Non-Toxigenic Penicillin and Cephalosporin-Resistant *Corynebacterium diphtheriae* Endocarditis in a Child: A Case Report and Review of the Literature

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Reports of invasive disease caused by non-toxigenic *Corynebacterium diphtheriae* are increasing; however, medical management has not been extensively studied. We describe what we believe is the first documented case of penicillin and cephalosporin-resistant *C. diphtheriae* endocarditis in a child successfully treated with vancomycin, meropenem, and valvular replacement surgery.

**Key words.** antibiotic resistance; *Corynebacterium diphtheriae*; endocarditis.

*Corynebacterium diphtheriae* was first described in 1884 as the causative agent in respiratory diphtheria, a toxin-mediated disease that has significantly decreased due to World Health Organization vaccination campaigns [1]. Despite campaign successes, toxigenic diphtheria remains an endemic disease in some countries. In addition, non-toxigenic (NT) *C. diphtheriae* has been increasingly found as a cause of invasive disease including endocarditis, and although the incidence remains low, infection is associated with high morbidity and mortality [1, 2]. Until 1985, all reported cases of diphtheria endocarditis describe penicillin (PCN)-sensitive strains, with few studies informing of effective strategies for the management of PCN-resistant (PCN-R) strains [1, 3]. We describe what we believe to be the first reported case of PCN and cephalosporin-resistant NT *C. diphtheriae* endocarditis in a child successfully treated by vancomycin and meropenem followed by late valvular replacement surgery.

**CASE**

A previously healthy 12-year-old, US-born male attending boarding school in Nigeria the previous 12 months presented to a Nigerian hospital with fever, headache, and fatigue for 8 days. He was treated for dehydration and anemia with intravenous fluids and red blood cell transfusion, and he was given amoxicillin for fevers. A fever workup was negative. His fevers persisted and he returned to the US on day 14 of illness. On day 15 of illness, he presented to his pediatrician and was subsequently hospitalized for persistent fevers and new heart murmur.

An echocardiogram revealed large vegetations on the aortic and mitral valve leaflets and the roof of the right atrium near the superior vena cava, moderate to severe mitral regurgitation, moderate to severe aortic insufficiency associated with dilation of the left atrium and ventricle, and a small pericardial effusion. His ejection fraction was normal (66%). Chest radiography showed cardiomegaly, pulmonary edema, and small bilateral pleural effusions. Electrocardiogram revealed predominantly sinus tachycardia and premature atrial complexes. Blood cultures (6 of 6) were preliminarily identified as *Corynebacterium* species. He was empirically treated with tobramycin and PCN G then transferred to our hospital on day 17 of illness for management of endocarditis.

On admission, his vital signs were temperature of 39.2°C, heart rate 130 beats/min, blood pressure 87/42 mm Hg,
respiratory rate 34, and oxygen saturation 99% on room air. Physical exam revealed a nervous child who was alert and oriented and in moderate distress due to pain. Oropharyngeal exam was normal. Axillary and inguinal lymph nodes were enlarged at 1–1.5 cm bilaterally. His cardiovascular exam was significant tachycardia, Grade III-IV harsh holosystolic murmur noted predominantly left apex with diastolic rumble, Grade II-III diastolic murmur right upper sternal border. Radial pulses were bounding, but there was a difference in lower extremity posterior tibial and dorsalis pedal pulses, with the right pulses being stronger than the left (2+ and 1+, respectively). His left foot was warm to touch with normal capillary refill, and sensation was grossly intact on initial examination. He had several well-healed, scattered, nonpruritic 1 × 1-cm circular hyperpigmented lesions over anterior tibias and dorsal forearms bilaterally, but palms and soles were spared. Also noted was appreciable fullness behind his left knee.

His initial laboratory evaluation was significant for a leukocyte count of 15.3/mm³; hemoglobin 9.0 g/dL; hematocrit 27.1%; platelet count 400/mm³; erythrocyte sedimentation rate 72 mm/h (normal, 0–20 mm/h); C-reactive protein 144 mg/dL (normal, 0–8 mg/L); and aspartate aminotransferase and alanine aminotransferase were 170 and 121 units/L (normal, 0–40 units/L), respectively. Malaria smears were negative. Therapy was changed to PCN G, gentamicin, and vancomycin. Shortly after arrival, the child developed absent left dorsalis pedal and posterior tibial pulses and severe pain in his left calf and foot. A Doppler ultrasound confirmed an occlusion (presumed septic emboli) of the left popliteal artery, and he underwent emergent embolectomy surgery.

