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***Corynebacterium jeikeium* endocarditis: a systematic overview spanning four decades**

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Abstract Skin flora is an important source of microorganisms that cause infective endocarditis. While staphylococcal and beta-hemolytic streptococcal species are well-recognized components of skin flora that can cause infective endocarditis, other skin flora rarely produce endocardial infection. One species of *Corynebacterium* has received the most attention, *Corynebacterium jeikeium*. This bacterium, a gram-positive rod that is a strict aerobe, is known to cause mechanical prosthetic valve infection and vancomycin is generally required for treatment of this multidrug-resistant organism. Following treatment of an unusual case of bioprosthetic valve endocarditis due to *C. jeikeium*, a Medline search for English-language articles published from January 1966 to October 2004 was performed. Reports of *C. jeikeium* endocarditis cases with culture of either blood or cardiac surgery tissue samples positive for *C. jeikeium* and with clinical and echocardiographic findings of infective endocarditis were reviewed. Clinical data and results of diagnostic procedures were examined. All 38 patients with *C. jeikeium* endocarditis reported in the literature had at least one predisposing condition for the development of infective endocarditis. The majority of patients (74%) had involvement of a pros-

thetic heart valve. The mortality attributed to *C. jeikeium* endocarditis was 33% and was similar in patients who did and did not undergo valve replacement. This relatively high mortality rate mandates that clinicians be aware of this rare endocardial infection. *C. jeikeium* is a rare cause of endocarditis and it more commonly infects prosthetic valves. Careful scrutiny is required when *C. jeikeium* is isolated from a blood culture, particularly in patients with underlying prosthetic cardiac valves.

Introduction

Skin flora is an important source of microorganisms that cause infective endocarditis (IE). Staphylococcal and beta-hemolytic streptococcal species are well-recognized components of skin flora that can cause IE. In contrast, other skin flora, including *Corynebacterium* species, rarely produce endocardial infection. One species of *Corynebacterium* has received the most attention, *Corynebacterium jeikeium* (formerly known as CDC group JK). This bacterium, a gram-positive rod that is a strict aerobe, is known to cause mechanical prosthetic-valve infection and vancomycin is generally required for treatment of this multidrug-resistant organism. Here, we describe a case of bioprosthetic valve endocarditis due to *C. jeikeium*, a clinical entity that has not been fully described previously, and we review the literature for cases of *C. jeikeium* IE in order to update knowledge of this condition.

Illustrative case

An 84-year-old man was transferred to our institution with complaints of low-grade fever and fatigue of 10 days' duration prior to admission. He had also experienced acute onset of left-sided weakness. He had undergone a porcine bioprosthetic aortic valve replacement for severe calcific aortic stenosis 10 months prior and more recently had experienced transient ischemic attacks. Transesophageal echocardiography (TEE) had been performed 3 months

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earlier and no clots or vegetations were seen; the bioprosthetic valve was functioning normally. Physical examination revealed no abnormalities other than a widely split second heart sound and a soft, 1 to 2/6 systolic ejection murmur at the right upper sternal border with an early peak ending before the second heart sound; this had remained unchanged since the valve replacement surgery. Laboratory test results showed hemoglobin of 11.2 g/dl, leukocytes $10.9 \times 10^9/l$, platelet count $177 \times 10^9/l$, arterial blood gases: $P O_2$ 74 mmHg, $P CO_2$ 31 mmHg. An electrocardiogram showed sinus rhythm and first-degree atrioventricular block. Computerized tomographic scans of the abdomen and head were negative. TEE revealed linear, independently mobile densities (largest 1.3×0.8 cm) on the aortic bioprosthetic valve. The vegetations were highly mobile and prolapsing in and out of the prosthesis funnel during the cardiac cycle.

Two separate sets of blood cultures performed 3 days apart grew *C. jeikeium* in 2/3 bottles after 24 h of growth. Despite aggressive antibiotic therapy with vancomycin and gentamicin, serial TEE examinations performed 5 and 8 days after the initial examination showed an increase in vegetation size and development of a perivalvular abscess. Therefore, aortic valve replacement with an aortic homograft was performed. Postoperative transthoracic echocardiography revealed normal functioning of the replaced prosthetic aortic valve and no signs of infection. Postoperative antibiotic treatment with vancomycin and rifampicin was continued for 6 weeks with no recurrence of fever and persistently negative blood cultures. The pathology report from examination of the explanted bioprosthesis tissue was consistent with endocarditis; gram-positive coccobacilli were identified, but tissue culture was negative since the patient had been on intravenous antibiotics for at least 2 weeks prior to surgery.

