

Effect of a Single Preoperative Dose of Oral Antibiotic to Reduce the Incidence of Surgical Site Infection Following Below-Knee Dermatological Flap and Graft Repair

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ABSTRACT Background: Surgical site infection (SSI) rates for below-knee dermatological surgery are unacceptably high, particularly following complex flap and graft closures. The role of antibiotic prophylaxis for these surgical cases is uncertain.

Objective: To determine whether SSI following complex dermatological closures on the leg could be reduced by antibiotic prophylaxis administered as a single oral preoperative dose.

Methods: A total of 115 participants were randomized to 2 g of oral cephalexin or placebo 40-60 minutes prior to surgical incision in a prospective, randomized, double-blind, placebo-controlled trial at a primary care skin cancer clinic in North Queensland, Australia.

Results: Overall 17/55 (30.9%) controls and 14/55 (25.5%) intervention participants developed infection ($P = 0.525$). There was no difference between the study groups in adverse symptoms that could be attributed to high-dose antibiotic administration ($P = 1$).

Conclusion: A single oral 2-g dose of cephalexin given before complex below-knee dermatological closure did not reduce SSI.

Introduction

The rate of surgical site infection (SSI) for clean dermatological surgery is usually less than 3% [1-3], which is significantly lower than the 5% acceptable SSI rate quoted by many

authorities [4,5]. The incidence of SSI is influenced by body site, and certain anatomical sites are at much higher risk than the acceptable rate [6-9], with lower limb surgery most consistently complicated by infection [3,10-16]. In tropical North Queensland, the infection rates following excisions from the

lower limb have ranged from 14.75% to 18.18% [13,16]. Below-knee surgery has been shown to have an even higher infection rate [13,16,17]. The reasons for this are unclear, but reduced perfusion pressure in the distal limbs [18], higher tension closures [19], as well as the frequent necessity for complex graft/flap surgery are postulated reasons.

More complex skin closures, such as flap and graft procedures, are known also to be independently associated with significantly higher risk of SSI [20]. Large observational prospective studies have shown that flap repair increases the likelihood of infection by 2 to 15 times compared with simple elliptical closure [3,18,20,21]. Graft repair has also been linked to much higher infection rates [3,18,20,21].

Established SSI may require multiple medical visits, can result in poorer cosmetic outcome and significant bacteremic complications [8,17], and also requires several days of treatment with antibiotics. Antibiotic treatment may be associated with unpleasant side effects, allergy, and the development of antibiotic resistance [8]. As a result of indiscriminate antibiotic prescribing, antibiotic resistance is increasing at a dramatic rate, causing significant morbidity and mortality globally [22,23]. A single, high-dose preoperative oral prophylactic antibiotic has been proposed for anatomical sites and dermatological procedures at high risk of SSI [8]. It is suggested that administration of such a single prophylactic dose may be less likely to result in antibiotic resistance than a longer-term course prescribed for established infection, with a resulting reduction in the quantity of antibiotics prescribed overall [17,19,24].

If antibiotic prophylaxis is to be effective, antibiotics should optimally be in the bloodstream and at the operative site at the time of incision [25,26]. The administration of antibiotics within 2 hours prior to incision is associated with the lowest risk of SSI [26].

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Flap or graft dermatologic surgery below knee • Over 18 years of age 	<ul style="list-style-type: none"> • Ingestion of any antibiotic (other than the intervention) within 48 hours of surgery • Suspected SSI at time of surgical closure • Allergy to protocol suture or dressing materials • Allergy to cephalosporins or penicillin • Intellectual or mental impairment • Previous participation in this study • Later exclusion if histology confirmed the need for wider excision

Figure 1. Inclusion and exclusion criteria for study. [Copyright: ©2019 Rosengren et al.]

Despite the importance of this topic, few randomized controlled trials (RCTs) have been published on the use of oral antibiotic prophylaxis in dermatological surgery [17]. The aim of our randomized, double-blind, placebo-controlled trial was to ascertain the effect of a single preoperative oral prophylactic antibiotic dose on SSI following complex below-knee dermatological surgery.

Methods

This randomized, double-blind, placebo-controlled trial recruited consecutive eligible patients booked for flap or graft closure following skin cancer excision below the knee at a primary care skin cancer clinic in Townsville, North Queensland, Australia, between January 2014 and February 2016. Each individual patient gave signed informed consent and was allowed to participate in the trial only once.

