EDITORIAL

Minimizing Surgical-Site Infections

Richard P. Wenzel, M.D.

Primitive ancestors of *Homo sapiens* and their colonizing bacteria have coevolved for approximately 500,000 years; some experts estimate that the total number of human cells is 10^{13} and the total number of colonizing microbes is 10^{14}. Despite this 10-to-1 inequity, the balance of power is influenced by an intact human immune system and the integrity of the skin and mucous membranes. Operative procedures disrupt this balance, resulting in a risk of surgical-site infections from endogenous flora, including colonizing strains of *Staphylococcus aureus*.

Each year in the United States, more than 30 million operative procedures are performed. The risk of infection depends on the skill of the surgeon, the degree of contamination defined by the type of surgery (i.e., clean, clean-contaminated, or contaminated), and the patient's status with respect to underlying coexisting conditions and carriage of *S. aureus*. Approximately 20 to 30% of surgical-site infections are caused by *S. aureus*, and over half of these arise from the endogenous flora.

In an attempt to reduce surgical morbidity, the Surgical Infection Prevention Project and the Surgical Care Improvement Project have outlined evidence-based recommendations, bundling several strategies into a comprehensive approach. They include the initial administration of perioperative antibiotics within 1 hour before surgery, the preoperative use of hair clippers or no hair removal (as opposed to shaving of hair), and the maintenance of normothermia during colorectal surgery.[1]

Because *S. aureus* is a virulent pathogen that can cause surgical-site infections, some studies have focused on eliminating nasal carriage of this organism preoperatively. Results of a recent meta-analysis suggested that topical mupirocin applied intranasally would reduce the rate of surgical-site infections due to *S. aureus* by 45% in the subgroup of patients who are carriers.[2] It is also known that the skin is an important extranasal reservoir not only for *S. aureus* but also for other organisms implicated in postoperative infections.

Two well-controlled, multicenter, randomized studies reported in this issue of the *Journal* offer valuable insights for controlling surgical-site infections. Bode and colleagues demonstrated the efficacy of rapid, preoperative screening for nasal carriage of *S. aureus* along with the prophylactic treatment of patients who had positive results with the use of intranasal mupirocin twice a day for 5 days and daily baths with chlorhexidine soap.[3] Patients scheduled to undergo simple operative procedures were excluded, and only those who were expected to remain in the hospital for at least 4 days were randomly assigned to either active treatment or placebo. The subgroup of surgical-site infections caused by *S. aureus* was reduced by 60% among those in the active treatment group as compared with those treated with the placebo nasal ointment plus placebo soap.

In the second study, Darouiche and colleagues found a greater than 40% reduction in total surgical-site infections among patients undergoing clean-contaminated surgery who had received a single chlorhexidine–alcohol scrub as compared with a povidone–iodine scrub.[4] No patients received intranasal mupirocin in this study, yet the rate of *S. aureus* surgical-site infections was reduced by approximately 50% in the chlorhexidine–alcohol group (see the Supplementary Appendix to the article by Darouiche et al., available at NEJM.org).

Chlorhexidine–alcohol has been recommended by the Centers for Disease Control and Preven-

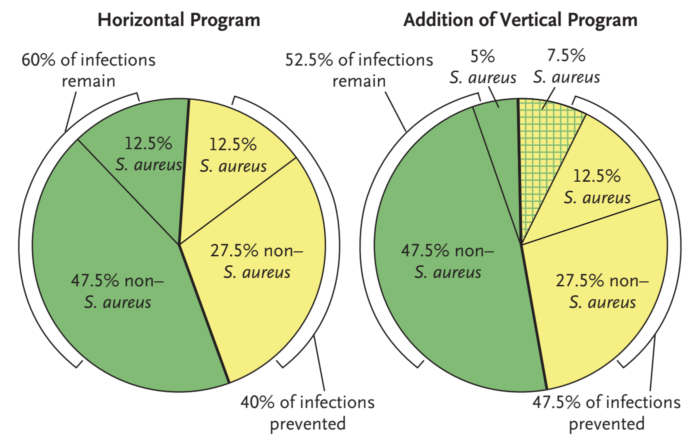

Figure 1. Estimates of *Staphylococcus aureus* Infections with the Use of Two Different Programs.

A horizontal program reduces all infections at a specific anatomic site, whereas a vertical program targets a single organism at that site. A horizontal program using chlorhexidine–alcohol surgical scrubs would prevent an estimated 40% of all surgical-site infections (pie chart on the left). A vertical program that focuses on *S. aureus* infections would add incremental value (pie chart on the right). The vertical program would prevent 60% of the 12.5% of *S. aureus* infections that remain when the horizontal program is used (i.e., a further reduction of 7.5 percentage points [cross-hatched area]). With both programs in place, 47.5% of surgical-site infections would be prevented.

tion as the antiseptic of choice to reduce vascular catheter–associated bloodstream infections.[5] As compared with povidone–iodine, the chlorhexidine–alcohol solution has been found to reduce catheter-associated infections by approximately 50%.[6] Recently, researchers in six intensive care units (ICUs) at four institutions examined the rates of colonization of and bloodstream infections due to methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) during a 6-month period during which patients were bathed daily with nonmedicated soap followed by a 6-month period of daily bathing with a chlorhexidine solution.[7] During the latter period, the MRSA acquisition rate decreased by 32%, VRE acquisition decreased by 50%, and the number of bloodstream infections due to VRE decreased by 73%. The same design was used in a study involving a single ICU, which showed an 87% reduction in all catheter-related bloodstream infections when patients were bathed with chlorhexidine.[8]

