Supplementary Online Content


Appendix 1. No-Difference Fabricated Manuscript
Appendix 2. Positive Fabricated Manuscript

This supplementary material has been provided by the authors to give readers additional information about their work.
Appendix 1. No-Difference Fabricated Manuscript

Prophylactic Perioperative Antibiotics
Twenty-Four Hours vs a Single Dose of Cefazolin: A Randomized Controlled Trial

Background: Surgical site infection (SSI) is one of the most severe complications of orthopedic surgery. Recommendations for the administration of perioperative antibiotic use vary, but the evidence driving these recommendations is relatively weak. This study tests the hypothesis that 24 hours of perioperative intravenous antibiotic administration during primary hip and knee arthroplasty or primary spinal fusion is more effective than is a single preoperative dose of the same antibiotic.

Methods: In this multi-institutional study, 3308 patients treated with primary total knee arthroplasty, primary total hip arthroplasty, or primary single-level spinal instrumentation and fusion were randomized into 2 groups. Group 1 received a single preoperative dose of 1 g of cefazolin administered 10 to 60 minutes before skin incision. Group 2 received the same preoperative dose and 3 subsequent doses every 8 hours after completion of the surgery. The prevalence of SSI was then compared between groups.

Results: A total of 2.78% of patients who received a single dose of cefazolin developed SSI, and 2.30% of patients who received 24 hours of antibiotic treatment developed SSI; this difference was not significant ($P = .18$). Subgroup analysis of the arthroplasty patients showed that the percentage of patients developing infection was 2.49% (n=22 of 829) in the single-dose group compared with 2.17% (n=18/829) in the 24-hour group; this difference was not significant ($P = .16$). Among patients treated with single-level spinal fusion, 2.91% (n=24 of 825) who received 1 dose of prophylactic cefazolin developed SSI compared with 2.42% (n=20 of 825) who received 24 hours of antibiotics; likewise, this difference was not significant ($P = .19$).

Conclusion: In primary total hip and knee arthroplasty and in primary single-level posterior spinal fusion, the administration of a single dose of cefazolin is as effective as 24 hours of cefazolin for perioperative SSI prophylaxis.

Level of Evidence: Therapeutic level I. See Instructions to Authors for a complete description of levels of evidence.

Surgical site infection (SSI) is one of the most serious complications of orthopedic surgery. The prevalence of infection complicating primary orthopedic surgery ranges from 1% to 10%, and its prevention is of utmost importance to patients and surgeons.1-14

Protocols for the administration of perioperative antibiotics vary widely. In a survey administered to cardiothoracic surgeons by LoCicero et al,15 the variability of protocols used by these surgeons was striking. For elective pulmonary resections, 40.3% (164 of 408)
chose 2 days, 21% (86 of 408) chose 3 days, 17% (69 of 408) chose 1 day, 15.9% (65 of 408) chose longer than 2 days, and nearly 6% (25 of 408) gave no perioperative antibiotics. Variability also exists in cardiothoracic trauma cases, where 43.8% (179 of 408) gave antibiotics for 3 days postoperatively, 19.2% (78 of 408) for 1 day, 15.4% (63 of 408) for longer than 3 days, and 11.8% (48 of 408) gave no antibiotics at all.

To our knowledge, there are no large, randomized orthopedic trials that can be used to guide the proper duration of perioperative antibiotic use for large, clean (primary) orthopedic procedures. This study tests the hypothesis that 24 hours of perioperative intravenous cefazolin for primary hip and knee arthroplasty or primary spinal fusion is more effective at preventing SSI than is a single dose of the same antibiotic.

**METHODS**

Internal review board approval was obtained for this multicenter study from all the participating institutions. All patients scheduled to undergo primary total knee arthroplasty, primary total hip arthroplasty, or primary single-level posterior spinal instrumentation and fusion were considered eligible for the study. Patients were excluded if they demonstrated established risk factors for SSI, including a preexisting diagnosis of diabetes mellitus, peripheral vascular disease, severe morbid obesity (body mass index >40), nicotine use, previous operation at the surgical site (either the joint in question or the spinal level scheduled for instrumentation and fusion), known allergy to cephalosporin drugs, known or suspected anaphylaxis to penicillin, or malnutrition (serum albumin concentration <3.0 g/dL). All the procedures were performed by high-volume (>50 cases per year) arthroplasty surgeons (hips and knees) or high-volume orthopedic spine subspecialists (spinal fusions). All participating hospitals were considered high volume (>100 cases per year) for the procedures in question.

