The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., Henry F. Chambers, M.D., Francis P. Tally, M.D., Gloria A. Vigliani, M.D., Christopher H. Cabell, M.D., M.H.S., Arthur Stanley Link, M.D., Ignace DeMeyer, M.D., Scott G. Filler, M.D., Marcus Zervos, M.D., Paul Cook, M.D., Jeffrey Parsonnet, M.D., Jack M. Bernstein, M.D., Connie Savor Price, M.D., Graeme N. Forrest, M.D., Gerd Fätkenheuer, M.D., Marcelo Gareca, M.D., Susan J. Rehm, M.D., Hans Reinhardt Brodt, M.D., Alan Tice, M.D., and Sara E. Cosgrove, M.D., for the *S. aureus* Endocarditis and Bacteremia Study Group

ABSTRACT

BACKGROUND

Alternative therapies for *Staphylococcus aureus* bacteremia and endocarditis are needed.

METHODS

We randomly assigned 124 patients with *S. aureus* bacteremia with or without endocarditis to receive 6 mg of daptomycin intravenously per kilogram of body weight daily and 122 to receive initial low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin. The primary efficacy end point was treatment success 42 days after the end of therapy.

RESULTS

Forty-two days after the end of therapy in the modified intention-to-treat analysis, a successful outcome was documented for 53 of 120 patients who received daptomycin as compared with 48 of 115 patients who received standard therapy (44.2 percent vs. 41.7 percent; absolute difference, 2.4 percent; 95 percent confidence interval, –10.2 to 15.1 percent). Our results met prespecified criteria for the noninferiority of daptomycin. The success rates were similar in subgroups of patients with complicated bacteremia, right-sided endocarditis, and methicillin-resistant *S. aureus*. Daptomycin therapy was associated with a higher rate of microbiologic failure than was standard therapy (19 vs. 11 patients, P=0.17). In 6 of the 19 patients with microbiologic failure in the daptomycin group, isolates with reduced susceptibility to daptomycin emerged; similarly, a reduced susceptibility to vancomycin was noted in isolates from patients treated with vancomycin. As compared with daptomycin therapy, standard therapy was associated with a nonsignificantly higher rate of adverse events that led to treatment failure due to the discontinuation of therapy (17 vs. 8, P=0.06). Clinically significant renal dysfunction occurred in 11.0 percent of patients who received daptomycin and in 26.3 percent of patients who received standard therapy (P=0.004).

CONCLUSIONS

Daptomycin (6 mg per kilogram daily) is not inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis. (ClinicalTrials.gov number, NCT00093067.)

From Duke University Medical Center, Durham, N.C. (V.G.F., G.R.C., C.H.C.); Tufts New England Medical Center (H.W.B.) and Beth Israel Deaconess Medical Center (A.W.K.) — both in Boston; Drexel University College of Medicine, Philadelphia (E.A.); University of Nebraska Medical Center, Omaha (M.E.R.); Wayne State University School of Medicine, Detroit (D.P.L.); San Francisco General Hospital, San Francisco (H.F.C.); Cubist Pharmaceuticals, Lexington, Mass. (F.P.T., G.A.V.); Forsyth Medical Center, Winston-Salem, N.C. (A.S.L.); Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (I.D.); Harbor–UCLA Medical Center, Torrance, Calif. (S.G.F.); William Beaumont Hospital, Royal Oak, Mich. (M.Z.); East Carolina University, Greenville, N.C. (P.C.); Dartmouth–Hitchcock Medical Center, Lebanon, N.H. (J.P.); Veterans Affairs Medical Center, Dayton, Ohio (J.M.B.); Denver Health Medical, Denver (C.S.P.); University of Maryland School of Medicine (G.N.F.), Johns Hopkins University School of Medicine (S.E.C.) — both in Baltimore; Klinikum, University of Cologne, Cologne, Germany (G.F.); Lehigh Valley Hospital Trauma and Critical Care Research, Allentown, Pa. (M.G.); Cleveland Clinic Foundation, Cleveland (S.J.R.); Johann Wolfgang Goethe Universität, Frankfurt, Germany (H.R.B.); and University of Hawaii, and Queens Medical Center — both in Honolulu (A.T.). Address reprint requests to Dr. Fowler at Box 3281, Division of Infectious Diseases, Duke University Medical Center, Durham, NC 27710, or at vance.fowler@duke.edu.

N Engl J Med 2006;355:653-65.

STAPHYLOCOCCUS AUREUS IS A LEADING CAUSE of bacteremia[1,2] and endocarditis.[3,4] *S. aureus* bacteremia is associated with serious complications, including endocarditis, in 30 to 40 percent of cases.[5,6] Treatment options for bacteremia and endocarditis caused by *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA), are limited. Vancomycin, the standard therapy for bloodstream infections attributable to MRSA, has been associated with suboptimal outcomes.[7-10] New agents for the treatment of *S. aureus* bacteremia and endocarditis are needed.

Daptomycin is a cyclic lipopeptide antibiotic that is rapidly bactericidal in vitro against most clinically relevant gram-positive bacteria, including *S. aureus*.[11-14] Daptomycin is approved for the treatment of complicated skin and skin-structure infections attributable to gram-positive organisms at a dose of 4 mg per kilogram of body weight intravenously per day,[15] but its efficacy in the treatment of *S. aureus* bacteremia and endocarditis and its safety at higher doses have not been established. We assessed the efficacy and safety of daptomycin as compared with standard therapy for *S. aureus* bacteremia and endocarditis.

METHODS

STUDY DESIGN

This open-label, randomized trial was conducted between August 28, 2002, and February 16, 2005. The institutional review board at each site approved the protocol, and all patients or their authorized representatives provided written informed consent. Eligible patients were 18 years of age or older and had one or more blood cultures that were positive for *S. aureus* within two calendar days before initiating study medication. Patients were ineligible if they had a creatinine clearance of less than 30 ml per minute, known osteomyelitis, polymicrobial bacteremia, or pneumonia. Full exclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

The adjudication committee of five infectious-disease experts (Drs. Abrutyn, Corey, Cosgrove, Fowler, and Karchmer) reviewed the data from each patient to establish the diagnosis and outcome. The committee was unaware of patients' treatment assignments.