Such data add credibility to the findings of more favorable outcomes among patients treated with chlorhexidine products before undergoing surgery. Nevertheless, researchers at a single institution tested three types of surgical-site scrubs, using a sequential-implementation study design. On primary analysis, the rate of surgical-site infections was lower with iodine povacrylex in alcohol than with either povidone–iodine or chlorhexidine–alcohol.[9]

From a population-based perspective, a program that substantially reduces all infections at a specific anatomical site (i.e., a horizontal program) is more valuable than one that targets a single organism at that site (i.e., a vertical program). Given a horizontal program (chlorhexidine–alcohol scrub) that reduces overall infection rates by 40% and eliminates 50% of *S. aureus* infections, one can estimate the incremental value of an additional vertical program that focuses on the remaining *S. aureus* infections. Assume that *S. aureus* infections represent 25% of all infections, that 50% of *S. aureus* infections remain, and that the number of these infections can be further reduced by 60%. The absolute improvement of 7.5 percentage points (i.e., [25%×50%]×60%) would be the maximal incremental effect of the vertical program on the total infection rate (Fig. 1).

The Darouiche study supports the value of a relatively inexpensive horizontal program, which was remarkably effective: the number of patients who would need to be treated to prevent one surgical-site infection was found to be 17.

Although the reduction in *S. aureus* surgical-site infections in the study by Bode et al. was impressive, the relative contributions of the intervention components — that is, decolonization in the nares and the use of chlorhexidine soap — are unclear. A total of 250 patients would need to be screened and 23 carriers would need to be treated to prevent one *S. aureus* infection. This organism is responsible for an important subgroup, yet still a minority, of surgical-site infections. Unfortunately, the influence on total infection rates at surgical sites was not recorded but could be estimated to be 15% (a 25% prevalence of *S. aureus*×60% reduction). The value of this well-conducted study is that it suggests a prophylactic approach for carriers of *S. aureus* who are candidates for surgical procedures associated with a high risk of deleterious outcomes should *S. aureus* infection develop at the surgical site. In this category, I would include all cases of open-heart surgery as well as any procedure in which a foreign body is placed (e.g., orthopedic and neurosurgical implant procedures) as especially high-risk operations, and I would also include any surgical procedure in patients whose immune systems are severely impaired.

In summary, the weight of evidence suggests that chlorhexidine–alcohol should replace povidone–iodine as the standard for preoperative surgical scrubs. The use of intranasal mupirocin and chlorhexidine baths for carriers of *S. aureus* who have been identified preoperatively by means of a real-time polymerase-chain-reaction assay could be reserved primarily for patients who are undergoing cardiac surgery, all patients receiving an implant, and all immunosuppressed surgical candidates. Currently, the incremental value of preoperative baths with chlorhexidine alone for all surgical patients is unclear, but this relatively straightforward procedure could be examined critically in future studies. In the meantime, the data reported in these two studies offer remarkably safer strategies for all patients who require surgery.

Dr. Wenzel reports receiving speaking fees from 3M and research funding and consultation fees from Pfizer. No other potential conflict of interest relevant to this article was reported.

From the Department of Internal Medicine, Virginia Commonwealth University, Richmond.

1. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis 2006;43:322-30.
2. van Rijen M, Bonten M, Wenzel RP, Kluytmans JA. Intranasal mupirocin for reduction of *Staphylococcus aureus* infections in surgical patients with nasal carriage: a systematic review. J Antimicrob Chemother 2008;61:254-61.
3. Bode LGM, Kluytmans JAJW, Wertheim HFL, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med 2010;362:9-17.
4. Darouiche RO, Wall MJ Jr, Itani KMF, et al. Chlorhexidine–alcohol versus povidone–iodine for surgical-site antisepsis. N Engl J Med 2010;362:18-26.
5. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Infect Control Hosp Epidemiol 2002;23:759-69.
6. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med 2002;136:792-801.
7. Climo MW, Sepkowitz KA, Zuccotti G, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococcus, and healthcare associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med 2009;37:1858-65.
8. Popovich KJ, Hota B, Hayes R, et al. Effectiveness of routine patient cleaning with chlorhexidine gluconate for infection prevention in the medical intensive care unit. Infect Control Hosp Epidemiol 2009;30:959-63.
9. Swenson BR, Hedrick TL, Metzger R, et al. Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. Infect Control Hosp Epidemiol 2009;30:964-71.

ORIGINAL ARTICLE

Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis

Rabih O. Darouiche, M.D., Matthew J. Wall, Jr., M.D., Kamal M.F. Itani, M.D., Mary F. Otterson, M.D., Alexandra L. Webb, M.D., Matthew M. Carrick, M.D., Harold J. Miller, M.D., Samir S. Awad, M.D., Cynthia T. Crosby, B.S., Michael C. Mosier, Ph.D., Atef AlSharif, M.D., and David H. Berger, M.D.

