

# Randomized, Controlled Trial of Topical Exit-Site Application of Honey (Medihoney) *versus* Mupirocin for the Prevention of Catheter-Associated Infections in Hemodialysis Patients

David Wayne Johnson, Carolyn van Eps, David William Mudge, Kathryn Joan Wiggins, Kirsty Armstrong, Carmel Mary Hawley, Scott Bryan Campbell, Nicole Maree Isbel, Graeme Robert Nimmo, and Harry Gibbs

*Department of Renal Medicine, University of Queensland at Princess Alexandra Hospital, Brisbane, Australia*

The clinical usefulness of hemodialysis catheters is limited by increased infectious morbidity and mortality. Topical antiseptic agents, such as mupirocin, are effective at reducing this risk but have been reported to select for antibiotic-resistant strains. The aim of the present study was to determine the efficacy and the safety of exit-site application of a standardized antibacterial honey *versus* mupirocin in preventing catheter-associated infections. A randomized, controlled trial was performed comparing the effect of thrice-weekly exit-site application of Medihoney *versus* mupirocin on infection rates in patients who were receiving hemodialysis via tunneled, cuffed central venous catheters. A total of 101 patients were enrolled. The incidences of catheter-associated bacteremias in honey-treated ( $n = 51$ ) and mupirocin-treated ( $n = 50$ ) patients were comparable (0.97 *versus* 0.85 episodes per 1000 catheter-days, respectively; NS). On Cox proportional hazards model analysis, the use of honey was not significantly associated with bacteremia-free survival (unadjusted hazard ratio, 0.94; 95% confidence interval, 0.27 to 3.24;  $P = 0.92$ ). No exit-site infections occurred. During the study period, 2% of staphylococcal isolates within the hospital were mupirocin resistant. Thrice-weekly application of standardized antibacterial honey to hemodialysis catheter exit sites was safe, cheap, and effective and resulted in a comparable rate of catheter-associated infection to that obtained with mupirocin (although the study was not adequately powered to assess therapeutic equivalence). The effectiveness of honey against antibiotic-resistant microorganisms and its low likelihood of selecting for further resistant strains suggest that this agent may represent a satisfactory alternative means of chemoprophylaxis in patients with central venous catheters.

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Central venous catheterization is an established method of providing rapid, temporary access for the provision of hemodialysis to patients with serious acute or chronic renal failure. Unfortunately, the clinical usefulness of this method is severely limited by the frequent occurrence of bloodstream infections in up to 40% of cases (1–3). A number of registry (4,5) and observational cohort studies (6) have indicated that there has been an increasing reliance on hemodialysis catheters in incident hemodialysis patients ranging from 30% of patients in Europe and Australia to 60% in the United States. Recent studies have suggested further that the use of hemodialysis catheters is associated with a 1.5- to 3-fold increase in both all-cause and infectious mortality (4,7,8). A number of randomized, controlled trials have demonstrated convincingly that tunneled, cuffed catheters are associated with a much lower risk for bacterial colonization, exit-

site infection, and bacteremia compared with nontunneled and noncuffed devices (9–14). Recently, our group demonstrated that the topical application of 2% mupirocin ointment to the exit sites of hemodialysis patients with tunneled, cuffed catheters engendered a further reduction in the rates of catheter-associated staphylococcal exit-site infection and bacteremia (3). Median infection-free survival time was increased from 55 to 108 d, such that one episode of bacteremia was prevented for every 3.7 patients treated. Unfortunately, a potentially significant disadvantage of mupirocin chemoprophylaxis is the appearance of resistant staphylococcal strains, which have been reported in a number of units in other hospitals (15). It would clearly be ideal to develop an alternative, safer strategy to mupirocin for preventing catheter-associated infections without selecting further resistant strains.

A promising agent in this regard is honey. Honey has been used from ancient times as a method of accelerating wound healing (16) and is mentioned for healing purposes in the Bible, the Koran, and the Torah (17). Anecdotally, honey has been claimed to reduce inflammation; debride necrotic tissue; reduce edema; and promote angiogenesis, granulation, and epithelialization (18). More recently, there have been a number of reports of honey being used successfully as a dressing for wounds, including burns, ulcers, infected surgical wounds, necrotizing

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**Address correspondence to:** Prof. David Johnson, Department of Renal Medicine, Level 2, Ambulatory Renal and Transplant Services Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland 4102, Australia. Phone: +61-7-3240-5080; Fax: +61-7-3240-5480; E-mail: david\_johnson@health.qld.gov.au

soft tissue infections, meningococcal wounds, and abdominal wound dehiscence (17,19–21). A meta-analysis of seven randomized, controlled trials involving the use of honey as a wound dressing showed it to be superior to antiseptics and/or systemic antibiotics for wound healing, maintenance of sterility, and eradication of infection (22).

