PERIOPERATIVE INTRANASAL MUPIROCIN FOR THE PREVENTION OF SURGICAL-SITE INFECTIONS: SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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ABSTRACT

OBJECTIVE: To review the evidence evaluating perioperative intranasal mupirocin for the prevention of surgical-site infections according to type of surgical procedure.

DESIGN: Systematic review and meta-analysis of published clinical trials.

SETTING: Studies included were either randomized clinical trial or prospective trials at a single institution that measured outcomes both before and after an institution-wide intervention (before–after trial). In all studies, intervention and control groups differed only by the use of perioperative intranasal mupirocin in the intervention group.

PATIENTS: Patients undergoing general or nongeneral surgery (eg, cardiothoracic surgery, orthopedic surgery, and neurosurgery).

MAIN OUTCOME MEASURE: Risk of surgical-site infection following perioperative intranasal mupirocin versus usual care.

RESULTS: Three randomized and four before–after trials met the inclusion criteria. No reduction in surgical-site infection rate was seen in randomized general surgery trials (summary estimates: 8.4% in the mupirocin group and 8.1% in the control group; relative risk [RR], 1.04; 95% confidence interval [CI_{95}], 0.81 to 1.33). In nongeneral surgery, the use of mupirocin was associated with a reduction in surgical-site infection in randomized trials (summary estimates: 6.0% in the mupirocin group and 7.6% in the control group; RR, 0.80; CI_{95}, 0.58 to 1.10) and in before–after trials (summary estimates: 1.7% in the mupirocin group and 4.1% in the control group; RR, 0.40; CI_{95}, 0.29 to 0.56).

CONCLUSIONS: Perioperative intranasal mupirocin appears to decrease the incidence of surgical-site infection when used as prophylaxis in nongeneral surgery. Given its low risk and low cost, use of perioperative intranasal mupirocin should be considered in these settings (*Infect Control Hosp Epidemiol* 2005;26:916-922).

Surgical-site infections (SSIs) are the most common nosocomial infection among surgical patients.[1] They are thought to complicate approximately 500,000 of the estimated 27 million operations performed annually in the United States.[2] These infections result in an excess cost of more than $1.6 billion in hospital charges alone and prolong hospital stays by more than 5 days per episode.[3,4] More importantly, patients with SSI are more than twice as likely as surgical patients without SSI to die in the postoperative period.[4]

Staphylococcus aureus is the most common cause of SSI, and it is believed that most of these infections originate from the patient's own flora.[5-7] This organism colonizes up to half of healthy adults, usually in the anterior nares.[8] Mupirocin is a topical antibiotic ointment that has activity against *Staphylococcus* species and has been demonstrated in randomized trials to nearly completely eradicate *S. aureus* from the anterior nares soon after treatment.[8-10] Complete eradication can be achieved with as little as one dose.[5]

Studies evaluating the use of perioperative intranasal mupirocin for the prevention of SSI have produced varied results. One explanation might be that many of these trials have included patients undergoing general surgery—surgeries in which gram-negative and anaerobic organisms may play a relatively larger role, thereby attenuating any potential benefit from mupirocin. To clarify the effect of mupirocin use for the prevention of SSI, we performed a systematic review and meta-analysis of the available evidence according to specific types of surgical procedures.

METHODS

Search Strategy

We searched the following databases during October and November 2004 to find appropriate articles: Medline (1966 to 2004), Cinahl (1982 to 2004), Biosis (1995 to 2003), and Cochrane Database of Systematic Reviews and Central Register of Controlled Trials. Our search was not restricted by language. The term "mupirocin" was combined with the keywords "postoperative complications," "surgical wound infection," "postoperative infection," or "surgical-site infec-

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tion." A bibliography review and a cited reference search were performed on relevant articles to identify additional studies. A total of 60 articles were identified.

