REVIEWS OF INFECTIOUS DISEASES • VOL. 11, NUMBER 1 • JANUARY FEBRUARY 1989

Infection Due to *Actinobacillus actinomycetemcomitans*: 15 Cases and Review

Andrew H. Kaplan, David J. Weber, Eugene Z. Oddone, and John R. Perfect

From the Pediatric and Adult Divisions of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill; and the Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina

Actinobacillus actinomycetemcomitans is a small fastidious gram-negative coccobacillus that fails to grow on MacConkey's agar. Slow growth in broth may lead to delays in diagnosis. First described in 1912, *A. actinomycetemcomitans* has been recognized since 1962 as capable of causing serious infections in humans. Such infections include periodontal infection, soft tissue abscess (often in association with *Actinomyces* species), and systemic infection, most commonly endocarditis. Fifteen cases and a review of the English-language literature are presented to define the epidemiology and clinical features of infection due to *A. actinomycetemcomitans*. Therapy for infection due to *A. actinomycetemcomitans* has most commonly involved ampicillin or penicillin, often in conjunction with an aminoglycoside. However, resistance to penicillin or ampicillin is common. Antimicrobial agents with a high degree of in vitro activity included cefazolin, cefotaxime, cetriaxone, aminoglycosides, and chloramphenicol. Therapy should be guided by clinical response and in vitro susceptibility testing.

Actinobacillus actinomycetemcomitans, a small gram-negative coccobacillus, was first described by Klinger in 1912 [1]. As its name indicates, it was initially thought that *A. actinomycetemcomitans* was unable to cause infection, except in conjunction with *Actinomyces israelii*. Several early studies reported that *A. actinomycetemcomitans* was cultured from a varying percentage of patients with infections due to *A. israelii* [2–6]. Before 1962 the few cases in which *A. actinomycetemcomitans* was the sole organism recovered were thought to represent elimination of *Actinomyces* from the infected site by previous antibiotic therapy [7]. In retrospect, the initial report of *A. actinomycetemcomitans* as the sole infecting agent in humans probably represented infection with a similar organism, *Haemophilus aphrophilus* [8]. In 1962 King and Tatum reported 32 well-documented infections with *A. actinomycetemcomitans* [9]; Page and King defined the epidemiology and clinical features of infections due to *A. actinomycetemcomitans* [10]. Since 1962 there have been 72 well-documented case reports of *A. actinomycetemcomitans* infection. We report herein an additional 15 cases at three North Carolina teaching hospitals: North Carolina Memorial Hospital in Chapel Hill, Duke University Medical Center in Durham, and Durham County General Hospital in Durham. Our goal is to analyze our cases and all detailed cases reported in the English-language literature to provide the clinician with a comprehensive review of the epidemiology, microbiology, clinical features, and therapy of infections due to *A. actinomycetemcomitans*.

Received for publication 12 February 1988 and in revised form 13 June 1988.

The authors wish to thank the following individuals for reviewing the manuscript: Myron Cohen, James Crawford, Peter Gilligan, Michael Kaplan and William Rutala. Editorial assistance was provided by Mollie Wise.

Please address requests for reprints to Dr. David J. Weber, CB# 7030 Burnett-Womack 229-H, Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599.

History

A. actinomycetemcomitans was first isolated by Klinger in 1912 [1] from five of 12 cutaneous lesions associated with *Actinomyces*. In the years following this initial description, many reports in the literature noted frequent recovery of *A. actinomycetemcomitans* from both pediatric and adult patients with infections due to *Actinomyces* [2–5, 11–15]. It is likely, however, that some of these isolates may have been organisms that were microbiologically similar to *A. actinomycetemcomitans*. The association of *A. actinomycetemcomitans* with infection due to *Actinomyces* led Bates to propose that *A. actinomycetemcomitans* lowered the oxygen tension in the surrounding tissues, thereby making the local environment more hospitable for the anaerobic *Actinomyces bovis* [2].

The pathogenicity of *A. actinomycetemcomitans* was vigorously debated by early investigators. In 1920 Colebrook isolated *A. actinomycetemcomitans* by culture from 10 of 30 patients with actinomycosis and injected pure cultures of the organism into the skin of a volunteer without producing infection [4]. Evaluation of the pathogenicity of *A. actinomycetemcomitans* in animals revealed that three of six guinea pigs injected intraperitoneally and subcutaneously with isolates of the organism developed an indurated inflammatory reaction [4]; intravenous injection resulted in the death of two of three rabbits but intraperitoneal or subcutaneous inoculation did not produce disease [4]. Despite the frequency with which it was detected in cultures from actinomycotic lesions—954 of 960 specimens in one series [6]—*A. actinomycetemcomitans* was commonly believed to be unable to initiate and maintain infection on its own.

In 1951 Holm suggested that *A. actinomycetemcomitans* alone might be pathogenic in humans after he had repeatedly isolated *A. actinomycetemcomitans* in pure growth from lesions in which *A. israelii* had been eliminated by penicillin [7]. He continued to recover *A. actinomycetemcomitans* up to 16 months after *Actinomyces* had been eliminated. Holm was also the first to report susceptibilities of an isolate of *A. actinomycetemcomitans* to antibiotic agents; his isolate was susceptible to sulfadiazine, sulfathiazole, and streptomycin but resistant to penicillin. The initial report by Thjøtta and Sydnes in 1950 of *A. actinomycetemcomitans* infection not associated with an actinomycotic lesion was probably spurious, as the isolate (recovered from a jaw abscess) fermented lactose and was therefore more likely to be *H. aphrophilus* [8]. The report of 32 well-documented cases of infection due to *Actinobacillus* by King and Tatum in 1962 provided conclusive evidence of the pathogenicity of *A. actinomycetemcomitans* [9]. Since 1962, 72 detailed cases of infection with *A. actinomycetemcomitans* have appeared in the English-language literature, further defining the epidemiologic and clinical features of the organism.

Microbiology

A. actinomycetemcomitans is a small (0.7 ± 0.1 × 1.0 ± 0.4 μm), gram-negative coccobacillus that is nonmotile, fermentative, and capnophilic and has no requirement for either X or V factor [16]. This organism reduces nitrate to nitrite, decomposes hydrogen peroxide, does not produce indole, and is oxidase-negative. *A. actinomycetemcomitans* gives positive fermentation reactions with glucose, fructose, and mannose but does not ferment lactose, sucrose, trehalose, or starch [17]. The guanine-plus-cytosine content of this species is between 0.449 and 0.487 mol [18]. DNA-DNA hybridization studies have demonstrated considerable homology between *A. actinomycetemcomitans* and *Haemophilus* species and a reassignment of the organism to the genus *Haemophilus* was proposed [18] but not favored by the Subcommittee of Pasteurellaceae and Related Organisms of the International Committee on Systematic Bacteriology [19].

The organism will grow in trypticase soy broth, brain-heart infusion broth with *p*-aminobenzoic acid, and Schaedler broth with 0.05% sodium polyanetholesulfonate and produces granules that often adhere to the bottom and the side of the tube. The broth itself, however, may remain clear for 72–96 hours, thereby delaying diagnosis. Optimal growth occurs at 37°C with little or no growth at 25°C or 42°C at 24 hours. The organism will grow on blood and chocolate but not MacConkey's agar [17]. Growth is markedly enhanced by 5% CO_2 and is either very poor or absent in an unenhanced atmosphere [20]. When grown on agar, small circular colonies (1 mm in diameter in 2–3 days) are formed that have a pattern described as star-like or crossed-cigars when examined under a dissecting microscope. A selective media for the isolation of *A. actinomycetemcomitans* has been developed that should increase the ease with which the organism can be recovered and identified [21, 22].

The genus *Actinobacillus* contains five species: *Actinobacillus equuli*, *Actinobacillus lignieresii*, *Actinobacillus hominis*, *Actinobacillus suis*, and *A. actinomycetemcomitans*. *A. equuli*, *A. lignieresii*, and *A. suis* are primarily animal pathogens, causing disease in horses, pigs, cattle, and sheep [17]. *A. lignieresii* has been rarely associated with horse bites [23] and *A. hominis* has been isolated from the sputa of patients with chronic lung disease [24]. *A. actinomycetemcomitans* may be separated from other members of the genus by its lack of growth on MacConkey's agar, fermentation of glucose but not lactose or sucrose, and a negative urease reaction [17]. Recently, gas chromatography has been used to differentiate between *Actinobacillus*, *Haemophilus*, and *Pasturella* species on the basis of analysis of whole-cell lysates [25].

The organism has been divided into eight biotypes by Pulverer and Ko on the basis of its ability to ferment mannitol, xylose, and galactose [26]. Three different serotypes (a, b, and c) have been identified by indirect immunofluorescence with use of rabbit antisera [27]. Blots of bacterial colonies on nitrocellulose paper have been used with monoclonal antibodies for the rapid identification of the organism [28]. Both biotyping and serotyping appear to be of limited clinical significance, although one group found a twofold greater incidence of serotype b among juvenile patients with periodontitis [29].

A fascinating array of potential virulence factors in *A. actinomycetemcomitans* have been characterized. Several groups have documented the existence of a leukotoxic extract that appears to lyse leukocytes in a dose-dependent fashion [30–33]. This activity is suppressed by the addition of sera from patients with juvenile periodontitis but unaffected by exposure to sera from patients with other dental conditions [31]. A polymorphonuclear leukocyte chemotaxis-inhibiting factor has also been identified [34]. Collagenolytic activity, as well as the capacity to resorb bone, which is probably prostaglandin-mediated, has also been reported in cell-free and capsular material preparations [35, 36]. The exact significance of these potential virulence factors in the establishment and maintenance of *A. actinomycetemcomitans* infection is unclear.

Evidence suggests that the humoral immune system is important in the host response to *A. actinomycetemcomitans* infection. Elevated levels of IgG in serum and fluid from the gingival crevice directed against *A. actinomycetemcomitans* have been noted by several investigators [37–42]. The role of cell-mediated immunity remains unclear [37]. Although some investigators have reported defects in cell-mediated immunity in patients with *A. actinomycetemcomitans*-associated periodontal disease [43, 44], other researchers have reported normal B cell and T cell numbers, ratios, and responsiveness to antigenic stimuli [37, 45]. It appears that the organism is capable of inducing acquired neutrophil defects as well [34].