ABSTRACT

BACKGROUND

Since the patient's skin is a major source of pathogens that cause surgical-site infection, optimization of preoperative skin antisepsis may decrease postoperative infections. We hypothesized that preoperative skin cleansing with chlorhexidine–alcohol is more protective against infection than is povidone–iodine.

METHODS

We randomly assigned adults undergoing clean-contaminated surgery in six hospitals to preoperative skin preparation with either chlorhexidine–alcohol scrub or povidone–iodine scrub and paint. The primary outcome was any surgical-site infection within 30 days after surgery. Secondary outcomes included individual types of surgical-site infections.

RESULTS

A total of 849 subjects (409 in the chlorhexidine–alcohol group and 440 in the povidone–iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection was significantly lower in the chlorhexidine–alcohol group than in the povidone–iodine group (9.5% vs. 16.1%; P=0.004; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine–alcohol was significantly more protective than povidone–iodine against both superficial incisional infections (4.2% vs. 8.6%, P=0.008) and deep incisional infections (1% vs. 3%, P=0.05) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups.

CONCLUSIONS

Preoperative cleansing of the patient's skin with chlorhexidine–alcohol is superior to cleansing with povidone–iodine for preventing surgical-site infection after clean-contaminated surgery. (ClinicalTrials.gov number, NCT00290290.)

From the Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine (R.O.D., S.S.A., A.A., D.H.B.), and Ben Taub General Hospital and Baylor College of Medicine (M.J.W., M.M.C., H.J.M.) — all in Houston; Veterans Affairs Boston Healthcare System and Boston University Medical School, Boston (K.M.F.I.); Veterans Affairs Medical Center and Medical College of Wisconsin, Milwaukee (M.F.O.); Veterans Affairs Medical Center, Atlanta (A.L.W.); and Cardinal Health, Leawood (C.T.C.), and Washburn University, Topeka (M.C.M.) — both in Kansas. Address reprint requests to Dr. Darouiche at the Center for Prostheses Infection, Baylor College of Medicine, 1333 Moursund Ave., Suite A221, Houston, TX 77030, or at rdarouiche@aol.com.

N Engl J Med 2010;362:18-26.

Despite the implementation of preoperative preventive measures, which include skin cleansing with povidone–iodine, surgical-site infection occurs in 300,000 to 500,000 patients who undergo surgery in the United States each year.[1-6] Since the patient's skin is a major source of pathogens, it is conceivable that improving skin antisepsis would decrease surgical-site infections.[7] The Centers for Disease Control and Prevention (CDC) recommends that 2% chlorhexidine-based preparations be used to cleanse the site of insertion of vascular catheters.[8] However, the CDC has not issued a recommendation as to which antiseptics should be used preoperatively to prevent postoperative surgical-site infection in the 27 million operations performed annually in the United States.[9] Furthermore, no published randomized studies have examined the effect of one antiseptic preparation as compared with another on the incidence of surgical-site infection. The main objective of this study was to compare the efficacy of chlorhexidine–alcohol with that of povidone–iodine for preventing surgical-site infections.

METHODS

STUDY DESIGN

We conducted this prospective, randomized clinical trial between April 2004 and May 2008 at six university–affiliated hospitals in the United States. The institutional review board at each hospital approved the study protocol, and written informed consent was obtained from all patients before enrollment. This investigator-initiated trial was conceived by the first author, who also acted as the study sponsor, recruited the sites, gathered the data, wrote the first and final versions of the manuscript, and decided in consultation with the other authors to submit the paper for publication. All authors vouch for the completeness and accuracy of the data. One of the authors, who is a statistician, analyzed the data. The single author from Cardinal Health (manufacturer of the antiseptic agents studied) substantially contributed to the design and conception of the study and critically revised the manuscript but played no role in data collection or analysis. All other authors had full access to the data and substantially contributed to the analysis and interpretation of the data and the writing of the manuscript.

PATIENTS

Patients 18 years of age or older who were undergoing clean-contaminated surgery (i.e., colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynecologic, or urologic operations performed under controlled conditions without substantial spillage or unusual contamination) were eligible for enrollment. Exclusion criteria were a history of allergy to chlorhexidine, alcohol, or iodophors; evidence of infection at or adjacent to the operative site; and the perceived inability to follow the patient's course for 30 days after surgery.

INTERVENTIONS

Enrolled patients were randomly assigned in a 1:1 ratio to have the skin at the surgical site either preoperatively scrubbed with an applicator that contained 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChloraPrep, Cardinal Health) or preoperatively scrubbed and then painted with an aqueous solution of 10% povidone–iodine (Scrub Care Skin Prep Tray, Cardinal Health). More than one chlorhexidine–alcohol applicator was used if the coverage area exceeded 33 by 33 cm. To help match the two groups and address potential interhospital differences, randomization was stratified by hospital with the use of computer-generated randomization numbers without blocking.