In laboratory studies, some honeys have been shown to exert an antimicrobial action against a broad spectrum of fungi and bacteria, including antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, multidrug-resistant gram negative organisms, and vancomycin-resistant enterococci (23,24). The reasons for this antibacterial activity include a relatively low water activity (0.56 to 0.59), low pH (3.2 to 4.5), the production of hydrogen peroxide on dilution (as a result of the presence of the enzyme glucose oxidase), and phytochemical components (including flavonoids and phenolic acids) (24). Despite a considerable accumulated experience of honey use in wound infections, antimicrobial resistance has not yet been reported, thereby making it very attractive as a potential means of antimicrobial prophylaxis (25). The aim of the present study was to determine the efficacy and the safety of topical exit-site application of standardized antibacterial honey (Medihoney) versus mupirocin in preventing infection secondary to tunneled, cuffed hemodialysis catheters.

## Materials and Methods

### Study Population

All adult patients who had acute or chronic renal failure and required hemodialysis via a newly inserted tunneled, cuffed central venous catheter at the Princess Alexandra Hospital between February 1, 2002, and July 28, 2004, were invited to participate in the study. Informed consent was obtained from all patients before their inclusion in the trial, and the study protocol was reviewed and approved by the Princess Alexandra Hospital Research Ethics Committee.

### Study Design

The study was a prospective, open-label, randomized, controlled trial. Patients who were enrolled in the study were randomly assigned to receive either topical  $\gamma$ -irradiated, commercially available, pooled antibacterial honeys including *Leptospermum sp* honey (Medihoney; Medihoney Pty Ltd, Brisbane, Australia) or standard 2% calcium mupirocin ointment (Bactroban; SmithKline Beecham Pharmaceuticals, Sydney, Australia; mupirocin group) in addition to standard exit-site care and 10% povidone iodine disinfection. The randomization was performed using sequentially numbered, opaque, sealed envelopes before catheter insertion. The sequence of interventions was obtained from a computer-generated random-number list with randomization blocks of 10.

All patients underwent ultrasound-guided placement of a subcutaneously tunneled, internal jugular venous hemodialysis catheter (PermCath; Quinton Instrument Company, Seattle, WA) by dedicated vascular access surgeons according to the method described by Schwab *et al.* (26). A prophylactic preoperative antibiotic (cephazolin 1 g intravenously) was prescribed in all cases. All catheters received 10% povidone iodine disinfection at the site of insertion (contact time 3 to 5 min followed by complete drying) and were covered by an opaque, air-permeable, nonwoven fabric dressing (Primapore, Smith & Nephew, Sydney, Australia). Chest radiographs were obtained after insertion to confirm the position of the catheter tip in the superior vena cava.

Central venous catheters were dedicated to hemodialysis use and were not accessed for other purposes. Subsequent catheter-site care was performed by trained hemodialysis registered nurses using a rigorous aseptic technique. Primapore dressings were changed thrice weekly at each hemodialysis treatment, and the sites were recleansed with 10% povidone iodine solution, in accordance with the Kidney Disease Outcomes Quality Initiative guidelines (27). Patients who were allocated to the honey group additionally received approximately 3 ml of Medihoney applied to their exit sites with each dressing change. Patients who were allocated to the mupirocin group had mupirocin ointment applied to their exit sites with each dressing change according to standard unit protocols (approximately 10 mm of ointment was squeezed directly on to their exit sites from a 15-g tube with an outlet diameter of 5 mm with each dressing change). Patients were treated with topical honey or mupirocin for the entire period that their catheter remained *in situ*. At the completion of each hemodialysis treatment, sodium heparin (1000 U/ml) was injected into each lumen in a volume equivalent to the priming volume of the catheter.

