Choice and Doses of Antibacterial Agents for Cement Spacers in Treatment of Prosthetic Joint Infections: Review of Published Studies

D. Iarikov,1 H. Demian,2 D. Rubin,3 J. Alexander,1 and S. Nambiar1

1Center for Drug Evaluation and Research, Office of New Drugs, Division of Anti-Infective Products, 2Center for Devices and Radiological Health, Office of Device Evaluation, Division of Surgical, Orthopedic, and Restorative Devices, and 3Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics, US Food and Drug Administration, Silver Spring, Maryland

Background. Addition of antibacterial drugs to interim antibacterial cement spacers (ACSs) is considered to be standard of care for surgical revision in prosthetic joint infections (PJIs). We reviewed published studies evaluating the choice and doses of antibacterials in spacers.

Methods. We conducted a PubMed search of all clinical study reports evaluating the use of ACSs in a 2-stage hip or knee arthroplasty for treatment of PJI (1988 through August 2011). The trial design, antibacterials used, and end points studied were analyzed.

Results. No randomized trials were found comparing either ACSs with different concentrations of antibacterials or ACSs with or without antibacterials. Most of the studies were uncontrolled and used various time points to evaluate the outcome. Twenty publications that reported doses of antibacterials in spacers and had a follow-up of ≥24 months after the second stage were selected for review. Most ACSs included vancomycin and aminoglycosides. The doses of aminoglycosides and vancomycin ranged from 0.25 to 4.8 g and from 1 to 4 g, respectively, per 40 g of cement. No association between reported eradication of the infection and antibacterial load was found.

Conclusions. Published data do not allow evaluation of whether antibacterials in temporary cement spacers provide additional benefits in the treatment of PJI, compared with systemic antibacterials, and are not sufficient to support recommendations on dosages. Complications of ACSs have not been consistently analyzed. Prospective randomized trials comparing spacers with and without antibacterials or spacers with different loads of antibacterials are needed to evaluate the safety and efficacy of ACSs.

Interim antibacterial cement spacers (ACSs) are considered standard of care for the treatment of late chronic prosthetic joint infection (PJI) [1–4]. The spacer is implanted during a 2-stage revision arthroplasty for approximately 6–8 weeks after removal of an infected prosthesis, to deliver antibiotics locally, stabilize the limb, and facilitate reimplantation of the permanent prosthesis. The patients also receive systemic antibacterials during this period.

The type of antibacterials used in ACSs varies, with aminoglycosides and vancomycin most commonly used. With regard to antibacterial load, ACSs have been divided into low and high dose, defined as ≤1 g and >3.6 g of powdered antibacterial, respectively per 40 g of bone cement [5]. Experts and professional societies recommend that only ACSs with higher antibiotic loads be used for the treatment of PJI [1, 2, 5, 6]. Thus, it has been suggested that the “minimum” dose of antibacterials should be 2 g of vancomycin and 2.4 g of tobramycin or gentamicin, whereas a “typical” dose should be 4 g of vancomycin and 4.8 g of an aminoglycoside (all doses per 40 g of cement) [1].

To evaluate the quality of evidence supporting the choice and doses of antibacterials for ACSs, we reviewed studies reporting the results of a 2-stage knee...
and/or hip arthroplasty and compared infection eradication rates associated with spacers of different antibacterial composition. We also reviewed literature on the safety of ACSs.

**MATERIALS AND METHODS**

A systematic review of journal articles in English was conducted by searching the PubMed database and by reviewing bibliographies of the selected articles. The key words “antibiotic spacers” and “two-stage arthroplasty” were used. The search period includes studies published since 1988. The database was last accessed in August 2011. Studies had to meet the following inclusion criteria: (1) the results of 2-stage hip and/or knee arthroplasties with ACSs were reported; (2) the ACS antibacterial content could be calculated per 40 g of cement; (3) all patients in a study received ACS of similar antibacterial composition; and (4) the follow-up period after the second stage of the procedure was ≥24 months.

