CLINICAL INFECTIOUS DISEASE ARTICLES

Enterococcal Endocarditis: A Comparison of Prosthetic and Native Valve Disease

Louis B. Rice, Stephen B. Calderwood, George M. Eliopoulos, Bruce F. Farber, and Adolf W. Karchmer

From the Infectious Disease Sections, Departments of Medicine, New England Deaconess Hospital and Massachusetts General Hospital, Boston, Massachusetts; and North Shore University Hospital, Manhasset, New York

Between 1973 and 1987, 36 patients with 41 episodes of enterococcal endocarditis were seen at our institution. There were 22 episodes of native valve endocarditis (NVE) and 19 episodes of prosthetic valve endocarditis (PVE). The overall mortality before completion of therapy was 15% (18% due to NVE and 11% due to PVE). Among patients with NVE, involvement of the aortic valve was significantly associated with death or complicated illness (defined as the need for valve replacement before completion of antibiotic therapy or relapse of endocarditis after completion of therapy). Among patients who survived episodes of PVE, 69% were cured without surgical intervention. Gentamicin was administered in combination with a penicillin or vancomycin in the majority of episodes (mean duration of therapy with aminoglycosides: 5 weeks). Renal dysfunction occurred in 44% of patients who received gentamicin and occurred more frequently in patients with elevated serum creatinine levels before treatment. Our results suggest that enterococcal PVE can often be successfully treated with antibiotics alone, and they confirm the efficacy of gentamicin when it is administered in combination with cell wall–active agents for the treatment of endocarditis due to enterococci that lack high-level resistance to this agent.

Although it is by now well accepted that effective antimicrobial treatment of enterococcal endocarditis requires the combination of a cell wall–active agent and an aminoglycoside, the relative efficacy of different aminoglycosides and the optimal duration of their use remain matters of debate [1, 2]. In addition, while earlier studies have included variable numbers of patients with enterococcal prosthetic valve endocarditis (PVE) [1–3], either the numbers have been small or the data for this subgroup of patients were not analyzed separately, which resulted in incomplete information on which to base therapeutic decisions regarding patients with this condition.

In order to better define the efficacy of gentamicin as the aminoglycoside used in combination therapy for enterococcal endocarditis and to describe the clinical course and response to treatment of enterococcal PVE, we reviewed all cases of enterococcal endocarditis that occurred at the Massachusetts General Hospital over a 14-year period.

Materials and Methods

Case identification and criteria for acceptance. Cases were identified by review of diagnoses from hospital discharge records, records from the infectious disease service, and data from the clinical microbiology laboratory. Cases were classified as enterococcal endocarditis if at least two blood cultures or cultures of valvular specimens were positive for enterococci and the patients presented with a clinical syndrome suggestive of endocarditis (fever with a pathologic cardiac murmur, evidence of peripheral or pulmonary embolization, or splenomegaly) or if the histopathology of the patients' valves was consistent with the diagnosis of endocarditis. Cases in which there was another identifiable focus of enterococcal infection were eliminated from consideration. One case of polymicrobial bacteremia was accepted because the number of blood cultures that yielded enterococcus (six) substantially exceeded the number of cultures (two) that yielded a second organism (*Candida albicans*).

Follow-up information was obtained from patients' hospital records, from conversations with primary physicians, and, when necessary, from patients or their families.

Definitions. Cure was defined as successful initial therapy that was followed by at least 6 months of disease-free survival. Recurrent episodes of enterococcal endocarditis were defined as relapses if they occurred within one year of completion of therapy for the initial episode and as reinfection if they occurred >1 year beyond completion of therapy.

Renal dysfunction was defined as an increase in serum creatinine >0.5 mg/dL above the patient's baseline value in association with aminoglycoside therapy. In many cases, the etiology of diminished renal function was probably multifactorial. No effort was made to distinguish between different etiologies of diminished renal function.

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Please address requests for reprints to Dr. Adolf W. Karchmer, Infectious Disease Section, New England Deaconess Hospital, 185 Pilgrim Road, Boston, Massachusetts 02215.