Epidemiology

A. actinomycetemcomitans is commonly demonstrated in human periodontal cultures. It has been implicated as the causative agent in localized juvenile periodontal disease [16, 42, 46–50], although its recovery from involved periodontal sites has not been uniform [51]. The organism may occasionally be isolated from sites in the tongue, cheek, saliva, and periodontal tissue in healthy adults and children [52, 53]. Zambon et al. isolated *A. actinomycetemcomitans* from 28 of 29 patients with localized juvenile periodontal disease, but only from 24 (17%) of 142 periodontally healthy individuals, 28 (21%) of 134 adult patients with periodontitis, and five of 98 patients with type 1 diabetes mellitus [54]. The organism is often isolated from sites in patients with progressive periodontal disease [55].

The ability of *A. actinomycetemcomitans* to colonize an oral site may depend on preexisting pathologic states, as attempts to transfer *A. actinomycetemcomitans* from infected to healthy periodontal sites in patients have been unsuccessful [56]. *A. actinomycetemcomitans* may be transmissible between individuals as ~50% of family members of patients with localized juvenile periodontal disease have been shown to harbor the organism, compared with <25% of the general population [56]. Most extraoral disease appears to occur as a result of hematogenous seeding from a periodontal source. This is supported by the high incidence (46%) of dental disease in patients with endocarditis due to *A. actinomycetemcomitans* revealed by our review of the English-language literature.

Methods

We attempted to ascertain all cases of infection due to *A. actinomycetemcomitans* seen in three central North Carolina teaching hospitals since 1971. Participating hospitals include North Carolina Memorial Hospital, a 530-bed teaching hospital, which is the main hospital for the School of Medicine, University of North Carolina at Chapel Hill; Duke University Medical Center, a 990-bed teaching hospital of the School of Medicine, Duke University in Durham; and Durham County Hospital, a 420-bed hospital affiliated with Duke University. Computer records of the microbiology laboratory of Memorial Hospital and Duke University Hospital and discharge records of all three hospitals were reviewed to distinguish patients with *A. actinomycetemcomitans* infection. In addition, records of the microbiology laboratory of the North Carolina Department of Health and Human Services were reviewed to distinguish cases in which isolates of *A. actinomycetemcomitans* from the three participating hospitals were identified by the state reference laboratory. Reports of *A. actinomycetemcomitans* infection appearing in English were identified by means of a comprehensive literature review with use of MEDLINE.

Case Reports and Review

A. actinomycetemcomitans has now been reported as the etiologic agent in a variety of clinical infections (table 1). However, periodontal infections, endocarditis, and local abscess formation often associated with infection due to *Actinomyces* appear to be the commonest. Fifteen cases of infection with *A. actinomycetemcomitans* have occurred at our hospitals since 1971 (table 2). These cases further delineate the infectious syndromes caused by this organism.

Endocarditis

Case 6. A 29-year-old man was admitted to the Duke University Medical Center emergency room on 12 January 1978 with fever, chills, cough, and vomiting. He was a West African native with a reported history of congenital aortic stenosis that led to dyspnea. An aortic valve replacement with a fascia lata femoris homograft was performed in Hamburg, Germany in 1971. He was well after surgery until he developed progressive dyspnea, cough, and fever during the 3 weeks before admission. Physical examination disclosed an acutely ill patient with a temperature of 39.7°C, blood pressure of 110/70 mm Hg, and heart rate of 108. His skin was without hemorrhages or Janeway lesions. Oral examination revealed severe periodontitis. There was no splenomegaly, eye grounds were normal, and his lungs were clear. His cardiac examination showed a 4/6 systolic murmur. His hemoglobin level was 9.3 mg/dL; platelet count, 144,000; white blood cell count, 15,600 cells/mm^3 (85% segmented, 2% band forms, 6% lymphocytes, 6% monocytes); erythrocyte sedimentation rate, 109 mm/h; urinalysis, normal; electrocardiogram showed left ventricular hypertrophy with strain, chest radiograph showed left ventricular prominence with cephalization of flow, and echocardiogram revealed concentric left ventricular hypertrophy with probable vegetations on the aortic valve and papillary muscle.

Specimens for eight blood cultures were drawn over a 36-hour period. The patient was given ampicillin (3 g every 6 hours) and streptomycin (1 g every 12 hours). All blood cultures yielded a gram-negative bacillus that was identified at the state laboratory as *A. actinomycetemcomitans.* The MICs of ampicillin, penicillin, and streptomycin were 0.4 µg/mL, 0.8 µg/mL, and 0.4 µg/mL, respectively. The MBC was identical to the MIC for both ampicillin and penicillin.

The patient was intermittently febrile for 7 days, but the white blood cell count decreased to normal in 48 hours. He received maintenance therapy consisting of both ampicillin and streptomycin for 30 days, when he was discharged on a regimen of amoxicillin, 750 mg three times daily for 3 weeks.

His recovery was complicated by increasing dyspnea in November 1978. Evaluation revealed both aortic and mitral valve insufficiency and he underwent replacement of both aortic and mitral valves with porcine xenografts. No vegetations were found at surgery.

Case 14. A 51-year-old man was seen in the infectious disease clinic at Memorial Hospital on 5 December 1985. He had no history of heart disease and was in his usual state of excellent health until 3–4 months before presentation, when he noted the acute onset of fevers, chills, and diffuse arthralgias. On 19 November he went to his physician who found him to be a well-appearing man except for poor dentition and an oral temperature of 101.8°F; physical

Table 1. Infectious syndromes caused by *Actinobacillus actinomycetemcomitans*.

Common	
	Endocarditis
	Soft tissue abscess*
	Periodontal infection
Uncommon	
	Brain abscess
	Thyroid abscess
	Parotitis
	Pneumonia
	Empyema
	Pericarditis
	Osteomyelitis
	Synovitis
	Urinary tract infection†
	Endophthalmitis†

* May be associated with infection due to *Actinomyces*.
† In association with endocarditis.

Table 2. Clinical features of the present series of 15 patients with infections due to *Actinobacillus actinomycetemcomitans.*

Case no.	Age/sex (year seen)	Infectious syndrome (additional pathogens)	Duration of symptoms	Predisposing factors	Treatment (duration)	Outcome
1	10/M (1971)	Chest wall abscess (none)	1 y	None	*Pen* 9 × 10^6 U (3 d); Pen 2 g (1 y)	Cured
2	31/M (1974)	Dental abscess (none)	3 w	Carious teeth, dental extraction	*Cm* 1.2 g (4 d); Clex 2 g (?)	Relapse after 3 mo; repeat therapy
3	39/M (1976)	Endocarditis (none)	3 w	Carious teeth	*Pen* 30 × 10^6 U + *Stm* 1 g; *Amp* 5 g (total 42 d)	Cured, late aortic valve replacement
4	58/M (1977)	Submandibular abscess (none)	1 y	Dental extraction	Surgical drainage and fistulectomy	Cured
5	36/M (1978)	Hand abscess (*Bacteroides corrodens*)	6 w	Puncture wound	*Pen* 10^7 U (?)	Cured
6	29/M (1978)	Endocarditis (none)	3 w	Homograft aortic valve	*Amp* 12 g (30 d) + *Stm* 2 g (30 d); Amox 2.25 g (21 d)	Cured, late aortic and mitral valve replacement
7	20/F (1978)	Mandibular abscess (*Staphylococcus aureus*)	2 w	Carious teeth, dental extraction	Pen 2 g (4 w)	Cured
8	16/F (1979)	Mediastinal and pulmonary abscesses, osteomyelitis of spine (*Actinomyces israelii, B. corrodens*)	7 mo	None	*Pen* 36 × 10^6 U (3 w); Pen 750 mg (4 w)	Cured
9	17/F (1981)	Empyema (none)	10 d	Cerebral palsy	*Amp* 12 g (4 d); *Amp* 12 g + *Gm* 240 mg (2 d)	Died
10	45/M (1981)	Endocarditis (none)	3 w	Alcohol abuse	*Pen* 12 × 10^6 U (42 d)	Cured
11	40/M (1984)	Submandibular abscess (none)	3 w	Carious teeth, dental extraction	Pen 3 g (10 mo); Dox 100 mg (10 w)	Prolonged infection, eventual cure
12	15/F (1984)	Brain abscess (*Eikenella corrodens, Haemophilus aphrophilus*)	2 w	Meningioma, CSF rhinorrhea, neurosurgery	*Chl* 4 g + *Metro* 2 g (1 mo)	Cured
13	39/M (1985)	Cervical adenitis (probable *Actinomyces*)	2 mo	Carious teeth, dental extraction	Pen 2 g (1 mo)	Cured
14	51/M (1985)	Endocarditis (none)	4 mo	Poor dentition	*Ctri* 2 g + Stm 1 g (42 d)	Cured
15	52/F (1986)	Septic embolus, endocarditis (none)	2 mo	Rheumatic heart disease, porcine mitral valve	*Pen* 12 g + *Stm* 2 g (3 w); *Pen* 12 g + *Amik* 1 g (6 w)	Cured

NOTE. Amik = amikacin, Amox = amoxacillin, Amp = ampicillin, Clex = cephalexin, Chl = chloramphenicol, Cm = clindamycin, Ctri = ceftriaxone, Dox = doxycycline, Pen = penicillin, Gm = gentamicin, Metro = metronidazole, Stm = streptomycin. Drugs administered intravenously are italicized.

examination was normal. Urinalysis revealed the presence of hemoglobin but his peripheral white blood cell count, hemoglobin levels, liver function tests, and chest radiograph were normal. Penicillin therapy (500 mg orally every 8 hours) was started.

Despite therapy the patient continued to have biweekly temperature elevations to 103°F and was referred to Memorial Hospital. The patient's medical history revealed that he worked on a farm and was exposed to dairy cows. However, he denied ingestion of unpasteurized milk. On examination he was noted to have carious teeth and a 1/6 systolic murmur at the apex. There was no presence of Osler's nodes, Janeway lesions, splinter hemorrhages, or splenomegaly. Results of a tuberculin skin test were negative with a positive control. Tests for antinuclear antigen and syphilis (Venereal Diseases Research Laboratory) were negative. An echocardiogram revealed focal thickening of the aortic and mitral valves. Three days after evaluation, a gram-negative bacillus was noted in three of nine blood cultures. A presumptive diagnosis of brucellosis was made, and the patient was given doxycycline (100 mg po two times a day) and streptomycin (1 g im every day).