The primary end point in our review was the infection eradication rate at the end of a 2-year follow-up, calculated as the ratio of joints remaining free of infection during follow-up to the total number of joints operated on. The 2-year follow-up period was selected based on estimations that PJI diagnosed up to 24 months postoperatively is caused by intraoperative contamination, but later infections are attributed to hematogenous seeding [7, 8]. Eradication rates were calculated per joint rather than per patient. Data for articulating and static spacers were combined.

Failure to eradicate infection was declared under any of the following circumstances: (1) persistent infection after spacer placement, defined as a need for repeated surgery or positive surgical culture at the time of permanent prosthesis implantation; (2) infection after implantation of the permanent prosthesis that occurred during a follow-up period of ≥2 years, including infections with a different organism; and (3) arthrodesis or amputation performed to control the infection during the follow-up period. Failure to complete 2-year follow-up because of loss to follow-up, death within 2 years after the second stage, or death after the first stage if a patient did not undergo the second stage by that time were also counted as noneradication of infection, because the absence of infection 2 years after surgery could not be reliably imputed. Patients who retained the spacer for >2 years without signs of infection or who underwent arthrodesis or amputation for reasons not related to infection were not considered to represent failures to eradicate infection.

Information on mortality and systemic toxicities associated with ACSs was reviewed. For this analysis, studies including case reports with information on renal, vestibular, or ototoxicity were reviewed, regardless of the duration of follow-up or differences in spacer antibacterial compositions. Complications related to mechanical failure of the ACSs were not analyzed. Information on pathogens cultured at the time of ACS implantation was collected.

**RESULTS**

Twenty publications met the inclusion criteria and reported the results of knee (n = 12), hip (n = 7), and both hip and knee (n = 1) arthroplasty Table 1. There were 824 patients and 836 infected joints, including 587 patients with 591 infected knee and 237 patients with 245 infected hip prostheses. No randomized clinical trials were found comparing either ACSs with different concentrations of antibacterials or with no antibacterials. All studies of knee spacers were case series without controls. One prospective randomized trial compared patients treated with or without ACSs for prosthetic hip infection [9].

The publications varied in terms of inclusion criteria, spacer antibiotic load, definition of infection and infection recurrence, duration of follow-up, and timing of assessment. Not all studies required positive pre- or intraoperative cultures as long as intraoperative tissue evaluations and clinical findings were consistent with PJI. Most studies included infections that occurred 30 days after arthroplasty without specifying the actual duration of the infection. One report included acute and hematogenous infections [10]. Information on patients’ immune status, baseline comorbid conditions, and the number of previous surgeries was frequently either lacking or incomplete.

Different criteria were used for outcome evaluation. Deaths, losses to follow-up, and refusals of reimplantation were excluded from calculation of infection rates in a number of studies [10–16]. Infection with a different microorganism in the same joint was not counted as failure in one study [17] but was considered failure in others [18–20]. Some investigators did not consider revision of ACSs due to infection or positive cultures at the time of reimplantation as a failure to eradicate infection if the patients eventually underwent reimplantation and remained infection free [15].

**Infection Eradication Rates**

Infection eradication rates were calculated using criteria specified in the Materials and Methods. These infection rates may differ from those reported by the authors (Table 1). Infection eradication rates ranged from 46% to 100% by our estimation and from 73% to 100% by authors’ estimation (Table 1). Retrospective design and different levels of detail provided do not allow a combined analysis. Overall, no obvious difference in infection eradication rates were seen when cements with different antibacterial loads and compositions were used.
The susceptibility of the PJI isolates was not reported in most publications. In some instances, however, a substantial proportion of isolates were resistant to antibacterials in spacers. A study of vancomycin-laden spacers reported that although 31.5% of the isolates were aerobic gram-negative rods, the infection eradication rate was 89.1% [9]. Another study of 10 patients, 3 of whom were infected with aerobic gram-negative rods, reported an infection eradication rate of 100% after implantation of vancomycin impregnated knee spacers [21]. It seems that in these cases infection was eradicated with systemic therapy without contribution of locally delivered antibacterials.