Study Selection

We included only those studies that were controlled trials with intranasal mupirocin as the sole intervention. The intervention had to include at least one preoperative dose of mupirocin, given regardless of *S. aureus* colonization status. We excluded studies if overall SSI rates could not be determined, if current Centers for Disease Control and Prevention criteria[11] (or equivalent criteria) to define SSI were not used, or if follow-up was less than 28 days. We also excluded studies that were solely about peritoneal dialysis catheter or central venous catheter placement and those performed during an outbreak of SSI. The figure shows the study selection process that resulted in the seven trials meeting all criteria.

All studies were reviewed by two independent investigators (AJK, CTW) and information was compiled using a standardized data extraction form. Discrepancies were resolved through discussion and, in one case, by a separate referee (RJL). For studies that included both as-treated and intent-to-treat analyses of the intervention group, only the intent-to-treat analysis was used. This was done to provide the most conservative estimate of mupirocin benefit and to better reflect its real-world use. One study, a before–after trial, included only an as-treated analysis and this was used in the summary analysis.[12] When possible, in studies that included gastrointestinal surgery, postoperative infections that were due to gastrointestinal leaks were excluded.

Categories of Surgery

We first broadly divided the studies into general surgery and nongeneral surgery. Where possible, we further separated the nongeneral surgery studies into the specific subcategories of cardiothoracic or orthopedic surgery.

The study by Perl et al. combined both general and nongeneral surgery.[13] We obtained data stratified by type of surgical procedure from one of the authors (M. B. Zimmerman, PhD, written communication, November 2004). Cardiothoracic and neurosurgery were combined in the nongeneral surgery category and the remaining cases, which included general, oncologic, and gynecologic surgery, were placed in the general surgery category.

Analysis

We separated trials into randomized and nonrandomized trials. All of the nonrandomized trials were prospective trials from a single institution that measured outcome before and after an institution-wide intervention (subsequently referred to as a before–after trial). The relative risk of SSI was calculated for patients treated with mupirocin versus control-patients in each study. When a prespecified category (ie, randomized general surgery trials) included more than one study, we tested for heterogeneity among the studies. If appropriate ($P > .10$), a random effects model was used to calculate a weighted summary relative risk (RR) and 95% confidence interval (CI_{95}) for SSI. Calculations were performed using meta-analysis software (RevMan 4.2, Update Software Ltd., Oxford, United Kingdom). All studies were assigned a strength that was adapted from U.S. Preventive Services Task Force criteria for evaluating the quality of studies.[14]

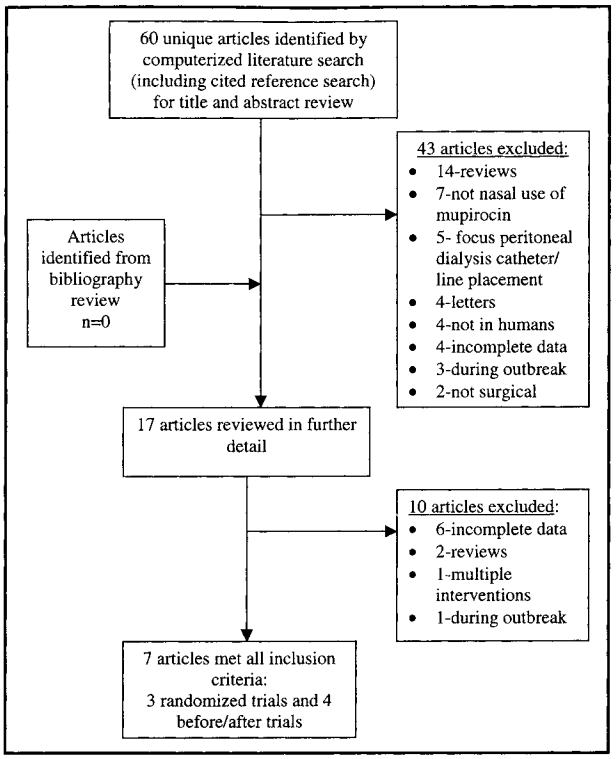

FIGURE. Study identification and selection criteria.

