Two-stage revision of infected hip arthroplasty using an antibiotic-loaded spacer: retrospective comparison between short-term and prolonged antibiotic therapy

Pang-Hsin Hsieh1,2*, Kuo-Chin Huang2,3, Po-Cheng Lee1,2 and Mel S. Lee1,2

1Department of Orthopedics, Chang Gung Memorial Hospital, Taoyuan, Taiwan; 2College of Medicine, Chang Gung University, Taoyuan, Taiwan; 3Department of Orthopedics, Chang Gung Memorial Hospital, Chia-Yi, Taiwan

Received 22 March 2009; returned 15 April 2009; revised 19 April 2009; accepted 23 April 2009

Objectives: The optimal duration of systemic antibiotic therapy in patients with prosthetic hip infection (PHI) undergoing staged exchange arthroplasty (SEA) has not been determined. We hypothesized that with an antibiotic-loaded cement spacer (ALCS), in the interim, short-term antibiotic therapy is as effective as a conventional prolonged treatment course.

Patients and methods: We reviewed 99 patients with PHI who were managed with SEA using an ALCS from February 2002 to October 2005. A standard (4–6 week) antibiotic treatment course was administered in the first 46 patients and a short-term (1 week) therapy was adopted in the subsequent 53 patients.

Results: Eight patients (four in each group) had persistent infection following the first attempt of surgery and antibiotic treatment; in three of them the infection was cured by additional debridement prior to re-implantation. Forty-two (91%) patients in the long-term group and 47 (89%) patients in the short-term group were free of infection (P = 0.67) at an average follow-up of 43 months (range, 24–60 months). Five (11%) patients developed complications related to prolonged antibiotic therapy. The short-term treatment resulted in a shorter hospital stay (18 versus 43 days, P < 0.001) and a lower direct medical cost (US$13732 versus US$21756, P < 0.001).

Conclusions: Short-term antibiotic therapy was not associated with a higher rate of treatment failure. Given the higher costs and incidence of complications, protracted courses of antibiotic administration may not necessarily be routine practice in patients with PHI undergoing SEA, provided that an ALCS is used.

Keywords: antibiotic policy, bone infections, joint infections, orthopaedic surgery

Introduction

Deep infection at the site of a joint implant is a devastating complication, typically resulting in painful disability, prolonged hospital stay and increased medical expenses.1 Treatment of such infection usually involves surgery and antimicrobial therapy. Although debridement alone and one-stage revision have gained some success in selected cases, the current standard surgical procedure in managing prosthetic hip infections (PHIs) is staged exchange arthroplasty (SEA), involving removal of all components with thorough debridement of the infected tissues, followed by a period of antibiotic treatment and re-implantation of a new prosthesis at a later stage.2 The application of an antibiotic-loaded cement spacer (ALCS) in the interim between the stages has become a common approach. The ALCS not only functions as a temporary hip joint implant, but can also be utilized for direct local antibiotic delivery.3

Although SEA has been successful, the optimal duration of systemic antibiotic therapy between stages has not been established. Reported durations vary significantly among studies, ranging from several days to months, with a 6 week period being the most common.3–7 However, most authors adopted a strict
Antibiotics in staged exchange of PHI

This retrospective cohort study included 107 consecutive patients (107 hips) with a clinical diagnosis of PHI who were managed with SEA using an interim ALCS at our institution between February 2002 and October 2005. Cases were identified using the hospital’s electronic database, by matching them to the International Classification of Diseases (ICD) Ninth Revision code, specific for prosthetic joint infection (PJI) (996.66) in the hip joint. After obtaining approval from the Institutional Review Board and informed consent from the participants, medical charts, radiographs and hospital bill records regarding treatment of PHI were reviewed. The series of patients were divided into two groups. Group I comprised 51 patients who were treated between February 2002 and December 2003 and received a 4 week intravenous antibiotic therapy regimen between stages. An additional 2 week oral antibiotic treatment was prescribed when an appropriate antibiotic was available in oral form. Group II comprised the subsequent 56 patients treated between January 2004 and October 2005. These patients received a 1 week intravenous antibiotic regimen after resection arthroplasty.