Physical examination, TEE and surveillance blood cultures were negative at the 3-month post-surgical follow-up. Telephone follow-up at 6 months revealed no symptoms, and the patient was doing well clinically.

Literature review

Methods

Cases of IE due to *C. jeikeium* reported in the English-language literature during the period 1 January 1966 to 1 October 2004 were identified by means of a computerized Medline search conducted using the following search words: «*Corynebacterium jeikeium*» and «*Corynebacterium JK*» (species name prior to 1976) combined with «endocarditis». In addition, relevant articles cited in the retrieved articles were examined and the case presented here was included. All cases included in this review had cultures of either blood or cardiac surgery tissue specimens that were positive for *C. jeikeium* and clinical and/or echocardiographic evidence of IE.

Because of the differences among individual cases, the era differences by decade and the small sample size included in each of the reports, a quantitative meta-analysis could not be performed. Instead, a qualitative systematic overview was conducted, and a formal test of heterogeneity was consequently not necessary.

Thirty-eight cases of IE from 14 articles [1–14] were identified in the literature search. Demographic and clinical data were collected from all reports for analysis. Complete clinical information was not available for many cases, so the denominator for each clinical feature was often lower than 38. Five additional cases (two French, one Polish, one Portuguese, one Spanish) of *C. jeikeium* IE were recovered from the non-English-language literature, but they were not included in this review.

Patient characteristics

Age and gender

The mean and median ages of patients were 52.2 and 54 years, respectively. Nineteen patients were between 17 and 84 years old, and 10 of these 19 (52.6%) patients were male.

Predisposing conditions for IE

Thirteen (65%) patients had one or more cardiac predisposing condition: prosthetic valve (ten patients), degenerative valve lesion (two patients), previous endocarditis, percutaneous coronary intervention, cardiac catheterization and pacemaker (one patient each). An indwelling device was present in six (30%) cases. Hemodialysis was identified as an associated comorbidity factor in five (25%) cases. Dental procedures preceded IE in four (20%) patients and three (15%) patients had undergone organ transplantation (liver, kidney or bone marrow). Urinary tract infection was present in two (10%) patients prior to the development of endocarditis, and one (5%) of the reported patients was an intravenous drug user.

Presenting symptoms and signs

Presenting symptoms and signs were described for 17 of the cases in the literature and in the current case report. Fever was the most common symptom and was present in 14 (78%) patients. An equal number of patients presented with dyspnea and presence of a new murmur (seven patients each or 39%), and angina pectoris was reported for three (17%) patients. Two (11%) patients had neurological symptoms, and skin manifestations (purpura and petechiae) were present in two (11%) patients. First-degree atrioventricular block and right-bundle branch block were each present in one (6%) patient. One (6%) patient presented with thigh pain as a complication of cardiac catheterization.

Valve involvement and time of presentation

The majority of patients (29 patients, 74%) with *C. jeikeium* endocarditis had a prosthetic heart valve; in eight (20%) of the patients a native valve was affected, and for the remaining case a vegetation on the right atrial wall without valve involvement was described [11]. The anatomical location of IE was not reported for one (3%) case [7]. Although one previous case of *C. jeikeium* involvement in a bioprosthesis infection [1] has been reported in the literature, it was not well-described; thus, the present case represents the only case described in detail in the literature to date.

The aortic valve was affected in most of the cases reviewed (17 patients or 46%) followed by the mitral valve (12 patients or 32%). Both the aortic and the mitral valves were involved in six (16%) cases. Only two (5%) patients had tricuspid valve involvement. In the group of patients with valve involvement, prosthetic valves were affected in 78% and native valves in 22%. The proportion of prosthetic valves in affected aortic valves was 82% and in affected mitral valves 83%. All of the involved tricuspid valves were native, as were cases with both aortic and mitral valve involvement.