**ANTIBIOTIC PROPHYLAXIS**

Patients were divided into primary arthroplasty (group A) and primary spinal fusion (group S) groups. These groups were then randomized via a computer-generated list to 1 of 2 subgroups. Groups A1 and A2 were composed of arthroplasty patients and groups S1 and S2 were composed of spinal fusion patients. Groups A1 and S1 received the same
preoperative dose and timing of cefazolin (2 g intravenously 10-60 minutes before skin incision or, for knee replacements, tourniquet inflation), with no postoperative doses. Groups A2 and S2 received 2 g of cefazolin intravenously 10 to 60 minutes before surgical incision (or tourniquet inflation, as appropriate) and 3 subsequent 2-g doses postoperatively every 8 hours for a total of 4 doses in a 24-hour period. No patient received an intraoperative redosing of antibiotics because the duration of all surgical procedures was less than 3 hours.

**PERIOPERATIVE PROCEDURES**

All the patients were instructed on the same preoperative protocol to include a bath or shower with chlorhexidine scrub brushes the night before or morning of surgery. When necessary, the surgical site was shaved using an electric shaver immediately before the sterile skin preparation. The skin preparation the day of surgery was performed by similar ancillary staff trained to perform an appropriate and adequate preparation using Chloraprep (chlorhexidine gluconate, 2% wt/vol, and isopropyl alcohol, 70% vol/vol) (Cardinal Health, Leawood, Kansas). Following the product instructions, repeated back-and-forth strokes of the sponge were used on the surgical site for approximately 30 seconds, ensuring that the surgical site was completely wet with antiseptic. The area was then allowed to dry for approximately 3 minutes, taking care to not blot or wipe away the antiseptic.

During the operation, monitoring by anesthesia ensured that patients were maintained at a normal body temperature. An FIO2 of 80% was used intraoperatively, except during extubation, and for 2 hours postoperatively using a nonrebreathing mask. The patient’s supplemental oxygen was administered via nasal cannula and was titrated to an oxyhemoglobin saturation of greater than 92%.

Surgical dressings consisted of petroleum gauze, dry gauze, and microfoam elastic surgical tape (3M, St Paul, Minnesota) for patients treated with hip arthroplasty. For knee arthroplasty patients, the dressing consisted of petroleum gauze, dry gauze, and an ACE wrap. Surgical wounds for spinal surgery patients were covered with a sterile Primapore dressing. Dressing changes and examination of the surgical site commenced on postoperative day 1, and, following recommendations of the Centers for Disease Control

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and Prevention, the first dressing change was performed using sterile technique and clean technique, with subsequent dressing changes throughout the patient’s hospitalization.

**CLINICAL ASSESSMENTS**

A preoperative baseline assessment of the patient was performed. Laboratory measurements included white blood cell count, C-reactive protein, erythrocyte sedimentation rate, urinalysis and urine culture, chemistry panel, and coagulation studies. A chest radiograph was obtained, and vital signs were recorded.

Postoperatively, vital signs were recorded every 8 hours. White blood cell count as part of a complete blood cell count was determined each day. Urinalysis and urine culture, blood culture, and chest radiographs were obtained postoperatively only if a temperature of at least 38.5°C was recorded on postoperative day 3 or later.

All the patients were followed clinically 10 days, 30 days, 3 months, 12 months, and 24 months postoperatively. Visits at intervals other than these were performed when clinically indicated. At follow-up clinic visits, a physical examination was performed. Laboratory tests, including complete blood cell count, C-reactive protein, and erythrocyte sedimentation rate, were performed 3 and 12 months postoperatively. The patients were asked questions to determine whether an unreported wound infection may have occurred (Table 1).

**CLASSIFICATION OF INFECTION**

All SSIs were classified according to guidelines proposed by the Centers for Disease Control and Prevention. A superficial SSI is said to have occurred if the infection develops within 30 days following the procedure and involves only skin or subcutaneous tissue of the incision. A deep incisional SSI is said to have occurred if within 30 days following the procedure (365 days if the procedure involved placement of a permanent implant) the infection involves deep soft tissue of the incision. An organ/space SSI is said to have occurred if within 30 after the procedure (365 days if the procedure involved placement of a permanent implant) the infection seems to be related to the procedure and involves any part of the anatomy other than the incision, which was opened or manipulated during the
Each of these infections, in addition to meeting the definition of the category, must include 1 of the signs or symptoms listed in Table 2.

