

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006;355:653-65.

## **SUPPLEMENTAL METHODS**

### ***Patient Exclusion Criteria***

A review of the screening logs at individual study sites demonstrated that patients were excluded from the study for the following reasons: 1) renal failure with creatinine clearance < 30 ml/min; 2) initial *S. aureus* blood culture outside the 2 day window; 3) inability to provide consent or unlikely to comply with study related procedures; 4) presence of an intravascular material (excluding cardiac stents) not intended to be removed within 4 calendar days; 5) receipt of non-study antibiotics potentially effective against *S. aureus*; 6) high likelihood of death or valve replacement surgery in the first 3 days following randomization; 7) refractory shock, significant hepatic insufficiency, or severe leucopenia; 8) weight <50 kg or >150 kg; 9) allergy to vancomycin or penicillin; or 10) infection with *S. aureus* with reduced susceptibility to vancomycin (minimum inhibitory concentration [MIC] >4 µg/ml). More than one exclusion criteria could be present in an individual patient.

### ***Enrollment of Patients with Left-sided IE***

Patients with suspected left-sided endocarditis were excluded until April 4, 2004, when an amendment to the protocol allowed enrollment of these patients. After April 4, 2004, patients with a high-likelihood of left-sided endocarditis at the time of enrollment were randomized centrally using a separate schedule without stratification by investigative site.

***Definitions***

All adverse events were to be coded using the Medical Regulatory Authorities (MedDRA) dictionary (Version 6.0). Potentially effective non-study antibiotics (PENS) were defined as any antibiotic received during or after study drug therapy that may have influenced the outcome. The Adjudication Committee recorded each antibiotic considered potentially effective after reviewing all available culture, susceptibility and antibiotic administration data.

***Plasma Drug Level Monitoring***

Plasma vancomycin levels were monitored according to standard practice of each participating site. Plasma levels of daptomycin were evaluated on day 5.

***Data Monitoring Committee (DMC)***

The Data Monitoring Committee (DMC) worked according to a standard operating procedure that was completed prior to their first meeting and evaluated ongoing safety data and efficacy data, only as it applied to safety. There were no stopping rules or interim efficacy analyses. The study was allowed to continue to completion by the Data Monitoring Committee.

***Statistical Analysis***

Several pre-specified strata analyses were performed on the primary endpoint, including MRSA, individual entry and final diagnoses as well as combined diagnostic groups; e.g., entry diagnosis of endocarditis; final diagnosis of right-sided endocarditis; final diagnosis

of complicated bacteremia plus right-sided endocarditis. Success at end of therapy (EOT) was also analyzed. Kaplan-Meier methodology was used to assess survival (log-rank test) and the time to clearance of bacteremia (Wilcoxon test).

## **SUPPLEMENTAL RESULTS**

### ***Retained prosthetic devices.***

Overall, 17 daptomycin and 21 comparator patients had intravascular prosthetic material, including intravascular stents, ports, pacemakers (permanent and temporary transvenous pacers), coronary stents, etc. Supplemental Table 1 shows success in patients with intravascular prosthetic material. Overall, similar numbers of patients in both treatment groups had retained prosthetic material.

### ***Adverse events.***

Adverse events that occurred in  $\geq 5\%$  of patients in either treatment group are provided in Supplemental Table 2.

Adverse events in the daptomycin and comparator treatment groups were compared (Supplemental Table 3). Terms were combined for post-hoc analyses where appropriate and medically relevant (i.e., peripheral neuropathy, renal impairment). Two of 300 MedDRA high level terms ("renal failure and impairment" and "bronchospasm and obstruction") were significant at a level of  $p \leq 0.05$ . Both of these terms were less frequent in daptomycin arm). Seven of the 580 MedDRA preferred terms were significant at a level of  $p \leq 0.05$ . Of these, "nausea", "decreased weight", and "arthralgia" were less

common in the daptomycin arm, and “bacteremia”, “CPK increased”, “pharyngolaryngeal pain”, and “sweating increased” were less common in the comparator arm. No adjustments for multiple comparisons were made for the statistical analyses of adverse events in the daptomycin and comparator treatment groups.

***Serious adverse events related to infections and infestation.***

There were more serious adverse events of infection in the daptomycin group than in the comparator group; 38/120 (31.7%) vs 23/116 (19.8%),  $p=0.053$ . The difference in incidence of serious adverse events related to infections is largely accounted for by a higher incidence of serious gram negative infections related to underlying diseases (e.g., Crohn’s disease, neurogenic bladder with recurrent urinary tract infection). The lower incidence of serious gram negative infections in comparator-treated patients may be related in part to the use of gentamicin in these patients. There may also be an element of open label bias in the reporting of serious adverse events related to *S. aureus* infection in the experimental study-drug arm.