EFFICACY OUTCOMES

The primary end point of the study was the occurrence of any surgical-site infection within 30 days after surgery. The operating surgeon became aware of which intervention had been assigned only after the patient was brought to the operating room. Both the patients and the site investigators who diagnosed surgical-site infection on the basis of criteria developed by the CDC[9] remained unaware of the group assignments. Secondary end points included the occurrence of individual types of surgical-site infections. These were classified as superficial incisional infection (which involved only skin and subcutaneous tissue and excluded stitch-related abscesses), deep incisional infection (which involved fascia and muscle), or organ-space infection (which involved any organ or space other than the incised layer of body wall that was opened or manipulated during the operation).[9]

CLINICAL ASSESSMENT

Preoperative evaluation included a medical history taking, physical examination, and routine hematologic and blood chemical laboratory tests. The surgical site and the patient's vital signs were assessed at least once a day during hospitalization, on discharge, at the time of follow-up evaluation, and whenever surgical-site infection occurred. After discharge, the investigators called the patients once a week during the 30-day follow-up period and arranged for prompt clinical evaluation if infection was suspected. Whenever surgical-site infection was suspected or diagnosed, clinically relevant microbiologic samples were cultured. Investigators who were unaware of the patients' group assignments assessed the seriousness of all adverse events and determined whether they were related to the study.

STATISTICAL ANALYSIS

The average baseline rate of surgical-site infection at the six participating hospitals was 14% after clean-contaminated surgery with povidone–iodine skin preparation, and we estimated that substituting chlorhexidine–alcohol for povidone–iodine would reduce this rate to 7%. Therefore, we planned to enroll approximately 430 patients in each study group who could be evaluated in order for the study to have 90% power to detect a significant difference in the rates of surgical-site infection between the two groups, at a two-tailed significance level of 0.05 or less.

The criteria for including patients in the intention-to-treat analysis included randomization and the possibility of applying each of the study antiseptic preparations (which required performance of surgery). Inclusion in the per-protocol analysis required the application of the study preparation before clean-contaminated surgery and completion of the 30-day follow-up. An independent data and safety monitoring board composed of an infectious-disease physician, a surgeon, and a statistician met annually to review the conduct of the study. No formal criteria were set for stopping the study.

The significance of differences between the two study groups in terms of patient characteristics was determined with the use of the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. For efficacy outcomes, we compared the proportions of patients in the two study groups who could be evaluated and who had any type of surgical-site infection, using Fisher's exact test and calculating the relative risk of infection and 95% confidence intervals. The consistency of the effects of the study intervention on infections across different types of surgery was examined with the use of an interaction test. To determine whether the results were consistent across the six participating hospitals, a prespecified Breslow–Day test for homogeneity was performed. To compare the proportions of patients in the two study groups who were free of surgical-site infection as a function of the length of time since surgery, we performed log-rank tests on Kaplan–Meier estimates based on analyses in which data for patients who did not have infections were censored 30 days after surgery. Both the frequency of isolating certain organisms and categories of organisms and the incidence of adverse and serious adverse events were compared between the study groups with the use of Fisher's exact test. All reported P values are based on two-tailed tests of significance and were not adjusted for multiple testing.

We conducted univariate and multivariate analyses to assess whether risk factors contributed to the occurrence of surgical-site infection. The univariate analysis for categorical factors was performed with the use of Fisher's exact test. For continuous factors, we used a single-variable logistic-regression model that involved generalized estimating equations (GEE) to account for hospital site as a random effect. A multivariate logistic-regression analysis that also adjusted for the hospital site as a random effect (by means of GEE) was performed to assess factors deemed significant ($P \leq 0.10$) by univariate analysis or considered clinically important. The assessed risk factors were prespecified in the protocol, and the statistical methods were preplanned except for the inclusion of hospital site as a random effect. Since some types of surgery did not result in infection in either study group, a dichotomous variable — "abdominal" surgery (including colorectal, biliary, small intestinal, and gastroesophageal operations) versus "nonabdominal" surgery (including thoracic, gynecologic, and urologic operations) — was created for the GEE logistic-regression model.