All surgical incisions were evaluated daily beginning on postoperative day 1 while in the hospital and at each follow-up interval. Using the Centers for Disease Control and Prevention criteria, SSI was deemed present if any of the following was present: purulent fluid, dehiscence, or erythema. Any wounds with visible drainage of any kind at 10-day follow-up were aspirated from a point away from the area of drainage, and any growth on culture was considered to be an SSI. All patients who were returned to the operating room for “lavage” or “drainage of hematoma” had the surgical wounds cultured before the drainage/lavage procedures. Any positive culture was considered indicative of SSI. Wounds with drainage of any kind beyond 10 days were considered infected. No empirical use of antibiotics for “cellulitis” was permitted without an aspirate of the joint or the surgical field (if a spine incision). If the culture was negative, the “cellulitis” was considered a superficial SSI.

For practical purposes, the clinical assessments were performed by the attending surgeons and their teams; however, the attending surgeons and the patients were blinded to the outcome of the randomization process.

**RANDOMIZATION AND STATISTICAL ANALYSIS**

Patients were assigned to groups based on a table of random numbers; sealed opaque study envelopes prepared by the study biostatistician were opened by study personnel other than the treating surgeon in the preoperative holding area to minimize the likelihood of subversion of randomization. Validation of blinding was performed by means of a survey administered to the attending surgeons and surgical patients at the time of hospital discharge of the first 200 patients enrolled in the trial; surgeons were asked to indicate which group they believed the patient in question was randomized to or whether they did not have any reason to form an opinion on that point. Statistical analyses were performed using an intention-to-treat analysis protocol. Results were analyzed strictly by study group (ie, group A1 only compared with group A2 and S1 compared with S2 and were calculated using a paired t test). Significance was set at $P < .05$. 

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SAMPLE-SIZE CALCULATION

Based on a review of the literature, SSI after primary arthroplasty and primary single-level fusion occurs in 1% to 10% of patients. To achieve 80% power, assuming a 5% loss to follow-up, an $\alpha$ value of .05, and a difference between groups of 1.5% (2.5% vs 1% among A1/S1 and A2/S2) required the inclusion of 1544 subjects in each group.

RESULTS

A total of 3308 patients were enrolled from the 5 participating institutions. There were 1658 arthroplasty patients (group A) and 1650 spinal fusion patients (group S). Patients were randomized using a computer-generated list: 829 patients to group A1, 829 to group A2, 825 to group S1, and 825 to group S2. Groups A1 and S1 received the same preoperative dose of cefazolin (2 g intravenously) but did not receive any postoperative doses. Groups A2 and S2 received 2 g of cefazolin intravenously 30 minutes before surgical incision and 3 postoperative doses of cefazolin at 8-hour intervals. There were 925 females and 733 males enrolled in group A and 749 females and 901 males in group S. The mean age was 62 years. There were no significant differences among groups regarding age, sex, and presence of comorbidities.

GROUP A

In group A1, 22 SSIs (2.49%) occurred (Table 3). Of these SSIs, 5 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 17 SSIs were deep infections. Two of these deep infections were diagnosed during the hospital stay, 10 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

In group A2, 18 SSIs (2.17%) occurred (Table 3). Of these SSIs, 4 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 14 SSIs were deep infections. Three of these deep infections were diagnosed during the hospital stay, 8 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.
The difference between groups A1 and A2 did not reach significance ($P = .16$). Complete follow-up was available for 97.0% of patients ($n = 804$ of 829) in group A1 and for 96.0% ($n = 796$ of 829) in group A2.

**GROUP S**

In group S1, 24 SSIs (2.91%) occurred (Table 3). Of these SSIs, 6 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 18 SSIs were deep infections. Four of these deep infections were diagnosed during the hospital stay, 8 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

In group S2, 20 SSIs (2.42%) occurred (Table 3). Of these SSIs, 3 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 17 SSIs were deep infections. Five of these deep infections were diagnosed during the hospital stay, 9 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

The difference between groups S1 and S2 was not significant ($P = .19$). Complete follow-up was available for 96.1% of patients ($n = 801$ of 825) in group S1 and in 97.9% ($n = 808$ of 825) in group S2.

**VALIDATION OF RANDOMIZATION**

For the first 200 hospital discharges in the study, the result of the surgeon survey found that in 182 the surgeon did not have a guess as to the group assigned. In the remaining 18 (9%), the surgeon identified the group correctly in 8 cases (4%) and incorrectly in 10 cases (5%). The result of the patient survey found that 190 patients (95%) did not have an idea as to which group they were randomized; 5 of the remaining 10 patients correctly identified the study group to which they were randomized, whereas the other 5 did not.
COMMENT

Preventing SSI in the setting of elective orthopedic surgery is important. In this study, the percentage of patients who developed SSI after elective orthopedic surgery who received 24 hours of antibiotic prophylaxis was 2.30% (n=38 of 1654). For patients who received a single dose of postoperative antibiotics, the prevalence was 2.78% (n=46 of 1654), a difference that was not significant (P=.18). Statistical power was ample to detect clinically meaningful differences in this multicenter randomized clinical trial. This suggests that 1 dose of perioperative prophylactic antibiotics is as effective as 24 hours of antibiotics in preventing SSI after clean, elective orthopedic surgical procedures involving the hip, knee, and spine.