Specific exclusion criteria (Figure 1) were age under 18, taking any antibiotic within 48 hours of the surgery, suspected SSI at the time of surgery, allergy to the protocol suture, dressing materials, cephalosporins or penicillin, intellectual or mental impairment, and previous participation in this study. If histology confirmed the need for a wider excision or participants received antibiotics for another SSI during the 30-day study period, participants were to be withdrawn from the study.

Capsules containing either 2 g of cephalexin or placebo were given 30 minutes prior to the excision appointment time, ensuring that skin incision would be within 60 minutes of ingestion of capsules. At the time of surgery baseline demographic data, pertinent medical and drug history, defect size, time from intervention to incision, and closure technique were documented. Histology was documented once it had been reported.

Intra- and Postoperative Protocol

If the wound required deep dermal absorbable sutures, Monosyn (B. Braun, Sydney, Australia) was used. All defects were closed superficially with nylon sutures (Dytek Pty Ltd., Hendon, South Australia). Following wound closure, Melolin (Smith and Nephew Medical Ltd, Hull, UK) and Fixomull (BSN Medical, Luxemburg) was applied.

Standardized verbal and written postoperative wound care instructions were given to all participants, stressing the importance of applying no topical creams, ointments, or antiseptics to the wound for the month after surgery. All participants were reviewed 7 days postoperatively for wound inspection and redressing. Information related to the use of postoperative oral analgesia (strongest analgesic used) was also recorded at this time. Early review at the study practice was encouraged in the event of discomfort, erythema, swelling, or discharge associated with the wound.

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|---|
| <p>1. At least ONE of the following:</p> <ul style="list-style-type: none"> • Purulent wound discharge • Erythema >1 cm from wound edges • Localized swelling, pain or heat |
| <p>2. Occurring within 30 days of surgery</p> |

Figure 2. Criteria for surgical site infection in dermatological surgery. [Copyright: ©2019 Rosengren et al.]

Sutures were removed 14 days after surgery. If at the time of suture removal the wound had not fully healed, it was dressed again and regularly reviewed until it had completely epithelialized.

Clinical Outcome

The wound was assessed at the time of suture removal (14 days postoperatively) by 1 of the 6 treating doctors. An adapted version of the 1988 Centers of Disease Control and Prevention of National Nosocomial Infections Surveillance System definition for dermatological surgical site infection was used [27]. Standardized criteria for surgical site skin infection included occurrence within 30 days of surgery and purulent discharge, erythema more than 1 cm from wound edges, OR presence of localized swelling, heat, pain, or tenderness (Figure 2).

If SSI was suspected, a swab was taken for microscopy, culture, and sensitivity and a 5-day course of cephalexin (500 mg 4 times a day) was prescribed pending swab results. Each participant was phoned by the study nurse 1 month after surgery to ensure no SSI was inadvertently missed.

Randomization and Blinding

The randomization sequence was generated electronically using IBM SPSS Statistics (V 22.0, IBM Corp., Armonk, NY, USA) by author and statistician (P.G.B.) and emailed to a compounding pharmacy where batches of generic gel capsules had been filled with either cephalexin or placebo (microcrystalline cellulose and calcium carbonate powder). Four identical-looking gel

capsules filled with either antibiotic (intervention) or placebo (control) were transferred to screw-top containers numbered according to the randomization sequence and sent to the recruiting practice in batches. Clinic staff and participants remained blind to group allocation during the trial.

Sample Size

A small prestudy observational trial at the practice had shown approximately 25% infection rates for flap and graft closures below the knee. Our hypothesis was that antibiotic prophylaxis would reduce the infection rate to 5%. Forty-four patients were required in each study group to show this with statistical confidence (power in excess of 80%; significance level 0.05). We planned to recruit a minimum of 110 participants (55 intervention and 55 placebo), allowing for a 25% drop out.

Statistical Analysis and Presentation

Statistical analysis and result preparation followed the CONSORT guidelines [28]. Numerical data were described using mean and standard deviation when symmetrically distributed and median and interquartile range when skewed. Categorical data were presented using absolute and relative frequencies.

Eligible nonparticipants were compared with participants using unpaired

t test, chi-square test, and Fisher exact test. Intervention and control group differences at baseline as well as treatment modality differences were assessed using unpaired t test, Mann-Whitney test, chi-square test, and Fisher exact test.

