Continuous versus Intermittent Infusion of Oxacillin for Treatment of Infective Endocarditis Caused by Methicillin-Susceptible *Staphylococcus aureus*

Darrel W. Hughes,1,2,3 Christopher R. Frei,2,3 Pamela R. Maxwell,1,2,3 Kay Green,1 Jan E. Patterson,4,5 George E. Crawford,4,5 and James S. Lewis II1,2,3,4*

Department of Pharmacy Services, University Health System, San Antonio, Texas3; The University of Texas at Austin College of Pharmacy, Austin, Texas2; Pharmacy Practice and Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, Texas2; Department of Medicine, Division of Infectious Diseases, The University of Texas Health Science Center at San Antonio, San Antonio, Texas4; and South Texas Veterans Health Care System, San Antonio, Texas5

Received 16 September 2008/Returned for modification 30 October 2008/Accepted 18 February 2009

Infective endocarditis (IE) is the fourth leading cause of life-threatening infection in the United States and imposes significant morbidity and mortality. The American Heart Association guidelines for the diagnosis and treatment of IE do not address continuous-infusion (CI) oxacillin. This retrospective study compares outcomes between CI oxacillin and intermittent-infusion (II) oxacillin in the treatment of IE caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). A total of 709 medical records were reviewed for inpatients with definitive IE treated between 1 January 2000 and 31 December 2007. Continuous data were analyzed by Student’s t test or the Wilcoxon rank sum test. The chi-square test or Fisher’s exact test was used to compare nominal data. A multivariate logistic model was constructed. One hundred seven patients met eligibility criteria for inclusion into the study. Seventy-eight patients received CI oxacillin, whereas 28 received II oxacillin. CI and II groups were similar with respect to 30-day mortality (8% versus 10%, P = 0.7) and length of stay (20 versus 25 days, P = 0.4) but differed in 30-day microbiological cure (94% versus 79%, P = 0.03). Sixty-three patients received synergistic gentamicin, whereas 44 did not. The gentamicin and no-gentamicin groups were similar with respect to 30-day mortality (11% versus 4%, P = 0.2) and 30-day microbiological cure (90% versus 89%, P = 0.8); however, times to defervescence (4 versus 2 days, P = 0.02) were significantly different. CI oxacillin is an effective alternative to II oxacillin for the treatment of IE caused by MSSA and may improve microbiological cure. This convenient and pharmacodynamically optimized dosing regimen for oxacillin deserves consideration for patients with IE caused by MSSA.

*MATERIALS AND METHODS*

**Study design and participants.** This retrospective cohort study performed at University Hospital, University Health System, San Antonio, TX, assessed the use of CI versus II oxacillin for the treatment of IE caused by MSSA. The two groups were comprised of patients who received either 2 g II oxacillin intravenously over 30 min every 4 h or 12 g CI oxacillin intravenously over 24 h once daily. The study was approved by both the hospital’s research department and the institutional review board of the University of Texas Health Science Center at San Antonio.
TABLE 1. Comparison of patients treated with CI and II for IE caused by MSSA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for patients treated with:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI or II (overall)</td>
<td>CI (n = 78)</td>
<td>II (n = 29)</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>41 (18–85)</td>
<td>40 (18–85)</td>
</tr>
<tr>
<td>Male gender</td>
<td>77 (72)</td>
<td>56 (74)</td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27 (25)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>76 (71)</td>
<td>60 (77)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Median body mass index (range)</td>
<td>24 (11–72)</td>
<td>24 (11–72)</td>
</tr>
<tr>
<td>Median creatinine clearance (range)</td>
<td>85 (15–262)</td>
<td>85 (15–248)</td>
</tr>
<tr>
<td>Risk factors/comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG†</td>
<td>4 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hemodialysis dependent</td>
<td>7 (7)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (23)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>IDU</td>
<td>86 (80)</td>
<td>63 (81)</td>
</tr>
<tr>
<td>Preexisting mechanical valve</td>
<td>8 (8)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>History of infective endocarditis</td>
<td>20 (19)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>HIV† positive</td>
<td>8 (8)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two major criteria</td>
<td>85 (79)</td>
<td>62 (79)</td>
</tr>
<tr>
<td>One major criterion</td>
<td>22 (21)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Presenting signs/symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever/temp of &gt;38°C†</td>
<td>91 (85)</td>
<td>65 (83)</td>
</tr>
<tr>
<td>Chills</td>
<td>60 (56)</td>
<td>48 (62)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>14.5</td>
<td>15</td>
</tr>
<tr>
<td>WBC count (×1,000 cells per μl)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Janeway’s lesions</td>
<td>8 (8)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Septic emboli</td>
<td>31 (29)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>59 (55)</td>
<td>43 (55)</td>
</tr>
<tr>
<td>Osler’s nodes</td>
<td>8 (8)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Splinter hemorrhage</td>
<td>7 (7)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Poor dentition</td>
<td>35 (33)</td>
<td>26 (33)</td>
</tr>
</tbody>
</table>