At the time of inclusion in the study, demographic and clinical data were recorded. Patients had their anterior nares cultured for *S. aureus*, but identified nasal carriers were not treated. Patients were followed up until the catheter was removed. The primary outcome measure was catheter-related bacteremia. Secondary outcome measures included catheter exit-site infection and adverse reactions (including mupirocin resistance among staphylococcal isolates). Data were censored at the time of catheter removal (when unrelated to catheter-associated infection), death (when unrelated to catheter-associated infection), or the end of the study on October 4, 2004.

### Definitions

Catheter-related infections were defined according to standard guidelines (9,28,29). Catheter-associated bacteremia was defined as either (1) a single positive blood culture together with a positive culture of the catheter tip or exit site with an identical organism or (2) two or more positive blood cultures (or a single positive blood culture for *S. aureus*) with no evidence of infection source other than the device. Exit-site infection was defined as purulent exit-site discharge or two of three of the following: Exit-site erythema, tenderness, and induration with a positive culture.

### Microbiology

Exit-site swabs were obtained using sterile, premoistened calcium alginate swabs in all suspected cases of catheter-associated infection. The swabs were streaked onto plates that contained blood agar, colistin-nalidixic acid agar, McConkey's media, and mannitol-salt agar. All cultures were incubated at 35°C for 48 h and examined daily for growth. Patients with suspected bacteremia (fever >38°C, rigors, leukocytosis, or clinically unwell) were investigated with exit-site swabs and at least two sets of blood cultures (20 ml). Staphylococcal isolates were screened routinely for mupirocin resistance by the disk susceptibility method (30). The laboratory was blinded to the patient's allocation group.

In cases of suspected catheter-associated bacteremia, the catheter was removed and the tip was sent for microbiologic culture. Approximately 50 mm of catheter tip was rolled across chocolate agar plates and processed according to the semiquantitative method of Maki *et al.* (29). Catheter colonization was defined as the recovery of >15 colony-forming units.

### Statistical Analyses

Normality of data was evaluated by the Kolmogorov-Smirnov test with Lilliefors's correction. Results are expressed as mean  $\pm$  SEM for

continuous parametric data, median (interquartile range) for continuous nonparametric data, and frequencies and percentages for categorical data. Comparisons between the honey and mupirocin groups were performed using *t* test or the Mann-Whitney *U* test, depending on data distribution. Differences in proportions were evaluated by  $\chi^2$  or Fisher exact test. Infection-free survival curves, survival probabilities, and estimated mean survival times were generated according to the Kaplan-Meier method. Differences in the survival curves between the two groups were evaluated using the log rank test. A multivariate Cox's proportional hazards model was also applied, which included allocated group, age, gender, race, body mass index, diabetic status, ischemic heart disease, presence of infection at the time of randomization, nasal staphylococcal colonization, and serum albumin as covariates. The proportional hazards assumption was checked both graphically and by hypothesis testing. Graphical examination was done using a log-cumulative hazard plot. The hypothesis test was carried out after generating Schoenfeld and scaled Schoenfeld residuals. All data were analyzed on an intention-to-treat basis using the statistical software package SPSS release version 10.0.5 (SPSS Inc., Chicago, IL).  $P < 0.05$  was considered significant.

Prospective power calculations for the infection-free survival analyses were performed using the software package PS version 1.0.17 (Vanderbilt University Medical Center, Nashville, TN). It was estimated prospectively that the study had adequate statistical power (80% probability) to detect at least a doubling in mean catheter-associated infection-free survival from a control (mupirocin) level of 320 d if 96 patients were recruited in the study (48 in each group), assuming an  $\alpha$  level of 0.05, accrual time of 730 d, and additional follow-up time after the end of recruitment of 90 d.

## Results

### Patient Characteristics

A total of 101 patients required insertion of tunneled, cuffed central venous catheters for the provision of hemodialysis at the Princess Alexandra Hospital between June 1, 2002, and July 31, 2004. All agreed to participate in the study, and none was lost to follow-up. No patients were excluded from the study. Fifty-one patients were randomly allocated to the honey group, and 50 patients received mupirocin. There were no significant differences between the two groups with respect to their baseline characteristics, except for a higher mean age and a trend toward a greater frequency of ischemic heart disease in the mupirocin group (Table 1). Median (interquartile range) follow-up was 95 (55 to 157) days.