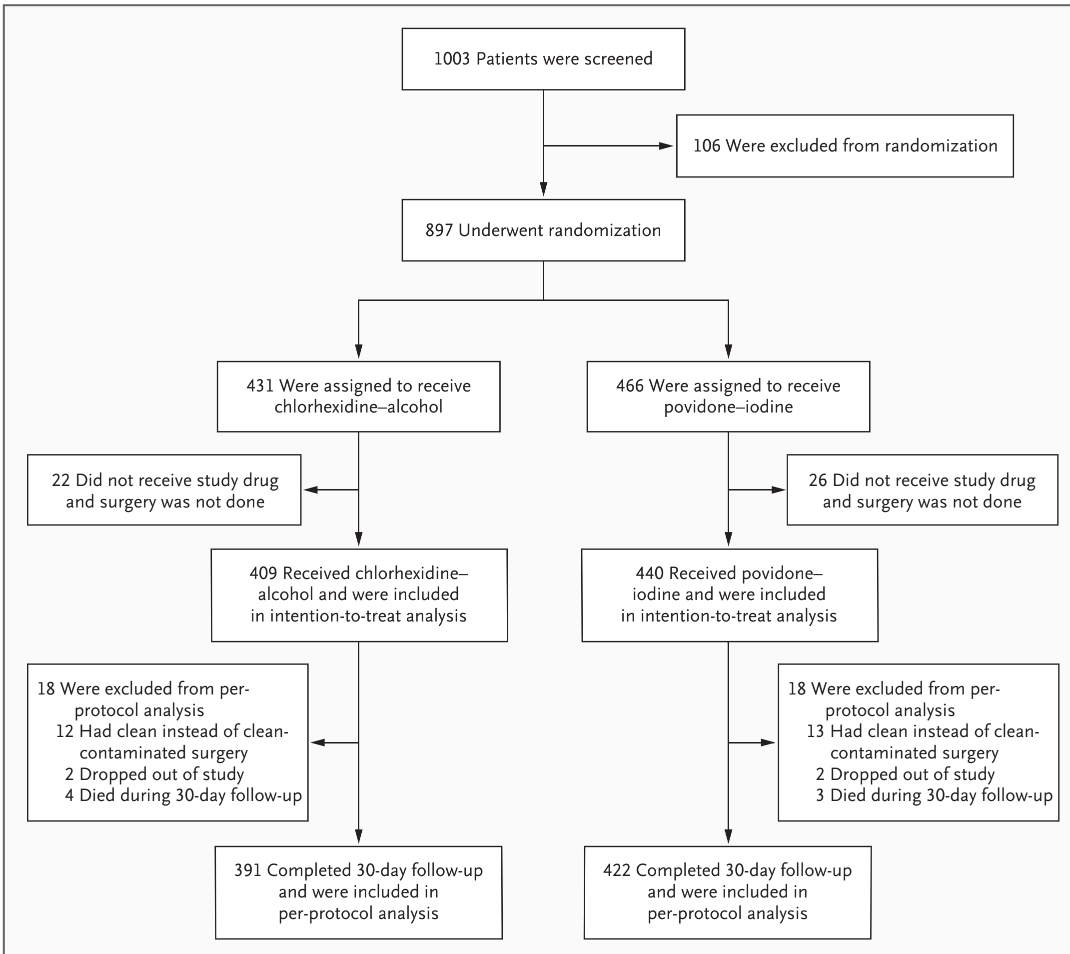

Figure 1. Screening, Randomization, and Follow-up of Study Participants.

Results

Patients

A total of 897 patients were randomly assigned to a study group: 431 to the chlorhexidine–alcohol group and 466 to the povidone–iodine group (Fig. 1). Of the 849 patients who qualified for the intention-to-treat analysis, 409 received chlorhexidine–alcohol and 440 received povidone–iodine. Thirty-six patients were excluded from the per-protocol analysis: 25 underwent clean rather than clean-contaminated surgery, 4 dropped out of the study 1 or 2 days after surgery, and 7 died before completion of the 30-day follow-up (4 in the chlorhexidine–alcohol group and 3 in the povidone–iodine group). Therefore, 813 patients (391 in the chlorhexidine–alcohol group and 422 in the povidone–iodine group) were included in the per-protocol analyses. The patients in the two study groups were similar with respect to demographic characteristics, coexisting illnesses, risk factors for infection, antimicrobial exposure, and duration and types of surgery (Table 1, and Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All patients received systemic prophylactic antibiotics within 1 hour before the initial incision, and there were no significant differences in the type or number of antibiotics given to the two study groups, even when only patients who underwent colorectal surgery were considered (Table 2 in the Supplementary Appendix).

Rates of Infection

For the patients in the intention-to-treat population, the overall rate of surgical-site infection was

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Chlorhexidine–Alcohol (N=409)	Povidone–Iodine (N=440)	P Value
Male sex (%)	58.9	55.9	0.40
Age (yr)	53.3+14.6	52.9+14.2	0.87
Systemic antibiotics			
Initiated preoperatively (%)	100	100	>0.99
Duration of preoperative administration (days)			
Mean	1.1±1.2	1.1±0.8	>0.99
Range	1–20	1–11	
Received postoperatively (%)	51.7	48.9	0.41
Duration of surgery (hr)	3.0±1.5	3.0±1.5	>0.99
Abdominal surgery (%)	72.6	70.0	0.41
Colorectal	45.5	43.4	0.58
Biliary	10.8	12.3	0.52
Small intestinal	10.0	7.7	0.28
Gastroesophageal	6.4	6.6	0.89
Nonabdominal surgery (%)	27.4	30.0	0.41
Thoracic	10.8	13.0	0.34
Gynecologic	10.3	9.1	0.56
Urologic	6.4	8.0	0.42
Preoperative shower (%)	26.7	27.0	0.94
With 4% chlorhexidine gluconate (%)	16.1	18.9	0.32
With 10% povidone–iodine (%)	7.3	5.2	0.26
With 0.6% triclocarban soap bar (%)	3.2	3.0	>0.99

* Plus–minus values are means ±SD.

significantly lower in the chlorhexidine–alcohol group (9.5%) than in the povidone–iodine group (16.1%, P=0.004) (Table 2). The relative risk of any surgical-site infection among patients whose skin was preoperatively cleansed with chlorhexidine–alcohol versus povidone–iodine was 0.59 (95% confidence interval [CI], 0.41 to 0.85). Similarly, chlorhexidine–alcohol was associated with significantly fewer superficial incisional infections (relative risk, 0.48; 95% CI, 0.28 to 0.84) and deep incisional infections (relative risk, 0.33; 95% CI, 0.11 to 1.01). However, there were no significant differences between the two study groups in the incidence of organ-space infection (relative risk, 0.97; 95% CI, 0.52 to 1.80) or sepsis from surgical-site infection (relative risk, 0.62; 95% CI, 0.30 to 1.29).