The mean time from cardiac valve placement to clinical presentation of IE was 6.04 months (range, 2 weeks–57 months). Early prosthetic valve endocarditis (arising within 2 months of surgery) and late prosthetic valve endocarditis occurred in 16 (57%) and 12 (43%) patients, respectively.

Data regarding the duration of presenting signs and symptoms prior to the diagnosis of IE was available for 13 (33%) cases. In the majority of cases (six cases, 46%) the symptoms were present for 1–3 months, in four (31%) cases between 1 week and 1 month and in three (23%) cases the diagnosis was established within 1 week following initial presentation.

Echocardiography

An echocardiographic examination was performed in 15 (38%) cases; 12 had undergone TTE and three TEE. An echocardiographic finding of IE was seen in 83% of cases examined by TTE and by TEE. Valvular vegetation was the most common TTE finding (six cases). Para prosthetic leak was present in two cases and mural vegetation in one case. Valvular vegetations were detected by TEE in all three cases.

Therapy

All but one of the reported patients received antibiotic therapy. The majority of cases (24 cases, 62%) underwent valve replacement, and 15 (38%) patients received only medical therapy. The aortic valve was replaced in 16 cases, the mitral valve in seven cases, and in one case, both the aortic and mitral valves were replaced. Gentamicin and

vancomycin were the two most commonly used antibiotics (58 and 55%, respectively), followed by penicillin in 46% of cases. Single-agent antibiotic treatment was administered in only nine (23%) of the cases, five of which were treated with vancomycin; only one patient was treated with a penicillin antibiotic (oxacillin) alone. All of the 19 patients treated with penicillin agents were reported in the two oldest articles (1977 and 1980) [1, 2] and there has been no report of penicillin administration (in any combination) since that time. In most of these cases, penicillin was administered in combination therapy (ten different combinations). Antibiotic susceptibility was reported in most of the cases and penicillin-sensitive strains were identified in only two (2%) of them [1].

Outcome

Overall mortality of patients with *C. jeikeium* endocarditis in the reviewed literature was 41% (16 patients) and infection-related mortality was 33% (13 patients). Twenty-three (59%) patients were cured. The infection-related mortality rate (33%) was similar for both groups of patients who were treated either medically or with combined medical and surgical intervention. In addition, the differences in mortality between the groups of patients with prosthetic and native valves (36 and 33%, respectively) and early and late prosthetic valve infection (38 and 33%) were similar.

Discussion

Corynebacterium group JK was first recognized as a distinct species in 1976 [15] and was later designated as *C. jeikeium* in 1987. It is part of the normal skin flora [16] and is commonly found in inguinal, axillary and perirectal sites. In rare instances it can become an opportunistic pathogen in immunosuppressed patients and patients with prosthetic material such as catheters and cardiac valves. *C. jeikeium* bacteria are pleomorphic, non-sporulate, gram-positive rods. They vary in shape from short coccobacilli to long bacillary forms with arrangement in V forms or palisades. Their colonies are punctate, smooth, and whitish in color. As a presumptive identification, *C. jeikeium* is one of the lipid-requiring species of *Corynebacterium* [17]; it produces turbid growth in brain-heart infusion broth supplemented with 1% Tween 80. A negative test for nitrate reduction, a negative urease test, and acid production from glucose plus resistance against many antibiotics are additional key characteristics of this species [17]. Further confirmation may require additional tests such as detection of pyrazinamidase and alkaline phosphatase.

Use of the API Coryne system (bioMérieux, La-Balme-les-Grottes, France) may result in incorrect identification [18]. Aerobic culture on Tryptone Soy broth followed by subculture on sheep blood agar grows *C. jeikeium* after 72 h of incubation [17]. Disk diffusion on plates and the E-test are used to determine the isolated

strain's antimicrobial susceptibility, but there are currently no Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) guidelines to interpret the antimicrobial susceptibility of *Corynebacterium* spp. other than *C. jeikeium*. The microorganism is typically susceptible to vancomycin and resistant to penicillin agents. It has demonstrated variable susceptibility to erythromycin, tetracycline, rifampin, and quinolones [19]. Telithromycin, linezolid and quinupristin/dalfopristin have shown good in vitro activity against *C. jeikeium* [20].

