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THE EFFECT OF EXIT-SITE ANTIBACTERIAL HONEY VERSUS NASAL MUPIROCIN PROPHYLAXIS ON THE MICROBIOLOGY AND OUTCOMES OF PERITONEAL DIALYSIS-ASSOCIATED PERITONITIS AND EXIT-SITE INFECTIONS: A SUB-STUDY OF THE HONEYPOT TRIAL

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♦ ***Background:*** **The HONEYPOT study recently reported that daily exit-site application of antibacterial honey was not superior to nasal mupirocin prophylaxis for preventing overall peritoneal dialysis (PD)-related infection. This paper reports a secondary outcome analysis of the HONEYPOT study with respect to exit-site infection (ESI) and peritonitis microbiology, infectious hospitalization and technique failure.**

♦ ***Methods:*** **A total of 371 PD patients were randomized to daily exit-site application of antibacterial honey plus usual exit-site care (*N* = 186) or intranasal mupirocin prophylaxis (in nasal *Staphylococcus aureus* carriers only) plus usual exit-site care (control, *N* = 185). Groups were compared on rates of organism-specific ESI and peritonitis, peritonitis- and infection-associated hospitalization, and technique failure (PD withdrawal).**

♦ ***Results:*** **The mean peritonitis rates in the honey and control groups were 0.41 (95% confidence interval [CI] 0.32 – 0.50) and 0.41 (95% CI 0.33 – 0.49) episodes per patient-year, respectively (incidence rate ratio [IRR] 1.01, 95% CI 0.75 – 1.35). When specific causative organisms were examined, no differences were observed between the groups for gram-positive (IRR 0.99, 95% CI 0.66 – 1.49), gram-negative (IRR 0.71, 95% CI 0.39 – 1.29), culture-negative (IRR 2.01, 95% CI 0.91 – 4.42), or polymicrobial peritonitis (IRR 1.08, 95% CI 0.36 – 3.20). Exit-site infection rates were 0.37 (95% CI 0.28 – 0.45) and 0.33 (95% CI 0.26 – 0.40) episodes per patient-year for the honey and control groups, respectively (IRR 1.12, 95% CI 0.81 – 1.53). No significant differences were observed between the groups for gram-positive (IRR 1.10, 95% CI 0.70 – 1.72), gram-negative (IRR: 0.85, 95% CI 0.46 – 1.58), culture-negative (IRR 1.88, 95% CI 0.67 – 5.29), or polymicrobial ESI (IRR 1.00, 95% CI 0.40 – 2.54). Times to first peritonitis-associated and first infection-associated hospitalization were similar in the honey and control groups. The rates of technique failure (PD withdrawal) due to PD-related infection were not significantly different between the groups.**

♦ ***Conclusion:*** **Compared with standard nasal mupirocin prophylaxis, daily topical exit-site application of antibacterial honey resulted in comparable rates of organism-specific peritonitis and ESI, infection-associated hospitalization, and infection-associated technique failure in PD patients.**

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KEY WORDS: Honey; peritonitis; exit-site infection; mupirocin; microbiology; hospitalization; technique failure; peritoneal dialysis related infection.

Peritoneal dialysis (PD)-related infections, including peritonitis and exit-site and tunnel infections, are serious complications of PD. These infections are associated with increased risks of mortality (1,2), catheter removal (3), hemodialysis transfer, and prolonged hospitalization (4).

Data from the ANZDATA Registry and from Hong Kong have shown that different spectra of microorganisms are associated with different outcomes (5–11). Compared with gram-negative organisms, gram-positive organisms account for higher proportions of both peritonitis and exit-site infections (ESI), but are also associated with better outcomes (3,8,12–15). Culture-negative peritonitis has generally better outcomes than culture-positive episodes (16) and single-organism peritonitis episodes have superior outcomes to polymicrobial peritonitis episodes (7, 8).

Topical application of mupirocin at either the exit site or intranasally has been recommended by the International Society for Peritoneal Dialysis (ISPD) in its guidelines (17) for prophylaxis against PD-related infections. Previous meta-analyses have found that mupirocin was effective in preventing *Staphylococcus aureus* exit-site infection and/or peritonitis (18,19). However, the agent is only active against gram-positive organisms, and has been found to be ineffective at preventing gram-negative PD-related infections (20). Furthermore, there are an increasing number of reports indicating that widespread use of mupirocin leads to the development of resistant organisms (18,21).

Over the past decade, honey has emerged as a promising therapeutic and preventive agent because of its broad-spectrum antibacterial coverage, particularly against multi-resistant organisms (22,23). Topical application of standardized antibacterial honey to hemodialysis catheter exit sites in hemodialysis patients has previously been demonstrated in a randomized controlled trial to result in infection rates similar to those with mupirocin, without the problems associated with mupirocin resistance (24).

Recently, the HONEYPOT study (25), a multi-center, multi-national, randomized controlled trial, reported that daily exit-site application of antibacterial honey was not superior to nasal mupirocin prophylaxis targeting nasal *S. aureus* carriers for preventing overall PD-related infections (unadjusted hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.83 – 1.51; $p = 0.47$). In order to further evaluate the impact of exit-site application of honey on peritonitis and ESI microbiology and outcomes, this pre-specified sub-study aimed to determine whether topical antibacterial honey and mupirocin exerted differential effects on peritonitis and ESI microbiology and/or outcomes (first peritonitis-associated hospitalization, first infection-associated hospitalization, and technique failure).