The per-protocol analysis yielded similar efficacy results. The Kaplan–Meier estimates of the risk of surgical-site infection (Fig. 2) showed a significantly longer time to infection after surgery in the chlorhexidine–alcohol group than in the povidone–iodine group (P=0.004 by the log-rank test).

The interaction between treatment group and type of surgery (abdominal vs. nonabdominal) was included in a logistic-regression model with the main effects of group and surgery type and was found not to be significant (P=0.41). When considered separately in a subgroup analysis (Table 3), the rate of infection after abdominal surgery was 12.5% in the chlorhexidine–alcohol group versus 20.5% in the povidone–iodine group (95% CI for the absolute difference [chlorhexidine–alcohol minus povidone–iodine], −13.9 to −2.1 percentage points). For patients undergoing nonabdominal surgery, the rate of infection was 1.8% in the chlorhexidine–alcohol group versus 6.1% in the

Table 2. Proportion of Patients with Surgical-Site Infection, According to Type of Infection (Intention-to-Treat Population).

Type of Infection	Chlorhexidine–Alcohol (N=409)	Povidone–Iodine (N=440)	Relative Risk (95% CI)*	P Value†
	no. (%)			
Any surgical-site infection	39 (9.5)	71 (16.1)	0.59 (0.41–0.85)	0.004
Superficial incisional infection	17 (4.2)	38 (8.6)	0.48 (0.28–0.84)	0.008
Deep incisional infection	4 (1.0)	13 (3.0)	0.33 (0.11–1.01)	0.05
Organ-space infection	18 (4.4)	20 (4.5)	0.97 (0.52–1.80)	>0.99
Sepsis from surgical-site infection	11 (2.7)	19 (4.3)	0.62 (0.30–1.29)	0.26

* Relative risks are for chlorhexidine–alcohol as compared with povidone–iodine. The 95% confidence intervals were calculated with the use of asymptotic standard-error estimates.
† P values are based on Fisher's exact test.

povidone–iodine group (95% CI for the absolute difference, –7.9 to 2.6 percentage points).

Both the intention-to-treat analysis (Table 3) and the per-protocol analysis showed lower rates of surgical-site infection in the chlorhexidine–alcohol group than in the povidone–iodine group for each of the seven types of operations studied. Although the trial was not powered to compare the rates of infection for subcategories of patients, infection occurred significantly less often in the chlorhexidine–alcohol group than in the povidone–iodine group in the intention-to-treat analysis for patients who underwent small intestinal surgery (P=0.04) or abdominal surgery (P=0.009) or who did not shower preoperatively (P=0.02).

The Breslow–Day tests indicated homogeneity in showing no significant differences between hospitals with respect to the incidence of either any type of surgical-site infection (P=0.35) or individual types of infection (P≥0.19). Even so, we accounted for hospital site in all logistic-regression models by including this term as a random effect through the use of GEE.

ANALYSES OF RISK FACTORS

The multivariate logistic-regression analysis identified the following risk factors for surgical-site infection in the intention-to-treat population: use of povidone–iodine, abdominal surgery, alcohol abuse, liver cirrhosis, cancer, diabetes mellitus, malnutrition, gastrointestinal disease, longer duration of surgery, longer duration of placement of surgical drain, and preoperative shower with povidone–iodine (Table 3 in the Supplementary Appendix). Since an analysis of risk factors other than the assigned intervention constitutes an exploratory analysis, which involves multiple simultaneous statistical tests, it could inflate the probability of a false positive finding (type II error).

MICROBIOLOGIC CAUSES OF INFECTION

Culture of the surgical site in 60 of 61 infected patients yielded growth of organisms (a total of 107 isolates), and similar proportions of infected patients in the two study groups (23 of 39 [59%] in the chlorhexidine–alcohol group and 37 of 71 [52%] in the povidone–iodine group) had an identifiable microbiologic cause of infection (Table 4 in the Supplementary Appendix). Gram-positive aerobic bacteria (63 isolates) outnumbered gram-negative aerobic bacteria (25 isolates) by a factor of 2.5, and 38% of cultures were polymicrobial. There were no significant differences in the frequency of isolating certain categories of organisms or particular organisms in the chlorhexidine–alcohol group (total of 44 isolates) as compared with the povidone–iodine group (total of 63 isolates), with the exception of streptococci, which were less common in the former group (1 of 44 [2.3%] vs. 10 of 63 [15.9%], P=0.03).

ADVERSE EVENTS

In the intention-to-treat analysis, adverse events occurred in equal proportions among the patients in the chlorhexidine–alcohol group and the povidone–iodine group (228 of 409 [55.7%] and 256 of 440 [58.2%], respectively), as did serious adverse events (72 of 409 [17.6%] and 70 of 440 [15.9%],

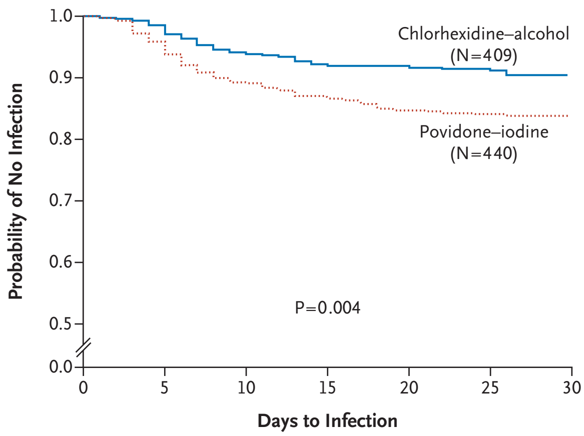

Figure 2. Kaplan–Meier Curves for Freedom from Surgical-Site Infection (Intention-to-Treat Population).