Five days later, the organism was identified as *A. actinomycetemcomitans*. Doxycycline was changed to ceftriaxone (2 g iv once daily). Streptomycin therapy was continued. The patient defervesced rapidly and improved clinically. Results of repeat blood cultures were negative. Therapy was continued for 6 weeks, at which time his echocardiogram was unchanged. He was seen again 3 months later and was doing well.

Case 15. A 52-year-old woman was admitted to Memorial Hospital on 1 June 1986 with a numb, cold right arm. She had had rheumatic fever as a child and underwent mitral valve replacement with a porcine xenograft in 1980. On 30 March she had her lower teeth cleaned and, because she reported an allergy to penicillin, received prophylactic treatment with erythromycin. About 3 weeks later she noted fevers and chills, which were treated with nitrofurantoin by her physician. Her symptoms persisted and four blood cultures of specimens drawn by her physician were reportedly negative.

One month later, she noted the acute onset of pain, numbness, and loss of function of her right arm. On arrival at the emergency room of Memorial Hospital she was ill-appearing, with an oral temperature of 101°F. Cardiac examination revealed no murmurs, pulmonary examination was unremarkable, and there were no peripheral stigmata of endocarditis. Her right arm was pale and pulseless. Her hemoglobin level was 12 mg/dL and erythrocyte sedimentation rate was 77 mm/h. Emergency embolectomy was performed and she was given vancomycin (600 mg every 6 hours) and gentamicin (70 mg iv every 8 hours). An echocardiogram revealed focal thickening of the aortic and mitral valves. Blood cultures and cultures of the excised clot yielded *A. actinomycetemcomitans* after 72 hours of incubation. The patient was desensitized to penicillin and antibiotic therapy was changed to penicillin (2 g iv every 4 hours) and streptomycin (2 g im every day). She responded clinically, regained function of her right hand, and was discharged 2 weeks later to continue intravenous antibiotic therapy at home.

Four days after discharge, she had an episode of shaking chills. In the emergency room she had an oral temperature of 103°F. Her physical examination was unchanged except for a petechial rash over her lower extremities. Four blood cultures were negative, and her antibiotic regimen was changed to penicillin (2 g iv every 4 hours) and amikacin (335 mg iv every 8 hours); peak serum bactericidal level was 1:32. Following an additional 6 weeks of intravenous antibiotic therapy, she was discharged as clinically well. When seen after 18 months she was without evidence of recurrent disease.

Comments. Our cases illustrate several characteristic features of *A. actinomycetemcomitans* endocarditis. The long delay between onset of symptoms and diagnosis is typical. Initially, none of the patients had any of the peripheral manifestations of endocarditis, although patient 15 developed a petechial rash, which may have represented a drug allergy. Poor dentition (case 14) and abnormal cardiac valves (cases 6 and 15) appear to be common predisposing factors. Although infection of a porcine valve, as noted in case 15, has been previously described [57–60], case 6 is the first reported case of homograft involvement with *A. actinomycetemcomitans*. Infection of an artificial valve does not appear to carry a worse prognosis than infection of a native valve.

The importance of considering endocarditis in patients presenting with septic emboli is demonstrated by case 15. Although mortality is higher in patients with clinically apparent emboli, embolization does not seem to be an absolute indication for valve replacement, as illustrated by this case.

All three patients were cured by antibiotic therapy alone. Case 14 documents the first reported use of ceftriaxone in *A. actinomycetemcomitans* endocarditis. In vitro data support the choice of this agent [61]. Given the varied susceptibilities of this organism, careful tests for in vitro susceptibilities to antibiotic agents should be performed for all patients with serious infection; clinical correlation during therapy is mandatory.

Review. Endocarditis has been the most frequently reported serious clinical infection caused by

A. actinomycetemcomitans. However, *A. actinomycetemcomitans* remains an unusual cause of endocarditis. Only three cases of *A. actinomycetemcomitans* infection of native valves were documented in a collection of 1,082 cases of endocarditis from six series [62–67]; 14 such cases were identified in a review of 348 cases of endocarditis caused by gram-negative organisms [68]. A compilation of major series revealed that 348 patients (2.9%) developed prosthetic valve endocarditis of a total patient population of 12,164 [69–74]. Only four episodes were due to *A. actinomycetemcomitans*. In King and Tatum's 1962 series of patients, 23 (72%) had clear evidence of endocarditis. Although only limited clinical information was provided, it was reported that endocarditis occurred in the setting of underlying heart disease in 18 patients (78%); ischemic heart disease, 14; and congenital heart disease, 4. Antibiotic agents used for therapy included penicillin, streptomycin, chloramphenicol, and tetracycline. The overall mortality rate was noted to be 33%.

Since 1962, 57 additional cases of *A. actinomycetemcomitans* endocarditis have been reported in the English-language literature (table 3) [57–60, 75–119]. *A. actinomycetemcomitans* endocarditis most commonly occurs in men: two-thirds of the initial cases reported by King and Tatum were in men, while more recently men have accounted for 77% of the cases. The mean age of patient with endocarditis was 48 years (range, 8–69 years). The condition of the patient at presentation is almost always subacute, with a mean time from onset of symptoms to diagnosis of 3 months. This delay is exacerbated by the slow growth of the organism. In the 34 cases for which the information was provided, the mean time to growth in culture was 7 days (range, 1.5–16 days).

Major predisposing factors appear to be underlying valvular heart disease and poor dentition. Valvular abnormalities have been noted in 60% of patients. Congenital heart disease (e.g., bicuspid aortic valve, ventricular septal defect, atrial-ventricular septal defects, idiopathic hypertrophic subaortic stenosis) was the commonest predisposing lesion (22% of patients), followed by rheumatic disease (12%). Fourteen of the patients (25%) had artificial valves, five of which were porcine. Two patients (4%) had permanent pacemakers that were involved by the infection.

Poor dentition has been commonly noted in patients with *A. actinomycetemcomitans* endocarditis; 46% of patients had carious teeth, periodontal dis-

Table 3. Clinical features of 57 patients with endocarditis due to *Actinobacillus actinomycetemcomitans*.

Clinical feature	No. of patients (%)
Age*† (y)	
≤20	7 (12)
21–40	12 (21)
41–60	31 (31)
>60	7 (12)
Sex	
Male	44 (77)
Female	13 (23)
Predisposing factors*	
Periodontal disease	12 (21)
Recent dental manipulation	14 (25)
Cardiac disorders†	
Prosthetic valve	14 (25)
Xenograft	5 (9)
Other	7 (12)
Unknown	2 (4)
Permanent pacemaker	2 (4)
Rheumatic valvular disease without prosthetic valve	7 (12)
Congenital heart disease‡	13 (22)
Murmur, etiology unknown	2 (4)
Other valvular disease	5 (9)
No underlying heart disease	10 (18)
No mention of underlying heart disease	4 (7)
Presenting symptoms*	
Fevers	33 (58)
Chills or rigors	22 (39)
Night sweats or diaphoresis	18 (32)
Weight loss	17 (30)
Malaise	13 (22)
Anorexia	13 (22)
Weakness	12 (21)
Fatigue	10 (18)
Dyspnea	7 (12)
Headache, confusion	6 (11)
Chest pain	4 (7)
Gastrointestinal symptoms	4 (7)
Presenting signs*	
Fever (>38°C)	25 (44)
Hepatomegaly	19 (33)
Splenomegaly	19 (33)
Peripheral manifestations§	20 (34)
Initial laboratory values‖#	
Anemia	44 (96)
Elevated erythrocyte sedimentation rate	32 (89)
Leukocytosis	21 (49)

(*continued*)

Table 3. *(continued)*

Clinical feature	No. of patients (%)
Duration (initial symptoms to diagnosis)	
0–7 d	3 (5)
8–30 d	10 (18)
1–2 mo	6 (11)
>2–4 mo	9 (16)
>4–6 mo	4 (7)
>6–8 mo	5 (9)
>8–10 mo	3 (5)
>10–12 mo	1 (2)
>1 y	1 (2)
Not specified	15 (26)
Outcome	
Survived	44 (77)
Prosthetic valve replacement*	13 (23)
Congestive heart failure	17 (29)
Patients with clinically significant emboli	22 (39)
Central nervous system	10
Eye	8
Kidney	5
Lung	3
Spleen	2

* Denominator includes all cases (n = 57).

† Percentages ≠ 100 because of rounding to the nearest digit.

‡ Bicuspid valve, three; idiopathic hypertrophic subaortic stenosis, two; mitral stenosis, two; mitral valve prolapse, one; and other, five.

§ Osler's nodes, Janeway lesions, petechiae, Roth's spots, subconjunctival hemorrhage.

‖ Denominator includes only cases providing the relevant information.

Normal values obtained from [119].

ease, or dental manipulation within 1 month of onset of symptoms. Of the 14 patients who reported some kind of dental manipulation, seven received prophylactic treatment, four with penicillin, one with vancomycin plus erythromycin, one with erythromycin alone, and one with an unknown intramuscular antibiotic. Two patients with endocarditis were immunocompromised, a 56-year-old man with systemic lupus erythematosus being treated with azathioprine and prednisone [85], and a man described only as immunocompromised [64]. A 12-year-old girl from Papua New Guinea, has been reported as coinfected with *A. actinomycetemcomitans* and *Plasmodium falciparum* [83].

Most patients reported constitutional symptoms including fever, chills, malaise, and anorexia. Peripheral stigmata of endocarditis were noted in 34% of patients. Hepatomegaly and splenomegaly were common. The erythrocyte sedimentation rate was invariably elevated and moderate anemia was nearly always present (96%).

Although the tendency of *A. actinomycetemcomitans* endocarditis to cause emboli has been noted in the literature [77, 81, 116], clinically recognized embolic events occurred in only 22 patients (39%). This is not significantly different from the 20%–50% reported in several large series of infectious endocarditis [64–66]. Complications of embolic phenomena were the presenting feature in five cases (9%). CNS emboli were the commonest (10 cases), followed by eye (eight), kidney (five), lung (three), and spleen (two). Multiple emboli were noted in five patients (9%). Clinically apparent embolization carried a poor prognosis; six of 22 patients with emboli, vs. three of 36 patients without emboli, died.