All data were analyzed using intention-to-treat analysis. Incidence of SSI was compared between intervention and control groups using chi-square test. The difference in infection rate was calculated and presented with 95% confidence interval (95% CI). The number needed to treat for benefit was calculated with 95% CI [29]. A sensitivity analysis was conducted including all 115 patients who were originally randomized by assuming various outcome scenarios for the 5 patients who were lost to follow-up. Logistic regression models were applied to assess potential confounding effects of all baseline characteristics on difference in incidence of infection between intervention and control groups.

Chi-square and Fisher exact tests were used to compare postoperative analgesia requirements, adverse effects, and treatment of occurring infections between intervention and control groups.

Analysis was conducted using StataIC12 (StataCorp LP, Lakeway Drive, College Station, TX, USA). A P value less than 0.05 was considered statistically significant.

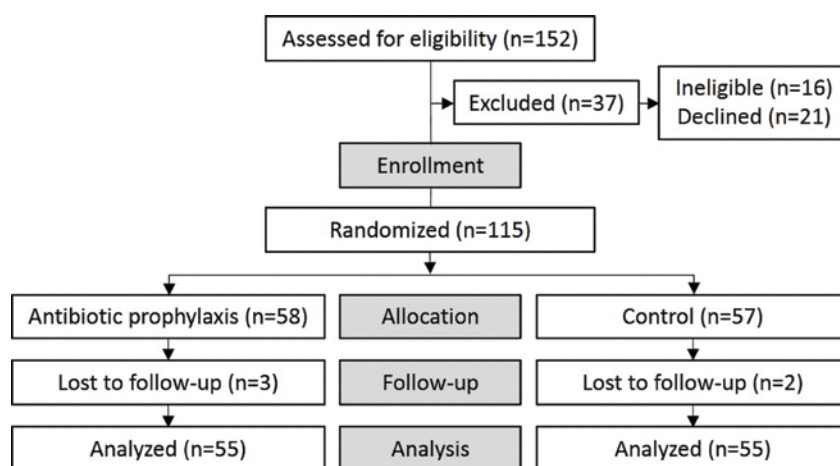


Figure 3. CONSORT Flow Diagram for Trial. [Copyright: ©2019 Rosengren et al.]

Table 1. Comparison of Nonparticipants Who Fulfilled Inclusion Criteria With Those Participating in the Study

Characteristic	Nonparticipants (n = 21)	Participants (n = 115)	P Value
Mean age (SD), years	71.9 (12.4)	69.4 (10.8)	0.336
Male (%)	10 (47.6%)	73 (63.5%)	0.171
Body site of lesion (%)			0.030
Foot	1 (4.8%)	8 (7.0%)	
Ankle	1 (4.8%)	6 (5.2%)	
Anterior leg	15 (71.4%)	44 (38.3%)	
Calf	4 (19.0%)	57 (49.6%)	
Histology ^a (%)			0.059
BCC	6 (30.0%)	54 (47.0%)	
SCC	11 (55.0%)	48 (41.7%)	
Keratoacanthoma	2 (10.0%)	7 (6.1%)	
Melanoma	1 (5.0%)	6 (5.2%)	
Active smoker ^a (%)	0	2 (1.7%)	1.0
Type 2 diabetes mellitus ^a (%)	1 (5.0%)	13 (11.3%)	0.693
User of anticoagulant medication ^a (%)	0	27 (23.5%)	0.065
User of immunosuppressive medication ^a (%)	0	1 (0.9%)	1.0

BCC = basal cell carcinoma; SCC = squamous cell carcinoma; SD = standard deviation.

^a Missing information for 1 nonparticipant.

Results

Sixteen of 152 consecutive patients requiring flap or graft closures below the knee were ineligible for this study because of penicillin or cephalosporin allergy (n = 9), taking antibiotics for unrelated reasons at the time of surgery (n = 4), and previous participation in this study (n = 3).

Twenty-one eligible patients declined to participate. The most common reasons given for nonparticipation were not wanting to take unnecessary tablets (n = 12) and fear of possible diarrhea (n = 3). Other reasons given (n = 6) were being too old, fear of allergy, and being unwell on the day of the procedure.