RESULTS

Study Characteristics

Seven studies involving a total of 11,088 patients met all inclusion criteria and were included in this analysis (Table 1).[12,13,15-19] Three were randomized clinical trials and four were before–after trials. We compared baseline characteristics for intervention and control groups using variables that were common to at least three studies (Table 2). As expected, the randomized clinical trials had intervention and control groups that were similar. However, several significant differences between the two groups were found in the before–after trials. One study had a significantly younger mupirocin group ($P = .023$),[17] another study had a significantly older mupirocin group ($P = .006$),[19] and a third study had a greater number of patients colonized with *S. aureus* in the control group ($P = .007$).[18]

General Surgery

General surgery trials were largely made up of patients undergoing gastrointestinal and general surgery (the study by Perl et al.[13] also included oncologic and gynecologic sur-

TABLE 1
CHARACTERISTICS OF TRIALS EVALUATING MUPIROCIN FOR THE PREVENTION OF SURGICAL-SITE INFECTIONS

Study	Study Strength*	Design	Dates	Site	Type of Surgery	Study Size		Mupirocin Dose	Usual Care†
						Mupirocin	Controls		
Perl et al.[13]	I, good	Randomized, double blind, placebo controlled	April 1995–December 1998	Iowa: university hospital and VA medical center	Cardiothoracic, general, oncologic, gynecologic, and neurosurgery	1,933	1,931	Twice daily up to 5 d (between 1 and 10 doses preoperatively)	"Standard therapy"
Kalmeijer et al.[15]	I, good	Randomized, double blind, placebo controlled	January 1997–July 1999	Netherlands: hospital	Orthopedic	315	299	Twice daily from admission to surgery (at least 2 preoperative doses)	Antibiotics: 1 dose preoperatively, 2 doses postoperatively
Suzuki et al.[16]	I, fair	Randomized, controlled trial	January 1996–January 1998	Japan: university hospital	Gastrointestinal	193	202	Three times daily for 3 d preoperatively	Preoperative chlorhexidine shower, 1 dose preoperative antibiotics then continued for 4 to 5 d
Gernaat-van der Sluis et al.[19]	II, fair	Nonrandomized, controlled trial	Before, July 1992–August 1994; After, August 1994–January 1996	Netherlands: teaching hospital	Orthopedic	1,044	1,260	3 doses preoperatively	IV antibiotic: 1 dose preoperatively, 1 dose postoperatively
Kluytmans et al.[17]	II, fair	Nonrandomized, controlled trial	Before, August 1989–February 1991; After, March 1991–August 1992	Netherlands: university hospital	Cardiothoracic	868	928	Twice daily for 5 d, beginning 1 d preoperatively	Preoperative antiseptic shower, 1 dose preoperative antibiotics then continued for 24 h
Cimochowski et al.[12]	II, fair	Nonrandomized, controlled trial	Before, January 1995–October 1996; After, December 1997–March 1999	Pennsylvania: community hospital	Cardiac	854	992	Twice daily for 5 d (2 preoperative doses)	Preoperative chlorhexidine shower, 1 dose preoperative IV antibiotics then continued for 48 h postoperatively
Yano et al.[18]	II, fair	Nonrandomized, controlled trial	Before, January –December 1996; After, February–March 1997	Japan: university hospital	Gastrointestinal	141	128	Three times daily for 3 d preoperatively	5 d postoperative antibiotics

VA = Veterans Affairs; IV = intravenous.
*Strength based on U.S. Preventive Services Task Force criteria for hierarchy of research design (roman numeral) and internal validity (rating).
†Given to both groups.

