

Ceftriaxone Once Daily for Four Weeks Compared with Ceftriaxone Plus Gentamicin Once Daily for Two Weeks for Treatment of Endocarditis Due to Penicillin-Susceptible Streptococci

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This randomized, multicenter, open-label study compared the efficacy and safety of monotherapy with 2 g of intravenous ceftriaxone once daily for 4 weeks with those of combination therapy with 2 g of intravenous ceftriaxone and 3 mg of intravenous gentamicin/kg once daily for 2 weeks as therapy for endocarditis due to penicillin-susceptible streptococci. Sixty-one patients were enrolled in the study. Clinical cure was observed for 51 evaluable patients both at termination of therapy and at the 3-month follow-up: 25 (96.2%) of 26 monotherapy recipients and 24 (96%) of 25 combination therapy recipients. Of the 23 patients in each treatment group who were microbiologically evaluable, 22 (95.7%) in each group were considered cured. No patient had evidence of relapse. Fourteen patients (27.5%) required cardiac surgery after initiation of treatment, including five monotherapy recipients and nine combination therapy recipients. Adverse effects were minimal in both treatment groups. We conclude that 2 g of ceftriaxone once daily for 4 weeks and 2 g of ceftriaxone in combination with 3 mg of gentamicin/kg once daily for 2 weeks are both effective and safe for the treatment of streptococcal endocarditis.

From 1970 to 1990, the standard treatment for infective endocarditis due to penicillin-susceptible streptococci in the United States was either 4 weeks of monotherapy with penicillin G, a first-generation cephalosporin, or vancomycin hydrochloride or 2 weeks of therapy with penicillin and an aminoglycoside [1]. These multidose regimens of parenteral antibiotics typically required prolonged hospitalization. More recently, there has been a growing trend to treat serious infectious diseases (including infective endocarditis) on an outpatient basis. Although amenable to outpatient parenteral therapy, the preceding regimens limited the number of infusion options because of the need to administer multiple doses of each drug per day.

Ceftriaxone, a third-generation cephalosporin, has excellent *in vitro* activity against viridans streptococci, including strains with reduced susceptibility to penicillin [2, 3]. The half-life of ceftriaxone is 6 to 9 hours, and once-daily dosing provides effective tissue and plasma levels for 24 hours after iv administration or im injection [4, 5]. In addition, the combination of ceftriaxone with an aminoglycoside is synergistic against

viridans streptococci in the treatment of experimental endocarditis, even when the aminoglycoside is administered once daily [6].

The preceding findings paved the way for clinical trials of once-daily ceftriaxone. In the early 1990s, researchers in Argentina and Switzerland demonstrated that patients with endocarditis due to penicillin-susceptible streptococci could be treated effectively, in some cases as outpatients, with a single daily dose of ceftriaxone [7, 8]. Stamboulis et al. [7] reported that 2 g of ceftriaxone, administered once daily either alone for 4 weeks or for 2 weeks followed by a course of 1 g of amoxicillin twice a day, was equally effective. In the latter study, 27 of the 30 patients were treated as outpatients, and a total of 380 days of hospitalization were avoided [9]. Francioli and colleagues [8] subsequently reported that therapy with 2 g of ceftriaxone once daily for 4 weeks was effective against streptococcal endocarditis. Twenty-three of the 55 patients in their trial were discharged from the hospital <2 weeks after admission. More recently, Francioli et al. [10] demonstrated that 2 weeks of therapy with the combination of once-daily ceftriaxone (2 g) and once-daily netilmicin (4 mg/kg) was safe and efficacious. This regimen allowed partial or complete outpatient treatment of 15 of 52 patients.

In 1995, an American Heart Association panel of experts recommended a 4-week course of monotherapy with ceftriaxone as one option for patients with endocarditis caused by penicillin-susceptible viridans streptococci or *Streptococcus bovis* [11]. Our study was undertaken to provide further data on the efficacy and safety of a regimen consisting of 2 g of

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ceftriaxone once daily for 4 weeks for the treatment of adults with penicillin-susceptible streptococcus endocarditis as defined by the Duke criteria [12, 13]. In a recent editorial, Wilson [1] posed the following question: "Can the duration of therapy for penicillin-susceptible streptococcal endocarditis be shortened from 28 days to 14 days by [combining] ceftriaxone and gentamicin sulfate, both administered in a single daily dose?" In response to this important question, our study assessed the efficacy and safety of 2 g of ceftriaxone plus 3 mg of gentamicin/kg once daily for 2 weeks.