Congestive heart failure was noted in 17 patients, of whom six died. Infection involved the aortic and/or mitral valve, except for one case of tricuspid involvement [93]. Thirteen patients required valve replacement (aortic, eight; mitral, two; and both, three).

A variety of antibiotic regimens were used, most of them containing either ampicillin alone or either ampicillin or penicillin with an aminoglycoside, usually streptomycin.

Soft Tissue Abscess with *Actinomyces*

Case 13. A 39-year-old man had several teeth extracted in February 1985 and ∼2 weeks later noted some swelling in his right cervical area without fever or chills. This swelling progressed and his local physician treated him with erythromycin. Because the patient's condition did not improve, he was referred to the otolaryngology clinic at Memorial Hospital on 1 April 1985, where a 10 cm × 12 cm mass with a fluctuant center on the right side of his neck was described. Stains obtained at the time of excision and drainage revealed sulfur granules, and cultures yielded *A. actinomycetemcomitans.* The patient was treated with penicillin VK, 500 mg po every 6 hours for one month. He is well 18 months later.

Case 8. A 16-year-old girl was transferred to Memorial Hospital on 13 June 1979 for evaluation of a posterior mediastinal mass. She had a 7-month history of increasing upper back pain with fevers, night sweats, anorexia, and a 7-kg weight loss. Upon admission to a local hospital on 6 June, she was reported to have a temperature of 102°F, markedly carious teeth, and a tender thoracic spine. Tomography of the thoracic spine revealed lucencies in the T-3 to T-7 vertebral bodies. Bone scan demonstrated increased uptake from T-2 to T-8 and chest tomography delineated a large, horseshoe-shaped mass extending from T-2 to T-8.

At thoracotomy a large, friable, necrotic mediastinal mass involving the posterior chest wall and right upper and lower lobes of the lung was removed. *A. israelii*, *Bacteroides corrodens* and *A. actinomycetemcomitans* were recovered from cultures of specimens obtained during the operation. The patient was treated with penicillin G (6 million units iv every 4 hours for 3 weeks) then penicillin VK (250 mg po three times a day for 1 month) with complete resolution of symptoms.

Comments. *A. actinomycetemcomitans* is often reported to be present with *Actinomyces*. Initially, 30%–40% of actinomycotic lesions were thought to contain *A. actinomycetemcomitans* but when improved cultural techniques are employed this percentage may be much higher. Cases similar to case 8 have been reported [120]. Lane et al. reported two patients with paravertebral infection and spinal osteomyelitis due to *A. israelii* and *A. actinomycetemcomitans* associated with pulmonary or pleural lesions. Typically, as in these cases, treatment directed at *Actinomyces* (i.e., penicillin and/or surgical drainage) will be curative.

Periodontal Infection

Case 4. A 58-year-old man was admitted to Memorial Hospital on 18 August 1977 for incision and drainage of a right submandibular mass. The patient's current medical problem began on 8 August 1976 when he underwent two right-molar odontectomies and several days later noted some right submandibular swelling. He was treated with lincomycin, without relief, and on 18 October surgical drainage of the abscess was performed. Cultures of the abscess were negative, and the patient was discharged on a regimen of tetracycline.

Over the next year he had several episodes of swelling below his right jaw. He remained afebrile throughout this period and in April 1977 he first noted the appearance of a fistulous tract with spontaneous drainage. Incision and drainage together with fistulectomy were performed at Memorial Hospital on 18 August 1977.

Cultures for mycobacteria and fungi were negative. Pathology revealed acute and chronic inflammation without sulfur granules. The patient was discharged without antibiotic agents and has done well without evidence of recurrent disease. Bacterial cultures sent to the state reference laboratory yielded a pure growth of *A. actinomycetemcomitans*.

Case 7. A 20-year-old woman presented to the Duke University Medical Center otolaryngology clinic in July 1978 with pain in her left jaw. Five weeks before presentation, she had three teeth removed from her left lower jaw for carious disease. She received oral penicillin for 1 week after the extraction. Two weeks before presentation the patient noticed pain in the area overlying the site of extraction; 3 days before presentation clear fluid began to drain from the site.

Physical examination revealed an afebrile, well-appearing woman. A small abcess of the left lower jaw was noted with a fistulous tract draining through her cheek. Drainage of the abscess and fistulectomy were performed and cultures of fluid from the abcess revealed *A. actinomycetemcomitans* and *Staphylococcus aureus*. Sulfur granules were not noted. Both organisms were susceptible to penicillin and the patient received penicillin (500 mg po four times a day for 4 weeks) with complete resolution of symptoms.

Comments. *A. actinomycetemcomitans* is isolated from 17% of healthy adults and 21% of adults with periodontal disease [54]. It appears that some initial insult predisposes a periodontal site to colonization, as investigators have encountered difficulties in the transfer of organisms from infected gum sites to healthy ones [56].

Other Infectious Syndromes

In addition to endocarditis, *A. actinomycetemcomitans* has been implicated as the infectious agent in brain [121–123], soft tissue [124], thyroid [121], and periodontal [125] abscesses; pericarditis [126]; pneumonia [127, 128]; empyema [120]; osteomyelitis [99, 129]; synovitis [130]; parotitis [131]; and skin [132] and urinary tract infections [26, 133]. The epidemiology of these cases is similar to that seen with endocarditis. All of the patients were men and the time from onset of symptoms to diagnosis ranged from several months to 1.5 years. Only one of the patients had an underlying disease, a 56-year-old man with multiple myeloma who was being treated with corticosteroids and an alkylating agent and who developed pneumonia [128].

The association with carious teeth and periodontal disease noted in *A. actinomycetemcomitans* endocarditis may be less pronounced for the patients who do not have cardiac disease. One patient developed chronic osteomyelitis following a fistfight during which his assailant's tooth became embedded in the patient's hand [99]. Synovitis of the wrist was reported in a patient with carious teeth who had injected the area with heroin [130]. This infection was possibly the result of the common practice of expectorating into the drug during its preparation. An additional case of a polymicrobial abscess of the brain that included *A. actinomycetemcomitans* has also been described in a 34-year-old man with periodontal disease.

Empyema

Case 9. A 17-year-old girl with severe cerebral palsy was admitted to Memorial Hospital on 15 February 1981 for evaluation of cough and fever. She was noncommunicative and had severe scoliosis, quadraplegia, and a poorly controlled seizure disorder. Her parents reported a 10-day history of fevers, chills, and chest congestion. These symptoms progressed, and on the day of admission the patient was febrile (39°C) and in respiratory distress with a rate of 58. On examination she had extremely carious teeth, severe scoliosis, and decreased breath sounds at the left lung base. Her white blood cell count was 20,000 cells/mm^3, with 11% band forms. Arterial blood gas while breathing room air showed a pH of 7.54, P_{CO_2} of 24 mm Hg and a P_{O_2} of 66 mm Hg. Chest radiography revealed a left pleural effusion. Ampicillin therapy (3 g iv every 6 hours) was begun. The next day, 500 mL of straw-colored fluid was aspirated from the left side of her chest. The fluid contained 19,000 white blood cells/mm^3, 82% of which were neutrophils. Chest radiographs taken after drainage revealed infiltrates in the right middle and lower lobes and the left lower lobe. All cultures were negative.

The patient improved immediately, but 4 days after admission, she had a temperature of 39°C with an increased respiratory rate. Repeat thoracentesis revealed frank pus and culture yielded *A. actinomycetemcomitans.* Gentamicin (80 mg iv every 8 hours) was added to her regimen. Her condition continued to worsen, and she died 2 days later. Permission to perform an autopsy was denied.

Comments. This is the first reported case of epyema solely due to *A. actinomycetemcomitans.* The infection progressed rapidly toward death. A patient with pulmonary infiltrates, paravertebral mass, and empyema due to *A. israelii* and *A. actinomycetemcomitans* who recovered with penicillin therapy has been reported [120].

Two cases of pneumonia have been reported [127, 128]: the previously described 56-year-old man with multiple myeloma and a 13-year-old boy without underlying disease. This latter patient had had anterior chest pain for 1 year before development of fever and chills. Chest radiographs revealed an infiltrate of the right upper lobe; only *A. actinomycetemcomitans* was recovered from specimens obtained by open lung biopsy. The patient was treated with ampicillin and there was a rapid resolution of symptoms [127]. Although *A. actinomycetemcomitans* may be a constituent of the normal oral flora, lower respiratory tract infections due to *A. actinomycetemcomitans* are rare.

Brain Abscess

Case 12. A 15-year-old girl was referred to the neurosurgery clinic of Memorial Hospital on 14 December 1984 after 2 years of decreasing vision in her right eye and several weeks of a worsening headache. Cranial computed tomography revealed a meningioma involving her right optic canal; a craniotomy with complete removal of the tumor was performed. The postoperative course was complicated by several episodes of CSF rhinorrhea that resolved spontaneously. The patient was sent home on a regimen of rapidly tapering doses of corticosteroids and did well until 1 week after discharge, when she began to have severe frontal headaches. These headaches progressed over the course of the next 2 weeks and, 2 days before admission, she developed a stiff neck and fever.

On admission she was febrile with a dilated right pupil and right-sided ptosis. Cranial computed tomography demonstrated the presence of right frontal abscess. Material obtained from a fine-needle aspirate yielded *Eikenella corrodens, H. aphrophilus*, and *A. actinomycetemcomitans.* A regimen of metronidazole (500 mg iv every 6 hours) and chloramphenicol (1 g iv every 6 hours) was begun.

The patient defervesced rapidly and repeat cranial tomography after 1 month of therapy showed dramatic resolution of the abscess. She is doing well after 2 years.

Comments. This patient probably developed an abscess as a result of spread of bacteria from her nasopharynx made possible by a dural tear. Despite her toxic appearance and a large abscess, she responded rapidly to antibiotic therapy and did not require open surgical drainage.