### Catheter-Associated Infections

Catheter-associated bacteremias occurred with similar frequencies in honey-treated ( $n = 6$ , 12%) and mupirocin-treated patients ( $n = 5$ , 10%;  $P = 0.78$ ). The causes of bacteremia in the honey and mupirocin groups were *S. aureus* (1 or 17% versus 1 or 20%), coagulase-negative staphylococci (2 or 33% versus 1 or 20%), micrococcus (1 or 17% versus 0 or 0%), *Serratia marcescens* (2 or 33% versus 0 or 0%), *Klebsiella pneumoniae* (0 or 0% versus 1 or 20%), and *Stenotrophomonas maltophilia* (0 or 0% versus 2 or 40%). The incidences of bacteremia in the two groups were 0.97 and 0.85 episodes per 1000 catheter-days, respectively (NS). Mean  $\pm$  SE actuarial bacteremia-free survival periods were  $367 \pm 42$  and  $334 \pm 17$  d, respectively (log rank 0.01,  $P = 0.92$ ; Figure 1). On univariate Cox proportional hazards model anal-

ysis, the type of prophylaxis administered (honey or mupirocin) was not significantly associated with bacteremia-free survival (unadjusted hazard ratio for honey, 0.94; 95% confidence interval, 0.27 to 3.24;  $P = 0.92$ ). Multivariate analysis did not alter this finding (data not shown). No exit-site infections were observed in any patients during the period of the study.

### Adverse Reactions and Cost

Medihoney and mupirocin both were well tolerated. Transient, mild local skin discomfort was observed in one patient who was treated with honey. This resolved within a few days despite continued administration of the agent. A similar transient local skin reaction associated with erythema was observed in one patient who received topical mupirocin ointment. No systemic adverse reactions to either honey or mupirocin ointment were noted during the study period.

Mupirocin-resistant strains were not detected in any staphylococcal isolates from study patients with catheter-associated bacteremias. During the period of the trial, the proportion of staphylococcal isolates from all microbiologic specimens within the hospital that were mupirocin resistant was 2.0% (26 of 1328 staphylococcal isolates). Approximately 70% of these mupirocin-resistant isolates were identified in patients from the Renal Unit, but none of these individuals was involved in the present study.

The median cost of exit-site application for the average life of a catheter was \$13.00 AUD per patient in the honey group and \$11.10 AUD per patient in the mupirocin group.

## Discussion

The present study demonstrated that regular, thrice-weekly, topical exit-site application of standardized antibacterial honey was safe and cost-effective and resulted in a comparable rate of catheter-associated infection to that obtained with topical mupirocin exit-site application in patients with tunneled, cuffed hemodialysis catheters. To our knowledge, this is the first randomized, controlled trial to have examined the potential utility of honey as an antimicrobial prophylactic agent. Moreover, the results of this study are potentially generalizable to the prevention of infections associated with a number of prosthetic devices (*e.g.*, central venous catheters, Hickman catheters, Tenckhoff catheters, T-tubes, nephrostomy tubes).

Previous randomized, controlled trials have shown convincingly that, compared with placebo or no treatment, topical mupirocin application was associated with a seven- to 13-fold reduction in catheter-associated bacteremias in patients with either noncuffed, nontunneled (2) or tunneled, cuffed hemodialysis catheters (3). Moreover, the observed rates of catheter-associated bacteremia in mupirocin-treated patients in those studies (0.7 and 1.6 episodes per 1000 catheter days, respectively) were similar to those observed in the present investigation (0.85 episodes per 1000 catheter-days). However, since the publication of these earlier investigations, there has been increasing concern regarding the emergence of mupirocin-resistant staphylococci (31) and the potential for therapeutic failure (15). After introducing mupirocin chemoprophylaxis in our own unit for the prevention of peritoneal dialysis and hemodi-