Eight patients did not complete the minimum 2 year follow-up. Of these, two Group I patients and one Group II patient died of unrelated causes, while three Group I and two Group II patients were lost to follow-up. The study group thus consisted of 99 (46 in Group I and 53 in Group II) patients, comprising 60 men and 39 women (Table 1). The average age at the time of the first-stage surgery was 61 years (range, 22 to 81 years). The average duration of follow-up was 43 months (range, 24 to 60 months).

### Definitions

PHI was defined by the presence of at least one of the following clinical criteria: (i) a discharging sinus communicating with the joint; (ii) operative findings of purulence; or (iii) positive laboratory and histopathological tests as well as the isolation of pathogens from at least two positive results of cultures of joint aspirate or intra-operative specimens. Persistent infection’ was defined as the presence of PHI after first-stage surgery. PHI that occurred after the completion of SEA and antimicrobial therapy was considered ‘re-infection’.

### Table 1. Patient data

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>Average age, years</td>
<td>59 (22–81)</td>
<td>62 (28–76)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>27/19</td>
<td>33/20</td>
</tr>
<tr>
<td>Average follow-up period, months</td>
<td>50 (24–60)</td>
<td>37 (24–48)</td>
</tr>
<tr>
<td>Previous surgerya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary total hip arthroplasty</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>revision total hip arthroplasty</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>bipolar hemiarthroplasty</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>unipolar hemiarthroplasty</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ASA status (I/II/III)b</td>
<td>1/10/35</td>
<td>0/12/41</td>
</tr>
</tbody>
</table>

*Values are given as the number of hips.

*ASA = American Society of Anesthesiologists (grades are as follows: I, good; II, fair; and III, poor).

### Table 2. Antibiotics used in the cement spacers

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=46)</th>
<th>Group II (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin + aztreonam</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Vancomycin + gentamicin</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values are given as the number of hips.

### Antibiotics in the ALCS

The choice of antibiotic(s) was based on the results of bacterial cultures obtained from the draining sinuses or preoperative joint aspirations (Table 2). The antibiotic(s) was/were hand-mixed at a concentration of 8 g per pack with 40 g of cement polymer (Stryker, Limerick, Ireland). If the infecting microorganism could not be identified preoperatively, or the infection was identified during a presumed aseptic operation, then a combination of 4 g of vancomycin (Eli Lilly, Indianapolis, ID, USA) and 4 g of aztreonam (Bristol-Myers Squibb, Princeton, NJ, USA) was added to each 40 g pack of cement.

### Treatment protocol

One senior surgeon performed all operations. The first stage consisted of the removal of the infected components, debridement and implantation of the ALCS, followed by systemic antibiotic therapy for 4–6 weeks (Group I) or a short-term, 1 week treatment course (Group II). The antibiotic was chosen according to the preoperative microbiological test. If the organism could not be identified before surgery, then a combination of a first-generation cephalosporin and gentamicin was given intravenously and then modified according to the results of cultures performed intra-operatively (Table 3). Laboratory monitoring, including complete blood cell counts and serum levels of creatinine, was performed weekly during hospitalization. The patients were discharged when the wound was dry and no
intravenous antibiotics were given. Adverse effects of antibiotic use, including nephrotoxicity (defined as a serum creatinine increase of 0.5 mg/dL or 50%, whichever was greater during the interim period) and neutropenia (defined as <1500 absolute neutrophil count per mL of blood), were recorded. Serum level of C-reactive protein (CRP) was checked every 2 weeks in the interim period. Infection was considered eradicated if CRP levels were <15 mg/L and there was no wound inflammation.