*Values are numbers (percentages) unless indicated otherwise.
†The body mass index was calculated as follows: weight (kg)/height (m²).
‡Creatinine clearance was determined by the Cockcroft-Gault method.
§CABG, coronary artery bypass graft.
¶HIV, human immunodeficiency virus.
∥The mean temperatures were 38.3°C for all patients treated with CI or II, 38.8°C for the patients treated with CI, and 38.3°C for the patients treated with II (P = 0.6).

Inclusion criteria. Data from patients admitted to University Hospital between 1 January 2000 and 31 December 2007 were included. Patients were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification codes for endocarditis (18a). Patients 18 years and older, with absolute neutrophil counts of ≥1,000 cells/mm³, who met modified Duke’s criteria for IE and bacteremia (≥2 positive cultures from blood samples drawn 12 h apart, all of 3 blood samples positive; or a majority of ≥4 separate cultures of blood positive) with MSSA were eligible for inclusion in the study. Definite IE caused by MSSA was defined, per AHA evidence-based guidelines and modified Duke’s criteria, as having two major, one major and three minor, or five minor criteria (6, 14). Inclusion was determined by review of microbiological data, echocardiographic imaging, physical exam, and vital signs contained in the patient’s electronic medical record. Patients also must have received oxacillin for treatment using one of the two dosing regimens described above or, for patients who had previously existing hepatic dysfunction or who developed hepatic dysfunction (12), a reduced daily dose of 8 g, the maximum manufacturer-recommended dose.

Exclusion criteria. Patients were excluded if they failed to meet modified Duke’s criteria for IE caused by MSSA, had IE due to an unidentifiable organism or an organism other than MSSA, or received IE treatment with a drug other than oxacillin (use of nafcillin was not evaluated). Other reasons for exclusion included incomplete medical records without follow up, such as for patients transferred to University Hospital during treatment or who transferred to an outside hospital from University Hospital prior to completion of their therapy. Patients who were switched from one method of drug administration to another (II to CI or CI to II) during treatment were also deemed ineligible for inclusion. Finally, patients who died in the hospital were excluded from analyses of length of stay and duration of antibiotic therapy.

Data. Data were collected from patients’ electronic medical records and documented on standardized data collection sheets. Patient demographics, baseline laboratory values, preexisting and predisposing conditions, signs and symptoms on admission, microbiology results, anti-infective therapy, evidence of fever (temperature of >38°C), lengths of hospital and ICU stays, and mortality data were collected.

TABLE 2. Sites of IE infection

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. (%) of patients treated with:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI or II (overall)</td>
<td>CI (n = 78)</td>
</tr>
<tr>
<td>Left side</td>
<td>37 (35)</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Right side</td>
<td>40 (37)</td>
<td>29 (37)</td>
</tr>
<tr>
<td>Both sides</td>
<td>7 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>None*</td>
<td>23 (21)</td>
<td>19 (24)</td>
</tr>
</tbody>
</table>

*Patients either did not demonstrate evidence of vegetation on the echocardiogram or did not receive an echocardiogram, having already met definitive IE criteria. The site of infection was determined by either a transthoracic echocardiogram or a transesophageal echocardiogram.
## RESULTS

Of the 709 patient charts reviewed, 528 were excluded because of bacteremia due to another organism or because an organism was not identified, 68 were excluded due to not meeting modified Duke’s criteria, and 6 were excluded because the patients had not received treatment with oxacillin. Comparisons of patient characteristics are presented in Table 1. The 107 adult patients had a median age of 41 (range, 18 to 85) years. Most patients were Hispanic (71%) and male (72%). Eighty percent had a history of intravenous drug use (IDU). Despite the high percentage of intravenous drug users in the study, the infected heart valves were evenly distributed between the left and right sides; 35% on the left side, 37% on the right side, 7% on both sides, and 21% having no identified vegetation either because echocardiography was negative or because the patients did not receive an echocardiogram, having already been diagnosed with IE by modified Duke’s criteria (e.g., one major and three minor criteria). See Table 2 for a complete breakdown of site of infection by method of administration.