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Organism identification. Identification of isolates was performed at the Massachusetts General Hospital's Clinical Microbiology Laboratory. Identification of enterococci before 1982 was accomplished by standard methods [4]. Isolates were not routinely identified by species during this period. Identification since 1982 has been performed with the use of the Vitek antimicrobial system (Vitek Systems, Inc., Hazelwood, Mo.). When necessary, confirmation of species identification was carried out with API rapid strep strips (Analytab Products, Plainview, N.Y.).

Statistical analysis. The χ^2 test, Fisher's exact test, and Student's *t*-test were used to compare numeric variables.

Results

From the available medical records, we identified 36 patients who experienced 41 episodes of enterococcal endocarditis between November 1973 and September 1987. Nineteen episodes of PVE occurred in 15 patients, and 22 episodes of native valve endocarditis (NVE) were diagnosed for 21 patients. There were 22 men (six with PVE) and 14 women (nine with PVE) in the study. The mean age of the men was 67 years (range, 42–88), and that of the women was 73 years (range, 36–78).

Clinical data. Predisposing valvular heart disease was identified for 14 (67%) of 21 patients with NVE. Rheumatic heart disease and aortic stenosis were the most common abnormalities (table 1). For patients with PVE, the mean duration of time from valve replacement to onset of symptoms was 4.83 years (range, 6 months to 15 years). A presumed portal of entry was identified in 75% of the patients, with the most common entry site being the gastrointestinal tract (nonmalignant lesions, 32%; malignant or premalignant lesions, 17%), the urinary tract, or site of instrumentation (29%). Wounds resulting from dental manipulation (12%) and abdominal surgery (2%) were uncommon portals of entry. The female genital tract was not believed to be the portal of entry for any female patient.

The most common presenting complaint was fever (88%), followed by anorexia (54%), chills (39%), and sweats (34%). Twenty-four percent of patients had congestive heart failure that was noted at the time of presentation. The mean duration of symptoms for all episodes was 23.6 days (range, 1–120 days); in 18 (44%) of episodes, hospitalization occurred within 10 days of the onset of symptoms. Only one patient presented with symptoms that lasted >3 months. This patient was cured of NVE with a 32-day course of penicillin and gentamicin. Analysis of symptom duration by type of endocarditis (NVE or PVE) revealed that patients with NVE had symptoms, on the average, approximately twice as long as patients with PVE (31.2 vs. 17.4 days) ($P = .214$).

Complications of endocarditis that occurred during the 40 assessable episodes of illness (one episode was excluded because the patient died on day 3 of hospitalization without receiving treatment) included a new heart murmur in 22 (55%); new-onset congestive heart failure (CHF) in 13 (32.5%); systemic emboli in six (15%), five of which involved the CNS; and new-onset heart block in three (7.5%).

Table 1. Predisposing valvular abnormalities in patients with enterococcal endocarditis.

Predisposing abnormality	No. of episodes
Prosthetic valve	19
Native valve	22
Rheumatic heart disease	6
Aortic stenosis	5
Mitral regurgitation/prolapse	2
Bicuspid aortic valve	1
No identifiable disease	8

Microbiology. In 17 episodes the isolates were identified merely as enterococci. In the remaining 24 episodes, 21 (87.5%) isolates were identified as *Enterococcus faecalis* and three (12.5%) were identified as *Enterococcus faecium*.

MICs for various antimicrobial agents were not determined routinely for enterococcal isolates during the period of the study.

Treatment and outcome. Treatment was initiated in 40 of the 41 episodes of endocarditis. (As noted above, one patient with relapse of PVE died after 3 days of progressive CHF without receiving antibiotic therapy. This patient's episode is included in the analysis of presenting complaints but excluded from all analyses of clinical course, treatment, and outcome; this results in a denominator of 40 [22 NVE, 18 PVE] episodes for these variables.) Each of the 40 patients received a cell wall–active agent in combination with an aminoglycoside. The choice of cell wall–active agents varied. Penicillin was used in 18 episodes, and vancomycin or ampicillin was used in four and two episodes, respectively. In the remaining 16 cases, several of these cell wall–active agents were used in sequence. The cell wall–active antimicrobial agents were administered iv in intermittent doses; penicillin doses ranged from 20 to 30 million U/d and ampicillin from 8 to 12 g/d. Therapy with vancomycin was initiated at a dosage of 2 g/d; doses were subsequently adjusted to maintain therapeutic serum levels. The mean duration of therapy with a cell wall–active agent was 5.5 weeks (5.4 for NVE and 5.6 for PVE). Streptomycin was administered im to three patients. Gentamicin was administered im to four patients. For the remaining patients, gentamicin, tobramycin, or amikacin was administered intravenously. Doses were adjusted to maintain serum concentrations within the standard therapeutic range for the respective agent. The mean dose of gentamicin was 220 mg/d.