DEFINITIONS

The diagnosis at baseline was determined with the use of the modified Duke criteria.[16] The adjudication committee determined final diagnoses (Table 1). Uncomplicated bacteremia was defined by the isolation of *S. aureus* from enrollment blood cultures in patients without endocarditis and without evidence of hematogenous spread. Patients with such infections received medication for a minimum of 10 to 14 days. In patients without definite endocarditis, complicated bacteremia was defined by the isolation of *S. aureus* from blood cultures on at least two days through study day 5, the presence of spread of infection, or infection involving prostheses not removed within four days. Such patients received medication for a minimum of 28 to 42 days. Uncomplicated right-sided endocarditis was defined as definite or possible[16] methicillin-susceptible *S. aureus* (MSSA) endocarditis in the absence of predisposing abnormalities or active infection of the mitral or aortic valve in a patient with active injection-drug use, a serum creatinine level of less than 2.5 mg per deciliter (221 μmol per liter), and no evidence of extrapulmonary sites of infection. Patients with uncomplicated MSSA right-sided endocarditis received medication for a minimum of 14 to 28 days. Complicated right-sided endocarditis was defined as definite or possible[16] endocarditis in the absence of predisposing abnormalities or active infection of the mitral or aortic valve, with extrapulmonary sites of infection, a serum creatinine level of at least 2.5 mg per deciliter, MRSA bacteremia, or the absence of injection-drug use. Patients with such infections were treated for a minimum of 28 to 42 days. Left-sided endocarditis was defined according to the criteria of Li et al.[16] Patients with such infections received medication for a minimum of 28 to 42 days.

The intention-to-treat population included all randomized patients. All patients in the intention-to-treat group who received at least one dose of the study medication were included in the safety analyses. The modified intention-to-treat population included all randomized patients who received at least one dose of study medication except those with a high likelihood of left-sided endocarditis who were enrolled before a protocol amendment allowing their inclusion. The per-protocol population included all patients in the

modified intention-to-treat group with documented adherence to the protocol (Fig. 1 of the Supplementary Appendix). Unless otherwise specified, all results presented are based on the modified intention-to-treat population, the primary efficacy population.

Patients were considered to have clinical failure if they had no response to the study drug on the basis of ongoing signs and symptoms of infection. Patients were considered to have microbiologic failure if they had persistent or relapsing *S. aureus* infection, defined as either ongoing positive cultures leading to discontinuation of the study drug or subsequent isolation of *S. aureus* of the same strain type after apparent clinical improvement.

RANDOMIZATION, TREATMENT, AND MONITORING

Patients were randomly assigned with the use of a block randomization schedule to receive either daptomycin or standard therapy; this centralized computer-generated schedule was designed to achieve a 1:1 ratio of patients, stratified according to investigative site.

Patients received daptomycin (Cubicin, Cubist Pharmaceuticals) (6 mg per kilogram of body weight intravenously once daily) or standard therapy with either vancomycin (1 g every 12 hours with appropriate dose adjustment) or an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) (2 g every 4 hours), depending on the susceptibility of the causative strain to methicillin. The duration of therapy was determined by the investigator on the basis of the working diagnosis. All patients who were randomly assigned to standard treatment and patients with left-sided endocarditis who were assigned to daptomycin were to receive gentamicin (1 mg per kilogram intravenously every eight hours or adjusted on the basis of renal function) for the first four days.

The investigators evaluated patients at baseline, at the end of therapy, and 42 days after the end of therapy (at the test-of-cure visit). Blood cultures were obtained daily until they were negative, as well as at the end of therapy and 42 days after the end of therapy (Fig. 1 of the Supplementary Appendix). Patients were required to undergo transesophageal echocardiography within five days after starting the study medication. All echocardiograms were reviewed by an independent expert unaware of the patient's treatment assignment; these results were used in all analyses.

An independent data and safety monitoring committee was established to regularly review the data and make recommendations regarding continuation of the study.

CLINICAL OUTCOMES

The primary outcome was the clinical success rate in each of the two treatment groups in the modified intention-to-treat population at the visit 42 days after the end of therapy. Failure at this visit was defined as clinical failure, microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective nonstudy antibiotics, or premature discontinuation of the study medication because of clinical failure, microbiologic failure, or an adverse event.

MICROBIOLOGIC METHODS

The species of all isolates was identified, and each isolate was tested for antimicrobial susceptibility by a central laboratory with the use of accepted interpretative criteria.[17] A minimal inhibitory concentration (MIC) of at least 2 μg of daptomycin per milliliter was considered to indicate a nonsusceptible isolate of *S. aureus*. *S. aureus* isolates from patients with persistent or recurrent infection were evaluated with repeated susceptibility testing and pulsed-field gel electrophoresis.

STATISTICAL ANALYSIS

Efficacy Assessments

In this noninferiority trial, the 95 percent confidence interval for the difference in success rates (daptomycin minus standard therapy) was calculated on the basis of the normal approximation to the binomial distribution. The noninferiority test was based on the lower bound of the confidence intervals being within the prespecified noninferiority margin of 20 percent and the upper bounds containing 0 percent. Assuming 65 percent efficacy in both treatment groups, a statistical power of 80 percent, and a one-sided significance level of 0.025, we estimated that 90 patients would need to be enrolled in each treatment group in the modified intention-to-treat population in order to test the null hypothesis (that the treatments differed by at least 20 percent). All reported P values were two-sided and not adjusted for multiple analyses.

Table 1. Characteristics of Patients in the Modified Intention-to-Treat Population.*

Characteristic	Daptomycin (N=120)	Standard Therapy (N=115)
Age — yr		
Median†	50.5	55.0
Range	21–87	25–91
Female sex — no. (%)	50 (41.7)	44 (38.3)
Race or ethnic group — no. (%)‡		
White	75 (62.5)	81 (70.4)
Black	32 (26.7)	23 (20.0)
Hispanic	8 (6.7)	5 (4.3)
Asian	1 (0.8)	2 (1.7)
Other	4 (3.3)	4 (3.5)
Body-mass index		
Median	26.9	25.7
Range	17.6–49.7	17.0–44.0
Creatinine clearance — ml/min		
Median	86.4	83.6
Range	28.0–246.9	17.9–277.0
Creatinine clearance <50 ml/min — no. (%)	19 (15.8)	22 (19.1)
Risk factor — no. (%)		
Diabetes mellitus	44 (36.7)	42 (36.5)
Systemic inflammatory response syndrome	89 (74.2)	87 (75.7)
Injection-drug use	25 (20.8)	25 (21.7)
Preexisting valvular heart disease	16 (13.3)	9 (7.8)
Surgery within previous 30 days	49 (40.8)	36 (31.3)
Extravascular foreign material§	28 (23.3)	29 (25.2)
Septic pulmonary emboli	10 (8.3)	13 (11.3)
HIV-positive¶	8 (6.7)	1 (0.9)

Safety Assessments

The incidence of adverse events was compared between treatment groups with the use of Fisher's exact test. Changes in laboratory values, in particular, changes in serum creatine kinase and creatinine clearance, were evaluated. Creatinine clearance was calculated at baseline and at regular intervals thereafter according to the Cockcroft–Gault formula.[18]

The study was designed by the sponsor (Cubist Pharmaceuticals) with the assistance of Drs. Chambers, Fowler, and Karchmer. Data were held and analyzed by the sponsor. However, the authors had complete and unfettered access to the data and vouch for the veracity and completeness of the data and analyses used for this article.