**Supplemental Table 1.** Adjudication Committee Success at Test of Cure in Patients with Intravascular Devices and Prosthetic Material.

	<b>Daptomycin</b>	<b>Comparator</b>
	Success n/N	
<b>Intravascular material</b>	<b>8/17</b>	<b>9/21</b>
Pacemaker / defibrillator	2/6	1/5
Removed	2/4	1/1
Not removed	0/2	0/4
Coronary stent(s)*	3/5	2/5
Tunneled catheter	2/4	4/7
Removed	2/4	2/4
Not removed	0	2/3
Abdominal aortic synthetic graft	0/1	0
Inferior vena cave filter	1/1	1/1
Peripheral vascular stent/Transjugular intrahepatic portosystemic shunt device	0	0/2
Intraaortic Balloon Pump	0	1/1

\*One patient in each group had coronary stents in place < 6 months, both failed

**Supplemental Table 2.** Adverse Events that Occurred in  $\geq 5\%$  of Patients in Either Treatment Group.

<b>Adverse Event</b>	<b>Daptomycin</b>	<b>Comparator</b>
<b>System Organ Class</b>	<b>(N=120)</b>	<b>(N=116)</b>
<b>Preferred Term</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Infections and infestations</b>	<b>65 (54.2%)</b>	<b>56 (48.3%)</b>
Urinary tract infection	8 (6.7%)	11 (9.5%)
Osteomyelitis	7 (5.8%)	7 (6.0%)
Sepsis	6 (5.0%)	3 (2.6%)
Bacteraemia	6 (5.0%)	0 (0%)
Pneumonia	4 (3.3%)	9 (7.8%)
<b>Gastrointestinal disorders</b>	<b>60 (50.0%)</b>	<b>68 (58.6%)</b>
Diarrhoea	14 (11.7%)	21 (18.1%)
Vomiting	14 (11.7%)	15 (12.9%)
Constipation	13 (10.8%)	14 (12.1%)
Nausea	12 (10.0%)	23 (19.8%)
Abdominal pain	7 (5.8%)	4 (3.4%)
Dyspepsia	5 (4.2%)	8 (6.9%)
Loose stools	5 (4.2%)	6 (5.2%)
Gastrointestinal haemorrhage	2 (1.7%)	6 (5.2%)
<b>General disorders and administration site conditions</b>	<b>53 (44.2%)</b>	<b>69 (59.5%)</b>
Oedema peripheral	8 (6.7%)	16 (13.8%)
Pyrexia	8 (6.7%)	10 (8.6%)
Chest pain	8 (6.7%)	7 (6.0%)
Oedema	8 (6.7%)	5 (4.3%)
Asthenia	6 (5.0%)	6 (5.2%)
Injection site erythema	3 (2.5%)	7 (6.0%)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>38 (31.7%)</b>	<b>43 (37.1%)</b>
Pharyngolaryngeal pain	10 (8.3%)	2 (1.7%)
Pleural effusion	7 (5.8%)	8 (6.9%)
Cough	4 (3.3%)	7 (6.0%)
Dyspnoea	4 (3.3%)	6 (5.2%)
<b>Skin and subcutaneous tissue disorders</b>	<b>36 (30.0%)</b>	<b>40 (34.5%)</b>
Rash	8 (6.7%)	10 (8.6%)
Pruritus	7 (5.8%)	6 (5.2%)
Erythema	6 (5.0%)	6 (5.2%)
Sweating increased	6 (5.0%)	0 (0%)
<b>Musculoskeletal and connective tissue disorders</b>	<b>35 (29.2%)</b>	<b>42 (36.2%)</b>
Pain in extremity	11 (9.2%)	11 (9.5%)
	8 (6.7%)	10 (8.6%)

Back pain	4 (3.3%)	13 (11.2%)
Arthralgia		
<b>Psychiatric disorders</b>	<b>35 (29.2%)</b>	<b>28 (24.1%)</b>
Insomnia	11 (9.2%)	8 (6.9%)
Anxiety	6 (5.0%)	6 (5.2%)
<b>Nervous system disorders</b>	<b>32 (26.7%)</b>	<b>32 (27.6%)</b>
Headache	8 (6.7%)	12 (10.3%)
Dizziness	7 (5.8%)	7 (6.0%)
<b>Investigations</b>	<b>30 (25.0%)</b>	<b>33 (28.4%)</b>
Blood CPK increased	8 (6.7%)	1 (<1%)
<b>Blood and lymphatic system disorders</b>	<b>29 (24.2%)</b>	<b>24 (20.7%)</b>
Anaemia	15 (12.5%)	18 (15.5%)
<b>Metabolism and nutrition disorders</b>	<b>26 (21.7%)</b>	<b>38 (32.8%)</b>
Hypokalaemia	11 (9.2%)	15 (12.9%)
Hyperkalaemia	6 (5.0%)	10 (8.6%)
<b>Vascular disorders</b>	<b>21 (17.5%)</b>	<b>20 (17.2%)</b>
Hypertension	7 (5.8%)	3 (2.6%)
Hypotension	6 (5.0%)	9 (7.8%)
<b>Renal and urinary disorders</b>	<b>18 (15.0%)</b>	<b>26 (22.4%)</b>
Renal failure	4 (3.3%)	11 (9.5%)
Renal failure acute	4 (3.3%)	7 (6.0%)