The mean duration of therapy with aminoglycosides was 5.0 weeks (4.9 for NVE and 5.3 for PVE). Among the patients who survived, only two (one with NVE and one with PVE) received <4 weeks of treatment with aminoglycosides. Therapy was discontinued after 17 and 19 days in these cases

as a result of marked rises in serum creatinine levels. Therapy with cell wall–active agents was continued, and the two patients were cured without surgery after completion of 4- and 5-week courses of therapy, respectively.

The outcome of therapy for enterococcal endocarditis was analyzed for 40 episodes (table 2). The one patient with PVE who was not treated is omitted from this analysis. Data on follow-up that continued for at least 6 months or until relapse occurred were available for 33 of the 34 episodes in which patients survived therapy.

Native valve endocarditis. During 22 episodes of NVE, four patients (18%) died before completion of therapy. One patient died on day 10 of therapy; at autopsy a myocardial abscess was found. Two patients died of unexplained cardiac arrest (postmortem examinations were refused) after 4 weeks of therapy. Blood cultures had been sterile before death. On day 18 of therapy, the fourth patient died of pneumonia due to infection with *Klebsiella pneumoniae* and *Staphylococcus aureus* after aortic valve replacement. Eighteen (82%) of 22 patients survived therapy and were discharged from the hospital. Three of the 12 patients who survived after treatment with antibiotics alone did not meet the criteria for cure. One had a relapse of endocarditis, one died of CHF 1 month after completion of therapy, and one patient was lost to follow-up 1 month after discharge from the hospital. All six of the patients who survived after therapy with antibiotics plus valve replacement were considered cured at follow-up 6 months later.

Six patients with infected aortic valves required semiemergent surgery before completion of a course of antibiotics. Indications for surgery were progressive heart failure in four patients, progressive heart failure and persistent fever in one, and new-onset left bundle-branch block and cerebral emboli in one. For all six patients, inspection of the valves revealed extensive vegetations. Myocardial abscesses were found in the patients with persistent fever and new-onset left bundle-branch block. Specimens of the vegetations from three of these six patients were cultured, and each yielded enterococci. These patients had received 28 days, 20 days, and 7 days of therapy with penicillin-gentamicin. In a seventh patient who required surgery, the mitral valve was replaced after 6 weeks of therapy with penicillin and gentamicin. The excised mitral valve was sterile.

The one relapse of NVE occurred 8 months after a 6-week course of penicillin and gentamicin and shortly after a colonoscopic examination. The isolates from each episode were not compared to determine if they were the same strain. The patient was cured with a second 6-week course of penicillin and gentamicin.

The aortic valve was involved in 13 episodes of NVE and the mitral valve in five episodes. In four episodes, valve involvement was indeterminate. Endocarditis resulted in death or a need for valve replacement before completion of antibiotic therapy in nine of 13 patients with aortic valve infection versus none of the five with mitral valve disease ($P = .035$, χ^2 test).

Table 2. Survival of patients with enterococcal endocarditis after initial hospitalization and therapy.

Mode of therapy	No. of patients who survived/no. who died after indicated type of episode: NVE (n = 22)	PVE (n = 18*)	Total (n = 40)
Antibiotic therapy only	12†/3	13‡/1	25/4
Antibiotic therapy plus surgery	6/1	3/1	9/2

* One episode not included due to patient's death 3 days after hospitalization.
† One patient relapsed, one patient was lost to follow-up after discharge, and one patient died 1 month after discharge.
‡ Three patients relapsed.