RESULTS

PATIENTS

Of the 246 randomized patients, 10 (6 assigned to daptomycin and 4 assigned to standard therapy) did not receive the study drug (Fig. 1 of the Supplementary Appendix); thus, 236 — 120 assigned to daptomycin and 116 assigned to standard therapy — were treated at 44 sites in four countries and represent the population used in the safety analyses. These 10 patients plus 1 patient who was treated with standard therapy and who enrolled before the amendment to allow patients with a high likelihood of left-sided endocarditis were excluded from the modified intention-to-treat population (120 assigned to daptomycin and 115

Table 1. (Continued.)

Characteristic	Daptomycin (N=120)	Standard Therapy (N=115)
Baseline pathogen — no. (%)		
Infection with MRSA	45 (37.5)	44 (38.3)
Diagnosis according to adjudication committee — no. (%)		
Baseline diagnosis		
Definite endocarditis	17 (14.2)	20 (17.4)
Possible endocarditis	73 (60.8)	71 (61.7)
Not endocarditis	30 (25.0)	24 (20.9)
Final diagnosis		
Uncomplicated bacteremia	32 (26.7)	29 (25.2)
Complicated bacteremia	60 (50.0)	61 (53.0)
Uncomplicated right-sided endocarditis	6 (5.0)	4 (3.5)
Complicated right-sided endocarditis	13 (10.8)	12 (10.4)
Left-sided endocarditis	9 (7.5)	9 (7.8)

* The standard-therapy group included 62 patients who received antistaphylococcal penicillins (50 nafcillin, 9 flucloxacillin, and 3 oxacillin) and 53 patients who received vancomycin. The body-mass index is the weight in kilograms divided by the square of the height in meters. HIV denotes human immunodeficiency virus.
† P=0.07 for the comparison between groups.
‡ Race or ethnic group was determined by the investigators.
§ Extravascular foreign material included orthopedic prostheses in 18 patients who received daptomycin and 12 patients who received standard therapy, neurologic devices in 1 patient who received daptomycin, and other extravascular foreign material (sternal wires; surgical drains, clamps, and stents; nonvascular catheters; and chest and endotracheal tubes) in 11 patients who received daptomycin and 22 patients who received standard therapy. More than one type of extravascular foreign material could be present in each patient. Orthopedic prostheses were infected in eight patients (six who received daptomycin and two who received standard therapy), six of whom underwent surgical therapy, and two of the six (both treated with daptomycin) had a successful outcome.
¶ P=0.04 for the comparison between groups.

assigned to standard therapy). Risk factors for *S. aureus* infection were similar in the two groups (Table 1). Clinical evidence of the systemic inflammatory response syndrome was present in 89 of 120 patients treated with daptomycin (74.2 percent) and in 87 of 115 patients treated with standard therapy (75.7 percent). The median duration of therapy was 14 days for daptomycin and 15 days for standard therapy (including early discontinuations). Gentamicin was administered to 107 of 115 patients in the standard-therapy group (93.0 percent) and to 1 patient in the daptomycin group (0.8 percent) for a median of four days. At entry, 75.0 percent of the daptomycin group and 79.1 percent of the standard-therapy group met modified Duke criteria for definite or possible endocarditis. The final diagnoses were distributed similarly in the treatment groups (Table 1). MRSA was isolated from 45 of 120 patients who were treated with daptomycin (37.5 percent) and 44 of 115 patients who were treated with standard therapy (38.3 percent).

OUTCOME

A successful outcome was documented 42 days after the end of therapy for 53 of 120 patients in the daptomycin group, as compared with 48 of 115 patients in the standard-therapy group (44.2 percent vs. 41.7 percent; absolute difference, 2.4 percent; 95 percent confidence interval for the difference, –10.2 to 15.1 percent). The lower limit of the 95 percent confidence interval was within the prespecified margin of –20 percent; thus, daptomycin was not inferior to standard therapy. Differences in success rates were similar across all of the prespecified analyses (Table 2 and Fig. 1). Success rates favored daptomycin over vancomycin among patients who were infected with MRSA (44.4 percent for daptomycin vs. 31.8 percent for standard therapy, P=0.28) but were higher among patients receiving standard therapy for MSSA infection (44.6 percent for daptomycin vs. 48.6 percent for standard therapy, P=0.74). At the end of therapy, the success rates were 61.7 percent in the daptomycin group, as compared with 60.9 per-

Table 2. Outcomes 42 Days after the End of Therapy, According to Prespecified Diagnostic Categories.