Patients who received chlorhexidine–alcohol were significantly more likely to remain free from surgical-site infection than were those who received povidone–iodine (P=0.004 by the log-rank test). In the chlorhexidine–alcohol group, 39 patients had events (9.5%) and data from 370 patients (90.5%) were censored; in the povidone–iodine group, 71 patients had events (16.1%) and data from 369 patients (83.9%) were censored.

respectively) (Table 4, and Table 5 in the Supplementary Appendix). Findings were similar in the per-protocol analysis. Three patients (0.7%) in each study group had an adverse event (pruritus, erythema, or both around the surgical wound) that was judged to be related to the study drugs; however, no serious adverse events were judged to be related to the study drugs. There were no cases of fire or chemical skin burn in the operating room. A total of seven patients died: four (1.0%) in the chlorhexidine–alcohol group who did not have surgical-site infections and three (0.7%) in the povidone–iodine group who died from sepsis due to organ-space infection.

DISCUSSION

Randomized studies have compared the efficacy of different types[10-13] or doses[14,15] of systemic antibiotics for preventing surgical-site infection but not the effect of preoperative skin antisepsis. In this randomized study, the application of chlorhexidine–alcohol reduced the risk of surgical-site infection by 41% as compared with the most common practice in the United States of using aqueous povidone–iodine.[7] This degree of protection is similar to the 49% reduction in the risk of vascular catheter–related bloodstream infection in a meta-analysis that showed the superiority of skin disinfection with chlorhexidine-based solutions versus 10% povidone–iodine.[16] Although the overall rates of surgical-site infection of 10 to 16% in this study are higher than those reported in some previous studies,[17,18] they are similar to the prestudy rates at the participating hospitals and those reported in other studies[13] and are lower than the rates reported in trials that used the CDC definition of infection and had adequate follow-up,[11,12,19] as we did in this trial. On the basis of our findings, the estimated number of patients who would need to undergo skin preparation with chlorhexidine–alcohol instead of povidone–iodine in order to prevent one case of surgical-site infection is approximately 17.

Although both the antiseptic preparations we studied possess broad-spectrum antimicrobial activity,[9] the superior clinical protection provided by chlorhexidine–alcohol is probably related to its more rapid action, persistent activity despite exposure to bodily fluids, and residual effect.[20] The superior clinical efficacy of chlorhexidine–alcohol in our study correlates well with previous microbiologic studies showing that chlorhexidine-based antiseptic preparations are more effective than iodine-containing solutions in reducing the bacterial concentration in the operative field for vaginal hysterectomy[21] and foot-and-ankle surgery.[22,23] Although the use of flammable alcohol-based products in the operating room poses the risk, though small, of fire or chemical skin burn, no such adverse events occurred in this study or the other studies.[21-23]

In this trial we universally enforced standard-of-care preventive measures (e.g., administering systemic prophylactic antibiotics within 1 hour before the first incision was made and, if needed, clipping hair immediately before surgery),[9,24] but hospitals were allowed to continue their preexisting practices, which offer potential but not established protective efficacy (e.g., preoperative showering).[25] However, we controlled the effect of differences in hospital practices by using hospital-stratified randomization, which ensured close matching of the two study groups as well as trial results that are applicable to a broadly representative population of hospitalized patients.

Because antiseptics act only against organisms

Table 3. Proportion of Patients with Surgical-Site Infection, According to Type of Surgery (Intention-to-Treat Population).

Type of Surgery	Chlorhexidine–Alcohol		Povidone–Iodine	
	Total No. of Patients	Patients with Infection	Total No. of Patients	Patients with Infection
		no. (%)		*no. (%)*
Abdominal	297	37 (12.5)	308	63 (20.5)
Colorectal	186	28 (15.1)	191	42 (22.0)
Biliary	44	2 (4.6)	54	5 (9.3)
Small intestinal	41	4 (9.8)	34	10 (29.4)
Gastroesophageal	26	3 (11.5)	29	6 (20.7)
Nonabdominal	112	2 (1.8)	132	8 (6.1)
Thoracic	44	2 (4.5)	57	4 (7.0)
Gynecologic	42	0	40	1 (2.5)
Urologic	26	0	35	3 (8.6)

Table 4. Clinical Adverse Events (Intention-to-Treat Population).