There is an extensive body of literature that shows the importance of administering perioperative prophylactic antibiotics in preventing SSI.\textsuperscript{20,25,26,31-52} Bodoky et al\textsuperscript{32} compared 2 doses of cefotiam with 2 doses of clindamycin in patients with hip fractures. The authors found that the prevalence of major (systemic) wound infection was 5% (n=6 of 115) in the clindamycin group and 1% (n=1 of 124) in the antibiotic group. Similarly, the prevalence of minor (local) wound infection was 11% (n=13 of 115) in the clindamycin group and 4% (n=5 of 124) in the antibiotic group, differences that were significant.

In Boyd et al’s study,\textsuperscript{34} patients with hip fractures were randomized to either a placebo group or a nafcillin group. The prevalence of infection in the nafcillin group was 0.8% (n=1/135) compared with a 4.8% (n=7 of 145) infection rate in the control group. Burnett et al\textsuperscript{37} compared the prevalence of infection in patients with proximal femur fractures randomized to a placebo group or a treatment group using 72 hours of cephalothin. A difference of 4.7% (n=6 of 126) infection rate in the placebo group vs 0.7% (n=1 of 135) rate in the treatment group was shown.

Pavel et al\textsuperscript{46} compared the effects of 1 dose of cephaloridine before incision and 1 dose of the same antibiotic intraoperatively with a placebo group on the prevalence of infection. The prevalence of infection in the treatment group was 2.8% (n=25 of 887) compared with 5% (n=35 of 704) in the placebo group (P=.03).
Henley et al. randomized patients undergoing elective orthopedic procedures without utilization of implants to a placebo group and to a treatment group receiving 24 hours of cefamandole. This study also demonstrated a difference in the prevalence of infection (placebo group = 4.2% [n = 15 of 338], treatment group = 1.6% [n = 6 of 349]; P < .05).

Despite the vast body of literature that exists regarding perioperative antibiotic prophylaxis, to our knowledge, few studies have compared varying durations of the same antibiotic with respect to efficacy in preventing SSI. In this study, we compared the efficacy of a 24-hour course with a single dose of perioperative prophylactic antibiotic administration in preventing SSI after elective orthopedic surgery. The present results suggest that the single-dose administration is as effective as the 24-hour course in preventing SSI.

This study should be viewed in light of several limitations. First, the study population was relatively homogeneous, consisting of primary arthroplasty and single-level spine fusions in patients who generally did not have severe risk factors that would predispose them to SSI; we do not assume that the results will generalize to smaller procedures (such as arthroscopy), more invasive operations (multilevel spine fusions or revision arthroplasty surgery), or orthopedic trauma. Similarly, this study analyzes only 1 dimension of intervention, the dosing regimen. These results may not be similar for different dosing schedules, different doses of the same antibiotic, or other antibiotics. It is also possible that the study method could have led to some subclinical, occult, or late-presenting infections being missed. That said, it seems likely that if SSIs are going to occur, most should present within the first 24 months postoperatively, and randomization should minimize any chance that the impact of this limitation would be felt dissimilarly between treatment groups. Finally, although steps were taken to blind surgeon and patient to the treatment that was randomly assigned, it is possible that in some cases surgeons (or patients) might have identified the antibiotic treatment rendered, and this could have resulted in a bias of assessment. However, the survey used to validate the randomization indicated that blinding was maintained; in most hospital discharges surveyed, neither the surgeon nor the patient had a sense for which duration of antibiotics was used, and in the remaining cases, the
wrong guess was made at least as often as the correct guess. Our sample-size calculation found sufficient power to demonstrate a decrease from 2.5% to 1% in the likelihood of SSI between the 24-hour and the single-dose groups. It is possible that this cohort is not large enough to show a statistically significant difference smaller than that. However, the single-dose group actually had a smaller percentage of patients with SSI; because there is no biologically plausible mechanism for the single dose to have fewer infections than the 4-dose group, it seems particularly unlikely that statistical power came into play with these results.

In conclusion, in primary total hip and knee arthroplasty and in primary single-level posterior spinal fusion, the administration of 1 preoperative dose of cefazolin is as effective as 24 hours of cefazolin for perioperative SSI prophylaxis.