Criteria	Daptomycin	Standard Therapy	Absolute Difference in Success Rates
	no. of patients/total no. (%)		*% (95% CI)**
Overall success (intention to treat)	53/124 (42.7)	48/122 (39.3)	3.4 (–8.9 to 15.7)
Overall success (modified intention to treat)	53/120 (44.2)	48/115 (41.7)†	2.4 (–10.2 to 15.1)
Success according to methicillin susceptibility of *Staphylococcus aureus*‡			
MSSA	33/74 (44.6)	34/70 (48.6)	–4.0 (–20.3 to 12.3)
MRSA	20/45 (44.4)	14/44 (31.8)	12.6 (–7.4 to 32.6)
Success according to final diagnosis			
Uncomplicated bacteremia	18/32 (56.2)	16/29 (55.2)	1.1 (–23.9 to 26.0)
Complicated bacteremia	26/60 (43.3)	23/61 (37.7)	5.6 (–11.8 to 23.1)
Uncomplicated right-sided endocarditis	3/6 (50.0)	1/4 (25.0)	25.0 (–33.3 to 83.3)
Complicated right-sided endocarditis§	5/13 (38.5)	6/12 (50.0)	–11.5 (–50.3 to 27.2)
Left-sided endocarditis¶	1/9 (11.1)	2/9 (22.2)	–11.1 (–45.2 to 22.9)
Success in predefined strata			
Baseline diagnosis: definite plus possible endocarditis			
Overall	41/90 (45.6)	37/91 (40.7)	4.9 (–9.5 to 19.3)
MSSA	26/54 (48.1)	26/53 (49.1)	–0.9 (–19.8 to 18.0)
MRSA	15/36 (41.7)	11/38 (28.9)	12.7 (–8.9 to 34.3)
Final diagnosis: right-sided endocarditis plus complicated bacteremia			
Overall	34/79 (43.0)	30/77 (39.0)	4.1 (–11.3 to 19.5)
MSSA	20/49 (40.8)	21/48 (43.8)	–2.9 (–22.6 to 16.7)
MRSA	14/30 (46.7)	9/29 (31.0)	15.6 (–8.9 to 40.2)
Final diagnosis: uncomplicated bacteremia‡			
Overall	18/32 (56.2)	16/29 (55.2)	1.1 (–23.9 to 26.0)
MSSA	12/21 (57.1)	11/17 (64.7)	–7.6 (–38.6 to 23.5)
MRSA	6/10 (60.0)	5/11 (45.5)	14.5 (–27.7 to 56.8)
Overall per-protocol success	43/79 (54.4)	32/60 (53.3)	1.1 (–15.6 to 17.8)

* CI denotes confidence interval.
† Success was reported in 20 of 53 patients who received vancomycin (37.7 percent) and 28 of 62 patients who received antistaphylococcal penicillin (45.2 percent).
‡ One patient in each treatment group had infection caused by gram-positive cocci other than *S. aureus*.
§ Complications included osteomyelitis in three patients who received daptomycin and one patient who received standard therapy, septic arthritis in two patients who received standard therapy, abscesses or empyema in eight patients who received daptomycin and four patients who received standard therapy, a pacemaker or defibrillator in one patient who received daptomycin and three patients who received standard therapy, and other complications in one patient who received daptomycin and two patients who received standard therapy.
¶ One patient who received daptomycin and three patients who received standard therapy had valve perforation, and two patients who received standard therapy had perivalvular abscesses. One of nine patients who received standard therapy and two of nine patients who received daptomycin underwent valve-replacement surgery; the patient who received standard therapy underwent surgery during the study and both of the patients who received daptomycin underwent surgery after the study. Surgery was relatively contraindicated for several patients because of the severity of illness.

cent in the standard-therapy group (74 of 120 patients vs. 70 of 115 patients; absolute difference, 0.8 percent; 95 percent confidence interval, –11.7 to 13.3 percent). Eighty-five percent of patients treated with daptomycin and 84 percent of patients treated with standard therapy survived to the end of the study (P=0.98).

Nine patients in each treatment group had a final diagnosis of left-sided endocarditis. Three patients had a successful outcome; one received

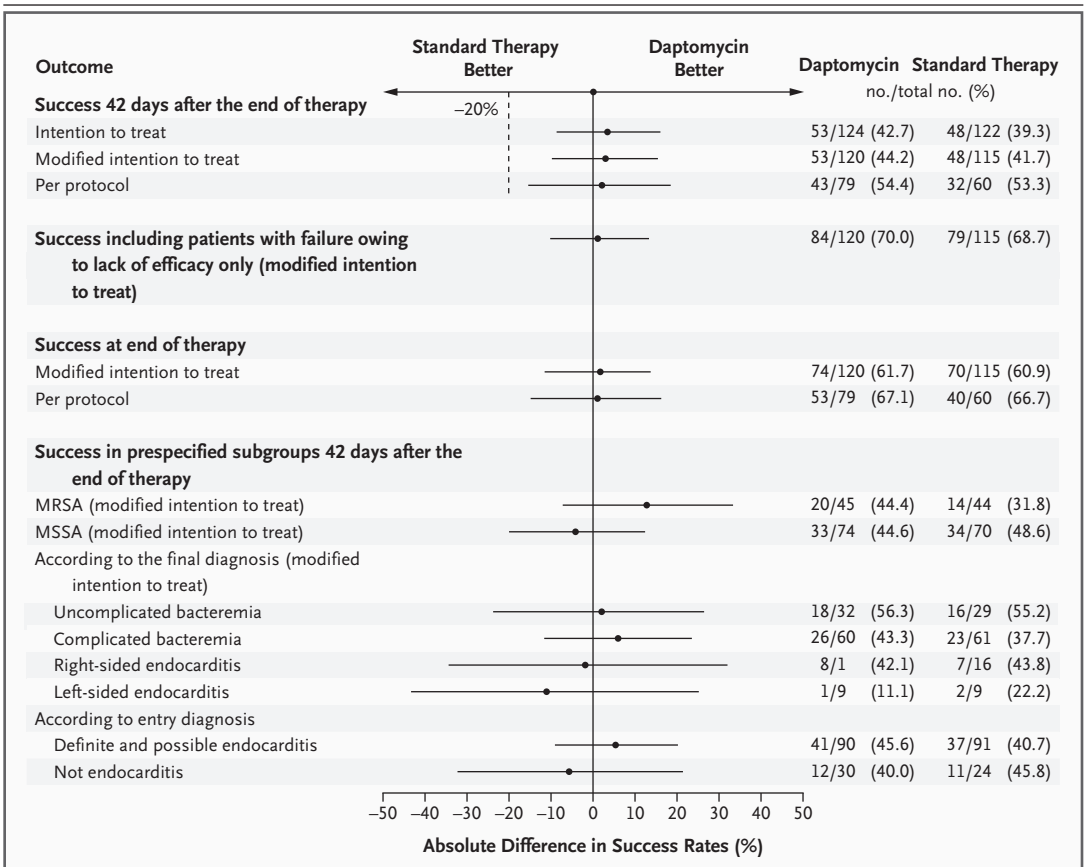

Figure 1. Comparison of the Rates of Success of Daptomycin and Standard Therapy for *Staphylococcus aureus* Bacteremia and Endocarditis.

Horizontal bars represent 95 percent confidence intervals.

daptomycin and two received standard therapy. Therapy failed in all nine patients with left-sided endocarditis caused by MRSA.

The median length of time to clearance of MRSA bacteremia (eight days and nine days, respectively; P=0.25) and MSSA bacteremia (four days and three days, respectively; P=0.28) did not differ significantly between the daptomycin and standard-therapy groups.

