sensitivity of 100%, a specificity of 66%, a PPV of 20%, and
an NPV of 100%.

**cTnT results.** cTnT levels were measured at the time of
hospital admission for 90 children (7 with fatal cases). Median
cTnT levels were higher at admission in those who died (0.09
ng/mL [range, 0–0.2 ng/mL] vs. 0 ng/mL [range, 0–0.07 ng/
ml]; OR, 160; 95% CI, 11.7–5101.5; \( P < .0001 \)). cTnT levels
were elevated (>0.01 \( \mu \text{g/L} \)) at hospital admission in 6 of the 7
patients with fatal cases in whom the levels were measured.
Therefore, the presence of cTnT in serum samples at hospital
admission predicted fatal outcome, with a sensitivity of 86%,
specificity of 99%, a PPV of 67%, and an NPV of 99%. How-
ever, all of these patients were identified by the clinical pre-
dictors of fatal outcome.

**Microbiology.** Thirty-four patients (22%) had *C. diphther-
iae* isolated from their nasopharynx. In all 34 cases, *C. diph-
theriae* was isolated from nasal swabs, but only 13 patients (38%)
had either nasal discharge or pseudomembrane present. *C.
diphtheriae* was more likely to be isolated from patients with
more extensive pseudomembrane (20 of 34 with positive cul-
ture results had pseudomembrane score of \( \geq 2 \) vs. 11 of 120
with negative results of culture; \( P < .001 \)). All of the isolates
were susceptible to penicillin, ampicillin, ceftriaxone, and ri-
fampicin. Although there are no clinically relevant break points
for *C. diphtheriae*, 9 of the isolates showed reduced suscepti-
bility or resistance to \( \geq 1 \) of the antimicrobials, on the basis of
a high MIC and no zone of inhibition in the disk susceptibility
test. Three isolates were resistant to tetracycline (MIC, >8 mg/
L); 1 was resistant to trimethoprim (MIC, 8 mg/L); 1 was
resistant to erythromycin (MIC, >16 mg/L) and azithromycin
(MIC, >16 mg/L); 3 were resistant to erythromycin (MIC, >16
mg/L), azithromycin (MIC, >16 mg/L), and tetracycline (MIC,
>8 mg/L); and 1 was resistant to erythromycin (MIC, >16 mg/
L), azithromycin (MIC, >16 mg/L), tetracycline (MIC, >8 mg/
L), and chloramphenicol (MIC, >4 mg/L). For 21% of the
34 children with a positive culture result, the isolate was re-
sistant to erythromycin. All of these children were treated with
penicillin.

**Follow-up.** Seventy-nine diphtheria survivors (56%) re-
turned for a follow-up visit 1 month after discharge (15 were
survivors of diphtheritic cardiomyopathy). All had normal 12-
lead electrocardiographic results. Only 1 child appeared unwell.
He was a survivor of diphtheritic cardiomyopathy, and ex-
amination findings revealed sinus tachycardia (rate, 120 beats/
min) and cranial nerve palsies. He had no other signs of cardiac
dysfunction, and the sinus tachycardia was assumed to be due
to autonomic neuropathy. Throat and nose swab culture results
were negative in all but 1 child—a sibling of the child with a
cleft palate [4].

**DISCUSSION**

Most descriptions of patients with diphtheria were published
>60 years ago, and their findings concentrated on 12-lead elec-
trocardiographic abnormalities. Many of these reports con-
cluded that the development of significant conduction defects,
such as bundle branch block and complete heart block, had a
poor prognosis [6–9, 18]. More recently, 24-h electrocardio-
graphic monitoring was performed for 15 children with severe
diphtheria from our center and was found to be useful in
predicting fatal outcome [5]. After the recent diphtheria epi-
demic in Russia, a study of diphtheritic cardiomyopathy in 122
children (9 with fatal cases) found that electrocardiographic

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**Table 5. Initial 12-lead electrocardiographic findings for 32 children with diphtheritic cardiomyopathy.**