Prosthetic valve endocarditis. Among 18 episodes of enterococcal PVE, two patients (11%) died before completion of therapy. Of these 18 episodes, one patient's episode is omitted from this analysis of clinical course, treatment, and outcome due to lack of treatment and death on day 3 of hospitalization. One patient died of progressive multisystem failure after replacement of an infected aortic valve. The second patient's death was attributed to progressive deterioration of a neurologic condition that predated her endocarditis. This patient also had two blood cultures that were positive for *C. albicans*. In 16 (89%) of 18 episodes, the patients survived therapy and were discharged from the hospital; 13 of these patients (72% of 18 PVE episodes) were cured. Three were cured with valve replacement plus antibiotic therapy. For one patient, an infected porcine aortic valve was replaced after 44 days of therapy with vancomycin and gentamicin because of severe aortic insufficiency and congestive heart failure. This patient received 21 days of therapy with vancomycin and gentamicin postoperatively. One fenestrated valve leaflet and one flail valve leaflet were found at surgery in addition to a paravalvular abscess cavity. The second patient's endocarditis was diagnosed when cultures performed on a Starr-Edwards mitral valve that was replaced to relieve valve obstruction yielded enterococci. This patient was cured with a 4-week course of penicillin and gentamicin. The third patient who relapsed after antibiotic therapy for PVE that involved a Bjork-Shiley tricuspid valve underwent surgery after 18 days of treatment with gentamicin plus either ampicillin or vancomycin. Cultures of valvular vegetations yielded enterococci. This patient received vancomycin treatment for 12 days postoperatively.

Among the 13 episodes in which patients were treated with antibiotics alone, 10 patients were cured and three relapsed. For one patient, relapse of infection of the aortic valve occurred 5 months after a 6-week course of penicillin and gentamicin; the patient was cured with a 40-day course of the same antibiotics. This patient became infected 2 years later, at which time small-cell carcinoma of the lung was also diag-

nosed. He was then treated with a 4-week course of gentamicin in combination with penicillin or vancomycin; however, he relapsed 10 days after completion of treatment and died without additional therapy for endocarditis. The third patient experienced relapse 2.5 months after a 6-week course of ampicillin and gentamicin for endocarditis that involved a Bjork-Shiley tricuspid valve. This relapse was successfully treated with antibiotics and valve replacement (see the above discussion of the third patient who was cured surgically).

The aortic valve was involved in 13 episodes, the mitral valve in four, and the tricuspid in two. No correlation between valve location and complications of endocarditis or response to therapy was found.

Prognostic factors. Death, need for surgery, and relapse all represented a bad outcome. We examined the appearance of new regurgitant murmurs and CHF as prognostic factors in the 39 patients with follow-up for ≥6 months or until relapse or death. Of the patients who developed both a new regurgitant murmur and CHF, 10 (83%) of 12 had a bad outcome (4/4 PVE, 6/8 NVE). In contrast, of 14 who presented with neither sign, only five (35.7%) had a bad outcome ($P = .04$, χ^2 test). Of those with a new murmur but no CHF, four (36.4%) of 11 had a bad outcome, while neither of two patients who had CHF but no regurgitant murmur had a bad outcome.

Toxicity. Increases in patients' serum creatinine concentration that were >0.5 mg/dL above the pretherapy concentration occurred in 18 (45%) of the 40 episodes. In 17 of these episodes, the increases occurred while the patient was being treated with gentamicin, and in one the increase occurred during therapy with streptomycin. Among patients treated with gentamicin, a comparison of patients who experienced significant elevations in concentrations of serum creatinine with those who did not revealed no difference in the mean initial dose (220 mg/d for patients with increased serum creatinine concentration vs. 219 mg/d in those without). The average baseline concentration of serum creatinine was higher in the group that experienced deterioration in renal function (1.5 mg/dL) compared to the group that did not (1.16 mg/dL) ($P = .015$, Student's t-test). Among patients who were treated with only one cell wall–active agent, the incidence of renal dysfunction was not significantly increased among patients who received the combination of vancomycin with gentamicin as compared to those treated with the combination of penicillin and gentamicin (three of four [75%] vs. six of fifteen [40%], respectively; $P = .495$, Fisher's exact test). The reversibility of renal dysfunction was not assessable for two patients (one died and the other's follow-up did not include repeated creatinine determinations). Of those patients for whom follow-up data were available, elevations in creatinine concentrations were reversible in all cases (in most instances they returned to baseline values). One patient suffered irreversible toxicity to the aural vestibule while being treated with vancomycin and gentamicin.