Peripheral blood cultures from the referral hospital were positive for *C diphtheriae*. The Illinois Department of Public Health special bacteriology laboratory confirmed organism identification as *C diphtheriae* by 16S DNA sequencing, and the Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory confirmed it as NT by ELEK assay. The isolate was identified as biotype gravis by API coryne strip test (bioMérieux, Marcy l’Etoile, France). Susceptibility testing was performed by broth microdilution according to the Clinical and Laboratory Standards Institute (CLSI) guidelines, and results were interpreted using CLSI criteria [4]. Isolate minimum inhibitory concentrations (MICs) revealed susceptibility to gentamicin (0.25 µg/mL), linezolid (<0.25 µg/mL), meropenem (0.25 µg/mL), and vancomycin (<0.5 µg/mL) and resistance to PCN (>16 µg/mL) and ceftriaxone (8 µg/mL). Antibiotics were changed to meropenem and vancomycin. The patient continued to have complications of the left popliteal artery, which required further embolization and thrombectomy of a pseudoaneurysm. Computerized tomography imaging demonstrated infarcts in the spleen, bilateral kidneys, and left parietal lobe of the brain. Due to worsening left ventricular function, the child underwent aortic cusp extension valvuloplasty, mitral valve ring posterior annuloplasty, and mitral valve anterior leaflet chordoplasty. He completed 6 weeks of meropenem and vancomycin therapy and recovered without further embolic event or neurologic sequelae; however, he continued on digoxin, lisinopril, and diuretics after surgery.

**DISCUSSION**

Reports of NT strains of *C diphtheriae* have been increasing over the past 30 years and cause infections such as endocarditis, discitis, septic arthritis, pharyngitis, and tonsillitis [1, 5, 6]. Infections with NT strains have been associated with alcoholism, homelessness, and intravenous drug use, and underlying heart disease is a major risk factor for endocarditis [1]. The increase in disease due to NT strains is hypothesized to be secondary to selective pressure after widespread immunization against toxigenic *C diphtheriae* [7]. Non-toxigenic strains carry novel virulence factors [6] and are not eradicated by the current vaccine, which protects against toxin-producing strains.

Case fatality rates from NT *C diphtheriae* endocarditis ranging from 35% to 47% [1, 8] are significantly higher than the CDC reported case fatality rates attributable to toxigenic strains. Early empiric antibiotic therapy and expanded antibiotic susceptibility criteria will be critical in preventing the significant morbidity and mortality associated with invasive infections as antibiotic resistance rises.

Penicillin has been the mainstay of therapy for *C diphtheriae*. The Clinical and Laboratory Standards Institute recommends PCN, vancomycin, gentamicin, and erythromycin as the agents to consider for primary testing. No resistance has been described for vancomycin. A Medline search using the Medical Subject Headings (MeSH) of antibiotic resistance and *C diphtheriae* limited to humans yielded 7 reports documenting 38 clinical and nonclinical isolates of PCN-R *C diphtheriae*. The majority of these were NT strains. Susceptibilities differed significantly by geographic region. A United Kingdom study found that 17 of 24 (71%) strains of NT *C diphtheriae* isolated from patients with pharyngitis between 1995 and 1996 were PCN-R [5]. In a Brazilian study, 26% (12 of 47) of strains of NT and toxigenic *C diphtheriae* between 1981 and 2002 were PCN-R [3]. A recent French study of NT *C diphtheriae* isolates between 2007 and 2010 reported 6 of 42 (14.3%) had intermediate sensitivity to PCN
<table>
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<th>Age/Sex</th>
<th>Risk Factors</th>
<th>Valve</th>
<th>Presentation</th>
<th>Treatment</th>
<th>MIC</th>
<th>Surgery&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 12/M    | None         | M, A  | Endocarditis | 1) Tobramycin, penicillin G  
2) Penicillin G, gentamicin, vancomycin  
3) Meropenem, vancomycin | Penicillin  
Ceftriaxone  
Vancomycin  
Linezolid  
Gentamicin  
Meropenem | 16<sup>a</sup>  
8<sup>a</sup>  
0.5  
0.25  
0.25  
0.25 | Y  | Fully recovered after surgery | PR |
| 38/M    | None         | M, A  | Endocarditis | 1) Amikacin, ciprofloxacin  
2) Amikacin, clindamycin | Ampicillin  
Gentamicin  
Ciprofloxacin  
Clindamycin  
Erythromycin  
Chloramphenicol  
Tetracycline | 0.5<sup>α</sup>  
0.38  
0.125  
0.25  
0.016  
2  
0.5 | Y  | Fully recovered after surgery | [7]<sup>α</sup> |
| 5/F     | Congenital Cyanotic Heart disease | M | Endocarditis | 1) Cefotaxime, gentamicin  
2) Cefotaxime, amikacin  
3) Cefotaxime, amikacin, ampicillin | Penicillin G | 0.25<sup>d</sup> | N  | Embolic stroke with residual left hemiplegia | [11] |
| 6/F     | Congenital Heart disease | NR | Endocarditis | 1) Bactrim  
2) Penicillin, streptomycin  
3) Cephalothin, gentamicin  
4) Ampicillin, amoxicillin | NR | N  | Recovered baseline cardiac function after regimen 3 | [12]<sup>α</sup> |