TABLE 2
PATIENT CHARACTERISTICS IN INCLUDED TRIALS

Study	Mean Age	Male	Diabetes Mellitus	Obesity	Length of Surgery	Prestudy Colonization With *Staphylococcus aureus*
Perl et al.[13]						
Mupirocin	53.8 y	50.6%	15.9%	Mean BMI, 28.9	Median, 168 min*	23.0%
Control	54.2 y	52.6%	16.7%	Mean BMI, 29.0	Median, 168 min*	23.1%
Kalmeijer et al.[15]						
Mupirocin	62.9 y	33.0%	1%†	Mean BMI, 27.0	Mean, 85 min	30.3%
Control	62.7 y	34.4%	0.3%†	Mean BMI, 27.2	Mean, 89 min	28.8%
Suzuki et al.[16]						
Mupirocin	63 y	65.8%	17.6%	No data	No data	No data
Control	62 y	66.8%	20.8%	No data	No data	No data
Gernaat-van der Sluis et al.[19,‡]						
Mupirocin	> 70 y, 36%	46.0%	6%	No data	≥ 2 h, 10%	No data
Control	> 70 y, 20%	44.0%	4%	No data	≥ 2 h, 20%	No data
Kluytmans et al.[17]						
Mupirocin	58.5 y§	No data‖	No data	No data	No data	No data
Control	60 y	No data	No data	No data	No data	No data
Cimochowski et al.[12]						
Mupirocin	66.1 y§	63.8%	31.2%	19.3%	No data	No data
Control	64.7 y	64.4%	27.9%	18.8%	No data	No data
Yano et al.[18]						
Mupirocin	60.1 y	75.2%	No data	No data	No data	12.0%§
Control	59.8 y	71.1%	No data	No data	No data	16.6%

BMI = body mass index.
*General surgery cases only.
†Insulin dependent only.
‡Evaluated patient characteristics only in a random subset of each group (N = 50).
§Significantly different.
‖Data not interpretable.

gery). We hypothesized that these surgeries would compromise procedures for which gram-negative and anaerobic organisms would play more of a role in causing SSI, therefore attenuating the effect of mupirocin. As demonstrated in Table 3, mupirocin use had no apparent effect in the randomized trials (summary estimates: 8.4% in the mupirocin group and 8.1% in the control group; RR, 1.04; CI_{95}, 0.81 to 1.33). The single small (n = 269) before–after trial showed a decrease in SSI incidence (11.3% in the mupirocin group and 18.0% in the control group; RR, 0.63; CI_{95}, 0.35 to 1.14). When randomized and before–after trials were combined, the RR approached 1.0 (summary estimates: 8.7% in the mupirocin group and 8.9% in the control group; RR, 0.95; CI_{95}, 0.70 to 1.29; test of heterogeneity, $P = .26$).

Nongeneral Surgery

Nongeneral surgery trials included patients undergoing cardiothoracic surgery, orthopedic surgery, and neurosurgery. We hypothesized that these surgeries would compromise procedures for which gram-positive organisms would play more of a role in causing SSI, therefore attenuating the effect of mupirocin. As demonstrated in Table 3, mupirocin use reduced the incidence of SSI in the randomized trials (summary estimates: 6.0% in the mupirocin group and 7.6% in the control group; RR, 0.80; CI_{95}, 0.58 to 1.10). For the before–after trials, mupirocin also reduced the incidence of SSI (summary estimates: 1.7% in the mupirocin group and 4.1% in the control group; RR, 0.40; CI_{95}, 0.29 to 0.56). A summary estimate combining the randomized and before–after trials did not meet our prespecified criteria for heterogeneity.