Patients and Methods

The study was approved by the institutional review boards of the participating institutions. Adult patients 18 years of age or older were eligible for the study if they had endocarditis diagnosed according to the Duke criteria [12, 13], had received <72 hours of parenteral antibiotic therapy before enrollment, and had provided written informed consent. Exclusion criteria included the presence of etiologic agents other than ceftriaxone-susceptible viridans streptococci or *S. bovis*; hypersensitivity to cephalosporins or aminoglycosides; prior treatment with antibiotics for >72 hours; New York Heart Association class IV heart failure; need for therapy for >2 weeks (e.g., patients with known or suspected cardiac or extracardiac abscesses); moderate-to-severe renal dysfunction (defined as an estimated serum creatinine clearance of <20 mL/min); prosthetic valve endocarditis; preexisting, clinically apparent moderate-to-severe hearing loss or vestibular dysfunction; or neutropenia (absolute neutrophil count, <1,000/mm³).

Patients were enrolled in the study between 29 January 1992 and 22 December 1996. A total of 67 patients from nine centers (range, 1–14 patients per center) were enrolled in the study. Patients were assigned randomly to receive either monotherapy with 2 g of iv ceftriaxone once daily for 4 weeks of combination therapy with 2 g of iv ceftriaxone plus 3 mg of iv gentamicin/kg of ideal body weight once daily for 2 weeks. Both ceftriaxone and gentamicin were infused over 30 to 60 minutes in an unblinded fashion.

Patients were assessed clinically within 48 hours after treatment initiation and on days 10 to 14 and day 28. At least one follow-up visit took place ~3 months after completion of therapy. The following tests were performed on blood or urine samples obtained within 48 hours of the start of treatment and during and after initiation of treatment: urinalysis and determinations of leukocyte and platelet counts, hemoglobin level, hematocrit, erythrocyte sedimentation rate, and serum creatinine clearance. The estimated serum creatinine clearance was calculated by means of the Cockcroft-Gault equation with use of the patient's age, sex, weight, and serum creatinine values. Peak and trough gentamicin concentrations in serum were measured at least twice: between days 3–4 and days 10–14 after therapy was begun.

Before the beginning of therapy, blood specimens for at least two cultures were obtained. Repeated blood cultures were performed between 1 and 2 weeks after initiation of antimicrobial therapy and at 3 months after completion of therapy. All blood cultures were incubated for at least 3 weeks before being defined as negative. The isolates were identified by the microbiology laboratory of the participating institution, and testing of in vitro susceptibility to penicillin and ceftriaxone was performed according to criteria established by the National Committee for Clinical Laboratory Standards [14].

An electrocardiogram and an echocardiogram were obtained at study entry and subsequently as clinically indicated. The decision as to whether to obtain a transthoracic or transesophageal echocardiogram (or both) was left to the discretion of individual investigators.

Microbiological cure was defined as negative blood cultures during therapy, 1–2 weeks after therapy, and at the follow-up visit 3 months after completion of therapy. Reinfection was defined as microbiological cure followed by a new episode of endocarditis caused by a different pathogen during the follow-up period. Clinical cure was defined as resolution of clinical findings of endocarditis with no evidence of active endocarditis both at the end of treatment and at the 3-month follow-up visit. Clinical cure with surgery was defined as clinical cure and completion of therapy according to the original randomization but a requirement of valve replacement(s) or other cardiac surgery during the study. The need for surgery was determined by the investigator on the basis of clinical evidence of worsening cardiac function. Adverse events were recorded for all patients enrolled in the study regardless of the relationship to the study drugs.

Results

Fifty-one of the 67 patients who were enrolled in the trial were evaluable for assessment of clinical efficacy. Of the 16 nonevaluable patients, seven were monotherapy recipients and nine were combination therapy recipients, including two patients in each treatment group who were excluded because of protocol violations. Other reasons that patients were nonevaluable were as follows: death before receiving study medication, self-discharge from the hospital against medical advice, resistance of the initial blood isolate to penicillin, concurrent metastatic infections, and failure to return for the follow-up visit.

Forty-one of 51 evaluable patients were male. The monotherapy group included 26 patients; the patients' ages ranged from 18 to 87 years (mean \pm SD, 52.5 \pm 17.8 years). The combination therapy group included 25 patients; the patients' ages ranged from 27 to 92 years (mean \pm SD, 59.5 \pm 15.5 years). All patients had native valve endocarditis. Predisposing congenital or acquired valvular abnormalities, as well as other risk factors for endocarditis, are summarized in table 1.

Identified pathogens included *S. bovis*, *Streptococcus morbillorum*, *Streptococcus mitis*, *Streptococcus mutans*, *Streptococ-*

Table 1. Risk factors for 51 clinically evaluable patients with endocarditis due to penicillin-susceptible streptococci who were treated with monotherapy with ceftriaxone for 4 weeks or combination therapy with ceftriaxone plus gentamicin for 2 weeks.

