Bacterial Endocarditis Caused by Actinomyces oris: First Reported Case and Literature Review

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Abstract
Actinomyces species are gram-positive, facultative anaerobic bacilli. Infection caused by Actinomyces species is usually limited to cervicofacial, thoracic, and abdominopelvic regions. Infective endocarditis due to Actinomyces species is extremely rare with only 30 reported cases since 1939. We report a case of Actinomyces oris endocarditis in a 14-year-old boy who had a 2-week history of dyspnea on exertion without other constitutional signs. Transthoracic echocardiography was suggestive of perforation of the right coronary cusp of aortic valve. No organisms were isolated from blood cultures. The patient underwent surgical valve repair due to deteriorated cardiac function. Valve tissue culture did not initially identify the organism. However, the terminal subculture in a thioglycolate broth grew gram-positive bacilli. The matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was compatible with Actinomyces oris. After 6 weeks of intravenous ampicillin, the patient remained well with improved cardiac function. We reviewed all reported cases of infective endocarditis caused by Actinomyces species, commenting on clinical characteristics and factors associated with unfavorable outcomes in infective endocarditis due to Actinomyces species. Although infective endocarditis caused by Actinomyces spp is rare, it could be considered in a case of culture-negative endocarditis since the clinical features might be indistinguishable from other bacterial endocarditis. Additionally, MALDI-TOF MS is a useful diagnostic tool for the identification of Actinomyces spp to improve the accuracy of diagnosis.

Keywords
Actinomyces infection, infective endocarditis, culture-negative endocarditis

Introduction
Actinomyces species are gram-positive, facultative anaerobic bacilli. They can be part of oral cavity, gastrointestinal tract, and vaginal flora. Infection caused by Actinomyces species is usually indolent and is typically limited to cervicofacial, thoracic, and abdominopelvic regions.1 Actinomycotic endocarditis is extremely rare. In this article, we describe the first case of infective endocarditis caused by Actinomyces oris.

Case Presentation
A previously healthy 14-year-old boy from the western part of Thailand presented with a 2-week history of dyspnea on exertion. He had no fever or other constitutional symptoms suggestive of infection. He denied history of cardiac diseases, recent dental procedures, or intravenous drug use. Physical examination at the referring hospital was notable for a systolic ejection murmur grade 3/6 at the left upper sternal border. The lungs were clear, and the liver was 3 cm below the right costal margin. Laboratory evaluation revealed a white blood cell count of 16200/µL with 76% neutrophils, hemoglobin of 13 g/dL, platelet count of 464000/µL, an erythrocyte sedimentation rate of 7 mm/h, and an anti-streptolysin O titer >400 IU. A chest X-ray revealed evidence of congestive heart failure. In addition to diuretics and inotropic drugs, benzathine penicillin, and oral prednisolone were given as presumed acute rheumatic fever. He later developed a high-grade fever without any foci of infection. Meropenem was started empirically without obtaining a blood culture. He did not respond to initial therapy and was referred to our hospital.

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Physical examination at our hospital revealed an afebrile child with stable vital signs but had gross dental caries. Subcutaneous nodules, Osler’s nodes, Janeway lesions, and splinter hemorrhages were absent. Cardiac examination showed both left and right ventricular heave, normal S1, loud P2, a to-and-fro murmur grade 3/6 at left upper sternal border, and a pansystolic murmur grade 3/6 at apex. Neurological and fundoscopic examinations were unremarkable. Laboratory findings included a white blood cell count of 6700/µL with 83% neutrophils, a hemoglobin level of 12 g/dL, platelet count of 242 000/µL, and an erythrocyte sedimentation rate of 6 mm/h. Urinalysis revealed 0 to 1 white blood cell/high-power field and over 20 red blood cells/high-power field. Chest X-ray showed cardiomegaly with pulmonary congestion. Transthoracic echocardiogram revealed biventricular hypertrophy with an ejection fraction of 49% with evidence of severe aortic valve (AV) regurgitation with a suspected perforation of both the right coronary cusp 5.2 × 5.6 mm and noncoronary cusp 5 × 8 mm, severe mitral valve (MV) regurgitation with an abnormal MV leaflet. No vegetations were seen. These findings suggested infective endocarditis according to the modified Duke criteria. Four sets of blood cultures were obtained, and he was empirically treated with ampicillin/sulbactam (3 g every 6 hours) and gentamicin (120 mg every 8 hours). No organisms were isolated after 5 days of incubation. He subsequently underwent surgical AV repair as indicated by worsening cardiac function. Operative findings revealed severely damaged MV and AV due to restriction and thickened cusps and a circular thinning lesion on the right coronary cusp. However, no vegetation or perforation was noted. The MV was repaired, and the AV was replaced (Figure 1).