REASONS FOR TREATMENT FAILURE

The overall rates of failure of daptomycin and standard therapy were similar (55.8 percent and 58.3 percent, respectively) (Table 3). The reasons for failure, however, were different. Failure of daptomycin treatment was more frequently attributable to persistent or relapsing *S. aureus* infection (19 of 120 patients [15.8 percent] vs. 11 of 115 patients [9.6 percent] in the standard-therapy group, P=0.17). In contrast, failure of standard therapy was somewhat, but not significantly more frequently, associated with treatment-limiting adverse events (occurring in 17 patients [14.8 percent] vs. 8 patients [6.7 percent] in the daptomycin group, P=0.06).

Nineteen patients who were given daptomycin and 11 patients who were given standard therapy (9 were given vancomycin, and 2 were given an antistaphylococcal penicillin) had persistent or relapsing infection (P=0.17). Microbiologic failure occurred after a mean of 12 to 13 days of therapy in both groups. Among patients with microbiologic failure, more patients who were treated with daptomycin (63.2 percent) than who were treated with standard therapy (45.5 percent) had a diagnosis of complicated bacteremia. The MIC of daptomycin of the *S. aureus* isolates increased from baseline values in seven patients who were

Table 3. Reasons for Treatment Failure According to the Adjudication Committee.*

Reason for Failure	Daptomycin (N=120)	Standard Therapy (N=115)	P Value†
	no. (%)		
Overall	67 (55.8)	67 (58.3)	
Microbiologic failure, clinical failure, or both	23 (19.2)	15 (13.0)	0.22
Microbiologic failure‡	19 (15.8)	11 (9.6)	0.17
Clinical failure without microbiologic failure§	4 (3.3)	4 (3.5)	1.00
Adverse event	8 (6.7)	17 (14.8)	0.06
Receipt of nonstudy antibiotics that could have influenced outcome	20 (16.7)¶	16 (13.9)‖	0.59
Death	13 (10.8)	13 (11.3)	1.00
No blood obtained for culture**	9 (7.5)	12 (10.4)	0.50
Patient could not be evaluated (e.g., withdrew consent, left hospital against medical advice)	9 (7.5)	14 (12.2)	0.27

* More than one reason may be indicated for each patient.
† The P value was calculated according to Fisher's exact test.
‡ This category includes 17 patients who received daptomycin and 10 patients who received standard therapy and who had both microbiologic failure and clinical failure and 2 patients who received daptomycin and 1 patient who received standard therapy who had microbiologic failure. Seven patients who received daptomycin and five patients who received standard therapy had complications of endocarditis, six patients who received daptomycin and one patient who received standard therapy had intravascular infection, two patients who received daptomycin had osteomyelitis, two patients who received daptomycin had septic arthritis, two patients who received daptomycin and three patients who received standard therapy had undrained abscesses, and two patients who received standard therapy had infected decubitus or T-cell lymphoma–associated ulcers.
§ Two patients in each group had osteomyelitis. In the daptomycin group, one patient had gangrene of the left leg, declined amputation, and died; metastatic breast cancer and septic thrombophlebitis developed in one 87-year-old woman, and she died. In the standard-therapy group, one patient with diabetes, chronic obstructive pulmonary disease, and obesity presented with sepsis in a leg infection, which progressed to multiorgan failure syndrome, and died; one patient with left-sided infective endocarditis died after neurologic complications developed.
¶ Indications for nonstudy antibiotics that could have been effective and may have influenced the outcome included *S. aureus* infection in 7 patients and other indications in 13 patients (e.g., urinary tract infection or gram-negative sepsis). Potentially effective nonstudy antibiotics included vancomycin in 6 patients, linezolid in 2, an antistaphylococcal β-lactam antibiotic in 12, a fluoroquinolone in 4, and other antibiotics with antistaphylococcal activity in 7. Patients may have received more than one potentially effective nonstudy antibiotic.
‖ Indications for nonstudy antibiotics that could have been effective and may have influenced the outcome included *S. aureus* infection in 13 patients and other indications in 3 patients. Nonstudy antibiotics that may have been effective included vancomycin in six patients, linezolid in four, an antistaphylococcal β-lactam antibiotic in five, a fluoroquinolone in five, and other antibiotics with antistaphylococcal activity in five. Patients may have received more than one nonstudy antibiotic that may have been effective.
** Treatment of patients who did not have blood obtained for culture was considered to have failed in all analyses. For 16 patients (7 who received daptomycin and 9 who received standard therapy), treatment failure was assessed only because of a lack of blood culture. Follow-up data on survival were available for all 7 patients who received daptomycin and for 7 of the 9 patients who received standard therapy; all 14 survived. Two patients who received standard therapy were lost to follow-up.

treated with daptomycin; six of these patients had microbiologic failure. Five of these six patients had isolates that were MRSA. In six patients with microbiologic failure, the baseline MIC was 0.25 μg of daptomycin per milliliter in five isolates and 0.5 μg per milliliter in one isolate and rose to 2 μg per milliliter in five isolates and 4 μg per milliliter in one isolate. In the central microbiology laboratory, the isolates from one of the nine patients treated with vancomycin who had microbiologic failure had an increase in the MIC of vancomycin to 2 μg per milliliter. An additional three of these nine isolates demonstrated similar rises in the MIC of vancomycin in the local microbiology laboratory only. Most patients whose treatment failed because of persistent or relapsing *S. aureus* infection had deep-seated infection and did not receive the necessary surgical intervention. No significant association was found between levels of plasma daptomycin or vancomycin and the occurrence of microbiologic treatment failure.

A sensitivity analysis was performed to define the relative contribution of individual reasons for failure. This analysis demonstrated similar success rates in the two groups when each reason for failure was considered, including failure of efficacy (e.g., microbiologic failure, death, or clinical failure) (Table 4). In addition, the overall success rates for daptomycin (49.2 percent) and standard therapy (48.7 percent) were similar when treatments that failed only because of treatment-limiting adverse events were classified as successes (absolute difference, 0.5 percent; 95 percent confidence interval, –12.3 to 13.3 percent) or were excluded from the analysis (data not shown).