Wound Infection

Case 5. A 36-year-old migrant farm worker was initially admitted to Memorial Hospital on 22 September 1978 for fever and painful swelling of the dorsum on his right hand. Six weeks before admission he reported suffering a puncture wound to the hand followed by painful swelling and progressive erythema with occasional purulent drainage. Symptoms continued despite therapy with erythromycin. On admission he was afebrile. A 6 cm × 6 cm erythematous, fluctuant area on the dorsum of his right hand was noted. Radiographs of the hand did not reveal evidence of osteomyelitis, and cultures from a needle aspirate of the lesion showed no growth at 72 hours. The lesion was excised, and the patient was discharged without antibiotic treatment.

His symptoms persisted and he was readmitted on 10 November. Review of the original culture reports revealed that *B. corrodens* and *A. actinomycetemcomitans* had been recovered. The patient was successfully treated with intravenous penicillin, 10 million units a day.

Comments. Although the source of the puncture wound was not specified, the site appears to have been contaminated by oral flora. Typically characterized by a chronic progression of symptoms, soft tissue infection with *A. actinomycetemcomitans* may take months to come to the attention of a physician. The long period between inoculation of cultures and the identification of the organism is also characteristic. *A. actinomycetemcomitans* was isolated only after the patient was discharged.

Four cases of bone and joint infections have been reported [99, 129, 130]. In addition to the case of wrist synovitis and osteomyelitis mentioned previously, two cases of osteomyelitis have been reported. One patient with severe periodontal disease developed spontaneous, draining sinuses of his chest, back, groin, and shoulder with progressive paraplegia. Radiographs revealed areas of erosion in his left fifth through seventh ribs. High-dose penicillin therapy resulted in resolution of the sinus tract and gradually increased function of the lower extremity [99]. Another patient was diagnosed with vertebral osteomyelitis due to *A. actinomycetemcomitans* after needle biopsy of a blastic lesion in his lumbar spine. He responded promptly to intravenous ampicillin therapy [129].

Chest Wall Abscess

Case 1. A 10-year-old boy from rural North Carolina was referred to the thoracic surgery service at Duke on 8 September 1971 for a right chest wall mass that had developed slowly for 1 year. He had been treated as an outpatient with an unknown antibiotic for 3 months without resolution. Physical examination showed him to be afebrile and in no distress. There was a 10 cm × 5 cm tender, red, fixed mass on the right anterior chest wall and a 2 cm × 2 cm right axillary lymph node. Otherwise the physical examination was normal. Laboratory findings were as follows: the white blood cell count was 8,300 cells/mm^3 with a normal differential count; hemoglobin level was 11 mg/dL; chest radiograph showed right hilar adenopathy; and chest tomography showed patchy right lung consolidation and hilar adenopathy.

The patient was admitted and a biopsy of the chest wall mass was performed. Cultures of the biopsy yielded *A. actinomycetemcomitans*. Sulfur granules were not noted. Mycobacterial and fungal cultures were negative. He received 30 days of intravenous penicillin G (1.5×10^6 units every 4 hours) followed by 1 year of penicillin VK (500 mg four times per day). The mass slowly resolved by 6 months of therapy. The right hilar adenopathy disappeared after 1 year of therapy, but the lung parenchymal changes remained. The patient had no recurrence 1 year after antibiotic therapy was discontinued.

Both acute-phase and convalescent-phase titers of antibody to *Brucella, Francisella tularensis, Coccidioides, Blastomyces*, and *Histoplasma* were negative.

Comments. There is one previous report of an anterior mediastinal abscess caused by *A. actinomycetemcomitans* [124]. That patient had no evidence of involvement of the lung parenchyma; however, the source of our patient's infection is unclear, and there was no evidence for tuberculosis or actinomycotic infection. A contiguous spread from pneumonia, possibly following an aspiration, seems most likely.

Additional Infections

A single case of urinary tract infection due to *A. ac-*

tinomycetemcomitans has been reported in a patient who had previously been treated for renal tuberculosis [133]. The patient responded to kanamycin therapy. An additional isolate of *A. actinomycetemcomitans* from urine has been reported, but no clinical information was provided [134]. Single cases of parotitis [131] and mediastinal abscess due to *A. actinomycetemcomitans* [124] have been reported. Both patients required surgical drainage and made uneventful recoveries.

Therapy

In vitro antibiotic susceptibility data reported since 1962 are summarized in table 4. This table combines the data reported in individual case reports of infection with *A. actinomycetemcomitans* [10, 57–60, 82, 87, 89, 103, 106–108, 111, 117, 128, 129, 133] and large microbiologic studies that used clinical isolates most commonly obtained from the oral cavity or actinomycotic lesions [61, 136, 137]. *A. actinomycetemcomitans* is generally susceptible to the cephalosporins, aminoglycosides, rifampin, chloramphenicol, and tetracycline. Susceptibility to ampicillin and penicillin is variable. *A. actinomycetemcomitans* is generally resistant to the semisynthetic penicillins, vancomycin, erythromycin, and clindamycin.

Table 4. Susceptibilities of clinical isolates of *Actinobacillus actinomycetemcomitans* to antibiotic agents.

Usually susceptible*†		Often susceptible‡		Rarely susceptible§	
Carbenicillin	(39)	Penicillin	(100)	Methicillin	(25)
Mezlocillin	(101)	Ampicillin	(145)	Vancomycin	(62)
Cefazolin	(14)			Erythromycin	(75)
Cefotaxime	(14)			Clindamycin	(74)
Ceftriaxone	(24)				
Gentamicin	(28)				
Tobramycin	(16)				
Rifampin	(15)				
Tetracycline	(114)				
Chloramphenicol	(81)				

NOTE. Values in parentheses are numbers of isolates tested.

* Derived from all reports in the literature of MBCs of agents for isolates of *A. actinomycetemcomitans*; includes both case reports and series of isolates specifically tested for antimicrobial susceptibility. Break points are based on those suggested by the National Committee for Clinical Laboratory Standards [135].

† More than 90% of isolates tested were susceptible to antibiotic.

‡ Fifty percent to 80% of isolates tested were susceptible to antibiotic.

§ Less than 30% of isolates tested were susceptible to antibiotic.

The most commonly employed antibiotic regimens reported in clinical infections have been either penicillin or ampicillin with or without an aminoglycoside. However, the multiplicity of antibiotic regimens that have been used and the small number of patients do not permit identification of the ideal therapeutic regimen. Because of the variable susceptibility of the organism to penicillin and ampicillin these agents probably should not be used unless in vitro testing suggests that the clinical isolate is susceptible. Endocarditis has been reported following penicillin prophylaxis for dental manipulation [77, 100, 103, 109] or minor skin surgery [60]. Further, it has been noted that patients with endocarditis do not respond to therapy with penicillin [78, 104, 117, 128]. Although most strains of *A. actinomycetemcomitans* are susceptible to tetracycline and chloramphenicol, these agents are bacteriostatic and only limited experience with the use of these agents in vivo is available.

An aminoglycoside has commonly been used in conjunction with penicillin or ampicillin for the therapy of endocarditis. However, the combination of ampicillin and an aminoglycoside has been reported as either being additive [103] or not being synergistic [76]. Rifampin has been shown to be synergistic in vitro with ceftriaxone or penicillin for 25%–33% of strains but only limited experience with the use of rifampin in vivo is available [107].

Cephalosporins (cephalothin, cefazolin, cefamandole) [60, 86, 91, 104] have been successfully used as part of the antibiotic regimen for endocarditis due to *Actinobacillus*, although one patient treated with cephalothin died [101]. No bacteria were visualized in this patient's vegetations at autopsy.

Review of the literature reveals that ampicillin plus an aminoglycoside has been the most commonly employed antibiotic combination for treatment of serious infection due to *A. actinomycetemcomitans*. However, therapeutic failures have been described. Limited clinical experience suggests that first- and second-generation cephalosporins may be used to treat endocarditis due to *Actinobacillus*. In vitro susceptibility data suggest that third-generation cephalosporins may be more efficacious. Animal studies would be useful to clarify the utility of these drugs.

The fastidious nature and slow growth of *A. actinomycetemcomitans* may at times make it impossible for clinical laboratories to perform in vitro susceptibility tests. In such cases a bactericidal antibiotic agent with a high degree of activity against *Actinobacillus* should be employed, and treatment should be guided by clinical response. In most cases, endocarditis due to *Actinobacillus* should be treated with 4–6 weeks of intravenous antibiotic agents. Prosthetic valve endocarditis may be cured medically [57, 58, 80, 92, 96, 99, 103, 104, 110, 132]; however, valve replacement may also be necessary [59, 60]. Of note, two of the patients with prosthetic valve involvement died [87, 106].

Seven patients reported since 1962 and one of the patients in our series received antibiotic prophylaxis before dental manipulations. It is unclear whether current recommendations for antibiotic prophylaxis were employed. Gordon et al. [138] and Slots et al. [139] have demonstrated that 250 mg of tetracycline given orally four times a day produces sufficient levels of antibiotic agent in the saliva and gingival fluid to inhibit all strains of *A. actinomycetemcomitans* tested. These investigators suggested that all patients with periodontal disease and underlying heart disease that would put them at risk for endocarditis have cultures of specimens obtained from their oral cavity performed to determine the presence of *A. actinomycetemcomitans* and, if the results are positive, the patient should receive 14 days of tetracycline before dental manipulation. If future case reports document the failure of currently recommended prophylactic regimens [140], then it would be reasonable to study the implementation of the suggestion of Slots et al.

Patients with *Actinobacillus* infections other than endocarditis usually respond well to short courses of appropriate antibiotic therapy and, if necessary, appropriate surgical intervention.

Discussion

This series of 15 cases, collected over 16 years from three hospitals, represents the largest collection of cases since King and Tatum's landmark report in 1962. In both our series and reports in the literature, the commonest serious infectious syndromes caused by *A. actinomycetemcomitans* are endocarditis and soft tissue abscesses, and the latter syndrome tends to occur in association with *Actinomyces*. *A. actinomycetemcomitans* is commonly isolated from the oral cavity of patients with periodontal disease, although its role in the pathogenesis of periodontitis is still unclear. Other less common illnesses due to *A. actinomycetemcomitans* include brain abscesses, pneumonia, osteomyelitis, and urinary tract infections.