Mitral valve and AV tissues were obtained for aerobic culture and 16s rRNA sequencing, which initially were unable to culture or identify an organism. The histopathologic examination of both valves revealed white myxomatous degeneration and fibrosis without vegetation or perforation, compatible with post-inflammatory valve disease. The terminal subculture in a thioglycolate broth grew gram-positive, small branching bacilli after 120 hours of incubation (Figure 2).

The biochemical tests and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) were compatible with Actinomyces, with the susceptibility test as shown in Table 1. The patient was diagnosed with Actinomyces endocarditis with suspected underlying rheumatic heart disease. Antibiotics were switched to intravenous ampicillin (12 g/day) for 6 weeks. The follow-up echocardiography showed an ejection fraction of 45% with trivial AV regurgitation and mild MV regurgitation. Ampicillin was switched to oral amoxicillin 2 g twice daily for a planned 12-month total course. At the follow-up visit 6 months later, he remained well and improved from functional class IV to II.

**Literature Review**

Previously reported cases of endocarditis caused by Actinomyces spp were searched by using the keywords “actinomyces spp” OR “actinomyces” OR “actinomycotic” AND “infective endocarditis” OR “endocarditis” in PubMed database.

**Discussion**

Actinomyces species is a gram-positive, filamentous, facultative anaerobic bacilli. Infective endocarditis caused by Actinomyces species is rare with only 30 reported cases since 1939. To date, 14 species of Actinomyces have been implicated in endocarditis: Actinomyces bovis, Actinomyces graminis, Actinomyces septicus, Actinomyces maris, Actinomyces
Actinomyces oris is one of the predominant organisms colonizing the oral cavity and plays a role in dental plaque formation. This species previously belonged to the *A. naeslundii/A. viscosus* group. However, the multilocus sequence analysis based on sequence comparisons for partial gene sequences has further speciated and proposed *A. oris* as a new species of *Actinomyces*. Furthermore, a phylogenetic tree based on 16s rRNA gene sequence of the genus *Actinomyces* has clearly showed that *A. oris* is genetically different from *A. naeslundii* and *A. viscosus*. However, it is also possible that *A. viscosus* or *A. naeslundii* in previous reports might be actually *A. oris* as the technology at that time might not be able to differentiate these species.

In a literature review, 31 cases of endocarditis caused by *Actinomyces* spp have been reported since 1939 including our case (Table 2). Of the previous case reports of actinomycotic endocarditis, there was only one pediatric case. The median age was 48 years (34-65 years), and 22 patients (71%) were male. Sixteen patients (52%) had underlying cardiac disease. Seven patients (22.6%) had a history of recent dental procedure or presence of dental caries. Twenty-eight cases (90.3%) involved a native valve. Of these 31 cases, 8 patients (25.8%) required cardiac surgery. The overall mortality associated with actinomycotic endocarditis was 25.8% (8 of 31 patients). Clinical characteristics, treatment, and outcome of patients with *Actinomyces* endocarditis are described in Table 3.