SAFETY AND TOLERABILITY

The overall incidence of adverse events in the two treatment groups was similar (Table 5). Most events were considered by the investigators to be unrelated to study treatment and were mild to moderate in severity. Of the 120 patients who received daptomycin, 62 (51.7 percent) had a serious adverse event, as did 52 of 116 patients who received standard therapy (44.8 percent). Adverse events that occurred in at least 5 percent of patients in either treatment group are listed in Table 2 of the Supplementary Appendix. All differences in the rates of adverse events between groups reaching a significance level of $P \leq 0.05$ are provided in Table 3 of the Supplementary Appendix. No statistical adjustments for multiple comparisons were made.

Creatine kinase elevations were significantly more common in the daptomycin group than the standard-therapy group (6.7 percent vs. 0.9 percent, $P=0.04$). Among patients with normal baseline levels of creatine kinase, elevations of creatine kinase were noted in 23 of 92 patients who received daptomycin, as compared with 12 of 96 patients who received standard therapy (25.0 percent vs. 12.5 percent, $P=0.04$). Among patients with data that could be evaluated, 2 of 111 patients who received standard therapy had elevations in creatine kinase to more than 500 IU per liter, as compared with 11 of 116 patients who received daptomycin (1.5 percent vs. 9.5 percent, $P=0.02$). Four of the 11 patients who received daptomycin had elevations that were greater than 10 times the upper limit of normal. Elevation of creatine kinase led to the discontinuation of treatment in 3 of 120 patients treated with daptomycin (2.5 percent). For 20 of the 24 patients who received daptomycin and who had increased levels of creatine kinase at baseline (83.3 percent), the level of creatine kinase returned to the normal range during treatment (18 patients) or after treatment (2 patients). Three patients had low-level elevations of creatine kinase (range, 114 to 451 U per liter) throughout the course of daptomycin therapy (one of whom had no follow-up data after treatment and two of whom had follow-up data approximately six weeks after treatment, with levels of creatine kinase of 215 and 389 U per liter). The fourth patient, who died on day 4, had a decrease in the creatine kinase level from 1004 U per liter on day 1 to 466 U per liter on day 4.

Eleven of 120 patients who received daptomycin had adverse events related to the peripheral nervous system (e.g., paresthesias, dysesthesias, and peripheral neuropathies) (9.2 percent), as compared with 2 of 116 patients who received standard therapy (1.7 percent, $P=0.02$). All of the events were classified as mild to moderate in severity; most were short-lived and resolved during continued treatment.

As compared with patients who received daptomycin, significantly more patients who received standard therapy had renal impairment as an adverse event, defined by the investigators as interstitial nephritis, toxic nephropathy, acute prerenal failure, acute or chronic renal failure, renal impairment, or renal tubular necrosis (18.1 percent vs. 6.7 percent, $P=0.009$) or on the basis of worsening creatinine clearance (46.8 percent vs. 19.8 percent, $P<0.001$). The incidence of renal impairment was similar among patients who received gentamicin and vancomycin (20.4 percent) and patients who received gentamicin and an antistaphylococcal penicillin (18.6 percent). In the safety analysis, renal impairment resulted in the discontinuation of treatment in 5 of 116 patients in the standard-therapy group (4.3 percent) and in 1 of 120 patients in the daptomycin group (0.8 percent). The proportion of patients with clinically significant decreases in renal function during treatment (a decrease in the creatinine clearance to less than 50 ml per minute or a decrease of more than 10 ml per minute from a baseline creatinine clearance of less than 50 ml per minute) was significantly higher in the standard-therapy group than in the daptomycin group by day 7 (14.2 percent vs. 5.2 percent, $P=0.03$) and through the end of the study (26.3 percent vs.

Table 4. Sensitivity Analyses of Success Rates 42 Days after the End of Therapy, According to the Reported Reasons for Failure as Determined by the Adjudication Committee.

Reason for Failure	Daptomycin (N=120)	Standard Therapy (N=115)	Absolute Difference in Success Rates
	no. of patients (%)		*% (95% CI)**
Patient could not be evaluated (e.g., withdrew consent, completed <4 days of therapy)	111 (92.5)	101 (87.8)	
Lack of efficacy†	84 (70.0)	79 (68.7)	1.3 (–10.5 to 13.1)
Other reasons			
Lack of efficacy or treatment-limiting adverse event	77 (64.2)	67 (58.3)	5.9 (–6.5 to 18.3)
Lack of efficacy, treatment-limiting adverse event, or receipt of potentially effective nonstudy antibiotic	62 (51.7)	58 (50.4)	1.2 (–11.6 to 14.0)
Lack of efficacy, treatment-limiting adverse event, receipt of potentially effective nonstudy antibiotic, or failure to obtain blood culture	55 (45.8)	49 (42.6)	3.2 (–9.5 to 15.9)
Lack of efficacy, treatment-limiting adverse event, receipt of potentially effective nonstudy antibiotic, failure to obtain blood culture, or discontinuation of treatment for other reason	53 (44.2)	48 (41.7)	2.4 (–10.2 to 15.1)

* CI denotes confidence interval.
† This category includes patients with microbiologic failure, patients with clinical failure, and those who died.

11.0 percent, P=0.004). Among patients who had clinically significant decreases in renal function, these decreases were reversible (defined by a final creatinine clearance within 10 ml per minute of the baseline value) in 5 of 13 patients who received daptomycin (38.5 percent) and 14 of 30 patients who received standard therapy (46.7 percent; 10 of 19 patients received an antistaphylococcal penicillin [52.6 percent], and 4 of 11 patients received vancomycin [36.4 percent]).

DISCUSSION

Our findings demonstrate that daptomycin is not inferior to standard therapy for the treatment of *S. aureus* bacteremia and right-sided endocarditis caused by MSSA or MRSA. Our findings were consistent among all efficacy populations and at assessments at both the end of therapy and 42 days after the end of therapy. The study population had high rates of complicated infections, coexisting conditions, and MRSA bacteremia.[3-6]

The growing problem of MRSA bacteremia and endocarditis is magnified by reports of clinical failure[19,20] and resistance[21-24] to vancomycin. The similar success rates among patients with MRSA bacteremia and right-sided endocarditis treated with daptomycin and such patients who were treated with vancomycin suggest that daptomycin may be considered an alternative to vancomycin in the management of these serious infections.

Although elevations of creatine kinase were documented in one quarter of the patients in the daptomycin group who had normal levels of creatine kinase at baseline, only three patients withdrew from the study for this reason. In our study, clinically significant daptomycin-associated elevations of creatine kinase occurred in 6.7 percent of recipients. Patients who are taking daptomycin should be monitored for elevations in creatine kinase and skeletal-muscle dysfunction.