Since *C. jeikeium* infections are mostly related to nosocomial sepsis, for which vancomycin has been the mainstay of therapy [21], there is very limited clinical experience with the use of oral agents that demonstrate in vitro activity, like rifampin, quinolones, tetracyclines and linezolid, for the treatment of these infections.

It is noteworthy that all patients included in this literature review had at least one predisposing condition for IE and that an underlying predisposing heart disease was present in 65% of cases. The presence of a prosthetic cardiac valve was the predominant risk factor for the subsequent development of IE and was identified in over three-fourths of the patients with predisposing conditions. There was a ratio of 4:1 among patients with prosthetic valves and native valves, respectively. To our knowledge, the case described here is the first case of bioprosthetic valve infection due to *C. jeikeium* to be fully characterized. In the one other report we located in the literature [1], mention of bioprosthetic endocarditis was made but specific details of the case were not provided.

Hemodialysis was another commonly associated comorbidity that was seen in one-quarter of *C. jeikeium* IE cases. It is not surprising that patients who required hemodialysis, particularly those who also had underlying prosthetic cardiac valves (20%), were identified as a group with *C. jeikeium* IE, since the serial direct access to the vascular tree in hemodialysis patients, either via percutaneous catheter or needle puncture, provides strong epidemiological support. Malignancies were reported in two cases of *C. jeikeium* IE: one patient had chronic myeloid leukemia, and in another, a history of malignant bladder polyps was noted. Finally, the occurrence of IE in three patients with organ transplantation affirms previous reports of common infection of immunocompromised hosts by *C. jeikeium* [22, 23].

In the majority of patients the time interval between the onset of signs and symptoms and the diagnosis of IE was 1–3 months, thus characterizing *C. jeikeium* IE as subacute. Early prosthetic valve endocarditis (i.e., within 60 days of surgery) occurred in 57% of cases and late prosthetic valve endocarditis in 43%. The related mortality rate was similar in cases of early and late prosthetic valve endocarditis (38 and 33%, respectively).

Although echocardiography has a well-established role in the diagnosis of IE, an echocardiogram was performed in only 38% of the reviewed cases (including the case we present), and 25% of the procedures were TEE. All patients in our review received antimicrobial therapy, except one who died before therapy was started. The agents used most

often were gentamicin and vancomycin, which is the suggested therapy for this type of infection. Since penicillin was mostly administered in combination therapy (ten different combinations), it is difficult to establish a relationship between penicillin therapy and failure; especially since the patients who received multiple different combinations were likely the most difficult to treat. Nevertheless, it was noted that three of four patients treated with a combination of penicillin and gentamicin were cured and the single death that occurred was due to post-operative complications. Despite a satisfactory choice of antibiotics, valve replacement surgery was carried out in 62% of the cases, with the aortic valve being replaced most often. It should be noted that the related mortality rate was equal among conservatively and surgically treated patients (33% in both groups).

The overall and infection-related mortality rates of *C. jeikeium* endocarditis were 41 and 33%, respectively. These outcomes are not surprising when one considers that prosthetic-valve, rather than native-valve, infection was present in the large majority of cases. This mandates that clinicians be aware of this potentially lethal complication of prosthetic valve placement. As with other retrospective reviews, reporting bias is highly probable given the fact that positive outcomes, rather than treatment failure, are more likely to be reported in the literature; thus, mortality may be underestimated. Furthermore, the frequency of *C. jeikeium* IE might be underestimated since the rarity of the pathogen might lead to its frequent interpretation as a potential contaminant. Given the high mortality associated with this species, every effort should be made to determine whether a *C. jeikeium* isolate represents true bacteremia or a skin contaminant, as with other types of skin flora isolated from blood cultures. In this regard, multiple sets of blood cultures should be obtained. If more than one set is positive, a further evaluation for endocarditis should be conducted, usually including TEE in patients with valvular prostheses. Evaluation of patients with both prosthetic cardiac valves and hemodialysis catheters or prosthetic grafts and *C. jeikeium* bacteremia presents more difficult challenges in terms of attempting to determine which cardiovascular device, or both, is serving as the primary nidus of bloodstream infection. In these cases, a team experienced in the management of cardiovascular device-related infections is crucial for devising diagnostic and treatment algorithms for the individual patient.

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