Similar to the present case, most of the patients in this review presented with subacute or chronic endocarditis that usually involved native heart valves. Predisposing factors for actinomycotic endocarditis include periodontal diseases or dental procedures in association with a preexisting cardiac valvular defect. Our patient might have had underlying rheumatic heart disease that he had not been aware of. This is a known risk factor for infective endocarditis. Additionally, the pathological findings from the MV and AV were suggestive of post-inflammatory change, which can be seen in rheumatic heart disease. Furthermore, the presence of dental caries, in this case, might be an attributable factor for developing infective endocarditis since *Actinomyces* species habitually colonize in the oral cavity.

The diagnosis of actinomycotic endocarditis primarily depends on the identification of *Actinomyces* species from blood cultures, which may be recognized within 5 to 7 days. However, the cultures should be held for up to 4 weeks to improve the yield of diagnosis. Moreover, blood cultures may fail to identify the organism since these facultative anaerobes require special specimen handling with minimal exposure to oxygen and a need for a CO2-enriched environments. The definitive diagnosis of *Actinomyces* spp has always been challenging. Over the past decade, 16s rRNA sequencing has been widely used for bacterial identification and the discovery of novel bacteria, especially uncultivable or slow-growing bacteria. This method has led to the classification and identification of *Actinomyces* spp, differentiating *Actinomyces* spp from other gram-positive anaerobic bacilli. However, accurate identification of certain species of actinomyces is still problematic. MALDI-TOF MS has emerged as a rapid and effective method for bacterial identification with the ability to speciate closely related organisms. A previous study has demonstrated the performance of MALDI-TOF MS in identification of endocarditis due to *A. neuii*. As in this case, MALDI-TOF MS was used to confirm the etiologic organism in subacute endocarditis.

The choice and optimal duration of antibiotics in actinomycotic endocarditis remains unclear. *Actinomyces* species are generally susceptible to β-lactam antibiotics. Penicillin or cephalosporins have been considered to be first-line agents for the treatment of actinomyces. According to previous reports, most patients with endocarditis tended to receive high doses and prolonged antibiotic therapy. In our literature review, duration of antibiotic therapy ranged from 1 to 12 months. Alternative agents, including chloramphenicol, erythromycin, clindamycin, doxycycline, or vancomycin, have been shown in vitro to be active against these organisms. In the present case, the patient was successfully treated with 6 weeks of intravenous ampicillin followed by oral amoxicillin for a planned 12-month course.

In conclusion, we describe a case of native valve *A. oris* endocarditis that was successfully treated with intravenous ampicillin and oral amoxicillin and surgical valve replacement. Although infective endocarditis caused by *Actinomyces* spp is rare, it could be considered in a case of culture-negative endocarditis since the clinical features might be indistinguishable from other bacterial endocarditis. Additionally, MALDI-TOF MS could be a useful diagnostic tool for the
Table 2. Summary of 30 Reported Cases Diagnosed With Infective Endocarditis Attributable to *Actinomyces* Species.