REFERENCES


31. Periti P, Stringa G, Mini E; Italian Study Group for Antimicrobial Prophylaxis in Orthopedic Surgery. Comparative multicenter trial of teicoplanin versus cefazolin for antimicrobial prophylaxis in


Table 1. Questions Concerning a History of Unreported Surgical Site Infection

Has the wound healed without any problems at all?
Has the wound been red?

Has the wound discharged clear yellow fluid?

Has the wound discharged pus?

Has the wound broken open?

Have you been given antibiotics for wound infection?

Has a nurse had to dress the wound?

Has a doctor opened/drained an abscess?

Have you been admitted to a hospital elsewhere?

Has the wound been opened and cleaned under general anesthetic in a hospital?
Table 2. Definition of Infection

**Superficial incisional surgical site infection:** Occurs within 30 days after procedure and involves only skin or subcutaneous tissues of the incision and must included at least one of the following:

- Purulent drainage from the superficial incision with or without laboratory confirmation
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the symptoms of infection
  - Pain or tenderness
  - Localized swelling
  - Redness
  - Heat

Diagnosis of superficial incisional SSI is made by the surgeon or attending physician after deliberately opening a superficial incision

**Deep incisional surgical site infection:** Occurs within 30 days after the procedure if no implant is left in place or within 1 year if an implant is left in place and involves deep soft tissues of the incision and includes at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms:
  - Fever > 38.4
  - Localized pain
  - Tenderness
  - Abscess or other evidence of infection involving the deep incision is found on direct examination, during re-operation, or by histopathologic or radiologic examination

A surgeon or attending physician diagnoses a deep incisional surgical site Infection
**Organ/Space surgical site infection:** Occurs within 30 days after the procedure is no implant is left in place or within 1 year if an implant is left in place, seems to be related to the procedure, involves any part of the anatomy, other than the incision, which was opened or manipulated during the procedure, and includes at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during re-operation, or by histopathologic or radiologic examination
- A surgeon or attending physician diagnoses an organ/space SSI
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Appendix 2. Positive Fabricated Manuscript

Prophylactic Perioperative Antibiotics
Twenty-Four Hours vs a Single Dose of Cefazolin: A Randomized Controlled Trial

Background: Surgical site infection (SSI) is one of the most severe complications of orthopedic surgery. Recommendations for the administration of perioperative antibiotic use vary, but the evidence driving these recommendations is relatively weak. This study tests the hypothesis that 24 hours of perioperative intravenous antibiotic administration during primary hip and knee arthroplasty or primary spinal fusion is more effective than is a single preoperative dose of the same antibiotic.

Methods: In this multi-institutional study, 3308 patients treated with primary total knee arthroplasty, primary total hip arthroplasty, or primary single-level spinal instrumentation and fusion were randomized into 2 groups. Group 1 received a single preoperative dose of 2 g of cefazolin administered 10 to 60 minutes before skin incision. Group 2 received the same preoperative dose and 3 subsequent doses every 8 hours after completion of the surgery. The prevalence of SSI was then compared between groups.

Results: A total of 2.78% of patients who received a single dose of cefazolin developed SSI, and 1.03% of patients who received 24 hours of antibiotic treatment developed SSI; this difference was significant ($P= .003$). Subgroup analysis of the arthroplasty patients showed that the percentage of patients developing infection was 2.49% ($n= 22$ of 829) in the single-dose group compared with 0.96% ($n= 8$ of 829) in the 24-hour group; this difference was significant ($P = .004$). Among patients treated with single-level spinal fusion, 2.91% ($n= 24$ of 825) who received 1 dose of prophylactic cefazolin developed SSI compared with 1.10% ($n= 9$ of 825) who received 24 hours of antibiotics; likewise, this difference was significant ($P = .002$).

Conclusion: In primary total hip and knee arthroplasty and in primary single-level posterior spinal fusion, the administration of 24 hours of cefazolin is significantly more effective than is a single dose of cefazolin for perioperative SSI prophylaxis.

Level of Evidence: Therapeutic level I. See Instructions to Authors for a complete description of levels of evidence.

Surgical site infection (SSI) is one of the most serious complications of orthopedic surgery. The prevalence of infection complicating primary orthopedic surgery ranges from 1% to 10%, and its prevention is of utmost importance to patients and surgeons.1-14

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**METHODS**

Internal review board approval was obtained for this multicenter study from all the participating institutions. All patients scheduled to undergo primary total knee arthroplasty, primary total hip arthroplasty, or primary single-level posterior spinal instrumentation and fusion were considered eligible for the study. Patients were excluded if they demonstrated established risk factors for SSI, including a preexisting diagnosis of diabetes mellitus, peripheral vascular disease, severe morbid obesity (body mass index >40), nicotine use, previous operation at the surgical site (either the joint in question or the spinal level scheduled for instrumentation and fusion), known allergy to cephalosporin drugs, known or suspected anaphylaxis to penicillins, or malnutrition (serum albumin concentration <3.0 g/dL). All the procedures were performed by high-volume (>50 cases per year) arthroplasty surgeons (hips and knees) or high-volume orthopedic spine subspecialists (spinal fusions). All participating hospitals were considered high volume (>100 cases per year) for the procedures in question.