Discussion

The epidemiology of enterococcal endocarditis has changed over the years, apparently as a result of a decrease in the number of young women who suffer from the infection. The average age of women in the study by Mandell et al. in 1970 was 37 years [5]. More recent series have shown an increased mean age overall, particularly for women [1, 2]. Our study confirms this trend; a possible explanation is the absence of pelvic infection or pelvic surgery as a predisposing factor. The absence of either of these factors may have resulted from changes in surgical technique, use of prophylactic antibiotics, or underlying differences between patient populations at different institutions. Alternatively, the increased age of our female patients may be the result of the high percentage (65%) of patients with PVE in this group.

Our study confirms the general impression that enterococcal endocarditis is a disease that occurs in the setting of prior valvular damage, usually with an identifiable risk factor for the development of bacteremia. Sixty-four percent of patients with NVE in our study had preexisting valvular abnormalities; rheumatic heart disease and aortic stenosis were the most prevalent. Sixty-eight percent of episodes occurred in patients with known predisposing causes for development of enterococcal bacteremia, most commonly gastrointestinal or genitourinary lesions or procedures. The 17% incidence of malignant or premalignant gastrointestinal lesions found among these patients is comparable to that seen with viridans streptococcal endocarditis [6] but considerably less than that noted with endocarditis due to *Streptococcus bovis* Type I [6].

In prior studies of NVE due to enterococci, mortality has ranged from 9% to 43%, with most studies reporting mortality of <20% [1–3, 5]. Moellering et al. noted that mortality was more often due to the severity of the patient's underlying disease than to uncontrolled infection [3]. It seems likely that the same is true in our study, in which only one of four deaths was associated with persistent enterococcal infection.

The association of aortic valve infection with an increased frequency of complicated endocarditis noted in our study highlights both the aggressive nature of this infection and the importance of an intact aortic valve in the maintenance of hemodynamic stability. Among patients with aortic NVE, nine (69%) of 13 either died or required emergent surgery, compared to none of the five with infection of the mitral valve. The high incidence of enterococcal NVE (32%, or 7 patients of 22 episodes) that required surgical intervention might be explained by the fact that Massachusetts General Hospital is a major referral center. In fact, five of the seven patients who underwent surgery were referred for that purpose. Of note, however, was the fact that no patients with mitral NVE due to enterococci were referred to our hospital for valve replacement. Furthermore, of the eight patients with aortic valve disease admitted directly to the hospital, two died and one underwent emergent valve replacement. Thus, although referral patterns may influence the frequency of surgical therapy

among our patients, these patterns do not explain the observed difference in the need for emergent surgical intervention between patients with aortic and mitral valve disease.

The 32% rate of surgery among our patients with NVE corresponds with that noted in a prior study in which surgical intervention is detailed [2]. The 83% cure rate associated with emergent valve replacement (five of six patients) and the absence of relapse, even for three patients whose cultures of valvular specimens yielded enterococci, suggest that replacement of an actively infected valve under the coverage of appropriate antibiotics is an effective and safe mode of therapy. The duration of preoperative antibiotic therapy should carry little weight in the determination of the optimal time for surgical intervention. Surgery to cure persistent infection or to halt deterioration of hemodynamic function should not be delayed to allow administration of additional preoperative antibiotic therapy.

The retrospective nature of our study and the relative uniformity of the antibiotic regimens do not permit comparative evaluations of different treatment regimens. Similarly, the lack of data on high-level resistance to aminoglycosides among the organisms that cause endocarditis prevents assessment of the adequacy of gentamicin-containing regimens for the treatment of endocarditis caused by strains that are highly resistant to streptomycin; the adequacy of such regimens has been questioned in a prior study [1]. Prior studies have shown a 54% rate of high-level resistance to streptomycin (>2,000 μg/mL) among enterococcal isolates at Massachusetts General Hospital [7]. High-level resistance to gentamicin was not recognized at our institution until after the period of study. Therefore, we suspect that the enterococci that caused endocarditis in our patients were susceptible to gentamicin but often resistant to streptomycin. The 72% cure rate in our study is comparable to rates reported by Wilson et al. (79%) and Herzstein et al. (73%) [1, 2]. Similarly, our rate of relapse is virtually identical to the 12.5% and 12% rates reported in the above-noted studies, respectively. These data suggest that gentamicin-containing regimens are effective in the treatment of endocarditis due to enterococci that do not possess high-level resistance to gentamicin.