| Case (Reference) | Year | Age | Sex | Duration of Illness (Months) | Valve(s) | Predisposing Factors | Organism | Therapy | Duration of Treatment (Months) | Outcome |
|------------------|------|-----|-----|----------------------------|----------|----------------------|----------|---------|-------------------------------|---------|
| 1 (17)           | 1939 | 24  | Male | 1                           | MV, AV   | None                 | *Actinomyces bovis* | Sulfathiazole | NA                             | Dead    |
| 2 (18)           | 1945 | 55  | Male | 9                           | MV, AV   | Aortic insufficiency, dental caries | *Actinomyces graminis* | None | NA                             | Dead    |
| 3 (19)           | 1946 | 39  | Male | 6 weeks                     | MV       | Cardiac murmur       | *Actinomyces septicus* | PCN | 10                             | Survived |
| 4 (20)           | 1947 | 37  | Male | NA                          | MV, AV   | None                 | *Actinomyces spp*   | Sulfaazolamide | 6                             | Dead    |
| 5 (20)           | 1947 | 71  | Female | NA                          | AV       | RHD                  | *Actinomyces spp*   | None | NA                             | Dead    |
| 6 (21)           | 1951 | 27  | Male | 2                           | MV       | RHD                  | *Actinomyces muris* | Chloramphenicol | 1                             | Survived |
| 7 (22)           | 1962 | 43  | Male | 2                           | MV, AV   | RHD, dental caries   | *Actinomyces bovis* | PCN | 5.5                           | Survived |
| 8 (23)           | 1968 | 6   | Male | NA                          | MV       | RHD                  | *Actinomyces israelii* | PCN | 8 days                        | Dead    |
| 9 (24)           | 1976 | 70  | Male | 5                           | MV       | Periodontitis        | *Actinomyces viscosus* | PCN | 2.5                           | Survived |
| 10 (25)          | 1993 | 65  | Male | 1                           | MV, AV   | RHD, H/O endocarditis | *Actinomyces israelii* | PCN | 7.5                           | Survived |
| 11 (26)          | 1996 | 48  | Male | 2 weeks                     | AV       | None                 | *Actinomyces meyeri* | PCN | 1.5                           | Survived |
| 12 (27)          | 1997 | 64  | Male | 1                           | AV       | AS                   | *Actinomyces pyogenes* | CTX $\rightarrow$ VAN + AMP + GEN | NA | Dead |
| 13 (15)          | 1998 | 81  | Male | 2-3 weeks                   | AV       | Poor dental hygiene  | *Actinomyces viscosus* | Ceftizoxime and CTX | 3 | Survived |
| 14 (28)          | 1998 | 55  | NA  | 2                           | NA       | None                 | *Actinomyces meyeri* | AMP/SUL | 1.5                           | Survived |
| 15 (29)          | 2001 | 38  | Male | 2                           | MV       | None                 | *Actinomyces viscosus* | VAN + GEN $\rightarrow$ CTM + PCN | NA | Survived |
| 16 (30)          | 2002 | 40  | Female | 2 weeks                     | TV       | Dental root infection, IVDU, H/O endocarditis | *Actinomyces funkei* | Cefuroxime + RIF + CLN $\rightarrow$ CTX + CLN | NA | Survived |
| 17 (31)          | 2005 | 33  | Male | 2                           | TV       | IVDU, dental procedure | *Actinomyces odontolyticus* | CTX $\rightarrow$ PCN + MET | NA | Survived |
| 18 (7)           | 2005 | 43  | Female | 2 weeks                     | AV       | Dental cleaning      | *Actinomyces viscosus* | AMP + azithromycin $\rightarrow$ VAN + GEN + + CTX | 1 | Survived |
| 19 (33)          | 2007 | 68  | Male | 3 weeks                     | AV       | Dental procedure     | *Actinomyces neuii* | AMP + GEN + CTX $\rightarrow$ AMP $\rightarrow$ doxycycline | 12 | Survived |
| 20 (33)          | 2007 | 34  | Male | NA                          | AV       | RHD                  | *Actinomyces spp*   | NA | NA                             | Dead    |
| 21 (34)          | 2008 | 27  | Female | 2 days                      | EV       | IVDU, H/O endocarditis | *Actinomyces israelii* | PCN $\rightarrow$ CTX $\rightarrow$ AMP | 8.5 | Survived |
| 22 (35)          | 2008 | 46  | Male | 1                           | MV       | None                 | *Actinomyces georgii* | PCN $\rightarrow$ CTX $\rightarrow$ AMP | NA | Survived |
| 23 (14)          | 2010 | 66  | Male | 2                           | PAV      | Aortic insufficiency | *Actinomyces neuii* | PCN + MER + ERY $\rightarrow$ amoxicillin | 12 | Survived |
| 24 (36)          | 2010 | 87  | Male | 2                           | MV       | Dental cleaning      | *Actinomyces israelii* | PCN | 7.5                           | Survived |
| 25 (37)          | 2013 | 49  | Male | 2                           | TV       | IVDU                 | *Actinomyces spp* | Van $\rightarrow$ CTX $\rightarrow$ ciprofloxacin + MET | NA | Survived |
| 26 (38)          | 2014 | 67  | Male | 6 weeks                     | PAV      | Prosthetics, dental cleaning | *Actinomyces naeslundii* | CTX | 1.5                           | Dead    |
| 27 (39)          | 2015 | 30  | Female | 1 week                      | EV       | None                 | *Actinomyces turicensis* | PCN $\rightarrow$ CTX | 2 | Survived |
| 28 (40)          | 2015 | 51  | Female | 2                           | PAV      | Prosthetics, dental caries | *Actinomyces naeslundii* | VAN + CTX $\rightarrow$ CTX $\rightarrow$ ERT $\rightarrow$ amoxicillin | 12 | Survived |
| 29 (41)          | 2018 | 55  | Female | 8                           | MV, AV   | HOCM with LVOT       | *Actinomyces israelii* | PCN | 11                           | Survived |
| 30 (13)          | 2019 | 61  | Male | 1 week                      | MV, AV   | H/O MV endocarditis  | *Actinomyces neuii* | VAN + PIP/TAZ $\rightarrow$ AMP + GEN $\rightarrow$ AMP $\rightarrow$ doxycycline | 12 | Survived |