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All the patients were instructed on the same preoperative protocol to include a bath or shower with chlorhexidine scrub brushes the night before or morning of surgery. When necessary, the surgical site was shaved using an electric shaver immediately before the sterile skin preparation. The skin preparation the day of surgery was performed by similar ancillary staff trained to perform an appropriate and adequate preparation using Chloraprep (chlorhexidine gluconate, 2% wt/vol, and isopropyl alcohol, 70% vol/vol) (Cardinal Health, Leawood, Kansas). Following the product instructions, repeated back-and-forth strokes of the sponge were used on the surgical site for approximately 30 seconds, ensuring that the surgical site was completely wet with antiseptic. The area was then allowed to dry for approximately 3 minutes, taking care to not blot or wipe away the antiseptic.

During the operation, monitoring by anesthesia ensured that patients were maintained at a normal body temperature. An FIO2 of 80% was used intraoperatively, except during extubation, and for 2 hours postoperatively using a nonrebreathing mask. The patient’s supplemental oxygen was administered via nasal cannula and was titrated to an oxyhemoglobin saturation of greater than 92%. The surgical dressings consisted of petroleum gauze, dry gauze, and microfoam elastic surgical tape (3M, St Paul, Minnesota) for patients treated with hip arthroplasty. For knee arthroplasty patients, the dressing consisted of petroleum gauze, dry gauze, and an ACE wrap. Surgical wounds for spinal surgery patients were covered with a sterile Primapore dressing. Dressing changes and examination of the surgical site commenced on postoperative day 1, and, following recommendations of the Centers for Disease Control
and Prevention, the first dressing change was performed using sterile technique and clean
technique, with subsequent dressing changes throughout the patient’s hospitalization.4

CLINICAL ASSESSMENTS

A preoperative baseline assessment of the patient was performed. Laboratory
measurements included white blood cell count, C-reactive protein, erythrocyte
sedimentation rate, urinalysis and urine culture, chemistry panel, and coagulation studies. A
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Postoperatively, vital signs were recorded every 8 hours. White blood cell count as
part of a complete blood cell count was determined each day. Urinalysis and urine culture,
blood culture, and chest radiographs were obtained postoperatively only if a temperature of
at least 38.5°C was recorded on postoperative day 3 or later.

All the patients were followed clinically 10 days, 30 days, 3 months, 12 months, and
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involves any part of the anatomy other than the incision, which was opened or manipulated
during the procedure. Each of these infections, in addition to meeting the definition of the category, must include 1 of the signs or symptoms listed in Table 2.

All surgical incisions were evaluated daily beginning on postoperative day 1 while in the hospital and at each follow-up interval. Using the Centers for Disease Control and Prevention criteria, SSI was deemed present if any of the following was present: purulent fluid, dehiscence, or erythema. Any wounds with visible drainage of any kind at 10-day follow-up were aspirated from a point away from the area of drainage, and any growth on culture was considered to be an SSI. All the patients who were returned to the operating room for “lavage” or “drainage of hematoma” had the surgical wounds cultured before the drainage/lavage procedures. Any positive culture was considered indicative of SSI. Wounds with drainage of any kind beyond 10 days were considered infected. No empirical use of antibiotics for “cellulitis” was permitted without an aspirate of the joint or the surgical field (if a spine incision). If the culture was negative, the “cellulitis” was considered a superficial SSI.

For practical purposes, the clinical assessments were performed by the attending surgeons and their teams; however, both the attending surgeons and the patients were blinded to the outcome of the randomization process.

**RANDOMIZATION AND STATISTICAL ANALYSIS**

Patients were assigned to groups based on a table of random numbers; sealed opaque study envelopes prepared by the study biostatistician were opened by study personnel other than the treating surgeon in the preoperative holding area to minimize the likelihood of subversion of randomization. Validation of blinding was performed by means of a survey administered to the attending surgeons and surgical patients at the time of hospital discharge of the first 200 patients enrolled in the trial; surgeons were asked to indicate which group they believed the patient in question was randomized to or whether they did not have any reason to form an opinion on that point. Statistical analyses were performed using an intention-to-treat analysis protocol. Results were analyzed strictly by study group (ie, group A1 only compared with group A2 and S1 compared with S2 and were calculated using a paired t test). Significance was set at P < .05.