<table>
<thead>
<tr>
<th>Electrocardiographic abnormality</th>
<th>Children with fatal cases (n = 12)</th>
<th>Survivors (n = 20)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree</td>
<td>1 (8)</td>
<td>1 (5)</td>
<td>.99</td>
</tr>
<tr>
<td>Second degree</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>.99</td>
</tr>
<tr>
<td>Third degree</td>
<td>4 (33)</td>
<td>0</td>
<td>.014</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>3 (25)</td>
<td>18 (90)</td>
<td>.0003</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>0</td>
<td>2 (10)</td>
<td>.51</td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>0</td>
<td>3 (15)</td>
<td>.27</td>
</tr>
<tr>
<td>QTc of ( &gt;0.44 ) s</td>
<td>2 (17)</td>
<td>6 (30)</td>
<td>.68</td>
</tr>
<tr>
<td>VE and/or SVE</td>
<td>4 (33)</td>
<td>8 (40)</td>
<td>.99</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>4 (33)</td>
<td>3 (15)</td>
<td>.38</td>
</tr>
<tr>
<td>Ischemic changes(^a)</td>
<td>10 (83)</td>
<td>3 (15)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients. Some children had >1 abnormal finding on electrocardiography. QTc, QT interval corrected for heart rate; SVE, supraventricular ectopic; VE, ventricular ectopic.

\(^a\) ST depression or T wave inversion.
abnormalities with ischemic changes resembling those seen in adults with an acute myocardial infarction, together with a high myoglobin level (>2000 ng/mL), were reliable markers for fatal outcome [19]. Other previously identified markers of a poor outcome in diphtheritic cardiomyopathy include extensive pseudomembrane in the oropharynx, extensive respiratory tract infection with subcutaneous edema, leukocytosis (leukocyte count, >25 × 10⁹ leukocytes/L), and elevated AST level (>80 IU/L) [20, 21]. Although previous studies have identified indicators of a fatal outcome, it is not known whether we can predict the development of diphtheritic cardiomyopathy and thus focus attention on patients with a potentially treatable complication, nor is it clear whether newer markers of cardiac damage, such as presence of cTnT, have anything useful to add. We therefore conducted a study to identify clinical, electrocardiographic, and laboratory features associated with the development of cardiomyopathy and fatal outcome.

Overall, 21% of our patients had diphtheritic cardiomyopathy, with most (60%) developing signs after admission to the hospital. Clinical features at presentation provided useful indicators of how patients will fare. The combination of the presence of a bull neck and a pseudomembrane score of >2 was the best predictor that patients would develop diphtheritic cardiomyopathy, whereas the combination of diphtheritic cardiomyopathy at hospital admission and a pseudomembrane score of >2 was the best predictor of a fatal outcome.

Ischemic changes on both 12-lead and 24-h electrocardiography were more common in patients who died. In addition, the number of different abnormalities on the 24-h electrocardiograph obtained at hospital admission was a good predictor of fatal cases. The admission 24-h electrocardiograph was also useful in predicting the development of symptomatic diphtheritic cardiomyopathy after hospital admission, identifying >90% of such patients.

As others have shown previously, we found that severe conduction defects, including complete heart block and bundle branch block, were associated with a poor outcome [18, 22, 23]. Tachyarrhythmias are reported less often in patients with diphtheritic cardiomyopathy [24], but we saw sinus arrhythmia, atrial flutter, prolonged ventricular tachycardia, and several unsustained episodes of supraventricular tachycardia. Although there are rare reports of the development of progressive conduction defects years after diphtheria [25, 26], we found no evidence of persistent cardiac dysfunction in our patients at follow-up, which included 15 of the 20 survivors of diphtheritic cardiomyopathy.

cTnT is a thin-filament contractile protein present in high concentrations in the myocardium and not in other tissues. It is released rapidly after myocardial injury in direct proportion to the extent of injury and is undetectable in healthy children [27]. Preliminary data showed that cTnT levels were elevated in patients with severe diphtheritic cardiomyopathy [10]. Therefore, we wondered whether it might be a useful early predictor of the development of diphtheritic cardiomyopathy, but it did not add to the clinical assessment. Other admission laboratory investigations useful in predicting fatal outcome included elevated serum creatinine (for age and sex) and AST (>47 IU/L) levels—both had a high sensitivity and NPV.

In summary, a high risk of developing cardiomyopathy or of dying can be predicted in children with diphtheria from both clinical and laboratory investigations and electrocardiographic findings. A simple score to document the amount of pseudomembrane visible at the time of admission, in combination with the presence of a bull neck, was the best predictor of the development of diphtheritic cardiomyopathy. The same pseudomembrane score in combination with presence of diphtheritic cardiomyopathy at presentation was the best predictor of a fatal outcome. Where available, 24-h electrocardiographic monitoring may help predict the development of symptomatic diphtheritic cardiomyopathy in some patients, and estimation of cTnT may help detect subclinical disease. Overall, however, the simple clinical predictors were as good as the newer cardiac diagnostic tools. When the availability of cardiac investigations is limited, these simple clinical predictors will enable doctors to target resources to the patients that need them most.

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References