The clinical setting of endocarditis due to *Actinobacillus* is now well described. Most patients are male, almost all patients have underlying valvular heart disease, and infection is commonly associated with periodontal disease or follows dental manipulation. Typically, the course of the infection is subacute, with fever, chills, anorexia, weight loss, and night sweats. Heart murmur is almost always present but may be ascribed to an underlying heart ailment. Physical examination frequently reveals fever, hepatosplenomegaly, and peripheral manifestations of endocarditis. Laboratory investigation will commonly reveal anemia, an elevated erythrocyte sedimentation rate, and microscopic hematuria. Leukocytosis may not be present. Although clinically apparent emboli may occur, the frequency of this complication does not appear greater than that with bacterial endocarditis caused by other organisms.

The fastidious nature and slow growth characteristics of *A. actinomycetemcomitans* may hamper the proper diagnosis. Endocarditis due to *Actinobacillus* may be misdiagnosed unless blood cultures are incubated in CO_2 and maintained for 2–3 weeks. Further, since the organism may grow at the top of the broth or along the sides of the bottle with clear broth being present, blind subcultures onto appropriate media should be considered. Once subcultured onto proper solid media, standard tests should allow separation of *A. actinomycetemcomitans* from biochemically similar organisms, especially *H. aphrophilus*.

Despite extensive in vitro data, the appropriate therapy for endocarditis due to *Actinobacillus* is unclear. Although ampicillin or penicillin (often in conjunction with an aminoglycoside) have been most commonly employed, *A. actinomycetemcomitans* demonstrates only variable susceptibility in vitro to penicillin or ampicillin. Further, synergy between ampicillin or penicillin and aminoglycosides has not been demonstrated. The use of third-generation cephalosporins should be examined in animal models and considered for use in patients who do not respond to "standard therapy" with ampicillin and an aminoglycoside. The question of the synergy of penicillin and ampicillin when used with aminoglycosides should be investigated in the laboratory. If future case reports demonstrate that the standard recommendations for the prophylaxis of endocarditis are inadequate to prevent endocarditis due to *A. actinomycetemcomitans*, then consideration should be given to employing the suggestions of Gordon et al. [138] and Slots et al. [139]: culture patients with periodontal disease and underlying heart disease that may predispose to endocarditis for *A. ac-*

tinomycetemcomitans, and treat culture-positive patients with tetracycline before dental manipulation.

Summary

A. actinomycetemcomitans, a small fastidious gram-negative coccobacillus, has been recognized since 1962 as capable of causing severe infections in humans. The organism grows best at 37°C and requires an atmosphere enriched with CO_2 for growth. Growth in broth is slow, leading to delays in diagnosis. *A. actinomycetemcomitans* produces small, circular colonies on blood or chocolate agar but will not grow on MacConkey's agar.

A. actinomycetemcomitans is commonly demonstrated in human periodontal cultures and has been implicated as the causative agent in localized juvenile periodontal disease. Major infectious syndromes include periodontal infections, soft tissue abscesses (often in association with *Actinomyces* species), and systemic infection. Fifteen cases have been summarized and the English-language literature reviewed to define the epidemiology and clinical features of *A. actinomycetemcomitans* infection.

Endocarditis is the commonest serious infection produced by *A. actinomycetemcomitans*. Predisposing factors include periodontal disease and/or recent dental manipulation and abnormal or prosthetic cardiac valves. A chronic course of infection before diagnosis is common. Complications include clinically significant emboli (39%), congestive heart failure (29%), prosthetic valve replacement (23%), and death (23%). Other infectious syndromes caused by *A. actinomycetemcomitans* include respiratory tract infections, bone or joint infections, and abscess formation.

Therapy for *A. actinomycetemcomitans* has most commonly involved ampicillin or penicillin, often in combination with an aminoglycoside. However, resistance to penicillin and ampicillin is common. Antimicrobial agents with a high degree of in vitro activity include cefazolin, cefotaxime, ceftriaxone, aminoglycosides, and chloramphenicol. Therapy should be guided by clinical response and results of tests in vitro for susceptibility.

References

1. Klinger R. Untersuchungen ubermenschliche Aktinomykose Zentralbl Bakteriol (Orig.) 1912;**62**:191–200
2. Bates R. Actinomycosis. Lancet 1933;**1**:571–3
3. Bayne-Jones S. Club-formation by *Actinomyces hominis* in glucose broth, with a note on *B. actinomycetemcomitans*. J Bacteriol 1925;**10**:569–76
4. Colebrook L. The mycelial and other microorganisms associated with human actinomycosis. Br J Exp Pathol 1920;**1**:197–212
5. Colebrook L. A report upon 25 cases of actinomycosis, with especial reference to vaccine therapy. Lancet 1921;**1**:893–9
6. Holm P. Studies on the etiology of human actinomycosis. I. The "other microbes" of actinomycosis and their importance. Acta Pathol Microbiol Scand 1950;**27**:736–51
7. Holm P. Studies on the etiology of human actinomycosis. II. Do the "other microbes" of actinomycosis possess virulence? Acta Pathol Microbiol Scand 1951;**28**:391–406
8. Thjøtta T, Sydnes S. *Actinobacillus actinomycetemcomitans* the sole infecting agent in a human being. Acta Pathol Microbiol Scand 1951;**28**:27–35
9. King EO, Tatum HW. *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*. J Infect Dis 1962; **111**:85–94
10. Page MI, King EO. Infection due to *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*. N Engl J Med 1966;**275**:181–8
11. Clemens HH. Actinomycosis: report of a case in a child with recovery following thymol therapy. J Pediatr 1940; **16**:487–94
12. Goldsworthy NE. *Bacterium actinomycetemcomitans*: a description of two strains. J Pathol Bacteriol 1938; **46**:207–8
13. Klaber R. Primary cutaneous actinomycosis: with a note on the *Bacillus actinomycetemcomitans*. Br J Dermatol 1934;**46**:12–9
14. Negroni P, Bonfiglioli H. Morphology and biology of *Actinomyces israelii*. J Trop Med Hyg 1937;**40**:226–33
15. Rosebury T. The parasitic actinomycetes and other filamentous microorganisms of the mouth. Bacteriological Reviews 1944;**8**:189–223
16. Zambon JJ. *Actinobacillus actinomycetemcomitans* in human periodontal disease. J Clin Periodontol 1985;**12**:1–20
17. Weaver RE, Hollis DG, Bottone EJ. Gram-negative fermentative bacteria and *Francisella tularensis*. In: Lennette EH, Balows A, Hausler WJ Jr, Shadomy HJ, eds. Manual of clinical microbiology. 4th ed. Washington, DC: American Society for Microbiology, 1985;309–29
18. Potts TV, Zambon JJ, Genco RJ. Reassignment of *Actinobacillus actinomycetemcomitans* to the genus *Haemophilus* as *Haemophilus actinomycetemcomitans* comb. nov. International Journal of Systematic Bacteriology 1985;**35**:337–41
19. Report of the International Committee on Systematic Bacteriology, Subcommittee on Pasturellaceae and Related Organisms. International Journal of Systematic Bacteriology 1987;**37**:474
20. Holm P. The influence of carbon dioxide on the growth of *Actinobacillus actinomycetemcomitans*. Acta Pathol Microbiol Scand 1954;**34**:235–48
21. van Steenbergen TJM, van Winkelhoff AJ, van der Mispel L, van der Velden U, Abbas F, de Graaff J. Comparison of two selective media for *Actinobacillus actinomycetemcomitans*. J Clin Microbiol 1986;**24**:636–8
22. Slots J. Selective medium for isolation of *Actinobacillus actinomycetemcomitans*. J Clin Microbiol 1982;**15**:606–9
23. Dibbs WL, Digranes A, Tonjum S. *Actinobacillus lignieresii* infection after a horse bite. Br Med J 1981;**283**:583–4
24. Friis-Moller A. A new *Actinobacillus* species from the human respiratory tract: *Actinobacillus hominis*. In: Kilian