Table 1. Baseline patient characteristics

Characteristic	Honey (n = 51)	Mupirocin (n = 50)	P Value
Age (years)	54.2 ± 16.8	60.9 ± 12.6	0.03
Female gender	22 (43%)	18 (36%)	0.46
White race	43 (84%)	45 (90%)	0.80
Body mass index (kg/m <sup>2</sup> )	28.1 ± 7.1	27.0 ± 5.1	0.35
Serum albumin (g/L)	32.7 ± 6.6	31.8 ± 6.8	0.81
Serum ferritin (μg/L)	256 (131 to 449)	206 (82 to 547)	0.64
Diabetes	16 (31%)	19 (38%)	0.48
Ischaemic heart disease	15 (29%)	24 (48%)	0.06
Cerebrovascular disease	8 (16%)	5 (10%)	0.39
Peripheral vascular disease	11 (22%)	16 (32%)	0.24
Smoking status			0.23
never	30 (59%)	27 (54%)	
former	20 (39%)	18 (36%)	
current	1 (2%)	5 (10%)	
Nasal staphylococcal carriage	9 (18%)	6 (12%)	0.43
Previous immunosuppression	9 (18%)	6 (12%)	0.43
Renal failure cause			0.90
acute-on-chronic renal failure	4 (8%)	6 (12%)	
diabetes	13 (25%)	15 (30%)	
glomerulonephritis	15 (29%)	9 (18%)	
polycystic kidney disease	4 (8%)	4 (8%)	
chronic tubulointerstitial nephritis	5 (10%)	5 (10%)	
other	10 (20%)	11 (22%)	
Catheter indication			0.66
acute temporary dialysis	4 (8%)	6 (12%)	
commencing chronic dialysis	27 (53%)	21 (43%)	
clotted vascular access	9 (18%)	13 (26%)	
failed peritoneal dialysis	10 (20%)	8 (16%)	
permanent access	1 (2%)	2 (4%)	
Infection at time of catheter insertion			0.56
none	46 (90%)	42 (84%)	
skin	2 (4%)	2 (4%)	
peritoneal dialysis peritonitis	3 (6%)	5 (10%)	
upper respiratory tract infection	0 (0%)	1 (2%)	

alysis catheter infections, high-level mupirocin resistance has emerged, ranging between 2 and 6% of all staphylococcal isolates. None of the isolates from patients in the present study displayed mupirocin resistance, although this may have been due to the relatively small patient numbers and short duration of follow-up. Another group (32) has not observed an increase in high-level resistance after topical mupirocin administration, but this finding is contradicted by several reports of disturbing increases in resistance (to between 12.4 and 66% of staphylococcal isolates) (31,33–35), particularly with widespread and prolonged mupirocin use (31). Furthermore, Perez-Fontan *et al.* (34) observed a greater incidence of exit-site infections in patients who were colonized with mupirocin-resistant *S. aureus* compared with those who were colonized with sensitive organisms, suggesting that the development of mupirocin resistance can have adverse clinical consequences.

Continued use of topical antimicrobial agents has provided the selective pressure that has led to the emergence of antibiotic-resistant strains, which, in turn, has driven the continued search for alternative, safer topical antiseptic agents with broad-spectrum antimicrobial activities. In this regard, standardized antibacterial honey seems to be a very promising candidate. Although mupirocin has been shown to be effective primarily against Gram-positive organisms, selected honeys have been found to be highly effective against fungi (including *Aspergillus fumigatus*, *Aspergillus flavus*, *Penicillium citrinum*, *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Candida albicans*), Gram-negative bacteria (including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas spp.*, *Proteus mirabilis*, *Haemophilus influenzae*, *Enterobacter cloacae*, and *Shigella dysenteriae*), and Gram-positive organisms (including streptococci, staphylococci, enterococci, and clostridia) (18,22). The minimum inhib-



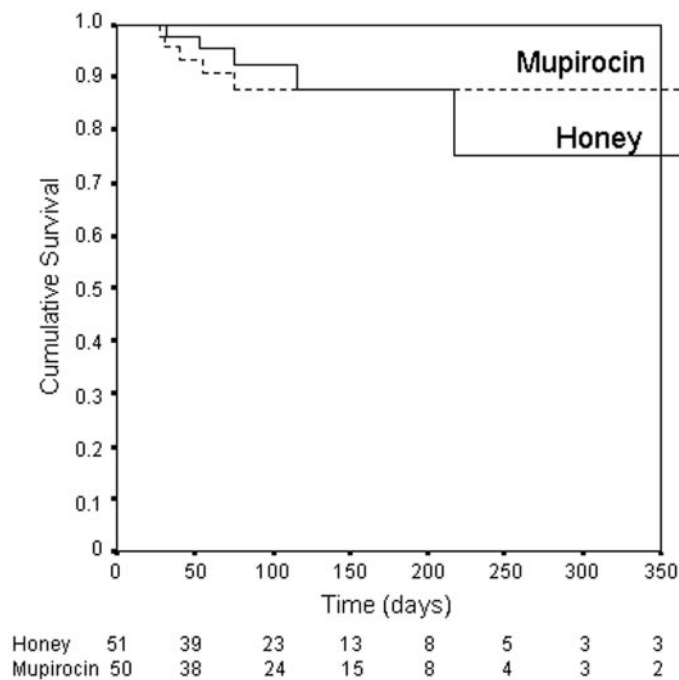


Figure 1. Catheter-associated bacteremia-free survival in honey- and mupirocin-treated patients. The difference between the groups was not statistically significant (log rank score 0.33,  $P = 0.87$ ). The number of patients at risk within each group is indicated beneath the corresponding time periods on the x axis.