The second stage of the procedure was conducted when the PHI was considered eradicated and surgery was medically feasible. If bone cement was used to fix the components at re-implantation, 2 g of antibiotic(s) (the same as used in the antibiotic spacer) was/were added to each 40 g pack of cement polymer. All patients were given intravenous antibiotics for 3 days following re-implantation. No additional antibiotics were given thereafter.

### Clinical, radiological and medical cost evaluation

The patients were examined at 1, 3 and 6 months and 1 year, and then annually after operation. Clinical data were collected by reviewing the medical records of the patients. The functional status of each patient was recorded before the operation and at the latest follow-up according to the d’Aubigné and Postel hip score in terms of pain, ambulation and mobility. A cup loosening was defined radiographically as any change in the cup angle of >3°, a cup migration of >5 mm or a complete radiolucency of >1 mm. The cemented femoral components were measured for loosening based on the criteria described by Harris, and the cementless stems were assessed according to the system developed by Engh et al.

The direct medical cost, including costs for surgical treatment, medication and hospitalization during hospital stays and outpatient visits, of all patients was determined by examining the hospital records of payments made by insurance providers and co-payments made by the patients.

### Statistical analysis

A $\chi^2$ analysis or a Fisher’s exact test was used where appropriate for analysing categorical data. For numerical data, an independent $t$-test or the non-parametric Mann–Whitney $U$-test were utilized for between-group comparisons. The Wilcoxon rank sum test was used to examine the variation of hip score pre- and post-surgery. Statistical significance was defined as $P<0.05$. All statistics were two-sided and performed using SAS software (version 9.1.3, SAS Inc., Cary, NC, USA).

### Results

#### Treatment of infection

Among the 99 patients in this series, infection was eradicated in 91 after the first-stage surgery and antibiotic treatment. Eight patients (four from each group) had persistent infection, as indicated by severe hip pain, high CRP levels and poor wound healing. The persistent infection was attributed to inadequate debridement with retained cement in five patients and an immunocompromised status (liver cirrhosis, chronic steroid use) in the other three patients. Three of these eight patients (two from Group I and one from Group II) required an additional debridement before final re-implantation. Infection persisted in four patients (two from each group) even after repeated debridement and re-implantation was contraindicated. One patient (from Group II) did not receive further surgery because of advanced cardiovascular disease. Specific information pertaining to each persistent infection case is summarized in Table 4.

The success rate of infection treatment, as defined by the eradication of infection, was 92% (91 of 99) after the initial surgery and antibiotic therapy. This rose to 95% (94 of 99) following additional debridement.

In these 94 patients (44 from Group I and 50 from Group II) who had undergone re-implantation surgery, re-infection was seen in five cases (two from Group I and three from Group II), occurring at an average of 11 months (range, 4 to 19 months) after re-implantation. All re-infection cases were treated with removal of the prosthesis without further re-implantation. No other patients received debridement, revision or antibiotic treatment for PHI during the follow-up period. Thus, a total of 89 patients (90%; 89 of 99) were free of infection at the latest follow-up; 91% (42 of 46; 95% CI: 83%–100%) in Group I, and 89% (47 of 53; 95% CI: 80%–97%) in Group II ($P=0.67$). The between-group difference in success rate was 2.6% (95% CI, −9.6%–14.7%).

### Table 3. Infecting microorganisms

<table>
<thead>
<tr>
<th></th>
<th>Group I ($n=46$)</th>
<th>Group II ($n=53$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus, methicillin-susceptible</strong></td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus, methicillin-resistant</strong></td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td><strong>Staphylococcus, coagulase-negative</strong></td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Streptococcus</strong></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Enterococcus</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Unidentified Gram-negative bacillus</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>No growth</strong></td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are given as the number of hips.
Clinical and radiological results

As Table 5 shows, both groups had similar average d’Aubigné and Postel hip scores before surgery ($P = 0.5$); both groups achieved major improvements over preoperative values (both $P < 0.001$). The hip scores were not significantly different at the final follow-up between groups ($P = 0.8$). The mean interim period duration was similar in both groups ($P = 0.25$). Patients in Group I had significantly more total hospitalization days (43 versus 18 days, $P < 0.001$) and had significantly higher direct medical costs (US$21756 versus US$13732, $P < 0.001$) than those in Group II.