With the exception of site tumor, there was no difference between eligible nonparticipants and participants (Table 1). Nonparticipants were more likely to have the neoplasm on the anterior leg whereas participants were more likely to have it on the calf (P = 0.030) (Table 1).

Of the 115 participants, 57 were randomized to administration of placebo (control group) and 58 to administration of cephalexin (intervention group). The 2 study groups were comparable at baseline for all variables measured (age, sex, diabetes, smoking status, anticoagulant or immunosuppressive medication, anatomical site and histology of tumor, defect size, and repair technique) (Table 2). Defect closure was with flap repair for 106 (52 control, 55 intervention) participants and graft repair for 8 (5 control, 3 intervention) participants. The remaining participant had an elliptical closure. Graft repair in all cases was with split thickness skin taken from the area surrounding the defect. This method of graft closure is referred to as a halo graft [30].

Two participants (both intervention) violated protocol and were withdrawn from the study, one because the treating doctor opted to close the defect with an ellipse and the other because of needing antibiotic treatment for an unrelated SSI

during the study follow-up period. Three participants (2 controls, 1 intervention) were lost to follow-up despite repeated attempts at phone contact. There were no demonstrable differences between the characteristics of the 5 participants who did not complete the study and the 110 who did.

Surgical Site Infection

The main analysis based on available cases at follow-up (Table 3) showed 17 (30.9%; n = 55) SSIs for control and 14 (25.5%; n = 55) for intervention participants (P = 0.525). A sensitivity analysis including all 115 initially randomized patients did not alter this result, regardless of whether the patients who were lost to follow-up were assumed to have had an infection or not to have had an infection (Table 3). Logistic regression analyses to assess effects of possible confounding variables did not alter the main result of the trial. Only 1 (intervention) of 8 split thickness graft closures developed SSI. All other cases of SSI occurred in flap closures.

The difference in infection rate between the control and intervention groups was 5.4% (95% CI: 11.4%-22.2%). Nineteen patients needed to be treated (number needed to benefit) to prevent an infection. The power to detect the 5.4% difference in infection rates between intervention and control groups was 9.6%. A sample size of 1,089 participants in each group would have been needed to reach a power of 80%.

Secondary Outcome Measures

There was no difference in analgesia requirement between study groups, with the majority of participants (81.8% of controls; 78.2% of intervention group) taking no postoperative analgesia (Table 4). One patient in the intervention group reported nausea in the follow-up period. No other symptoms that might have been attributable to the intervention were recorded in either study group.

Swab Results for SSI Cases

All patients with clinical SSI were treated with antibiotics, the majority (16/17 controls and 12/14 intervention participants) receiving cephalexin (Table 4).

Doctors forgot to take swabs for microscopy, culture, and sensitivity in 5 participants presenting to the study clinic with suspected SSI. A further 5 study participants presented to clinicians elsewhere (hospital in 2 cases, own family doctor in 3 cases) with suspected SSI and were treated with antibiotics without first taking swabs.

Of the 10 participants (5 control, 5 intervention) with suspected SSI not confirmed on microscopy, 8 were treated with cephalexin and 1 with dicloxacillin. In the final case, we were unable to ascertain what antibiotic had been prescribed. Clinical SSI settled in all 10 cases without the need for further intervention.

Of the 21 swabs taken, 12 (8 control, 4 intervention) grew *Staphylococcus aureus* sensitive to cephalexin, 1 (intervention) produced *Stenotrophomonas maltophilia* sensitive to cephalexin, and a further 4 (2 control, 2 intervention) developed no organism. Clinical SSI in all of these 17 swabbed cases responded fully to cephalexin which had been prescribed.

Table 2. Baseline Comparison of Control Group (n = 57) With Intervention Group (n = 58)