itory concentrations of honey for all of these species were generally well below 10% vol/vol (18,22,24,36) and did not seem to be appreciably different in antibiotic-resistant strains, such as methicillin-resistant *S. aureus*, multidrug-resistant Gram-negative organisms, and vancomycin-resistant enterococci (18,24). The lack of significant variance in the sensitivity to some honeys of a large number of isolates collected from a wide range of clinical settings contrasts markedly with the variations seen in antimicrobial sensitivities to antibiotics and strongly suggests that there is no mechanism of resistance to the antibacterial activity of honey (37). Indeed, despite a considerable accumulated experience of honey use in wound infections, antimicrobial resistance has not yet been reported.

The mechanisms of action of honey have not been fully elucidated, but hyperosmolality, acidity, hydrogen peroxide generation, and phytochemical components (including flavonoids and phenolic acids) have been considered to be important (17,36). The floral source of the honey also seems to be crucial, because some honeys (e.g., manuka honey from New Zealand and a related *Leptospermum* honey from Australia) can be up to 100 times more active against microorganisms than others (36). Honey has also been demonstrated to possess a number of additional advantages over conventional topical antiseptics, including the promotion of wound healing (22), activation of lymphocytes and neutrophils (38), and the lack of significant toxicity to human tissues (39). Sterilization of honey by  $\gamma$ -irradiation does not cause loss of antimicrobial activity (40) but is recommended before clinical use because honey has

occasionally been reported to contain viable spores of *Clostridium botulinum* (41).

The potential weaknesses of this trial were its open-label design, the possibility of type 2 statistical error, and the lack of statistical power to confirm therapeutic equivalence of honey and mupirocin. The absence of blinding could have potentially introduced co-intervention and observer biases. For example, Wagman *et al.* (42) showed an eightfold higher rate of infections associated with tunneled, cuffed catheters that were managed outside study protocol compared with those that were managed using the technique required by the study. Such protocol deviations were strictly avoided in the present study by ensuring that nursing staff adhered to a standardized exit-site care protocol and carefully documented their actions at each dressing change. Moreover, observer bias was minimized by the use of clearly defined, objective outcome measures and by blinding to the patient's study group assignment the microbiology laboratory staff who processed culture samples. As stated in the Materials and Methods section, the study was adequately powered to have detected a halving (or doubling) of risk in the honey arm compared with the mupirocin arm. A smaller significant difference between the two groups could not be excluded because of the possibility of a type 2 statistical error. In particular, it is important to emphasize that the study lacked statistical power to have determined confidently that honey and mupirocin were therapeutically equivalent. Although the limits for establishing equivalence are arbitrary, to have had an 80% probability of determining that the differences between honey and mupirocin were no greater than 10% using the assumptions of the original power calculations, a minimum of 4688 patients in total would have been required. The results of the present trial therefore should be considered preliminary, such that much larger studies will be needed to confirm that honey offers prophylactic efficacy that is equivalent to mupirocin.

In conclusion, the present investigation demonstrated that the application of honey (Medihoney) to the exit sites of tunneled, cuffed hemodialysis catheters was safe and effective compared with topical 2% calcium mupirocin, although our investigation did not have sufficient statistical power to confirm therapeutic equivalence. This study has potentially important implications for the treatment of hemodialysis patients with temporary hemodialysis catheters and possibly for the treatment of patients with other types of catheters and prosthetic devices, who are at greatly increased risk for morbidity and mortality from catheter-related sepsis. The finding that honey administration to such patients is safe, inexpensive, unlikely to select for further antibiotic-resistant strains, and associated with acceptably low catheter-related bacteremia rates suggests that this agent may represent a satisfactory, alternative means of preventing hemodialysis catheter infections. Future much larger trials are recommended to confirm the equivalence of honey and mupirocin chemoprophylaxis.

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