Because 6 of the reviewed studies used spacers with aminoglycosides only [11, 14, 18, 19, 22, 23], we reviewed publications on aminoglycoside resistance among PJI isolates (Table 2).

<table>
<thead>
<tr>
<th>Study by Arthroplasty Site</th>
<th>Patients, No./ Joints, No.</th>
<th>Spacer Antibiotic Content (Dose, g/40 g Cement)</th>
<th>Infection Eradication Ratea By Review As Reported by Authors Deathsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[17]c</td>
<td>1995–2002</td>
<td>12/23</td>
<td>18/23 (78)</td>
</tr>
<tr>
<td>[48]</td>
<td>Not reported</td>
<td>12/12</td>
<td>12/12 (100)</td>
</tr>
<tr>
<td>[12]c</td>
<td>1998–2001</td>
<td>22/22</td>
<td>20/22 (90)</td>
</tr>
<tr>
<td>[10]c</td>
<td>1993–1997</td>
<td>24/24</td>
<td>24/24 (88)</td>
</tr>
<tr>
<td>[23]c</td>
<td>2001–2006</td>
<td>40/40</td>
<td>38/40 (95)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

a The joint eradication rate is given as No. of joints of joints free of infection/No. of joints operated on (%).

b Deaths within 2 years after the second stage of arthroplasty.

c Only infections with original organisms were included in the authors’ outcome evaluation.

d Not every death, loss to follow-up, or refusal of reimplantation was included in the authors’ assessment of outcome.

e The timing of death was not clearly indicated.

f Patients in the study received 2 weeks of systemic antibiotics between the first and second stages, compared with ≥6 weeks in most studies.

g Prospective randomized trial comparing antibacterial cement spacers with 2-stage arthroplasty without spacers; the other studies are case series without controls.

h In this study, 2 g of vancomycin was added to a pack of cement used to fixed the proximal part of the spacer.
The safety of ACSs was further evaluated in studies otherwise not meeting inclusion criteria for the efficacy review but providing information on systemic adverse events [28–32] (Table 3). In addition, case reports of renal impairment associated with ACSs were reviewed [33–36]. Rates of renal impairment after ACS placement ranged from 0% to 10%. A retrospective analysis of 82 patients implanted with hip spacers reported 5 cases of acute renal failure (6%) and no cases of otoxicity or hepatic failure [31]. Two patients required dialysis and 1 died. Most spacers were impregnated with 0.5 g of gentamicin and 2 g of vancomycin per 40 g of bone cement. However, a noncomparative retrospective design of the study does not allow conclusions to be drawn regarding the relationship between spacers and renal failure.

A retrospective study of 34 patients reported a case of transient rise in serum creatinine and no other systemic side effects after implantation of knee spacers loaded with 4.8 g of gentamicin and 4 g of vancomycin per batch of cement per 40 g [28]. Serum concentrations of gentamicin or vancomycin were not reported. Another study reported no renal, vestibular, or hearing changes after [18]. Some support for the recommended doses was provided by a study reporting that the intra-articular concentrations of

Four reports described 5 patients with acute renal insufficiency attributed to ACSs [33–36]. Four of 5 patients had normal renal functions before surgery, and the other patient had a history of renal insufficiency. All of the spacers included gentamicin or tobramycin with addition of vancomycin [34, 36], vancomycin and cefuroxime [34] or cefazolin [35]. The amount of aminoglycosides and vancomycin per 40 g of cement ranged from 0.5 to 3.6 g and from 2 to 3 g, respectively. Four patients had aminoglycoside levels ranging from 2.0 to 5.5 μg/mL while they were not receiving systemic aminoglycosides [33–35]. Three patients required hemodialysis. The spacers were removed in 4 cases, with subsequent improvement in renal function. One patient treated with hemodialysis retained the spacer, and her renal function normalized within 2 months after surgery [30].