Earlier studies have either included few cases [1, 3] or limited analysis [2] of the clinical course and response to therapy of patients with enterococcal PVE. Our cases of enterococcal PVE would be classified as late-onset infections that occur >60 days after valve replacement. Although early studies reported a mortality of 45% associated with late-onset PVE [8, 9], studies of more recent episodes of PVE have cited a mortality of 21% and have attributed much of the improvement in survival to more-aggressive surgical intervention [10]. For late-onset PVE that is due to a variety of organisms and is treated with medical therapy alone, mortality ranges from 31% to 70% [11]. In this setting, the low overall mortality in our series (two [11%] of 18 patients) and in particular among the subgroup treated with medical therapy alone (one [7%] of 14 patients) is notable. These data suggest that the course of enterococcal PVE is more comparable to that of PVE caused by less destructive organisms, such as fastidious gram-negative rods and viridans streptococci, than to that of PVE due to staphylococci and enteric gram-negative bacilli. Since cure rates with medical therapy alone for enterococcal PVE are relatively high, surgical intervention plays a less prominent role in successful management.

It is curious that the same organism that produces such aggressive disease on native aortic valves should respond so readily to medical therapy alone when it infects prosthetic valves. One possible explanation is the prolonged symptomatic period prior to diagnosis observed for patients with native valve disease. The mean duration of symptoms prior to diagnosis for the PVE group was 17.4 days, approximately half the mean duration of symptoms (31.2 days) prior to the establishment of the diagnosis for patients with enterococcal NVE. Although this difference is not statistically significant, the trend toward earlier diagnosis for patients with PVE reflects a heightened awareness of the risk of this disease among patients who comprise this subpopulation and may explain the apparent difference in severity of disease between enterococcal PVE and NVE. An earlier study suggested that a prolonged duration of symptoms prior to diagnosis is associated with an increased incidence of relapse and death [1].

The incidence of renal dysfunction among patients who received gentamicin in our study (44%) is comparable to the incidence reported by Wilson et al. (60%) [1]. We were unable to define a relationship between the dose of gentamicin and renal dysfunction, which may merely reflect the relative uniformity of the dosages of gentamicin in our study. Increases in serum creatinine concentration did occur more commonly in patients with preexisting, underlying renal dysfunction as defined by the serum creatinine level at admission to the hospital.

An emerging issue in the treatment of enterococcal infection that is not addressed by the findings of this study is the growing prevalence of enterococcal strains that are highly resistant to currently available aminoglycosides. These strains are characteristically resistant to the synergistic bactericidal action of cell wall–active agents and aminoglycosides, a factor likely to be of considerable significance in the treatment of infections, such as endocarditis, when bactericidal therapy is required. One center has reported high-level resistance to gentamicin in 55% of strains studied [12], and reports of cases of endocarditis due to enterococci that are highly resistant to gentamicin are beginning to appear in the literature [13, 14]. Our experience in the treatment of a patient with endocarditis due to one of these strains is instructive.

A 40-year-old man was admitted to a hospital for treatment of renal failure presumably due to poststreptococcal glomerulonephritis. His initial course was complicated by enterococcal bacteremia associated with the placement of a temporary hemodialysis catheter. The bacteremia was suppressed by

treatment with chloramphenicol but recurred when treatment was discontinued. He was given a 5.5-week course of ampicillin and gentamicin, and adequate serum bactericidal levels (1:64, trough) were documented. Three and one-half weeks after the completion of therapy, enterococcal bacteremia recurred, so he was transferred to our hospital. The isolate from his blood was highly resistant to all aminoglycosides tested (MIC, >2,000 μg/mL) but was susceptible to ampicillin (MIC, 1 μg/mL). During the first week of therapy, he developed CHF that worsened due to aortic insufficiency. He underwent aortic valve replacement followed by 5 weeks of continuous infusion of ampicillin (110 mg/h; serum ampicillin level, 18–20 mg/L). Culture of the excised valve yielded enterococci with susceptibilities identical to those of the initial isolate. He is currently well, without any signs of relapse, >1 year after surgery.