Overall, microbiological cure, 30-day mortality, and median time to clearance of bacteremia were 90.7% (97/107 patients), 8.4% (9/107 patients), and 7 (1 to 42) days, respectively (see Table 3 for complete results).

### CI versus II oxacillin

Seventy-eight patients received CI oxacillin, whereas 29 received II oxacillin (Table 4). CI and II groups were similar with respect to 30-day mortality (8% versus 10%, respectively; P = 0.7) and length of hospital stay (20 versus 25 days, respectively; P = 0.4) but differed for microbiological cure at 30 days (94% versus 79%, respectively; P = 0.03).

#### Synergistic gentamicin versus no gentamicin

Because synergistic gentamicin is an optional treatment modality per guidelines, a subgroup analysis was performed to detect whether the use of synergistic gentamicin influenced mortality, hospital length of stay, microbiological cure at 30 days, clearance of bacteremia, or time to defervescence. The intended length of gentamicin therapy was physician specific and was not controlled in this study. The median number of days of gentamicin therapy was 4, with a range of 1 to 14 days. Overall, the gentamicin versus no-gentamicin groups were similar with respect to outcomes tested; however, the median times to defervescence and hospital length of stay were longer in the no-gentamicin group.

---

### TABLE 3. Subgroup analysis of synergistic gentamicin use overall

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of patients or days</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With gentamicin (n = 63)</td>
<td>Without gentamicin (n = 44)</td>
<td></td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>7 (11)</td>
<td>2 (5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>20</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>30-Day microbiological cure</td>
<td>57 (91)</td>
<td>39 (89)</td>
<td>0.8</td>
</tr>
<tr>
<td>Clearance of bacteremia</td>
<td>7</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td>Time to defervescence</td>
<td>4</td>
<td>2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Results represent the numbers of days (median values for clearance of bacteremia), except results for 30-day mortality and 30-day microbiological cure, which represent the numbers (percentages) of patients.

### TABLE 4. Primary and secondary outcomes for patients receiving CI versus II oxacillin

<table>
<thead>
<tr>
<th>Outcome or parameter</th>
<th>CI or II (overall)</th>
<th>CI (n = 78)</th>
<th>II (n = 29)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day microbiological cure</td>
<td>97 (91)</td>
<td>73 (94)</td>
<td>23 (79)</td>
<td>0.03</td>
<td>3.8 (1.06–13.6)</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>21</td>
<td>20</td>
<td>25</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>9 (8)</td>
<td>6 (8)</td>
<td>3 (10)</td>
<td>0.7</td>
<td>0.7 (0.2–3.1)</td>
</tr>
<tr>
<td>Clearance of bacteremia</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Time to defervescence</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>42</td>
<td>42</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent administration of gentamicin</td>
<td>63 (59)</td>
<td>40 (51)</td>
<td>23 (79)</td>
<td>0.009</td>
<td>0.3 (0.1–0.8)</td>
</tr>
</tbody>
</table>

* Results represent the numbers of days (median values for clearance of bacteremia and time to defervescence), except results for 30-day microbiological cure, 30-day mortality, and concurrent administration of gentamicin, which represent the numbers (percentages) of patients.

* LOS, length of stay.

* Gentamicin was administered at 1 mg/kg of body weight for every 8-h dosing period.

---
between patients who received synergistic gentamicin (n kidney injury (chronic kidney disease were excluded from analyses of acute patients receiving hemodialysis and those having preexisting noted. These results are shown graphically in Fig. 1. Rates of acute kidney injury were also compared for those patients vs II oxacillin without gentamicin), no statistically sig-
ificant differences in the primary or secondary outcomes were
comparing within groups (CI oxacillin with gentamicin versus CI oxacillin without gentamicin and II oxacillin with gentamicin versus II oxacillin without gentamicin), no statistically significant differences in the primary or secondary outcomes were noted. These results are shown graphically in Fig. 1. Rates of acute kidney injury were also compared for those patients receiving synergistic gentamicin and those that did not. Patients receiving hemodialysis and those having preexisting chronic kidney disease were excluded from analyses of acute kidney injury (n = 7). Rates of acute kidney injury were similar between patients who received synergistic gentamicin (n = 60) and those who did not receive synergistic gentamicin (n = 40) (18% versus 7%, respectively; P = 0.1).