In 3 cases, elevated creatinine levels were noticed within days after surgery. Two patients, however, developed renal insufficiency 1.5 and 5 months after surgery [34]. The latter patient received hip spacers with an unknown amount of tobramycin and vancomycin and subsequent multiple debridements for recurrent infection. Her renal function was preserved until about 5 months after surgery when she acute renal failure developed, and her tobramycin level was 5.5 μg/mL. The patient was not receiving systemic tobramycin at that time. The spacer was explanted with subsequent improvement in renal function and decrease in tobramycin levels.

One study reported “vestibular damage” in 1 of 50 patients [18]. The authors attributed this complication to a high vancomycin level from systemic administration. Patients in this study received knee spacers loaded with 4.8 g of tobramycin per 40 g of cement. Serum levels of tobramycin were reported as “therapeutic” on postoperative day 1 and undetectable by day 3. One study reported liver dysfunction and bone marrow suppression each occurring in 2 patients and resolving after withdrawal of systemic antibacterials [10].

## DISCUSSION

The addition of antibacterials to interim spacers for the treatment of PJI has become the standard of care with the emphasis to use at least 3.6–4 g of antibacterials per 40 g of cement [1, 2, 5, 6, 37]. However, no clinical data supporting these recommendations have been identified. The publications recommending at least 3.6 g of tobramycin and 1 g of vancomycin [37] or at least 3.6 g of antibacterials per 40 g of bone cement [2] refer to 2 in vitro studies [38, 39]. However, these studies compared elution characteristics of 2 cements and used only 2.4 g tobramycin and 1.0 g vancomycin per 40 g of cement without recommending any particular dose for clinical use [38, 39].

Some support for the recommended doses was provided by a study reporting that the intra-articular concentrations of

### Table 2. Gentamicin Resistance in Isolates From Prosthetic Joint Infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Species (No. of tested isolates)</th>
<th>Resistant Isolates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>[16]</td>
<td>All cultured pathogens (44)</td>
<td>50</td>
</tr>
<tr>
<td>[24]</td>
<td><em>Staphylococcus</em> spp. a (30)</td>
<td>74</td>
</tr>
<tr>
<td>[27]</td>
<td><em>Staphylococcus</em> spp. b (93)</td>
<td>41</td>
</tr>
<tr>
<td>[25]</td>
<td>Coagulase-negative staphylococci (74)</td>
<td>45</td>
</tr>
<tr>
<td>[26]</td>
<td>Coagulase-negative staphylococci (91)</td>
<td>43</td>
</tr>
</tbody>
</table>

a *Staphylococcus aureus* in 4 of 30 isolates.

b Methicillin-resistant *S. aureus* in 21 isolates, methicillin-susceptible *S. aureus* in 38, and coagulase-negative staphylococci in 37.

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tobramycin at the time of spacer removal was above susceptibility break points when $\geq 3.6 \text{ g}$ of tobramycin was added to $40 \text{ g}$ of cement but was below the break points when $2.4 \text{ g}$ was used [40]. Another study reported concentrations of gentamicin in the membrane formed between the spacer and bone at 6 weeks after implantation of “low-dose” hip spacers containing $1 \text{ g}$ of gentamicin and $1 \text{ g}$ of clindamycin [41]. The concentration of gentamicin in the membrane was below the minimum inhibitory concentration for several isolates of Staphylococcus epidermidis, Staphylococcus aureus, and Streptococcus group B. However, the clinical significance of this finding is not clear.