Radiographic results indicated evidence of loosening with a complete radiolucency in one cementless acetabular cup (in Group I) at 3 years. Two acetabular cages appeared to be unstable with evidence of migration and broken screws (one in each group). There was no evidence of infection in any of these patients (aspirations were negative and CRP levels normal); hence, they were deemed to be aseptic failures. All three patients underwent re-revision surgery and recovered without incident. All femoral components appeared stable on the radiographic examination.

Complications

Early complications included eight persistent infections after the first-stage procedure as mentioned earlier. Five patients (all from Group I) developed complications related to systemic antibiotic therapy. Four patients had nephrotoxicity, and the remaining patient had both nephrotoxicity and neutropenia. All five patients were given intravenous vancomycin, and three of them had combined therapy of vancomycin and gentamicin. The nephrotoxicity and neutropenia resolved following discontinuation of antibiotics or a change of antibiotic regimen.

Late complications included re-infection in five patients and aseptic loosening in three patients, as already described. Two patients (from Group II) suffered periprosthetic fractures of the femur after re-implantation and thus required further fracture repair surgery. These patients thereafter recovered without further incident.

Discussion

To our knowledge, this investigation is the first to compare the outcomes of short-term and prolonged antibiotic therapy in patients with an infected hip arthroplasty treated by using SEA with an interim ALCS. The rate of successful treatment for infection was 90%. This compares favourably with outcomes reported by others.3–7,19,20 Although we were initially concerned that short-term antibiotic treatment would provide insufficient antimicrobial coverage, this approach was not associated with a higher rate of re-infection when performed with an ALCS in situ.

Studies have demonstrated that the release of antibiotics from an ALCS is ample and sustained.8,9 Masri et al.5 in a study of the in vivo antibiotic elution from ALCSs in hips and knees, noted that high therapeutic levels of antibiotics in the joint fluid continued for at least 4 months when at least 3.6 g of tobramycin and 1 g of vancomycin were loaded per 40 g package of bone cement. Hsieh et al.9 analysed (in 46 hips) the elution of antibiotics from custom-made, cement-on-cement ALCSs containing 4 g of vancomycin and 4 g of aztreonam per batch of bone cement.
cement. Their results indicated that the release was prompt and abundant, and that the antibiotics maintained their therapeutic activity for several months.

A radical debridement is essential to the success of infection treatment. Five of the eight patients who failed the first-stage surgery had inadequate debridement with retained cement. McDonald et al., in a report on the results of SEA in 82 patients with PHI, indicated that recurrence of infection occurred in three of seven patients who had retained cement, while only eight recurrences were found from the other 75 patients from whom the cement had been completely removed. We recommend creating cortical windows on the femur as soon as retained cement is suspected in the medullary canal.

The optimal timing of the re-implantation surgery continues to be controversial. Previous reports have recommended various intervals between stages, ranging from 1 month to 1 year.5,6,21 We prefer adopting the CRP level as an indicator to monitor the efficacy of treatment, which we believe is a more practical strategy than adhering to a fixed interval. Although the measurement of CRP is not specific to infection, it is sensitive, readily available and most valuable when serially monitored.22 In this study, no difference was observed in the interim period duration between the two groups when CRP level was applied to guide the timing of the second-stage surgery.