Multivariable analysis. Patient characteristics identified as being statistically different between the two treatment groups (CI versus II oxacillin) were included in a multivariable regression model. Results of the model are included in Table 6. The antibiotic regimen (i.e., CI versus II) was the only independent factor responsible for microbiological cure at 30 days after a stepwise logistic regression analysis (P = 0.04). Neither antibiotic regimen (i.e., CI versus II) nor any of the clinically relevant factors (i.e., age, WBC count, chills, hemodialysis, synergistic gentamicin, or days on gentamicin therapy) were independently responsible for time to defervescence after a stepwise logistic regression analysis.

Comparative safety profiles. The safety of the study drug was also examined. There were two patients in each arm of the analysis who experienced transaminitis (CI group, n = 2; II group, n = 2), defined as normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increasing to greater than three times the upper limits of normal or, if AST/ALT levels were elevated at the start of therapy, doubling from baseline.

All of the patients experiencing transaminitis were included in the analysis of all outcomes. Each of the four patients had at least one risk factor for developing transaminitis at the start of

### TABLE 5. Subgroup analysis of synergistic gentamicin use per method of administration

<table>
<thead>
<tr>
<th>Group a</th>
<th>Outcome</th>
<th>No. (% of patients or days b</th>
<th>P value</th>
<th>OR (95% CI) c,d</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI-gent (n = 41) vs CI-no gent (n = 37)</td>
<td>30-Day mortality</td>
<td>With gentamicin: 5 (12)</td>
<td>0.2</td>
<td>2.0 (0.3–11.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without gentamicin: 1 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital LOS d</td>
<td>18</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-Day microbiological cure</td>
<td>39 (95)</td>
<td>0.7</td>
<td>4.5 (0.5–43)</td>
</tr>
<tr>
<td></td>
<td>Clearance of bacteremia</td>
<td>6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to defervescence</td>
<td>4</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of gentamicin treatment</td>
<td>3</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>II-gent (n = 23) vs II-no gent (n = 6)</td>
<td>30-Day mortality</td>
<td>With gentamicin: 3 (13)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Without gentamicin: 0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospital LOS d</td>
<td>30</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-Day microbiological cure</td>
<td>18 (78)</td>
<td>1</td>
<td>0.7 (0.1–7.7)</td>
</tr>
<tr>
<td></td>
<td>Clearance of bacteremia</td>
<td>7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to defervescence</td>
<td>5</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of gentamicin treatment</td>
<td>5</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

a CI-gent, CI oxacillin with gentamicin; CI-no gent, CI oxacillin without gentamicin; II-gent, II oxacillin with gentamicin; II-no gent, II oxacillin without gentamicin.

b Results represent the numbers of days (median values for clearance of bacteremia, time to defervescence, and duration of gentamicin treatment), except results for 30-day mortality and 30-day microbiological cure, which represent the numbers (percentages) of patients.

c OR, odds ratio; 95% CI, 95% confidence interval.

d LOS, length of stay.

![FIG. 1. Outcomes of oxacillin therapy for patients with IE caused by MSSA. CI-Gent, CI oxacillin with gentamicin; CI-No Gent, CI oxacillin without gentamicin; II-Gent, II oxacillin with gentamicin; II-No Gent, II oxacillin without gentamicin.](http://aac.asm.org/)

### TABLE 6. Results of multivariable logistic fit for microbiological cure

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>0.01</td>
</tr>
<tr>
<td>Synergistic gentamicin treatment</td>
<td>0.32</td>
</tr>
<tr>
<td>Days on gentamicin therapy</td>
<td>0.13</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.52</td>
</tr>
<tr>
<td>Chills</td>
<td>0.45</td>
</tr>
<tr>
<td>WBC count</td>
<td>0.48</td>
</tr>
<tr>
<td>Age</td>
<td>0.89</td>
</tr>
</tbody>
</table>
therapy. Risk factors included hepatitis C infection, a history of ethanol abuse, and a history of cirrhosis. Two patients, both in the CI group, had normal AST/ALT levels at the start of therapy, while the other two patients in whom transaminitis occurred were in the II group and had elevated AST/ALT levels at the start of therapy. One patient in each treatment group was switched from oxacillin to another antibiotic after receiving at least 31 days of CI oxacillin and 35 days of II oxacillin. The two patients who switched therapies completed 42 days of treatment on vancomycin and ceftazolin, respectively. All four patients remained culture negative at 30 days, and none of the four died within 30 days of completing therapy. The transaminitis resolved (returned to start-of-therapy baseline) for all patients.

