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Perspective

Corynebacterium diphtheriae endocarditis: a case series and review of the treatment approach

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SUMMARY

Objectives: Infective endocarditis due to non-toxigenic *Corynebacterium diphtheriae* is uncommon; we report 10 cases occurring over a 14-year period in Auckland, New Zealand and review the approach for treatment.
Case series: Eight of the 10 patients had known prosthetic valves or homografts in situ. Three patients required surgical intervention for infective endocarditis. Seven patients were treated with a combination of β-lactam and aminoglycoside, and one each was treated with a combination of vancomycin and an aminoglycoside, a β-lactam alone, and vancomycin alone. All patients survived and none relapsed.
Review of literature: The antibiotic treatment of 46 previously reported cases was reviewed; patients treated with a β-lactam and aminoglycoside ($n = 25$), and without the addition of an aminoglycoside ($n = 11$) were compared. The differences in length of treatment within each group make the comparison of outcome (mortality, need for surgical intervention, disease and treatment complications) difficult. However, regardless of the length of treatment, there was no difference in mortality or need for surgical intervention between the two groups in the currently published cases.
Conclusions: Current evidence suggests that endocarditis of either native or prosthetic valves, caused by penicillin-susceptible *C. diphtheriae*, demonstrates a favorable outcome when treated with either a β-lactam alone or in combination with an aminoglycoside. Patient-specific factors will determine which approach is more appropriate for each individual patient.

1. Introduction

Corynebacterium diphtheriae was first described in 1884 by Loeffler as the causative agent of diphtheria.[1] The first case of infective endocarditis caused by this organism was reported in 1893.[2] *C. diphtheriae* is an uncommon cause of endocarditis, mycotic aneurysm, septic arthritis, splenic abscess, and osteomyelitis.[2–27] However, reports of infective endocarditis due to non-toxigenic strains have been increasing in the literature of late, with 63 of the 76 reported cases reported after 1980.[2,6]

C. diphtheriae endocarditis has been described as an aggressive disease requiring urgent surgical intervention, especially in those with prosthetic valves.[2] Most patients with *C. diphtheriae* endocarditis have underlying cardiac disease, prosthetic valves, or a history of intravenous drug use.[2] Recommendations for treatment based on expert opinion suggest that 4–6 weeks of a β-lactam antibiotic in conjunction with an aminoglycoside be given.[28]

Ten cases of *C. diphtheriae* endocarditis from two hospitals in Auckland, New Zealand occurring over a 14-year period are reported, and the outcome of treatment for published cases of endocarditis, in particular the benefit of combination therapy with a β-lactam and aminoglycoside, is reviewed.

2. Methods

2.1. Case series

In the present study, the medical notes of patients with *C. diphtheriae* infection identified from the Microbiology Department records at Auckland City Hospital and Middlemore Hospital were reviewed. Patients included had to have had *C. diphtheriae* isolated from one or more sets of blood cultures, isolated from cardiac valve tissue, or *C. diphtheriae* DNA detected by 16S rDNA PCR from cardiac valve tissue. Cases met the definition of definite or possible infective endocarditis as determined by the Modified Duke Criteria for Endocarditis.[29]

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Table 1
Clinical features and outcome of patients with *Corynebacterium diphtheriae* endocarditis in this report ($n = 10$)

Patient No.	Age (years)/ sex	Biotype/penicillin MIC	Risk factors	Antibiotics (duration)	Surgery	Complications (disease or treatment)	Outcome
1	12/F	NA	Tetralogy of Fallot Prosthetic AV	Vancomycin (4 weeks)	No	Neutropenia (treatment)	Survived
2	12/F	gravis/0.25 mg/l	Rheumatic fever Prosthetic AV and MV	Penicillin (6 weeks) Gentamicin (2 weeks)	Yes	Nil	Survived
3	9/M	gravis/NA	Congenital MR Prosthetic MV	Ceftriaxone (6 weeks) Gentamicin (6 weeks)	No	Nil	Survived
4	4/F	gravis/NA	Hypoplastic left heart	Penicillin (4 weeks) Gentamicin (4 weeks)	No	Macular rash (treatment) Neutropenia (treatment) Renal tubular damage (treatment)	Survived
5	28/M	gravis/0.25 mg/l	Transposition of the great arteries Aortic homograft	Penicillin (6 weeks) Gentamicin (6 weeks)	No	Nil	Survived
6	62/M	gravis/0.25 mg/l	Nil	Penicillin (4 weeks) Gentamicin (2 weeks)	No	Nil	Survived
7	10/M	gravis/NA (identified through sequencing; no culture isolate)	Nil	Amoxicillin (5 weeks pre-op) Vancomycin (5 weeks) Gentamicin (5 weeks) Amoxicillin (2 weeks post-op) Vancomycin (2 weeks) Amikacin (2 weeks)	Yes	Congestive cardiac failure (disease)	Survived
8	57/F	gravis/0.25 mg/l	Rheumatic fever with MR Prosthetic MV	Vancomycin (6 weeks) Gentamicin (2 weeks)	No	Nil	Survived
9	5/F	gravis/0.5 mg/l	Congenital VSD	Penicillin (6 weeks) Gentamicin (2 weeks)	No	Osteomyelitis – calcaneum (disease) Renal and cerebral infarction	Survived
10	28/M	NA/NA	Rheumatic fever with prosthetic MV and AV	Penicillin (5 weeks) Gentamicin (5 weeks)	Yes	Pleural effusion (treatment)	Survived