M, Frederidson W, Biberstein EL, eds. *Haemophilus, Pasturella* and *Actinobacillus*. New York: Academic Press, 1981;151–7
25. Brondz I, Olsen I. Differentiation between *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus* based on carbohydrates in lipopolysaccharide. J Chromatogr 1984;**310**:261–72
26. Pulverer G, Ko HL. *Actinobacillus actinomycetemcomitans*: fermentative capabilities of 140 strains. Appl Microbiol 1970;**20**:693–5
27. Pulverer G, Ko HL. Serological studies of *Actinobacillus actinomycetemcomitans*. Appl Microbiol 1972;**23**:207–10
28. McArthur WP, Stroup S, Wilson L. Detection and serotyping of *Actinobacillus actinomycetemcomitans* isolates on nitrocellulose paper blots with monoclonal antibodies. J Clin Periodontol 1986;**13**:684–91
29. Zambon JJ, Slots J, Genco RJ. Serology of oral *Actinobacillus actinomycetemcomitans* and serotype distribution in human periodontal disease. Infect Immun 1983;**41**:19–27
30. Baehni P, Tsai C-C, McArthur WP, Hammond BF, Taichman NS. Interaction of inflammatory cells and oral microorganisms. VIII. Detection of leukotoxic activity of a plaque-derived gram-negative microorganism. Infect Immun 1979;**24**:233–43
31. Taichman NS, Wilton JMA. Leukotoxicity of an extract from *Actinobacillus actinomycetemcomitans* for human gingival polymorphonuclear leukocytes. Inflammation 1981; **5**:1–12
32. Taichman NS, McArthur WP, Tsai CC, Baehni PC, Shenker BJ, Berthold P, Evian C, Stevens R. Leukocidal mechanisms of *Actinobacillus actinomycetemcomitans*. In: Genco RJ, Mergenhagen SE, eds. Host-parasite interactions in periodontal disease. Washington, DC: American Society for Microbiology, 1982;261–9
33. Taichman NS, Shenker BJ, Tsai C-C, Glickman LT, Baehni PC, Stevens R, Hammond BF. Cytopathic effect of *Actinobacillus actinomycetemcomitans* on monkey blood leukocytes. J Periodont Res 1984;**19**:133–45
34. Van Dyke TE, Bartholomew E, Genco RJ, Slots J, Levine MJ. Inhibitions of neutrophil chemotaxis by soluble bacterial products. J Periodontol 1982;**53**:502–8
35. Robertson PB, Lantz M, Marucha PT, Kornman KS, Trummel CL, Holt SC. Collagenolytic activity associated with *Bacteroides species* and *Actinobacillus actinomycetemcomitans*. J Periodont Res 1982;**17**:275–83
36. Wilson M, Kamin S, Harvey W. Bone resorbing activity of purified capsular material from *Actinobacillus actinomycetemcomitans*. J Periodont Res 1985;**20**:484–91
37. Chen P, Park B, Genco RJ. Immunological profile of patients with juvenile periodontitis [abstract no. 933]. J Dent Res 1983;**62**:273
38. Ebersole JL, Frey DE, Taubman MA, Smith DJ. An ELISA for measuring serum antibodies to *Actinobacillus actinomycetemcomitans*. J Periodont Res 1980;**15**:621–32
39. Ebersole JL, Taubman MA, Smith DJ, Genco RJ, Frey DE. Human immune response to oral microorganisms and association of localized juvenile periodontitis with serum antibody responses to *Actinobacillus actinomycetemcomitans*. Clin Exp Immunol 1982;**47**:43–52
40. Johnson RJ, Matthews JL, Stone MJ, Hurt WC, Newman J. Immunopathology of periodontal disease. I. Immunological profiles in periodontitis and juvenile periodontitis. J Periodontol 1980;**51**:705–12
41. Murray PA, Genco RJ. Serum and gingival fluid antibodies to *Actinobacillus actinomycetemcomitans* in localized juvenile periodontitis [abstract no. 245]. J Dent Res 1980;**59**(Special Issue A)
42. Zambon JJ, Sammond P, Huber P, Slots J, Genco RJ. *Actinobacillus* and *Haemophilus:* serology and serum immune response in patients with periodontal disease [abstract no. 253]. J Dent Res 1983;**62**
43. Lehner T, Wilton JMA, Ivanyi C, Manson JD. Immunological aspects of juvenile periodontitis (periodontosis). J Peridont Res 1974;**9**:261–72
44. Waldrup TC, Mackler BF, Schur P, Killoy W. Immunological study of human periodontosis (peridontitis). J Periodont 1981;**52**:8–15
45. Miyaski KT, Wilson ME, Brunetti AJ, Genco RJ. Oxidative and nonoxidative killing of *Actinobacillus actinomycetemcomitans* by human neutrophils. Infect Immunol 1986;**53**:154–60
46. Fine DH, Mandel ID. Indicators of periodontal disease activity: an evaluation. J Clin Periodontol 1986;**13**:533–46
47. Slots J. Bacterial specificity in adult periodontitis: a summary of recent work. J Clin Periodontol 1986;**13**:912–7
48. Slots J, Bragd L, Wikstrom M, Dahlen G. The occurrence of *Actinobacillus actinomycetemcomitans, Bacteroides gingivalis* and *Bacteroides intermedius* in destructive periodontal disease in adults. J Clin Periodontol 1986; **13**:570–7
49. Smith DJ, Ebersole JL, Taubman MA, Gadalla L. Salivary IgA antibody to *Actinobacillus actinomycetemcomitans* in a young adult population. J Periodontol Res 1985; **20**:8–11
50. Zambon JJ, Christersson LA, Genco RJ. Diagnosis and treatment of localized juvenile periodontitis. J Am Dent Assoc 1986;**113**:295–9
51. Moore WEC, Holdeman LV, Cato EP, Smibert RM, Burmeister JA, Palcanis KG, Ranney RR. Comparative bacteriology of juvenile periodontitis. Infect Immun 1985; **48**:507–19
52. Kilian M, Schiott CR. Haemophili and related bacteria in the human oral cavity. Arch Oral Biol 1975;**20**:791–6
53. Slots J, Reynolds HS, Genco RJ. *Actinobacillus actinomycetemcomitans* in human periodontal disease: a cross-sectional microbiological investigation. Infect Immun 1980;**29**:1013–20
54. Zambon JJ, Christersson LA, Slots J. *Actinobacillus actinomycetemcomitans* in human periodontal disease: prevalence in patient groups and distribution of biotypes and serotypes within families. J Periodontol 1983;**54**:707–11
55. Bragd L, Dahlen G, Wikstrom M, Slots J. The capability of *Actinobacillus actinomycetemcomitans, Bacteroides gingivalis* and *Bacteroides intermedius* to indicate progressive periodontitis: a retrospective study. J Clin Periodontol 1987;**14**:95–9
56. Christersson LA, Slots J, Zambon JJ, Genco RJ. Transmission and colonization of *Actinobacillus actinomycetemcomitans* in localized juvenile periodontitis patients. J Periodontol 1985;**56**:127–31
57. Affias S, West A, Stewart JW, Haldane EV. *Actinobacillus*

actinomycetemcomitans endocarditis. Can Med Assoc J 1978;**118**:1256–60
58. Lalonde G, Hand R. Infective endocarditis due to *Actinobacillus actinomycetemcomitans* in a patient with a porcine prosthetic mitral valve. Can Med Assoc J 1980;**122**:316–9
59. Siegman-Igra Y, Schwartz D, Ophir O, Konforti N. Endocarditis caused by *Actinobacillus actinomycetemcomitans*. Eur J Clin Microbiol 1984;**3**:556–9
60. Wilson JH, Franco I, Keys TF. Endocarditis due to *Actinobacillus actinomycetemcomitans* of both a prosthetic valve and a native valve in the same patient. Cleve Clin Q 1986;**53**:193–5
61. Yogev R, Shulman D, Shulman ST, Glogowski WG. In vitro activity of antibiotics alone and in combination against *Actinobacillus actinomycetemcomitans*. Antimicrob Agents Chemother 1986;**29**:179–81
62. Baddour LM, Bisno AL. Infective endocarditis complicating mitral valve prolapse: epidemiologic, clinical and microbiologic aspects. Rev Infect Dis 1986;**8**:117–37
63. Finland M, Barnes MW. Changing etiology of bacterial endocarditis in the antibacterial era: experiences at Boston City Hospital 1933–1965. Ann Intern Med 1970;**72**:341–8
64. Garvey GJ, Neu HC. Infective endocarditis—an evolving disease. A review of endocarditis at the Columbia-Presbyterian Medical Center 1968–1973. Medicine 1978; **57**:105–27
65. Lowes JA, Hamer J, Williams G, Houang E, Tabaqchali S, Shaw EJ, Hill IM, Rees GM. 20 years of infective endocarditis at St. Bartholomew's hospital: analysis of clinical features and treatment in relation to prognosis and mortality. Lancet 1980;**1**:133–6
66. Pelletier LL Jr, Petersdorf RG. Infective endocarditis: a review of 125 cases from the University of Washington hospitals 1963–72. Medicine 1977;**56**:287–313
67. Weinstein MP, Stratton CW, Ackley A, Hawley HB, Robinson PA, Fisher BD, Aleid DV, Stephens DS, Reller LB. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am J Med 1985;**78**:262–9
68. Cohen PS, Maguire JH, Weinstein L. Infective endocarditis caused by gram-negative bacteria: a review of the literature, 1945–1977. Prog Cardiovasc Dis 1980;**22**:205–42
69. Calderwood SB, Swinski LA, Waternaux CM, Karchmer AW, Buckley MJ. Risk factors for the development of prosthetic valve endocarditis. Circulation 1985;**72**:31–7
70. Dismukes WE, Karchmer AW, Buckley MJ, Austen WG, Swartz MN. Prosthetic valve endocarditis: analysis of 38 cases. Circulation 1973;**48**:365–77
71. Ivert TSA, Dismukes WE, Cobbs CG, Blackstone EH, Kirklin JW, Bergdahl LAL. Prosthetic valve endocarditis. Circulation 1984;**69**:223–32
72. Masur H, Johnson WD Jr. Prosthetic valve endocarditis. J Thorac Cardiovasc Surg 1980;**80**:31–7
73. Slaughter L, Morris JE, Starr A. Prosthetic valvular endocarditis—a 12 year review. Circulation 1973;**47**:1319–26
74. Wilson WR, Jaumin PM, Danielson GK, Giuliani ER, Washington JA II, Geraci JE. Prosthetic valve endocarditis. Ann Intern Med 1975;**82**:751–6
75. Ah Fat LNC, Patel BR, Pickens S. *Actinobacillus actinomycetemcomitans* in hypertrophic obstructive cardiomyopathy. J Infect 1983;**6**:81–4
76. Anolik R, Berkowitz RJ, Campos JM, Friedman AD. *Actinobacillus actinomycetemcomitans* endocarditis associated with periodontal disease. Clin Pediatr 1981;**20**: 653–5
77. Blair TP, Seibel J Jr, Oldfield E, Berg SW, Karney W, Barker WP. Endocarditis caused by *Actinobacillus actinomycetemcomitans*. South Med J 1982;**75**:559–61
78. Block PJ, Fox AC, Yoran C, Kaltman AJ. *Actinobacillus actinomycetemcomitans* endocarditis: report of a case and a review of the literature. Am J Med Sci 1973;**266**:387–92
79. Boulton-Jones JM, Sissons JGP, Evans DJ, Peters DK. Renal lesions of subacute infective endocarditis. Br Med J 1974;**2**:11–4
80. Chalmers BE, Rosenbaum JT, Fraunfelder FT, Cowger RC. Iris manifestations of bacterial endocarditis. Arch Ophthalmol 1986;**104**:1548–9
81. Chong Y, Lee KW, Lee SY, Cho SY. Isolation of *Actinobacillus actinomycetemcomitans* from the blood of a patient with subacute bacterial endocarditis. Yonsei Med J 1983;**24**:54–8
82. Chowdury MNH, Al-Nozha M, Husain IS, Akhtar J. Endocarditis due to *Actinobacillus actinomycetemcomitans*. J Infect 1985;**10**:158–62
83. Davis M, Gratten M, Ree GH. Infective endocarditis caused by *Actinobacillus actinomycetemcomitans* and *Achromobacter xylosoxidans*. Papua New Guinea Med J 1982; **25**:7–11
84. Dibbs WL, Halstensen A, Sorheim JI. *Actinobacillus actinomycetemcomitans* endocarditis. J Infect 1983;**7**:168–9
85. Donzis PB, Rappazzo JA. Endogenous *Actinobacillus actinomycetemcomitans* endophthalmitis. Ann Ophthalmol 1984;**16**:858–60
86. Ellner JJ, Rosenthal MS, Lerner PI, McHenry MC. Infective endocarditis caused by slow-growing, fastidious, gram-negative bacteria. Medicine 1979;**58**:145–58
87. Eng RHK, Smith SM, Goldstein EJ, Miyasaki KT, Quah E-S, Buccini F. Failure of vancomycin prophylaxis and treatment for *Actinobacillus actinomycetemcomitans* endocarditis. Antimicrob Agents Chemother 1986;**29**: 699–700
88. Felius A, Fleer A, Moulaert A. *Actinobacillus actinomycetemcomitans* endocarditis in a child with a prosthetic heart valve. Infection 1984;**12**:260–1
89. Geraci JE, Wilson WR, Washington JA II. Infective endocarditis caused by *Actinobacillus actinomycetemcomitans*—report of four cases. Mayo Clin Proc 1980;**55**:415–9
90. Goss JE, Gutin RS, Dickhaus DW. Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. Am J Med 1967;**43**:636–8
91. Gould L, Gopalaswamy C, Kim BS, Patel C, Freiberg K. Infectious endocarditis caused by *Actinobacillus actinomycetemcomitans*. Angiology 1985;**36**:64–6
92. Hansen W, Glupczynski Y, Lemper JC, Yourassowsky E. Infective endocarditis due to *Actinobacillus actinomycetemcomitans*. Acta Clin Belg 1984;**39**:97–102
93. Hirsh PD, Nixon JV. Right-sided native valve endocarditis caused by *Actinobacillus actinomycetemcomitans*. Chest 1983;**84**:494–5