On subanalysis, nongeneral surgery studies were further subdivided into studies of cardiothoracic surgery and orthopedic surgery (Table 4). Among the subset of cardiothoracic surgery patients from the single randomized trial, mupirocin reduced the incidence of SSI (incidence: 9.9% in

TABLE 3
EFFECT OF MUPIROCIN USE ON SURGICAL-SITE INFECTIONS IN NONGENERAL AND GENERAL SURGERY

Study	No. of Patients	Infection Rate		RR (CI_{95})*
		Mupirocin	Control	
Nongeneral surgery				
Randomized trials				
Perl et al.,[13] 2002	1,456	7.0%	8.8%	
Kalmeijer et al.,[15] 2002	614	3.8%	4.7%	
Subtotal	2,070	6.0%	7.6%	0.80 (0.58–1.10)
Nonrandomized trials				
Gernaat-van der Sluis et al.,[19] 1998	2,304	1.3%	2.7%	
Cimochowski et al.,[12] 2001	1,846	0.9%	2.7%	
Kluytmans et al.,[17] 1996	1,796	2.8%	7.3%	
Subtotal	5,946	1.7%	4.1%	0.40 (0.29–0.56)
General surgery				
Randomized trials				
Perl et al.,[13] 2002	2,408	8.4%	8.3%	
Suzuki et al.,[16] 2003	395	8.8%	6.9%	
Subtotal	2,803	8.4%	8.1%	1.04 (0.81–1.33)
Nonrandomized trial				
Yano et al.,[18] 2000	269	11.3%	18.0%	0.63 (0.35–1.14)

RR = relative risk; CI_{95} = 95% confidence interval.
*< 1, mupirocin is favored; > 1, control is favored.

TABLE 4
EFFECT OF MUPIROCIN USE ON SURGICAL-SITE INFECTIONS IN CARDIOTHORACIC AND ORTHOPEDIC SURGERY

Study	Total No.	Infection Rate		RR (CI_{95})*
		Mupirocin	Control	
Cardiothoracic surgery				
Randomized trial				
Perl et al.[13]	724	9.9%	14.4%	0.69 (0.46–1.03)
Nonrandomized trials				
Kluytmans et al.[17]	1,796	2.8%	7.3%	
Cimochowski et al.[12]	1,846	0.9%	2.7%	
Subtotal	3,642	1.9%	4.6%	0.37 (0.25–0.55)
Orthopedic surgery				
Randomized trial				
Kalmeijer et al.[17]	614	3.8%	4.7%	0.81 (0.38–1.73)
Nonrandomized trial				
Gernaat-van der Sluis et al.[19]	2,304	1.3%	2.7%	0.50 (0.27–0.92)

RR = relative risk; CI_{95} = 95% confidence interval.
*< 1, mupirocin is favored; > 1, control is favored.

the mupirocin group and 14.4% in the control group; RR, 0.69; CI_{95}, 0.46 to 1.03). In two before–after trials involving cardiothoracic surgery patients, mupirocin also decreased the incidence of SSI (summary estimates: 1.9% in the mupirocin group and 4.6% in the control group; RR, 0.37; CI_{95}, 0.25 to 0.55). A summary estimate combining the randomized and before–after trials did not meet prespecified criteria for homogeneity. Only two studies evaluated orthopedic

patients (one randomized and one before–after). The summary estimate for this subset of patients combining the randomized and the before–after trial showed a reduced SSI incidence in the mupirocin group (summary estimates: 1.9% in the mupirocin group and 3.1% in the control group; RR, 0.61; CI_{95}, 0.38 to 0.98; test for heterogeneity, $P = .32$).

Resistance and Side Effects

Four trials included information on the development of mupirocin resistance.[12,13,15,17] In two of the trials,[15,17] no mupirocin resistance was identified in any *S. aureus* isolated. The study by Cimochowski et al. evaluated resistance in 100 patients after completion of the study (6 to 22 months after treatment).[12] Twenty-five (96.2%) of 26 *S. aureus* isolates remained sensitive to mupirocin. In the study by Perl et al., among 1,021 *S. aureus* isolates obtained from cultures of both wounds (n = 90) and nares (n = 931), 1,015 (99.4%) remained sensitive.[13]

Only the study by Perl et al. reported side effect information.[13] In this trial, study-related side effects (primarily rhinorrhea and itching at the application site) were reported by 4.8% of mupirocin recipients and 4.8% of placebo recipients. Although five patients withdrew due to adverse events, only one of these patients was in the mupirocin group.[13]