Risk factor	No. of patients	
	Monotherapy recipients	Combination therapy recipients
Structural cardiac abnormality		
Aortic insufficiency	2	0
Aortic stenosis	3	0
Aortic valve disease (unspecified)	1	0
Bicuspid aortic valve	3	1
Mitral insufficiency	8	5
Ventricular septal defect	2	0
Other risk factors		
Previous endocarditis	4	1
Intravenous devices (e.g., central catheters)	1	1
Intracardiac devices (pacemaker)	1	0
Intravenous drug use	2	1
History of rheumatic heart disease	3	3

NOTE. Some patients had more than one risk factor.

cus sanguis (untyped), *S. sanguis* I, *S. sanguis* II, and a nutritionally deficient streptococcus (table 2). All pathogens isolated from evaluable patients were susceptible to ceftriaxone and gentamicin.

No relapses occurred. Clinical cure was observed in 25 (96.2%) of 26 monotherapy recipients and 24 (96%) of 25 combination therapy recipients (table 3). The single patient for whom monotherapy failed had a pedunculated mobile vegeta-

Table 2. Pathogens identified at initiation of therapy for 51 clinically evaluable patients with endocarditis due to penicillin-susceptible streptococci who were treated with monotherapy with ceftriaxone for 4 weeks or combination therapy with ceftriaxone plus gentamicin for 2 weeks.

Pathogen	No. of patients	
	Monotherapy recipients	Combination therapy recipients
Viridans streptococci, species level not determined	12	10
<i>Streptococcus bovis</i>	1	1
<i>Streptococcus mitis</i>	1	1
<i>Streptococcus mutans</i>	3	0
<i>Streptococcus sanguis</i> (no further typing)	1	1
<i>S. sanguis</i> I	4	6
<i>S. sanguis</i> II	4	4
<i>Streptococcus morbillorum</i>	0	1
Nutritionally deficient streptococcus	0	1

Table 3. Clinical outcome for 51 evaluable patients with endocarditis due to penicillin-susceptible streptococci who were treated with monotherapy with ceftriaxone for 4 weeks or combination therapy with ceftriaxone plus gentamicin for 2 weeks.

Clinical outcome	No. (%) of patients	
	Monotherapy recipients (n = 26)	Combination therapy recipients (n = 25)
Cure without surgery	21 (80.8)	15 (60)
Cure with surgery	4 (15.4)	9 (36)
Treatment failure	1 (3.8)	1 (4)

tion at the time of surgery. The single patient for whom combination therapy failed had fever that persisted for 4 weeks. Gram staining of the mitral valve following replacement surgery revealed 4+ gram-positive cocci, but cultures of preoperative blood and operative valve specimens were negative.

Microbiological outcome was assessable for a total of 46 patients (23 in each group). In each group, 22 (95.7%) of the 23 patients were cured (table 4). Blood cultures for one monotherapy recipient treated for endocarditis due to viridans streptococci were positive for *Enterococcus faecalis* 37 days after initiation of therapy. A transesophageal echocardiogram obtained at the time of enterococcal bacteremia revealed a pedunculated mobile vegetation on the mitral valve. This patient was subsequently treated for presumed enterococcal endocarditis.

A total of five monotherapy recipients required cardiac surgery a mean \pm SD of 37.1 \pm 27.1 days after the institution of antimicrobial therapy. In contrast, nine combination therapy recipients required cardiac surgery at a mean \pm SD of 22.4 \pm 17.2 days (table 5). Although the relative risk for surgery was 1.87 for the combination therapy group vs. the monotherapy

Table 4. Microbiological outcome for 46 patients with endocarditis due to penicillin-susceptible streptococci who were treated with monotherapy with ceftriaxone for 4 weeks or combination therapy with ceftriaxone plus gentamicin for 2 weeks.

Microbiological outcome	No. (%) of patients	
	Monotherapy recipients* (n = 23)	Combination therapy recipients† (n = 23)
Cure	22 (95.7)	22 (95.7)
Reinfection	1 (4.3)	0
Treatment failure	0	1 (4.3)

* Three patients in this group were not evaluable for microbiological outcome.

† Two patients in this group were not evaluable for microbiological outcome.

Table 5. Surgical interventions for 51 clinically evaluable patients with endocarditis due to penicillin-susceptible streptococci who were treated with monotherapy with ceftriaxone for 4 weeks or combination therapy with ceftriaxone plus gentamicin for 2 weeks.

Procedure	No. of patients	
	Monotherapy recipients	Combination therapy recipients*
Aortic valve replacement	4	2
Coronary artery bypass grafting	1	1
Ventricular defect repair	1	0
Aortic valve excision, homograft	0	1
Mitral valve repair	0	2
Mitral valve replacement	0	6
Total (%) who underwent surgery	5/26 (19.2)	9/25 (36.0) [†]

* One patient underwent mitral valve repair on treatment day 10 and later required mitral valve replacement 63 days after initiation of treatment.