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SAMPLE-SIZE CALCULATION

Based on a review of the literature, SSI after primary arthroplasty and primary single-level fusion occurs in 1% to 10% of patients.\textsuperscript{1-14} To achieve 80% power, assuming a 5% loss to follow-up, an $\alpha$ value of .05, and a difference between groups of 1.5% (2.5% vs 1% among A1/S1 and A2/S2) required the inclusion of 1544 subjects in each group.

RESULTS

A total of 3308 patients were enrolled from the 5 participating institutions. There were 1658 arthroplasty patients (group A) and 1650 spinal fusion patients (group S). Patients were randomized using a computer-generated list: 829 patients to group A1, 829 to group A2, 825 to group S1, and 825 to group S2. Groups A1 and S1 received the same preoperative dose of cefazolin (2 g intravenously) but did not receive any postoperative doses. Groups A2 and S2 received 2 g of cefazolin intravenously 30 minutes before surgical incision and 3 postoperative doses of cefazolin at 8-hour intervals. There were 925 females and 733 males enrolled in group A and 749 females and 901 males in group S. The mean age was 62 years. There were no significant differences among groups regarding age, sex, and presence of comorbidities.

GROUP A

In group A1, 22 SSIs (2.49%) occurred (Table 3). Of these SSIs, 5 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 17 SSIs were deep infections. Two of these deep infections were diagnosed during the hospital stay, 10 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

In group A2, 8 SSIs (0.96%) occurred (Table 3). Of these SSIs, 1 was superficial and was diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 7 SSIs were deep infections. None of these deep infections were diagnosed during the hospital stay, 5 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.
The difference between groups A1 and A2 was significant ($P=.004$). Complete follow-up was available for 97.0% of patients (n=804 of 829) in group A1 and for 96.0% (n = 796 of 829) in group A2.

**GROUP S**

In group S1, 24 SSIs (2.91%) occurred (Table 3). Of these SSIs, 6 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 18 SSIs were deep infections. Six of these deep infections were diagnosed during the hospital stay, 8 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

In group S2, 9 SSIs (1.10%) occurred (Table 3). Of these SSIs, 2 were superficial and were diagnosed as cellulitis. They were treated 10 to 30 days postoperatively without sequelae or apparent infection at 24-month final follow-up. The remaining 7 SSIs were deep infections. Two of these deep infections were diagnosed during the hospital stay, 3 were diagnosed within a month, and the remainder were diagnosed 3 to 12 months postoperatively.

The difference between groups S1 and S2 was significant ($P=.002$). Complete follow-up was available for 96.1% of patients (n=801 of 825) in group S1 and in 97.9% (n = 808 of 825) in group S2.

**VALIDATION OF RANDOMIZATION**

For the first 200 hospital discharges in the study, the result of the surgeon survey found that in 182 the surgeon did not have a guess as to the group assigned. In the remaining 18 (9%), the surgeon identified the group correctly in 8 cases (4%) and incorrectly in 10 cases (5%). The result of the patient survey found that 190 patients (95%) did not have an idea as to which group they were randomized; 5 of the remaining 10 patients correctly identified the study group to which they were randomized, whereas the other 5 did not.
COMMENT

Preventing SSI in the setting of elective orthopedic surgery is important. In this study, the percentage of patients who developed SSI after elective orthopedic surgery who received 24 hours of antibiotic prophylaxis was 1.03% (n = 17 of 1654). For patients who received a single dose of postoperative antibiotics, the frequency of infection was 2.78% (n = 46 of 1654), a difference that was significant (P = .003). This suggests that 1 dose of perioperative prophylactic antibiotics is not as effective as 24 hours of antibiotics in preventing SSI after clean, elective orthopedic surgical procedures involving the hip, knee, and spine.

There is an extensive body of literature that shows the importance of administering perioperative prophylactic antibiotics in preventing SSI. Bodoky et al compared 2 doses of cefotiam with 2 doses of clindamycin in patients with hip fractures. The authors found that the prevalence of major (systemic) wound infection was 5% (n = 6 of 115) in the clindamycin group and 1% (n = 1 of 124) in the antibiotic group. Similarly, the prevalence of minor (local) wound infection was 11% (n = 13 of 115) in the clindamycin group and 4% (n = 5 of 124) in the antibiotic group, differences that were significant.