Evaluation of the efficacy of spacers with different antibacterial loads based on published reports is difficult, even when predefined inclusion criteria are applied. We excluded many large studies because the composition of ACSs was not similar across the study participants or the follow-up period was short. The vast majority of publications are noncontrolled case series with different inclusion criteria and definitions of infection recurrence, limited patient data, and differences in the timing of assessments and duration of follow-up. In addition, differences in systemic antibacterial regimens, timing of surgery, surgical technique, type of antibacterial(s) mixed into different polymethylmethacrylate cements, preoperative prophylaxis, and decolonization strategies confound the comparison of different spacers with low and high antibacterial loads as well as the evaluation of the added benefit or risk of local antibacterials compared with their systemic administration in the treatment of PJI. A recent systematic review of exchange knee arthroplasty similarly concluded that “most reports on exchange arthroplasty performed for infected knee arthroplasty are of poor methodological quality, and no unbiased comparative studies exist” [42].

Nevertheless, our review did not reveal apparent association between antibacterial composition of ACSs and infection eradication rates. Moreover, our analysis suggests that PJI may be successfully treated when antibacterials added to spacers are not active against infecting organisms. Thus, PJI was eradicated in patients treated with vancomycin-laden spacers, whereas a significant proportion of isolates were aerobic gram-negative rods [9, 21]. The same may be true for spacers impregnated only with aminoglycosides [11, 14, 18, 19, 22, 23]. Although resistance to aminoglycosides among PJI isolates was reported to be 41%–74% [16, 24–27], infection eradication rates were similar whether spacers included aminoglycosides alone or a vancomycin-aminoglycoside combination. Although one may argue that aminoglycosides were still effective owing to higher local concentrations, the infection may have been eradicated mainly by surgical debridement and postoperative systemic antibacterials.

The safety of ACSs has not been consistently analyzed. In the absence of comparative clinical trials, no conclusion can be made on the incidence of systemic complications associated with ACSs. A report of renal insufficiency with detectable concentrations of tobramycin 5 months after the surgery suggests that spacers may elute aminoglycosides for a prolonged time, which may result in significant systemic levels of the drugs [34].

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No./Joints, No.</th>
<th>ACS Composition (Dose, g/40 g cement)</th>
<th>Patients With Systemic Toxicity, No. (%)</th>
<th>Renal</th>
<th>Vestibular</th>
<th>Liver Dysfunction and Bone Marrow Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9]</td>
<td>38/38 hips</td>
<td>Vancomycin (1)</td>
<td>0</td>
<td>NC</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>44/54 hips</td>
<td>Tobramycin (4.6) + vancomycin (4)</td>
<td>0</td>
<td>0</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td>50/50 knees</td>
<td>Tobramycin (4.8)</td>
<td>0</td>
<td>1 (2)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>[10]</td>
<td>24/24 hips</td>
<td>Gentamicin (1) + vancomycin (1) + ceftoxame (1)</td>
<td>NC</td>
<td>NC</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>43/44 hips</td>
<td>Gentamicin (0.25) + vancomycin (2)</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[28]</td>
<td>34/36 knees</td>
<td>Gentamicin (4.8) + vancomycin (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[29]</td>
<td>42/42 hips</td>
<td>Liquid gentamicin (480 mg; 24 patients); liquid gentamicin (480 mg) and vancomycin (3.0; 18 patients)</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>[30]</td>
<td>110/115 knees</td>
<td>Not specified</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[31]</td>
<td>82/88 hips</td>
<td>Gentamicin (0.5) + vancomycin (2)</td>
<td>5 (6)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>[32]</td>
<td>10/10 hips</td>
<td>vancomycin (2–3)</td>
<td>1 (10%)</td>
<td>NC</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACS, antibacterial cement spacer; NC, no specific comments provided.
In conclusion, current recommendations on the doses and types of antibacterials are based on expert opinions and in vitro studies rather than on the results of randomized controlled clinical trials. Published data do not allow evaluation of whether antibacterials in temporary cement spacers provide additional benefits in the treatment of PJI, compared with systemic antibacterial therapy, and are not sufficient to support recommendations on dosages. Prospective randomized trials comparing either spacers with and without antibacterials or at least spacers with different load of antibacterial agents are needed to evaluate the safety and efficacy of ACSs.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References