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; M, A, mitral, aortic valves; MIC, minimum inhibitory concentration; N, No; NR, not reported; PCN, penicillin; PCN-R, penicillin-resistant; PR, present report; Y, Yes.

<sup>a</sup>CLSI defines PCN-R and ceftriaxone-R if >4 µg/mL [4].

<sup>b</sup>Valvular replacement surgery.

<sup>c</sup>No MIC results were provided for PCN or ceftraxone. The strain was reported to be resistant to PCN and ceftazidime and intermediate to cefuroxime axetil and ceftriaxone.

<sup>d</sup>This result was determined to be PCN-intermediate based on a minimum bactericidal concentration of 1 µg/mL, not PCN-resistant based on CLSI criteria.

<sup>α</sup>These reports were published before the 2006 CLSI interpretive criteria for diphtheria susceptibility testing.
(MIC, 0.38–0.5 mg/L) [9], although by 2006 CLSI criteria for these would be considered PCN-sensitive.

We additionally conducted a Medline search using the MeSH C diphtheriae and endocarditis limited to humans, which produced 47 articles. Since Belko et al [1] reported 48 cases of C diphtheriae endocarditis in 2000, there have been 7 additional pediatric cases (including the one reported here) and 8 adult cases, representing a total of 63 cases since 1950. Of the additional endocarditis cases, 4 NT isolates had complete or intermediate resistance to PCN (Table 1).

The 4 additional PCN-R NT C diphtheriae ranged in age from 6 to 38 years old, with a median age of 10 years. In the Belko et al [1] review, 37% of patients had no known predisposing factors and of nonintravenous drug users, 47% had underlying heart disease. This result is consistent with recent cases in which 2 of 4 (50%) patients had underlying heart disease and none were drug users. The mortality rates for C diphtheriae endocarditis range from 14% to 43% with a complication rate of 58%, the majority (45%) of which are endovascular [8, 10]. In the PCN-R cases, 2 of 4 (50%) underwent surgical intervention, all 4 patients survived, and 1 of 4 (25%) had a significant morbidity of persistent neurological deficits after embolic stroke.

Few reports offer guidance on PCN-R C diphtheriae management, and a variety of antibiotic combinations has been used in endocarditis cases. Synergy between PCN and gentamicin in PCN-susceptible C diphtheriae isolates has been demonstrated in vitro; however, the clinical benefit of combination therapy is unclear [2]. Aminoglycosides were used in 3 of 4 (75%) PCN-R C diphtheriae endocarditis cases in combination with beta-lactams and fluoroquinolones. Our case was unique when the isolate’s additional resistance to ceftriaxone, which necessitated broader treatment with vancomycin and meropenem. Synergy testing was not performed. Our case represents the first PCN and cephalosporin-resistant isolate based on 2006 CLSI interpretive criteria for diphtheria susceptibility testing (see Table 1 footnotes).

In summary, non-toxigenic C diphtheriae is a cause of invasive infections including endocarditis. Our case elucidates the need for awareness of the increasing frequency of NT C diphtheriae infections and the potential need for broad empiric antibiotic therapy due to developing PCN and cephalosporin resistance of these organisms. An expansion of antibiotic interpretive criteria due to resistant invasive C diphtheriae may be warranted.

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