Clinical Adverse Event	Chlorhexidine–Alcohol (N=409)	Povidone–Iodine (N=440)	Absolute Difference*	P Value†
	no. (%)		*percentage points (95% CI)*	
Adverse events in ≥5% of patients in either group	228 (55.7)	256 (58.2)	−2.4 (−9.1 to 4.2)	0.49
Drug-related adverse events‡	3 (0.7)	3 (0.7)	0.1 (−1.1 to 1.2)	>0.99
Serious adverse events in >1% of patients in either group	72 (17.6)	70 (15.9)	1.7 (−3.3 to 6.7)	0.52
Serious drug-related adverse events	0	0	—	—
Death	4 (1.0)	3 (0.7)	0.3 (−0.9 to 1.5)	0.72

* The absolute difference is shown as the rate in the chlorhexidine–alcohol group minus the rate in the povidone–iodine group.
† P values were calculated with the use of Fisher's exact test.
‡ Drug-related adverse events included pruritus, erythema, or both around the surgical wound and are reported even though the rate was not 5% or higher in either group.

that reside on the patient's integument, the overall superior protection afforded by chlorhexidine–alcohol was attributed primarily to a reduction in the rates of superficial and deep incisional infections that were caused mostly by gram-positive skin flora. Since two thirds of surgical-site infections are confined to the incision,[9,11] optimizing skin antisepsis before surgery could result in a significant clinical benefit.

Dr. Darouiche reports receiving research and educational grants from Cardinal Health; Dr. Wall, receiving a research grant from Cardinal Health; Dr. Itani, receiving consulting fees from Klein and Company and a research grant from Cardinal Health; Dr. Otterson, receiving consulting fees and a research grant from Cardinal Health; Dr. Webb, receiving a research grant from Cardinal Health; Dr. Awad, receiving consulting and lecture fees from Cardinal Health; Ms. Crosby, being employed by Cardinal Health; and Dr. Berger, receiving a research grant from Cardinal Health. No other potential conflict of interest relevant to this article was reported.

References

1. Wolf JS Jr, Bennett CJ, Dmochowski RR, Hollenbeck BK, Pearle MS, Schaeffer AJ. Best practice policy statements on urologic surgery antimicrobial prophylaxis. J Urol 2008;179:1379-90. [Erratum, J Urol 2008;180:2262-3.]
2. Hawn MT, Itani KM, Gray SH, Vick CC, Henderson W, Houston TK. Association of timely administration of prophylactic antibiotics for major surgical procedures and surgical site infection. J Am Coll Surg 2008;206:814-9.
3. Belda FJ, Aguilera L, Garcia de la Asunción J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA 2005;294:2035-42. [Erratum, JAMA 2005;294:2973.]
4. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996;334:1209-15.
5. Yasunaga H, Ide H, Imamura T, Ohe K. Accuracy of economic studies on surgical site infection. J Hosp Infect 2007;65:102-7.
6. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol 1999;20:725-30.
7. Napolitano LM. Decolonization of the skin of the patient and surgeon. Surg Infect (Larchmt) 2006;7:Suppl 3:S3-S15.
8. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Infect Control Hosp Epidemiol 2002;23:759-69.
9. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78.
10. Ishizaka K, Kobayashi S, Machida T, Yoshida K. Randomized prospective comparison of fosfomycin and cefotiam for prevention of postoperative infection following urological surgery. J Infect Chemother 2007;13:324-31.
11. Itani KMF, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Engl J Med 2006;355:2640-51.
12. Milsom JW, Smith DL, Corman ML, Howerton RA, Yellin AE, Luke DR. Double-blind comparison of single-dose alatrofloxacin and cefotetan as prophylaxis of infection following elective colorectal surgery. Am J Surg 1998;176:6A Suppl:46S-52S.
13. Arnaud JP, Bellissant E, Boissel P, et al. Single-dose amoxycillin-clavulanic acid vs. cefotetan for prophylaxis in elective colorectal surgery: a multicentre, prospective, randomized study. J Hosp Infect 1992;22:Suppl A:23-32.
14. Fujita S, Saito N, Yamada T, et al. Randomized, multicenter trial of antibiotic prophylaxis in elective colorectal surgery: single dose vs 3 doses of a second-generation cephalosporin without metronidazole and oral antibiotics. Arch Surg 2007;142:657-61.
15. Mohri Y, Tonouchi H, Kobayashi M, et al. Randomized clinical trial of single- versus multiple-dose antimicrobial prophylaxis in gastric cancer surgery. Br J Surg 2007;94:683-8.
16. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med 2002;136:792-801.
17. Uchiyama K, Takifuji K, Tani M, et al. Prevention of postoperative infections by administration of antimicrobial agents immediately before surgery for patients with gastrointestinal cancers. Hepatogastroenterology 2007;54:1487-93.
18. Greif R, Akça O, Horn E-P, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161-7.
19. Smith RL, Bohl JK, McElearney ST, et al. Wound infection after elective colorectal resection. Ann Surg 2004;239:599-605.
20. Denton GW. Chlorhexidine. In: Block SS, ed. Disinfection, sterilization, and preservation. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:321-36.
21. Culligan PJ, Kubik K, Murphy M, Blackwell L, Snyder J. A randomized trial that compared povidone iodine and chlorhexidine as antiseptics for vaginal hysterectomy. Am J Obstet Gynecol 2005;192:422-5.
22. Ostrander RV, Botte MJ, Brage ME. Efficacy of surgical preparation solutions in foot and ankle surgery. J Bone Joint Surg Am 2005;87:980-5.
23. Bibbo C, Patel DV, Gehrmann RM, Lin SS. Chlorhexidine provides superior skin decontamination in foot and ankle surgery: a prospective randomized study. Clin Orthop Relat Res 2005;438:204-8.
24. Tanner J, Woodings D, Moncaster K. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev 2006;2:CD004122.
25. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. Cochrane Database Syst Rev 2007;2:CD004985.