Patients in the standard-therapy group may have had significantly greater increases in serum creatinine because of the addition of gentamicin to the treatment regimen.[25] This observation suggests that even a few days of low-dose gentamicin may result in considerable renal dysfunction in this high-risk population. Our findings provide support for the position of recent guidelines[26] that the use of gentamicin in the treatment of native-valve *S. aureus* endocarditis should be considered optional. However, our study was not designed to examine the contribution of gentamicin to the efficacy or toxicity of standard treatment.

Nineteen of 120 patients who received daptomycin (15.8 percent) had microbiologic failure, defined as persistent or relapsing *S. aureus* infec-

Table 5. Results of the Safety Analysis.

Adverse Event	Daptomycin (N=120)	Standard Therapy (N=116)	P Value*
	no. of patients (%)		
Any drug-related adverse event	42 (35.0)	49 (42.2)	0.29
Any serious adverse event	62 (51.7)	52 (44.8)	0.30
Any drug-related serious adverse event	3 (2.5)	6 (5.2)	0.33
Death	18 (15.0)	19 (16.4)	0.86
Stopped study drug because of drug-related adverse event	10 (8.3)	13 (11.2)	0.51
Most common adverse events (≥10% incidence in either group)†			
Anemia	15 (12.5)	18 (15.5)	0.58
Diarrhea	14 (11.7)	21 (18.1)	0.20
Vomiting	14 (11.7)	15 (12.9)	0.84
Constipation	13 (10.8)	14 (12.1)	0.84
Nausea	12 (10.0)	23 (19.8)	0.04
Hypokalemia	11 (9.2)	15 (12.9)	0.41
Renal impairment‡	8 (6.7)	21 (18.1)	0.009
Headache	8 (6.7)	12 (10.3)	0.36
Peripheral edema	8 (6.7)	16 (13.8)	0.09
Arthralgia	4 (3.3)	13 (11.2)	0.02
Serious adverse events according to system organ class†§			
Blood and lymphatic system disorders	1 (0.8)	3 (2.6)	0.36
Cardiac disorders	9 (7.5)	8 (6.9)	1.00
Gastrointestinal disorders	2 (1.7)	6 (5.2)	0.17
General disorders and conditions at the injection site	3 (2.5)	4 (3.4)	0.72
Infections and infestations¶	38 (31.7)	23 (19.8)	0.05
Injury, poisoning, and procedural complications	2 (1.7)	3 (2.6)	0.68
Laboratory abnormalities	3 (2.5)	0	0.25
Metabolism and nutrition disorders	2 (1.7)	5 (4.3)	0.28
Benign and malignant neoplasms	1 (0.8)	3 (2.6)	0.36
Nervous system disorders	4 (3.3)	5 (4.3)	0.75
Psychiatric disorders	4 (3.3)	1 (0.9)	0.37
Renal and urinary disorders	1 (0.8)	9 (7.8)	0.009
Respiratory, thoracic, and mediastinal disorders	8 (6.7)	5 (4.3)	0.57
Vascular disorders	2 (1.7)	2 (1.7)	1.00

* The P value was calculated according to Fisher's exact test.
† Each patient may have had more than one event.
‡ The renal-impairment category includes interstitial nephritis, toxic nephropathy, acute prerenal failure, acute or chronic renal failure, renal impairment, and renal tubular necrosis.
§ In addition, one patient who received daptomycin had a hepatobiliary disorder. One patient who received standard therapy had an eye disorder, one had a disorder of the immune system, one had a musculoskeletal and connective-tissue disorder, one had a skin and subcutaneous-tissue disorder, and one did not comply with treatment.
¶ See the Supplementary Appendix for additional information.

tion. In six of these patients, *S. aureus* isolated during or after treatment became less susceptible to daptomycin. In contrast, 11 of 115 patients (9.6 percent) who received standard therapy had microbiologic failure, including 9 of 53 patients who received vancomycin and 2 of 62 patients who received an antistaphylococcal penicillin. In four of these nine patients who received vancomycin, the MIC of vancomycin increased to 2 μg per milliliter from baseline values of 0.5 or 1 μg

per milliliter. Most patients with persistent or relapsing infection had complicated bacteremia associated with osteomyelitis or indwelling prostheses. Given the complicated nature of these infections, the contribution of decreased antimicrobial susceptibility to clinical failure is difficult to determine. However, these observations, as well as reports of clinical failures associated with reduced susceptibility to vancomycin[20] and daptomycin,[27] underscore the importance of adjunctive therapy, especially surgical intervention, in optimizing outcomes.

Because of the strict definition for success based on findings 42 days after the completion of therapy, treatment in many cases failed for reasons other than lack of efficacy. For example, not having blood cultures drawn at the visit 42 days after the end of therapy, despite a lack of evidence of persistent or relapsing *S. aureus* infection, contributed to the high failure rates seen in both groups. In addition, gentamicin therapy may have contributed to the likelihood of both microbiologic success and treatment failure associated with adverse effects in the patients who received standard therapy. However, the overall success rates 42 days after the end of therapy in both groups were similar when treatments that failed only because of treatment-limiting adverse events were classified as successes and when outcomes were assessed according to measures of efficacy (e.g., microbiologic failure, death, or clinical failure).

The open-label nature of the study might have led to bias if investigators were more likely to withdraw a patient in one of the treatment groups than in the other.[28] The effect of this potential bias was minimized by including an objective microbiologic end point as part of the assessment and by the use of a blinded adjudication committee to establish the final outcome. Another limitation was the small number of patients with left-sided *S. aureus* endocarditis and the poor clinical outcome among these patients in both treatment groups. Additional studies are required to optimize medical and surgical therapies in the management of this life-threatening infection.

In conclusion, our results suggest that daptomycin at a dose of 6 mg per kilogram once daily is not inferior to standard therapy for the treatment of bacteremia and right-sided endocarditis caused by MSSA or MRSA.

Supported by Cubist Pharmaceuticals.