AV, aortic valve; F, female; M, male; MIC, minimum inhibitory concentration; MR, mitral regurgitation; MV, mitral valve; NA, not available; VSD, ventricular septal defect.

Statistical analysis was done to compare the clinical outcomes in patients with different antibiotic regimes using GraphPad Instat software and employing the Fisher's exact test.

Ethical approval for the study was provided by the Northern Region X Ethics Committee.

2.2. Literature review

In addition to the cases reported, a Medline search (MESH terms 'Corynebacterium diphtheriae endocarditis' English literature) was performed to identify cases of *C. diphtheriae* endocarditis reported in the literature. Cases were accepted where information regarding the demographics, clinical outcomes, and treatment was provided.

3. Results

3.1. Case series

Ten patients with *C. diphtheriae* endocarditis from 1994 to 2007 were identified. Table 1 summarizes the demographics, clinical features, treatment, and outcome of these cases. Modified Duke criteria were complete for definite ($n = 6$) or possible ($n = 4$) infective endocarditis in all cases.

3.2. Literature review

A Medline search (MESH terms 'Corynebacterium diphtheriae endocarditis' English literature) identified 76 cases of infective endocarditis caused by *C. diphtheriae*.[2,24,27] Seventy of these cases have been reviewed extensively elsewhere.[2] Treatment data were available for 46 of these cases.[2,27] Twenty-nine of the 46 cases received either β-lactam monotherapy ($n = 11$) or a β-lactam with an aminoglycoside ($n = 18$); these cases are summarized in Tables 2 and 3, respectively. Five cases received β-lactam and aminoglycoside with a third antimicrobial agent active against *C. diphtheriae*: vancomycin ($n = 3$), erythromycin ($n = 1$), and rifampin ($n = 1$). These five cases were excluded from further analysis. Of the remaining 12 cases, nine received a β-lactam with a non-aminoglycoside agent: chloramphenicol ($n = 3$),[19,20] vancomycin ($n = 3$),[16,18,24] erythromycin ($n = 1$),[11] trimethoprim–sulfamethoxazole ($n = 1$),[20] and doxycycline and rifampin ($n = 1$),[22] and three were treated with non-β-lactam regimens: erythromycin,[8,27] clindamycin–ciprofloxacin combination therapy,[27] and sulphapyridine.[19,21]

Treatment duration was available for 29 cases and mostly ranged from 4 to 8 weeks (18 of 29), but longer durations have been reported.[19]

There are no recommended guidelines for the treatment of infective endocarditis caused by *C. diphtheriae*. Therapy in reported cases has varied depending on local practice. The 11 cases who received β-lactam only (Table 2) and the 25 cases who received β-lactam and aminoglycoside (Table 1, $n = 7/10$ and Table 3, $n = 18/23$), were compared for patient outcomes. Four patients died in both groups ($p = 0.39$) and there was no significant difference in the number of patients requiring surgical intervention ($p = 0.62$). No relapses were reported in either group.

4. Discussion

This case series of *C. diphtheriae* endocarditis demonstrates a number of similarities with the 76 previously published cases and the species-specific risk factors recently identified for Corynebacterium endocarditis.[30] Firstly, all cases but two were caused by non-toxigenic strains of *C. diphtheriae* biotype *gravis*. Secondly, the median age was 12 years (range 4–62 years). This is in keeping with previous cases, of which approximately 80% occurred in patients aged less than 30 years. Thirdly, eight patients had pre-existing cardiac abnormalities with prosthetic valves or homografts in situ. Cardiac abnormalities, including congenital cardiac anomalies and prosthetic heart valves have been described as risk