Five patients in our series developed adverse events related to the prolonged administration of systemic antibiotics. All of these patients were given intravenous vancomycin, and three of them had concurrent use of gentamicin. Reported incidence of nephrotoxicity from vancomycin alone ranged from 6.5% to 10.7%, but the risk can be up to 35% among patients receiving concomitant vancomycin and aminoglycoside therapy.12,23 Vancomycin-induced neutropenia is a rare but potentially serious adverse drug reaction, and all reported cases were associated with prolonged use (>12 days).24 Although in the present series nephrotoxicity and neutropenia appeared asymptomatic and self-limiting, our current practice is to avoid the combined use of vancomycin and aminoglycoside; restrict vancomycin use to no more than 1 week and switch to another structurally related agent, such as teicoplanin, when long-term parenteral antibiotic therapy is absolutely necessary.

The treatment of PHI can have substantial economic implications for patients, payers and health-care providers. Bozic and Ries18 observed that, an infected hip arthroplasty increased the average of direct medical costs by 2.8 and 4.8 times and increased the length of hospital stay by 3.5 and 4.5 times compared with revision arthroplasty because of aseptic loosening and primary total hip arthroplasty, respectively. In the present study, a shortened antibiotic protocol was linked with 25 fewer hospitalization days and 37% lower total direct medical costs than the traditional 4–6 weeks of antibiotic therapy. Satisfactory clinical outcome was not compromised by the shortened treatment duration. Our findings indicate that decreasing the duration of antibiotic treatment may reduce the economic burden associated with treating this devastating complication and, as a consequence, facilitate improved healthcare resource utilization.

The use of a shortened antibiotic therapy between stages is not new.4,25–27 Stockley et al.26 reported a success rate of 87.7% (100 of 114) in infection control with depot antibiotic treatment in the absence of long-term antibiotic therapy in PHI. Nelson et al., in a study of 28 patients who had an infection at the site of a hip or knee arthroplasty, reported that patients who were managed with the implantation of antibiotic cement beads in conjunction with <5 days of parenteral antibiotic therapy, and those who were managed with 6 weeks of intravenous antibiotic therapy, had comparable results.

A weakness of the present study is its retrospective nature with the inherent limitations of such a study design. The analysis could only be conducted on the basis of the numbers of patients available, the treatment of each patient was not randomized, follow-up was relatively short and patients treated later might have benefited from improved techniques acquired over time. The strengths include a relatively large series of patients with a high rate of follow-up and the fact that a single surgeon treated all of these patients with similar techniques.

Data from our retrospective study demonstrate that short-term (as compared with longer-term) antibiotic therapy in SEA does not lead to a higher rate of treatment failure in patients who have PHI. The hospitalization days and the medical costs could be reduced, provided radical debridement is performed and an ALCS is implanted. These findings imply that the routine use of

---

**Table 5. Summary and comparison of clinical variables between the two patient groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (95% CI)</th>
<th>Group II (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hips</td>
<td>46</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Hip score (points)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preoperative</td>
<td>8.2 (7.6–8.7)</td>
<td>7.9 (7.4–8.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>final follow-up</td>
<td>15.1 (14.7–15.5)</td>
<td>15.0 (14.6–15.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Interim period duration (days)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>93 (89–97)</td>
<td>90 (86–94)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hospital stay (days)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>43 (41–45)</td>
<td>18 (16–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Direct medical cost (US$)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>21 756 (20 715–22 796)</td>
<td>13 732 (12 740–14 724)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are presented as means (ranges).

<sup>b</sup>According to the d’Aubigné and Postel scoring system.13

<sup>c</sup>There were five pieces of missing data due to persistent infection without re-implantation.

<sup>d</sup>Significantly different, P < 0.05.
protracted antibiotic treatment courses may not be warranted. There is a need for a large scale, prospective, longer duration randomized clinical trial to confirm the findings reported herein.

Acknowledgements

We thank Zoe Chen for her assistance with data collection and statistical analysis.

Funding

This study was carried out as part of our routine practice and received no funding.

Transparency declarations

Conflicts of interest: none to declare.

References