**DISCUSSION**

The results of this study suggest an improved microbiological cure in patients with IE caused by MSSA treated with CI oxacillin compared to that in patients treated with II oxacillin. Outcomes between treatment groups were similar with respect to 30-day mortality, length of hospital stay, median time to clearance of bacteremia, median time to defervescence, and duration of antibiotic therapy. These findings demonstrate that CI oxacillin is an effective alternative to II oxacillin for the treatment of IE caused by MSSA. The CI method of administration was found to be statistically different from the II method for the primary outcome of microbiological cure at 30 days. Furthermore, the statistical superiority of CI versus II was preserved in a stepwise logistic regression model. Although statistically different for the primary outcome, these results do not indicate a clinical superiority of CI over II, especially since no difference in mortality between the two groups was seen.

These results are important considering that *S. aureus* has become the primary cause of IE in many parts of the world (4, 9). While methicillin-resistant *S. aureus* has become a concern, MSSA still accounts for the majority of cases of IE caused by *S. aureus* in many recent series (4, 8, 9, 19, 20). Also, other studies have shown that CI of a β-lactam reduces pharmacy preparation time, reduces nursing administration time, and maximizes antimicrobial pharmacodynamics (7). However, difficulties with CI administration do exist, namely, difficulty associated with the requirement for continuous venous access. This can be potentially problematic in patients with limited venous access or in critical-care settings, where patients require the administration of multiple intravenous agents.

A subgroup analysis of concurrent, synergistic gentamicin use illustrated no benefit concerning microbiological cure and an association with higher rates of mortality and acute kidney injury. Our analysis was consistent with previously reported data suggesting that synergistic gentamicin reduces the total number of days that individuals are bacteremic by about 1 day (13). Hastening the time to clearance of bacteremia did not improve overall mortality, and in fact, this investigation highlights a disturbing trend of higher mortality, in both arms and overall, for patients receiving synergistic gentamicin. Further exploration of this practice is warranted.

The decision to use synergistic gentamicin is one of the major limitations of this retrospective investigation. By nature, retrospective studies are more prone to bias than prospective studies. It may be that clinicians treated patients who appeared clinically worse with gentamicin but not those who seemed less ill.

This study population had high rates of IDU and previous endocarditis but was balanced with regard to site of infection (right versus left side). This is surprising considering that previous reports describe mainly right-sided disease in patients that were intravenous drug users (1, 4, 9). Our population had a higher-than-expected incidence of left-sided disease, which is important because these patients tend to have higher failure rates than patients with right-sided IE; however, this did not appear to affect our outcomes (8).

Safety analyses were supportive of the treatment guideline recommendation that synergistic gentamicin be regarded as an optional treatment, as our study found no clinical benefit and numerically high but not statistically different rates of acute kidney injury in the gentamicin-treated group compared to the no-gentamicin group (1).

Hepatotoxicity, although a known side effect of oxacillin, was infrequent, with only 4% (4/107) of patients experiencing transaminitis (3, 10). All cases were limited and reversible, with positive outcomes (microbiological cure and patient survival) in all instances. Although two patients were switched to different drugs to complete therapy, this was unlikely to have affected the patient outcomes.

**Limitations.** There are several limitations to this study. First, this was a single-center analysis with a limited number of patients in the II arm of the study. Second, this analysis was conducted retrospectively; however, a prospective study of this nature requires prohibitive amounts of both time and money. As a result of the retrospective study design, we were unable to control for bias between the two treatment groups and also within a treatment group, such as is seen with the duration of gentamicin therapy in patients that received gentamicin. Also, this study had a relatively large population of intravenous drug users, which in addition to limiting the external validity of the study might account for some microbiological failure. Another limitation is that it is very difficult to assess compliance with home health antibiotic therapy. Despite these limitations, this is, to our knowledge, the first and only study to address the suitability of CI oxacillin for the treatment of IE.

**Conclusion.** CI oxacillin offers a pharmacodynamically optimized treatment regimen for the management of patients with IE caused by MSSA. These results indicate that CI oxacillin is a suitable alternative to II oxacillin and possibly results in better microbiological outcomes. These results are significant when considering the costs associated with prolonged antibiotic therapy. Other evaluations of CI β-lactam antibiotics have found that CI reduces pharmacy preparation time, reduces nursing administration time, maximizes antimicrobial pharmacodynamics, and costs less to prepare and administer (3). More data, including prospective randomized trials, comparing the two methods of oxacillin administration for IE and other serious infections caused by MSSA would be of value to further validate these findings.

**ACKNOWLEDGMENTS**

We thank James H. Jorgensen and Michael W. Ellis for their critical review of this study as well as their helpful comments and suggestions.
No financial support was provided for this study.
We declare no conflicts of interest.

REFERENCES