**This case**

| Case (Reference) | Year | Age | Sex | Duration of Illness (Months) | Valve(s) | Predisposing Factors | Organism | Therapy | Duration of Treatment (Months) | Outcome |
|------------------|------|-----|-----|----------------------------|----------|----------------------|----------|---------|-------------------------------|---------|
|                  | 2019 | 13  | Male | 2                           | MV, AV   | Dental caries, probable RHD *Actinomyces oris* | AMP/SUL $\rightarrow$ AMP $\rightarrow$ amoxicillin | 12 | Survived |

**Abbreviations:** NA, not applicable; H/O, history of; RHD, rheumatic heart disease; IVDU, intravenous drug use; MV, mitral valve; AV, aortic valve; TV, tricuspid valve; PAV, prosthetic aortic valve; EV, eustachian valve; HOCM, hypertrophic cardiomyopathy; LVOT, left ventricular outlet obstruction; PCN, penicillin; AMP, ampicillin; CTX, ceftriaxone; CTM, cefotaxime; VAN, vancomycin; ERT, ertapenem; MER, meropenem; GEN, gentamicin; AMPSUL, ampicillin/sulbactam; CLN, clindamycin; ERY, erythromycin; RIF, rifampicin; MET, metronidazole; PIP/TAZ, piperacillin/tazobactam.
identification of Actinomyces spp to improve the accuracy of speciation and diagnosis.

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Ethics Approval
Ethical approval to report this case was obtained from the Institutional Review Board of Mahidol University (Approval Number: COA.MURA2019/1101).

Informed Consent
Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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Table 3. Clinical Characteristics, Treatment, and Outcome of Endocarditis Cases Caused by Actinomyces Species.

| Clinical Characteristics                                      | N (%) |
|--------------------------------------------------------------|-------|
| Age, years, (range)                                          | 48 (34-65) |
| Sex (male)                                                   | 22 (71) |
| Underlying cardiac disease                                   | 16 (52) |
| History of recent dental procedures or presence of dental caries | 7 (22.6) |
| Native valve                                                  | 28 (90.3) |
| Mitral valve                                                  | 11 (35.5) |
| Aortic valve                                                  | 6 (19.4) |
| Mitral and aortic valve                                      | 6 (19.4) |
| Eustachian valve                                              | 2 (6.5) |
| Prosthetic valve                                              | 3 (9.7) |
| Treatment with non–β-lactams antibiotics                     | 6 (19.4) |
| Required surgery                                              | 8 (25.8) |
| Duration of treatment (months) (range)                        | 1-12 |
| Death                                                        | 8 (26.7) |
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