Characteristic	Control (n = 57)	Intervention (n = 58)	P Value
Mean age (SD), years	69.4 (11.6)	69.4 (10.1)	0.982
Male (%)	34 (59.6%)	39 (67.2%)	0.398
Body site of lesion (%)			0.633
Foot	3 (5.3%)	5 (8.6%)	
Ankle	2 (3.5%)	4 (6.9%)	
Anterior leg	21 (36.8%)	23 (39.7%)	
Calf	31 (54.4%)	26 (44.8%)	
Histology (%)			0.412
BCC	30 (52.6%)	24 (41.4%)	
SCC	18 (33.4%)	29 (50%)	
Keratoacanthoma	5 (8.8%)	2 (3.4%)	
Melanoma	3 (5.3%)	3 (5.2%)	
Active smoker (%)	1 (1.8%)	1 (1.7%)	1.0
Type 2 diabetes mellitus (%)	7 (12.3%)	6 (10.3%)	0.777
User of anticoagulant medication (%)	10 (17.6%)	17 (29.3%)	0.248
Repair technique			0.970
Ellipse	0	1 (1.7%) ^a	
ROM flap	31 (54.4%)	28 (48.3%)	
Keystone flap	6 (10.5%)	7 (12.1%)	
Rotation	6 (10.5%)	7 (12.1%)	
A-T flap	6 (10.5%)	8 (13.8%)	
Other transposition flap	2 (3.5%)	3 (5.2%)	
Other advancement flap	1 (1.8%)	1 (1.7%)	
Split thickness (halo) graft	5 (8.8%)	3 (5.2%)	
Median average diameter defect size	20.0	20.0	0.335
(IQR), mm	(16, 22)	(16, 24.5) ^b	

BCC = basal cell carcinoma; IQR = interquartile range; SCC = squamous cell carcinoma; SD = standard deviation; ROM = reducing opposed multilobed flap.

^a Patient receiving ellipse repair technique was removed from follow-up.

^b Based on 57 patients.

Table 3. Sensitivity Analysis of Surgical Site Infection by Intention to Treat

	Control Group	Intervention Group	Difference: Control Minus Intervention	Two-Sided 95% CI	P Value
Participants who completed follow-up	17/55 (30.9%)	14/55 (25.5%)	5.4%	-11.4, 22.2	0.525
Sensitivity analysis					
Assuming all lost to follow-up did not develop SSI	17/57 (29.8%)	14/58 (24.1%)	5.7%	-10.5, 21.9	0.492
Assuming all lost to follow-up did develop SSI	19/57 (33.3%)	17/58 (29.3%)	4.0%	-12.9, 20.9	0.642

CI = confidence interval; SSI = surgical site infection.

Table 4. Comparison of Analgesia Requirements, Adverse Symptoms, Follow-up Treatment, and Swab Results for Intervention and Control Study Participants

Characteristic	Control (n = 55)	Intervention (n = 55)	P Value
Surgical site infection	17 (30.9%)	14 (25.5%)	0.525
Analgesia requirements (%)			0.329
None	45 (81.8%)	43 (78.2%)	
Strongest paracetamol	8 (14.5%)	11 (20.0%)	
Strongest Panadeine ^a	0	0	
Strongest Panadeine Forte ^a	2 (3.6%)	0	
Strongest Endone ^b	0	1 (1.8%)	
Adverse symptoms (%)			
Nausea following ingestion of study capsules	0	1 (1.8%)	1.0
Diarrhea following ingestion of study capsules	0	0	1.0
Antibiotics started (%)			0.753
None	38 (69.1%)	41 (74.5%)	
Cephalexin	16 (29.1%)	12 (21.8%)	
Dicloxacillin	0	1 (1.8%)	
Unknown antibiotic started by nonpractice doctor	1 (1.8%)	1 (1.8%)	
Swab result (%) (n = 21)			0.879
<i>S aureus</i> sensitive to cephalexin	8 (%)	4 (%)	
<i>S aureus</i> sensitive to cephalexin + 2nd organism not sensitive to cephalexin	1 (%)	1 (%)	
Other organism sensitive to cephalexin	0	1 (%)	
Other organism not sensitive to cephalexin	1 (%)	1 (%)	
Normal skin flora	2 (%)	2 (%)	

^a Paracetamol and codeine.

^b Oxycodone.

In 4 participants with SSI, the infection did not respond to cephalexin. Swabs in 2 cases (1 intervention, 1 control) isolated organisms not sensitive to cephalexin (*Pseudomonas aeruginosa* in one case, *Enterobacter cloacae* in the other). In a further 2 participants (1 control, 1 intervention), 2 organisms were isolated on microscopy and culture: the *S aureus* found in each case was sensitive to cephalexin but the second organism isolated (*P aeruginosa* in one case and *Streptococcus C* in the other) was not sensitive to cephalexin. Ciprofloxacin was introduced for each SSI not responding to cephalexin, in accordance with swab sensitivity results.