[†] RR, 1.87; 95% CI, 0.73–4.82.

group, the 95% confidence interval for such risk was 0.73–4.82; therefore, this risk could not be considered statistically significant.

In the monotherapy group, three patients had diarrhea, one had drug-related fever, and one had nausea. In the combination therapy group, one patient had diarrhea. Two combination therapy recipients had elevations in their serum creatinine levels: one had a rise from 0.7 mg/dL to 1.5 mg/dL by treatment day 11 and one had a rise from 0.9 mg/dL to 1.3 mg/dL by treatment day 12. All of these adverse events were thought by the investigators to be related to the study drugs. However, no patients in this study required discontinuation of therapy because of treatment-related adverse effects. Mean peak and trough serum concentrations of gentamicin \pm SD for the combination therapy group were 9.2 ± 2.7 μ g/mL and 1.75 ± 0.4 μ g/mL, respectively.

The median duration of hospitalization was 8 days for the monotherapy group and 14.5 days for the combination therapy group.

Discussion

Selection of the regimens used in the present study was based on the pharmacokinetic properties of ceftriaxone and the results of previous studies on endocarditis in South America and Europe [7–10]. Consolidated dosing with either gentamicin or tobramycin (usually 5 mg/kg every 24 hours for patients with normal renal function) has gained popularity for the treatment of many infections [15–17]. To our knowledge, this is the first application of consolidated dosing of gentamicin and ceftriaxone for the treatment of endocarditis. In animal models of infective endocarditis, the success of once-daily dosing of aminoglycosides appears to be organism-dependent. Once-

daily dosing is generally reported as equally efficacious to multiple-dose regimens for streptococcal and staphylococcal species. In contrast, once-daily dosing has been reported as less efficacious for animals with enterococcal endocarditis [18]. Moreover, the American Heart Association endorses a therapeutic regimen consisting of a 2-week course of 1 mg of iv or im gentamicin/kg every 8 hours and 12–18 million U of iv penicillin G every 24 hours either continuously or in six equally divided doses for the treatment of endocarditis [11].

The results of the present study confirm and extend the findings of previous trials conducted outside the United States. The 4-week regimen of once-daily ceftriaxone and the 2-week regimen of once-daily ceftriaxone plus gentamicin were both highly efficacious in the treatment of penicillin-susceptible streptococcus endocarditis. Such regimens are more practical and more convenient than prior regimens utilizing six-times-a-day therapy with penicillin. Furthermore, once-daily dosing of aminoglycosides holds the promise of reducing the risk of nephro- and ototoxicity, although our study was not specifically designed to address this issue.

An important advantage of these once-daily regimens is their simplicity for use in therapy administered to outpatients. We believe that patients meeting the following criteria can be safely and appropriately treated as outpatients with these regimens: unequivocal clinical response to initial therapy, stable hemodynamic status, absence of metastatic or intracardiac complications, and ability to comply with the mechanics and scheduling of outpatient antibiotic therapy.

In our study, nine combination therapy recipients required cardiac surgery in contrast to five monotherapy recipients, and the mean time since completion of therapy for the combination therapy group was longer than that for the monotherapy group. The significance of these findings is unknown. Patients in both treatment groups underwent cardiac surgery for a variety of reasons, including coronary artery bypass grafting and valve replacement, closure of ventricular septal defect, and mitral valve repair. More combination therapy recipients underwent valve replacement surgery, but this procedure was performed late in the course of therapy for most patients. Furthermore, active infection (as defined by positive gram staining or valve cultures) was found in only one patient. Valve replacement surgery during therapy is commonly undertaken in the treatment of infective endocarditis, and we do not consider the rate of surgery in either of the two treatment groups to be unusually high.

Because our patients were selected with use of highly specific criteria, caution should be exercised in generalizing these treatment regimens to all patients with penicillin-susceptible streptococcus endocarditis. For example, short-term therapy should be administered with caution to patients with prosthetic valve endocarditis, intracardiac or extracardiac complications, or long-standing disease of >1 to 2 months in duration.

In future studies, it will be important to assign patients to outpatient and inpatient regimens on the basis of response to

initial therapy, the absence or presence of hemodynamic instability, and the absence or presence of extra- or intracardiac complications. In addition, patients who undergo surgery during medical treatment should be categorized as cured if cultures of valves obtained 14 days after completion of medical therapy are negative and no relapse occurs during 3 months of follow-up.

In conclusion, a 4-week regimen of once-daily ceftriaxone and a 2-week regimen of once-daily ceftriaxone plus gentamicin are both efficacious and safe for the treatment of penicillin-susceptible streptococcus endocarditis. These simple regimens allow partial or complete outpatient management in selected cases. Outpatient therapy is usually more comfortable and less expensive for the patient and requires less time away from work, school, and other daily activities.

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