Drs. Fowler, Boucher, Corey, Abrutyn, Karchmer, Rupp, Levine, Chambers, Cabell, Link, Price, and Cosgrove report having served as consultants for Cubist Pharmaceuticals. Drs. Tally and Vigliani are employees of Cubist Pharmaceuticals. Dr. Fowler reports having received grant support from Inhibitex, Merck, Nabi, and Theravance; Dr. Corey, from Inhibitex, Merck, and Theravance; Dr. Abrutyn, from Tenet Healthcare Foundation; Dr. Karchmer, from Cubist, Merck, Theravance, and Pfizer; Dr. Rupp, from Becton Dickinson and 3M; Dr. Levine, from Cubist; Dr. Chambers, from Cubist and Ortho-McNeil; Dr. Filler, from Amgen; Dr. Zervos, from Merck and Elan; Dr. Parsonnet, from Procter & Gamble; Dr. Bernstein, from Theravance, Cubist, and Peninsula; Dr. Price, from Denver Health Medical Center, Fujisawa, GlaxoSmithKline, and Cubist; Dr. Rehm, from Cubist; Dr. Tice, from Cubist, Roche, and Merck; and Dr. Cosgrove, from Merck. Dr. Fowler reports having received lecture fees from Cubist, Nabi, and Pfizer; Dr. Boucher, from Pfizer, Schering-Plough, and Cubist; Dr. Karchmer, from Cubist; Dr. Rupp, from Aventis, Ortho-McNeil, Cubist, Schering-Plough, and Bayer; Dr. Levine, from Cubist; Dr. Chambers, from Basilea and Pfizer; Dr. Link, from Cubist; Dr. Zervos, from Pfizer, Aventis, Cubist, and Wyeth; Dr. Bernstein, from Cubist and Ortho-McNeil; Dr. Price, from Ortho-McNeil; Dr. Forrest, from AdvanDx; Dr. Rehm, from Wyeth and Cubist; and Dr. Tice, from Cubist. No other potential conflict of interest relevant to this article was reported.

APPENDIX

In addition to the authors, the following persons participated in the *S. aureus* Endocarditis and Bacteremia Study: **Patient Enrollment:** *Amarillo, Tex.* — R. Akins; *Atlanta* — H. Albrecht; *Denver* — M. Barron, M. Bessesen; *Fargo, N.D.* — P. Carson; *New York* — D. Fierer; *Danville, Pa.* — M. Foltzer; *St. Louis* — D. Goodenberger; *Winston-Salem, N.C.* — K. High; *Manhasset, N.Y.* — B. Hirsch; *Besançon CEDEX, France* — B. Hoen; *Buffalo, N.Y.* — C. Hsiao; *San Francisco* — H. Lampiris; *Philadelphia* — M. Levison, B. Suh; *Bethlehem, Pa.* — T.P. Le; *Leuven, Belgium* — W. Peetermans; *Chicago* — D. Pitrak, J.P. Quinn, J. Segreti; *Louisville, Ky.* — J. Ramirez; *Boston* — P.A. Rice; *Regensburg, Germany* — B. Salzberger; *Cumberland, Md.* — J. Stone; *Akron, Ohio* — J. Tan; *Rochester, Minn.* — Z. Temesgen; **Data and Safety Monitoring Committee**: *New York* — K. Freeman; *Charleston, S.C.* — J. John, Jr.; *Springfield, Mass.* — D. Longworth; **Cubist Pharmaceuticals Study Team**: J. Alder, D. Anastasiou, R. Arbeit, J. Aziz, K. Blackerby, E. Campanaro, M. Campion, B. Eisenstein, J. Lufkin, S. Luperchio, C. Otradovec, C. Rundlett, U. Stoutenburgh, G. Thorne, P. Tipirneni.

REFERENCES

1. Fluit AC, Jones ME, Schmitz FJ, Acar J, Gupta R, Verhoef J. Antimicrobial susceptibility and frequency of occurrence of clinical blood isolates in Europe from the SENTRY Antimicrobial Surveillance Program, 1997 and 1998. Clin Infect Dis 2000; 30:454-60.

2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-17. [Erratum, Clin Infect Dis 2004;39:1093.]

3. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA 2005; 293:3012-21. [Erratum, JAMA 2005;294: 900.]

4. Miro JM, Anguera I, Cabell CH, et al. *Staphylococcus aureus* native valve infective

endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. Clin Infect Dis 2005;41:507-14. [Erratum, Clin Infect Dis 2005;41:1075-7.]
5. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) 2003;82:322-32.
6. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med 2003;163:2066-72.
7. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore) 2003;82:333-9.
8. Fowler VG Jr, Kong LK, Corey GR, et al. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. J Infect Dis 1999;179:1157-61.
9. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med 1991;115:674-80.
10. Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. Antimicrob Agents Chemother 1990;34:1227-31.
11. Barry AL, Fuchs PC, Brown SD. In vitro activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers. Antimicrob Agents Chemother 2001;45:1919-22.
12. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin Infect Dis 2004;38:994-1000.
13. Critchley IA, Blosser-Middleton RS, Jones ME, Thornsberry C, Sahm DF, Karlowsky JA. Baseline study to determine in vitro activities of daptomycin against gram-positive pathogens isolated in the United States in 2000-2001. Antimicrob Agents Chemother 2003;47:1689-93.
14. Snydman DR, Jacobus NV, McDermott LA, Lonks JR, Boyce JM. Comparative in vitro activities of daptomycin and vancomycin against resistant gram-positive pathogens. Antimicrob Agents Chemother 2000;44:3447-50.
15. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38:1673-81.
16. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
17. Performance standards for antimicrobial testing: 15th informational supplement. CLSI/NCCLS document M100-S15. Wayne, Pa.: Clinical and Laboratory Standards Institute, 2005.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
19. Fowler VG Jr, Sakoulas G, McIntyre LM, et al. Persistent bacteremia due to methicillin-resistant *Staphylococcus aureus* infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. J Infect Dis 2004;190:1140-9.
20. Howden BP, Ward PB, Charles PG, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. Clin Infect Dis 2004;38:521-8.
21. *Staphylococcus aureus* resistant to vancomycin — United States, 2002. MMWR Morb Mortal Wkly Rep 2002;51:565-7.
22. Vancomycin-resistant *Staphylococcus aureus* — Pennsylvania, 2002. MMWR Morb Mortal Wkly Rep 2002;51:902.
23. Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis 2004;38:448-51.
24. Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. N Engl J Med 1999;340:493-501.
25. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. Ann Intern Med 1982;97:496-503.
26. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association — executive summary. Circulation 2005;111:3167-84. [Erratum, Circulation 2005;112:2373.]
27. Hayden MK, Rezai K, Hayes RA, Lolans K, Quinn JP, Weinstein RA. Development of daptomycin resistance in vivo in methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 2005;43:5285-7.
28. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. N Engl J Med 1994;331:1325-30.