DISCUSSION

Intranasal mupirocin has been used in several specific clinical situations to decrease subsequent infections, including both peritoneal and hemodialysis infections, and in patients with recurrent gram-positive skin infections.[20] Investigation of its use in the prevention of SSI seemed a natural progression from these other indications, but, to date, the results of such studies have been inconsistent due to small sample sizes, design differences, and mixing of different surgical subgroups. As a result, routine use of perioperative intranasal mupirocin has not been recommended in practice guidelines.[1]

We found that perioperative intranasal mupirocin reduced the risk of SSI in studies of nongeneral surgery but had no apparent effect in general surgery. We hypothesized that because mupirocin affects gram-positive organisms colonizing the nares, the potential benefit of mupirocin would be minimized in trials involving general surgery—surgeries that often involve the bowel, where organisms such as gram-negative rods and anaerobes would be anticipated to play a greater role in SSI. For this reason, we thought it was important to analyze the available data on mupirocin according to type of surgery.

Our review has several limitations. First, there were few trials that met our inclusion criteria. Rigorous inclusion criteria were necessary to ensure that trials addressed our specific study questions, had high-quality study designs, and were comparable. For this reason, we excluded those that described a reaction to an outbreak or evaluated more than one intervention at a time. Second, although our search was systematic and extensive, it is possible that unpublished studies could have been missed. Third, the baseline "usual care" (eg, other perioperative antibiotics) differed among studies. Although these differences could potentially affect baseline SSI rates across studies, they will have little effect within studies as the same standard was applied to both the mupirocin and the control groups.

Due to the limited number of trials, we included nonrandomized trials in our analysis. These trials were prospective single-institution studies that measured outcomes both before and after an institution-wide intervention, all of which would be ranked just below randomized trials for quality. Nevertheless, we analyzed the randomized and before–after trials separately to acknowledge the differences in the level of quality of the two study designs. Although in some of the before–after trials the intervention and control groups had slight differences in baseline characteristics, there was no clear pattern to the apparent effect of these differences, with approximately half favoring mupirocin and half favoring controls.

Some might point out that the finding in the randomized nongeneral surgery trials could be due to chance alone (because the CI_{95} included 1.0). However, we believe that type 2 error is likely if the null hypothesis of no difference between the mupirocin and the control groups is accepted. These two randomized trials, one solely involving orthopedic patients and the other a subset of a larger study, were relatively small. Yet both trials had a consistent 20% reduction in SSI incidence, suggesting some reproducibility. Others might argue that the positive results in the before–after trials might be due to some unrecognized bias. We think that the before–after trials in our review were all well done and, although certainly subject to some bias, are not likely to be biased to such a degree as to eliminate all of the considerable effect reported here.

There are few reasons not to use mupirocin. It has side effects similar to placebo and has been found to be acceptable to patients.[8] Additionally, although the development of mupirocin resistance has been reported following periods of long-term use, this did not appear to be an important problem for short-term use. Perioperative intranasal mupirocin is also an inexpensive intervention. Two studies have estimated the cost for a course of this medication to be less than $15.[12,21] For context, a deep sternal wound infection has been estimated to cost more than $80,000.[12]

In the current healthcare environment where medical complications such as SSI have a high profile in terms of both cost and quality, it is important to carefully consider all of the options available to prevent them. The findings of this meta-analysis suggest a benefit from the use of perioperative intranasal mupirocin to prevent SSI in patients undergoing nongeneral surgery. Because of the expense, further randomized trials among the patients most likely to benefit (eg, those undergoing cardiothoracic and orthopedic surgery) may not be forthcoming. A calculation of the standard sample size demonstrates that such a study would require approximately 14,000 patients to show a 20% reduction in SSI given a baseline SSI rate of 5%. Pending any further evaluation, we believe our analysis supports the use of

perioperative intranasal mupirocin for the prevention of SSI in clean surgeries where the risk of *S. aureus* is high.

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