94. Hofstad T, Stallemo A. Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. Scand J Infect Dis 1981;**13**:78–9
95. Ishak MA, Zablit KV, Dumas J. Endogenous endophthalmitis caused by *Actinobacillus actinomycetemcomitans*. Can J Ophthalmol 1986;**21**:284–6
96. Juffe A, Miranda AL, Rufilanchas JJ, Maronas JM, Figuero D. Prosthetic valve endocarditis by opportunistic pathogens. Arch Surg 1977;**112**:151–3
97. Lass JH, Varley MP, Frank KE, Speck WT. *Actinobacillus actinomycetemcomitans* endophthalmitis with subacute endocarditis. Ann Ophthalmol 1984;**16**:54–61
98. Macklon AF, Ingham HR, Selkon JB, Evans JG. Endocarditis due to *Actinobacillus actinomycetemcomitans*. Br Med J 1975;**1**:609–10
99. Mauff AC, Miller S, Kuhnle V, Carmichael M. Infections due to *Actinobacillus actinomycetemcomitans*. S Afr Med J 1983;**63**:580–1
100. Mitchell RG, Gillespie WA. Bacterial endocarditis due to an actinobacillus. J Clin Pathol 1964;**17**:511–2
101. Moorthy K, Prakash R, Aronow WS. Endocardiographic appearance of aortic valve vegetations in bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. JCU 1977;**5**:49–51
102. Overholt F. *Actinobacillus actinomycetemcomitans* endocarditis. Arch Intern Med 1966;**117**:99–102
103. Panwalker AP, Akalin HE, Zimelis V, Jackson GG. *Actinobacillus actinomycetemcomitans* endocarditis in a patient with a prosthetic aortic valve. Infection 1977;**5**:104–6
104. Peters J, Robinson F, Dasco C, Gentry LO. Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. Am J Med Sci 1983;**286**:35–41
105. Peirce CS, Bartholomew WR, Amsterdam D, Neter E, Zambon JJ. Endocarditis due to *Actinobaciilus actinomycetemcomitans* serotype C and patient immune response. J Infect Dis 1984;**149**:479
106. Reider J, Wheat J. Endocarditis caused by *Actinobacillus actinomycetemcomitans*. South Med J 1979;**72**:1219–20
107. Schack SH, Smith PW, Penn RG, Rapoport JM. Endocarditis caused by *Actinobacillus actinomycetemcomitans*. J Clin Microbiol 1984;**20**:579–81
108. Serra P, Tonato M. Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. Am J Med 1969;**47**:809–12
109. Shah GM, Winer RL. Glomerulonephritis associated with endocarditis caused by *Actinobacillus actinomycetemcomitans*. Am J Kidney Dis 1981;**1**:113–5
110. Stauffer JL, Goldman MJ. Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans* in a patient with a prosthetic aortic valve. California Medicine 1972;**117**:59–63
111. Stockman K, McKinnon G, Bower S, Davidson A. *Actinobacillus endocarditis*. Med J Aust 1985;**143**:130–1
112. Symbas PN, Schlant RC, Hatcher CR, Lindsay J. Congenital fistula of right coronary artery to right ventricle complicated by *Actinobacillus actinomycetemcomitans* endarteritis. J Thorac Cardiovasc Surg 1967; **53**:379–84
113. Thomas JR. *Actinobacillus actinomycetemcomitans* endocarditis in a patient with bicuspid aortic valve and coarctation of the aorta. South Med J 1967;**60**:783–4
114. Underhill EE. Endocarditis due to *Actinobacillus actinomycetemcomitans*. Canadian Journal of Medical Technology 1968;**30**:125–7
115. Vandepitte J, Decraene P, Kesteloot H, Maris J, Eyckmans L. Bacterial endocarditis caused by *Actinobacillus actinomycetemcomitans*. Acta Clin Belg 1970;**25**:109–15
116. Vandepitte J, DeGeest H, Jousten P. Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. J Clin Pathol 1977;**30**:842–6
117. Vogelzang RM. Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. Arch Intern Med 1967;**120**:99–101
118. Wilson APR, Scott GM, Prouse PJ, Gumpel JM, Shah LP, Webster ADB. Endocarditis with a rare parvobacillus: host response and difficulty in diagnosis. J R Soc Med 1984;**77**:1048–50
119. Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. Harrison's principles of internal medicine. 10th ed. New York: McGraw-Hill, 1983:A1–9
120. Lane T, Goings S, Fraser GW, Ries K, Pettrozzi J, Abrutyn E. Disseminated actinomycosis with spinal cord compression: report of two cases. Neurology 1979;**29**:890–3
121. Burgher LW, Loomis GW, Ware F. Systemic infection due to *Actinobacillus actinomycetemcomitans*. Am J Clin Pathol 1973;**60**:412–5
122. Ingham HR, High AS, Kalbag RM, Sengupta RP, Tharagonnet D, Selkon JB. Abscesses of the frontal lobe of the brain secondary to covert dental sepsis. Lancet 1978;**2**:497–9
123. Martin BF, Derby BM, Budzilovich GN, Ransohoff J. Brain abscess due to *Actinobacillus actinomycetemcomitans*. Neurology 1967;**17**:833–7
124. Garland SM, Prichard MG. *Actinobacillus actinomycetemcomitans* causing a mediastinal abscess. Thorax 1983;**38**:472–3
125. Peel MM, Rich AM, Reade PC. *Actinobacillus actinomycetemcomitans* infection in the oral cavity. Oral Surg 1981;**52**:591–3
126. Horowitz EA, Pugsley MP, Turbes PG, Clark RB. Pericarditis caused by *Actinobacillus actinomycetemcomitans*. J Infect Dis 1987;**155**:152–3
127. Carlile JR, Beckman EN, Arensman RM. *Actinobacillus actinomycetemcomitans* pneumonia. Clin Pediatr 1984;**23**:578–80
128. Meyers BR, Buttone E, Hirschman SZ, Schneierson SS, Gershengorn K. Infection due to *Actinobacillus actinomycetemcomitans*. Am J Clin Pathol 1971;**56**:204–11
129. Muhle I, Rau J, Ruskin J. Vertebral osteomyelitis due to *Actinobacillus actinomycetemcomitans*. JAMA 1979;**241**:1824–5
130. Bromley GS, Solender M. Hand infection caused by *Actinobacillus actinomycetemcomitans*. J Hand Surg 1986;**11A**:434–6
131. Patel PK, Seitchik MW. *Actinobacillus actinomycetemcomitans:* a new cause for granuloma of the parotid gland and buccal space. Plast Reconstr Surg 1986;**77**:476–8
132. Fenichel S, Bodino C, Kocka F. Isolation of *Actinobacillus actinomycetemcomitans* from a skin lesion. Eur J Clin Microbiol 1985;**4**:428–30

133. Townsend T, Gillenwater JY. Urinary tract infection due to *Actinobacillus actinomycetemcomitans*. JAMA 1969; **210**:558
134. Sakazaki R, Yoshizaki E, Tamura K, Kuramochi S. Increased frequency of isolation of *Pasteurella* and *Actinobacillus* species and related organisms. Eur J Clin Microbiol 1984;**3**:244–8
135. Thornsberry C, Anhalt J, Barry AL, Gerlack EH, Hossom J, Jones RN, Matson JM, Moellering RC, Nortan R. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards 1983;**3**:67
136. Hoffler U, Niederau W, Pulverer G. Susceptibility of *Bacterium actinomycetemcomitans* to 45 antibiotics. Antimicrob Agents Chemother 1980;**17**:943–6
137. Slots J, Evans RT, Lobbins PM, Genco RJ. In vitro antimicrobial susceptibility of *Actinobacillus actinomycetemcomitans*. Antimicrob Agents Chemother 1980;**18**: 9–12
138. Gordon JM, Walker CB, Murphy JC, Goodson JM, Socransky SS. Tetracycline: levels achievable in gingival crevice fluid and in vitro effect on subgingival organisms. Part I. Concentration in crevicular fluid after repeated doses. J Periodontol 1981;**52**:609–13
139. Slots J, Rosling BG, Genco RJ. Suppression of penicillin-resistant oral *Actinobacillus actinomycetemcomitans* with tetracycline: considerations in endocarditis prophylaxis. J Periodontol 1983;**54**:193–6
140. American Heart Association Committee Report. Prevention of bacterial endocarditis. Circulation 1977;**56**:139A–43A