Discussion

The results of this trial did not show any clinically or statistically significant reduction in the rate of SSI from a single dose of cephalexin administered 40-60 minutes before skin incision. There was no increase in adverse outcomes related to antibiotic administration in the intervention group.

These results contrast to the only previously identified study examining the effect of antibiotic prophylaxis in lower limb ellipse skin excisions, which showed a reduction in the incidence of SSI from a similar baseline rate of 35.7% to a

rate of 12.5% in the intervention group, although this study was underpowered to produce statistical significance [17]. Our study differed in that we included only below-knee excisions, which are at higher risk than the entire lower limb, and flap and graft surgery, which are at higher infection risk than ellipse excisions.

Other studies examining antibiotic prophylaxis for surgical sites elsewhere have also demonstrated the effectiveness of antibiotic prophylaxis, in contrast with our study. Two RCTs—one involving flap and graft repairs in a dermatological surgery setting [31] and the other involving ear and nose only [32]—confirmed that single-dose oral antibiotic prophylaxis prevented SSI. Although a further RCT involving graft repairs on the nose was underpowered to show a reduction in SSI, graft survival was better for those randomized to antibiotic prophylaxis [33]. A recent meta-analysis of 12 RCTs studying antibiotic prophylaxis in dermatological surgery demonstrated that preoperative antibiotic prophylaxis was effective in preventing SSI and furthermore that single antibiotic use is of adequate efficacy and safety for preventing SSI [34]. It should be noted, however, that only 2 of these RCTs investigated oral antibiotic prophylaxis, with intravenous antibiotics investigated in the remaining 10 studies [34].

The recruited cases for this study were at particularly high infection risks, and we postulate that this was the reason for the failure of antibiotic prophylaxis in our study. First, the anatomical site studied was below the knee, which has been shown to have higher risk of infection than other anatomical sites [13,16]. Second, only flap and graft surgery was included, which is known to be of higher SSI risk than simpler surgical techniques [20]. Third, the study was conducted in a tropical setting, where infection rates have previously been shown to be increased (8.6% and 11.7% in studies in the Mackay region) [35,36]. The reason for this remains unclear, but might be related to tropical humidity. We hypothesize that a single-dose antibiotic prophylaxis was simply insufficient in dose and duration to prevent SSI in these circumstances.

Minimizing antibiotic dose and duration is an increasingly important focus of research [37]. Given the advantages of prophylactic antibiotics in reducing morbidity, and potentially reducing the total amount of antibiotic prescribed [17], we would recommend that future research investigate other prophylactic regimens, such as larger or multiple pre- or perioperative doses of antibiotic or antibiotic mixed with local anesthetic and injected directly into the wound site preoperatively [38,39].

The strengths of our study were a blind, randomized design with placebo control, a standardized protocol for excision and follow-up, as well as the collection of a large amount of demographic, medical, and excision-related data for comparison of groups.

We must, however, acknowledge some limitations to our study. Infection may have been underreported, with participants presenting to doctors outside the study practice after surgery. Various characteristics influence SSI, and although information on as many variables as possible was recorded, it is difficult to ensure that all possible variables are comparable at baseline. Despite the intention to take swabs for microscopy culture and sensitivity for all cases of clinical SSI, only 21 swabs were taken in 31 suspected SSI cases.

There may also be limitations to generalizing our findings. This study included complex procedures only, and we do not know the effect of this regimen for elliptical excisions albeit that few nasal and aural skin cancers can be effectively excised with an ellipse. The climate in North Queensland is hot and humid, with a mean daily maximum temperature ranging between 24.2°C and 30°C during the summer months and a relative humidity of 75%-79%. The results may not necessarily be generalizable to a temperate climate with a lower baseline infection rate.

The diagnosis of infection, even when guidelines are used, is subjective, and interobserver and intraobserver variation may occur [40]. However, the definition we used is the most widely implemented standard definition of wound infection [27].

Conclusions

Despite confirmation that the majority of complex below-knee closure SSIs responded effectively to oral cephalexin postoperatively, we were unable to demonstrate that a single preoperative 2-g dose of cephalexin could prevent SSI from occurring.

Infection rates for below-knee surgery are unacceptably high, even in temperate climates. As antibiotic prophylaxis has been shown to be helpful for other dermatological high-risk areas, further research experimenting with different antibiotic prophylactic regimens is worthwhile.

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