This case amply demonstrates the difficulty associated with the treatment of enterococcal endocarditis with bacteriostatic antimicrobial agents and evokes memories of the era before it was recognized that bactericidal synergism could be achieved by the combination of penicillin and streptomycin, an era when treatment with penicillin alone was associated with unacceptable cure rates [15]. At present, there are no agents or combinations of agents that are bactericidal against those enterococci that are highly resistant to all aminoglycosides. One new agent, daptomycin, has shown promising activity in vitro against these organisms, both alone and in combination with fosfomycin [16]. However, daptomycin has been inconsistently effective in the treatment of experimentally induced enterococcal endocarditis [17, 18] and has not been used clinically for this purpose. Likewise, although therapy with a continuous infusion of ampicillin has shown promise for the treatment of experimental endocarditis in the rat model, there is scant clinical experience with this approach [19].

Of the three patients with endocarditis due to enterococci that were highly resistant to gentamicin who were reported in the literature, two were treated with antimicrobial therapy. One received a 9-day course of ampicillin and gentamicin followed by an additional 19 days of therapy with ampicillin (12 g/d) alone. The minimal inhibitory and bactericidal concentrations for ampicillin against this organism were 1 μg/mL and 2 μg/mL, respectively. Despite achievement of adequate levels of bactericidal titers in serum, the patient's condition deteriorated after 4 weeks of therapy and he required replacement of his aortic valve, which yielded enterococci on culture. He received therapy with ampicillin for 6 weeks and was cured. The second patient was apparently cured (follow-up of only 2 months) with a 6-week course of ampicillin (9 g/d) alone. The outcome of therapy with ampicillin in these cases, in addition to the case reported herein, suggests that it would be advisable to omit aminoglycosides from regimens for the treatment of endocarditis due to enterococci that are highly resistant to aminoglycosides and to consider early surgical intervention in an attempt to maximize the possibility of cure and minimize antibiotic-related toxicity.

The recent reports of enterococcal strains capable of producing β-lactamase [20] and demonstrating high-level resistance to vancomycin [21] cause further concern. Already, episodes of bacteremia due to both types of strains have been reported [22, 23]. Widespread dissemination of these resistant strains would make even successful bacteriostatic therapy more difficult to achieve.

Enterococcal NVE, particularly of the aortic valve, is an aggressive disease that frequently requires both bactericidal antimicrobial therapy and surgical intervention to maximize the chance of cure. In contrast to NVE and to the general conceptions about PVE due to aggressive or antibiotic-resistant organisms, enterococcal PVE is associated with a low mortality and frequently responds to medical therapy alone, although a tendency toward a higher relapse rate is observed than that seen with native valves. With the growing prevalence of enterococcal strains that are highly resistant to all aminoglycosides, it is imperative that all enterococcal strains associated with endocarditis be tested for high-level resistance to these agents. Traditional therapy is unlikely to be as effective for the treatment of endocarditis due to enterococci that are highly resistant to aminoglycosides. Optimal regimens for treatment in such cases are as yet undefined.

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References

1. Wilson WR, Wilkowske CJ, Wright AJ, Sande MA, Geraci JE. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. Ann Intern Med **1984**;100:816–23
2. Herzstein J, Ryan JL, Mangi RJ, Greco TP, Andriole VT. Optimal therapy for enterococcal endocarditis. Am J. Med **1984**;76:186–91
3. Moellering RC Jr, Watson BK, Kunz LJ. Endocarditis due to group D streptococci: comparison of disease caused by *Streptococcus bovis* with that produced by the enterococci. Am J Med **1974**;57:239–50
4. Isenberg HD, Washington JA II, Balows A, Sonnenwirth AC. Collection, handling, and processing of specimens. In: Lennette EH, Balows A, Hausler WJ Jr, Shadomy HJ, eds. Manual of clinical microbiology. 4th ed. Washington, DC: American Society for Microbiology, **1985**:91–2
5. Mandell GL, Kaye D, Levison ME, Hook EW. Enterococcal endocarditis: an analysis of 38 patients observed at the New York Hospital-Cornell Medical Center. Arch Intern Med **1970**;125:258–64
6. Ruoff KL, Miller SI, Garner CV, Ferraro MJ, Calderwood SB. Bacteremia with *Streptococcus bovis* and *Streptococcus salivarius*: clinical correlates of more accurate identification of isolates. J Clin Microbiol **1989**;27:305–8
7. Calderwood SA, Wennersten C, Moellering RC Jr, Kunz LJ, Krogstad DJ. Resistance to six aminoglycosidic aminocyclitol antibiotics among enterococci: prevalence, evolution, and relationship to synergism with penicillin. Antimicrob Agents Chemother **1977**;12:401–5