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**Supplemental Table 3.** Adverse Events with a Statistically Significant Difference in Incidences ( $p \leq 0.05$ ) between Treatment Groups in the High Level and/or Preferred Terms. For all Preferred Terms reaching statistical significance, the corresponding High Level Term is provided. For all created and modified High Level Terms reaching statistical significance, the associated Preferred Terms are provided.

<b>System Organ Class</b> <b>High Level Term</b> <b>Preferred Term</b>	<b>Daptomycin</b> <b>(N=120)</b> <b>n (%)</b>	<b>Comparator</b> <b>(N=116)</b> <b>n (%)</b>	<b>P</b> <b>Value*</b>
Gastrointestinal disorders			
Nausea and vomiting symptoms	21 (17.5%)	26 (22.4%)	0.42
Nausea	12 (10.0%)	23 (19.8%)	0.04
Infections and infestations			
Sepsis, bacteraemia and viraemia	15 (12.5%)	8 (6.9%)	0.19
Bacteremia	6 (5.0%)	0	0.03
Investigations			
Skeletal and cardiac muscle analyses	8 (6.7%)	2 (1.7%)	0.10
Blood creatine phosphokinase increased	8 (6.7%)	1 (<1%)	0.04
Physical examination procedures	1 (<1%)	6 (5.2%)	0.06
Weight decreased	0	5 (4.3%)	0.03
Musculoskeletal and connective tissue disorders			
Joint related signs and symptoms	7 (5.8%)	14 (12.1%)	0.11
Arthralgia	4 (3.3%)	13 (11.2%)	0.02
Nervous system disorders			
Peripheral neuropathy <sup>†</sup>	11 (9.2%)	2 (1.7%)	0.02
Hypokinesia	1 (<1%)	0	1.00
Facial paresis	1 (<1%)	0	1.00
Peroneal nerve palsy	1 (<1%)	0	1.00
Hypoaesthesia	2 (1.7%)	1 (<1%)	1.00
Paraesthesia	3 (2.5%)	1 (<1%)	0.62
Brachial plexus lesion	1 (<1%)	0	1.00
Peripheral neuropathy	2 (1.7%)	0	0.50
Neuropathic pain	0	1 (<1%)	0.49
Sensory loss	1 (<1%)	0	1.00
Renal and urinary disorders			
Renal impairment <sup>‡</sup>	8 (6.7%)	21 (18.1%)	0.009
Interstitial nephritis	0	1 (<1%)	0.49
Toxic nephropathy	0	1 (<1%)	0.49
Acute prerenal failure	1 (<1%)	0	1.00
Renal failure	4 (3.3%)	11 (9.5%)	0.06
Acute renal failure	4 (3.3%)	7 (6.0%)	0.37
Chronic renal failure	0	1 (<1%)	0.49
Renal impairment	1 (<1%)	3 (2.6%)	0.36
Renal tubular necrosis	0	1 (<1%)	0.49
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract signs and symptoms	10 (8.3%)	3 (2.6%)	0.08

Pharyngolaryngeal pain	10 (8.3%)	2 (1.7%)	0.03
Bronchospasm and obstruction	3 (2.5%)	10 (8.6%)	0.05
Skin and subcutaneous tissue disorders			
Apocrine and eccrine gland disorders	7 (5.8%)	1 (<1%)	0.07
Sweating increased	6 (5.0%)	0	0.03

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\* Fisher's exact test

† High Level Term created to include hypokinesia, facial paresis, peroneal nerve palsy, hypoaesthesia, paraesthesia, brachial plexus lesion, peripheral neuropathy, neuropathic pain, and sensory loss.

‡ MedDRA High Level Term of Renal failure and impairment modified to also include interstitial nephritis, toxic nephropathy, and renal tubular necrosis.

**FIGURE LEGEND**

**Supplemental Figure 1.** Study design, diagnoses, outcomes and patient disposition in the *S. aureus* bacteremia and endocarditis study. Ten patients did not receive study drug: five withdrew consent, two had bacteremia due to coagulase-negative staphylococci, one had known osteomyelitis, one deteriorated clinically and one withdrew for another reason.