In Boyd et al’s study, patients with hip fractures were randomized to either a placebo group or a nafcillin group. The prevalence of infection in the nafcillin group was 0.8% (n = 1 of 135) compared with a 4.8% (n = 7 of 145) infection rate in the control group. Burnett et al compared the prevalence of infection in patients with proximal femur fractures randomized to a placebo group or a treatment group using 72 hours of cephalothin. A difference of 4.7% (n = 6 of 126) infection rate in the placebo group vs 0.7% (n = 1 of 135) rate in the treatment group was shown.

Pavel et al compared the effects of 1 dose of cephaloridine before incision and 1 dose of the same antibiotic intraoperatively with a placebo group on the prevalence of infection. The prevalence of infection in the treatment group was 2.8% (n = 25 of 887) compared with 5% (n = 35 of 704) in the placebo group (P = .03).

Henley et al randomized patients undergoing elective orthopedic procedures without utilization of implants to a placebo group and to a treatment group receiving 24 hours of
This study also demonstrated a difference in the prevalence of infection (placebo group = 4.2% [n = 15 of 338], treatment group = 1.6% [n = 6 of 349]; P < .05).

Despite the vast body of literature that exists regarding perioperative antibiotic prophylaxis, to our knowledge, few studies have compared varying durations of the same antibiotic with respect to efficacy in preventing SSI. In this study, we compared the efficacy of a 24-hour course with a single dose of perioperative prophylactic antibiotic administration in preventing SSIs after elective orthopedic surgery. The present results suggest that single-dose administration is not as effective as the 24-hour course in preventing SSI.

This study should be viewed in light of several limitations. First, the study population was relatively homogeneous, consisting of primary arthroplasty and single-level spine fusions in patients who generally did not have severe risk factors that would predispose them to SSI; we do not assume that the results will generalize to smaller procedures (such as arthroscopy), more invasive operations (multilevel spine fusions or revision arthroplasty surgery), or orthopedic trauma. Similarly, this study analyzes only 1 dimension of intervention, the dosing regimen. These results may not be similar for different dosing schedules, different doses of the same antibiotic, or other antibiotics. It is also possible that the study method could have led to some subclinical, occult, or late-presenting infections being missed. That said, it seems likely that if SSIs are going to occur, most should present within the first 24 months postoperatively, and randomization should minimize any chance that the impact of this limitation would be felt dissimilarly between treatment groups. Finally, although steps were taken to blind surgeon and patient to the treatment that was randomly assigned, it is possible that in some cases surgeons (or patients) might have identified the antibiotic treatment rendered, and this could have resulted in a bias of assessment. However, the survey used to validate the randomization indicated that blinding was maintained; in most hospital discharges surveyed, neither the surgeon nor the patient had a sense for which duration of antibiotics was used, and in the remaining cases, the wrong guess was made at least as often as the correct guess.
In conclusion, in primary total hip and knee arthroplasty and in primary single-level posterior spinal fusion, the administration of 1 preoperative dose of cefazolin is not as effective as 24 hours of cefazolin for perioperative SSI prophylaxis.

REFERENCES


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**Table 1. Questions Concerning a History of Unreported Surgical Site Infection**

- Has the wound healed without any problems at all?
- Has the wound been red?
- Has the wound discharged clear yellow fluid?
- Has the wound discharged pus?
- Has the wound broken open?
- Have you been given antibiotics for wound infection?
- Has a nurse had to dress the wound?
- Has a doctor opened/drained an abscess?
- Have you been admitted to a hospital elsewhere?
- Has the wound been opened and cleaned under general anesthetic in a hospital?
Table 2. Definition of Infection

Superficial incisional surgical site infection: Occurs within 30 days after procedure and involves only skin or subcutaneous tissues of the incision and must included at least one of the following:

- Purulent drainage from the superficial incision with or without laboratory confirmation
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the symptoms of infection
  - Pain or tenderness
  - Localized swelling
  - Redness
  - Heat
- Diagnosis of superficial incisional SSI is made by the surgeon or attending physician after deliberately opening a superficial incision

Deep incisional surgical site infection: Occurs within 30 days after the procedure if no implant is left in place or within one year if an implant is left in place and involves deep soft tissues of the incision and includes at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- Deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms:
  - Fever > 38.4
  - Localized pain
  - Tenderness
  - Abscess or other evidence of infection involving the deep incision is found on direct examination, during re-operation, or by histopathologic or radiologic examination
- A surgeon or attending physician diagnoses a deep incisional surgical site Infection
Organ/Space surgical site infection: Occurs within 30 days after the procedure is no implant is left in place or within 1 year if an implant is left in place, seems to be related to the procedure, involves any part of the anatomy, other than the incision, which was opened or manipulated during the procedure, and includes at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during re-operation, or by histopathologic or radiologic examination
- A surgeon or attending physician diagnoses an organ/space SSI
Table 3

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