8. Watanakunakorn C. Prosthetic valve infective endocarditis. Prog Cardiovasc Dis **1979**;22:181–92
9. Mayer KH, Schoenbaum SC. Evaluation and management of prosthetic valve endocarditis. Prog Cardiovasc Dis **1982**;25:43–54
10. Dismukes WE. Prosthetic valve endocarditis: factors influencing outcome and recommendations for therapy. In: Bisno AL, ed. Treatment of infective endocarditis. New York: Grune and Stratton, **1981**:167–91
11. Karchmer AW. Treatment of prosthetic valve endocarditis. In: Sande MA, Kaye D, Root RK, eds. Contemporary issues in infectious diseases. Vol 3. New York: Churchill Livingstone, **1984**:163–82
12. Zervos MJ, Kauffman CA, Therasse PM, Bergman AG, Mikesell TS, Schaberg DR. Nosocomial infection by gentamicin-resistant *Streptococcus faecalis*: an epidemiologic study. Ann Intern Med **1987**; 106:687–91
13. Frenandez-Guerrero ML, Barros C, Rodriguez Tudela JL, Frenandez Roblas R, Soriano F. Aortic endocarditis caused by gentamicin-resistant *Enterococcus faecalis*. Eur J Clin Microbiol Infect Dis **1988**;7:525–7
14. Lipman ML, Silva J Jr. Endocarditis due to *Streptococcus faecalis* with high-level resistance to gentamicin. Rev Infect Dis **1989**;11:325–8
15. Koenig MG, Kaye D. Enterococcal endocarditis: report of nineteen cases with long-term follow-up data. N Engl J Med **1961**;264:257–64
16. Rice LB, Eliopoulos GM, Moellering RC Jr. In vitro synergism between daptomycin and fosfomycin against *Enterococcus faecalis* isolates with high-level gentamicin resistance. Antimicrob Agents Chemother **1989**;33:470–3
17. Bush LM, Boscia JA, Kaye D. Daptomycin (LY146032) treatment of experimental enterococcal endocarditis. Antimicrob Agents Chemother **1988**;32:877–81
18. Eliopoulos GM, Willey S, Reiszner E, Spitzer PG, Caputo G, Moellering RC Jr. In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic. Antimicrob Agents Chemother **1986**;30:532–5
19. Thauvin C, Eliopoulos GM, Willey S, Wennersten C, Moellering RC Jr. Continuous-infusion ampicillin therapy of enterococcal endocarditis in rats. Antimicrob Agents Chemother **1987**;31:139–43
20. Murray BE, Church DA, Wanger A, Zscheck K, Levison ME, Ingerman MJ, Abrutyn E, Mederski-Samoraj B. Comparison of two beta-lactamase-producing strains of *Streptococcus faecalis*. Antimicrob Agents Chemother **1986**;30:861–4
21. Shlaes DM, Bouvet A, Devine C, Shlaes JH, al-Obeid S, Williamson R. Inducible, transferable resistance to vancomycin in *Enterococcus faecalis* A256. Antimicrob Agents Chemother **1989**;33:198–203
22. Patterson JE, Colodny SM, Zervos MJ. Serious infection due to β-lactamase–producing *Streptococcus faecalis* with high-level resistance to gentamicin. J Infect Dis **1988**;158:1144–5
23. Bingen E, Lambert-Zechovsky N, Mariani-Kurkdjian P, Cezard JP, Navarro J. Bacteremia caused by a vancomycin-resistant enterococcus. Pediatr Infect Dis J **1989**;8:475–6