METHODS

STUDY DESIGN AND PARTICIPANTS

The study design and methodology (26), including the statistical analysis plan (27), have previously been described, as have the main study results (25). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12607000537459). The study protocol was approved by ethics committees at all participating centers and all patients provided written informed consent prior to trial participation.

Adults and children of all ages with end-stage kidney disease undergoing PD were included in the trial. The exclusion criteria were ESI, tunnel infection, or peritonitis within the preceding month; current or recent (within the preceding 4 weeks) treatment with an antibiotic administered by any route; nasal carriage of mupirocin-resistant *S. aureus*; known hypersensitivity to, or intolerance of, honey or mupirocin; inability to provide informed consent; and history of psychological illness or disorder that interfered with the ability to understand or comply with the requirements of the study.

Participants were randomized in a 1:1 ratio to either daily exit-site application of antibacterial honey (Medihoney Antibacterial Wound Gel, Comvita, Paengaroa, New Zealand) or intranasal mupirocin prophylaxis (Bactroban, GlaxoSmithKline Limited, Melbourne, Australia) in nasal *S. aureus* carriers only (control; self-application twice daily to both anterior nares for 5 consecutive days each month). Usual exit-site care was performed according to local unit protocols. Randomization was stratified by study site, PD status (incident versus prevalent), and nasal carriage of *S. aureus*. Participants underwent a medical review and exit-site inspection in accordance with the Twardowski classification system every 2 months (28). They were followed until either completion of 24 months of follow-up, the occurrence of a study-terminating event, or the end of the study (16 June 2012), whichever came first.

The trial was open label, although microbiology staff were blinded to treatment allocation. Exit-site swabs were obtained using sterile, premoistened swabs in all suspected cases of exit-site infection (erythema, tenderness,

induration, or discharge). In all cases of suspected peritonitis (e.g. abdominal pain, cloudy bags, fever, etc.), dialysate effluents were collected and inoculated in blood culture bottles. All samples were promptly sent for microscopy and culture at the local microbiology laboratory (including mupirocin-sensitivity testing of any *S. aureus* isolates using standard disc diffusion techniques) (26).

The primary efficacy endpoint for the trial was time to first catheter-associated infection (ESI, tunnel infection, or peritonitis, whichever came first). In this sub-study, organism-specific peritonitis and ESI rates were compared between the honey and control groups. All (first and subsequent) catheter-associated infection events were analyzed. Comparisons were also made between the 2 groups with respect to the outcomes of time to first peritonitis-associated hospitalization, time to first infection-associated hospitalization (hospitalization due primarily to peritonitis or ESI), time to PD withdrawal due to PD-related infection and causes of infection-associated technique failure (conversion from PD to hemodialysis for any duration due to peritonitis or ESI).

First peritonitis-associated hospitalization was defined as hospitalization primarily for treatment of peritonitis. First infection-associated hospitalization was defined as hospitalization primarily for treatment of any infections, including PD-related infection and non PD-related infection.

STATISTICAL ANALYSIS

Organism-specific peritonitis and ESI rates were analyzed by treatment group using a Poisson regression model. The incidence rate ratios (IRRs) and 95% CIs from the model were reported. Within each treatment group, infection rates were calculated as the number of infections divided by the total time at risk and expressed as episodes per patient-year at risk. In addition to analysis of individual organisms, analyses were also grouped according to larger categories, such as gram-positive, gram-negative, and polymicrobial, to increase event numbers and statistical power.

Times from randomization to first peritonitis- and first infection-associated hospitalization and time to PD withdrawal due to PD-related infection were displayed using Kaplan-Meier survival curves by treatment group. Survival curves for treatment groups were summarized using median survival times and statistically compared using the log-rank test. Unadjusted HRs were estimated from Cox proportional hazards regression models. Participants who did not have a peritonitis- or infection-associated hospitalization or PD withdrawal due to PD-related infection were censored in the survival analyses. Since the events of death, transfer to hemodialysis, renal transplant, and spontaneous recovery of renal function either prevent or alter the probability of occurrence of the PD withdrawal due to PD-related infection, competing risk survival analyses were done to test the sensitivity of results to the risk of PD withdrawal due to PD-related infection.

Results for the causes of withdrawal from PD are presented as frequencies (percentages) by intervention group. Group comparisons were performed using the chi-square test. *P* values less than 0.05 were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

The HONEYPOT study randomized 371 participants from 26 centers to receive either honey (n = 186) or mupirocin prophylaxis (n = 185). All of these participants were included in the intention-to-treat analysis in the present sub-study. As previously reported (25), the 2 groups were well matched for all baseline characteristics. In particular, the proportion of nasal *S. aureus* carriers was 22% in both groups. The nasal *S. aureus* carriers in the control group received nasal mupirocin prophylaxis. Mupirocin-resistant *S. aureus* isolates were detected in 2 participants in the control group and no participants in the honey group.

ORGANISM-SPECIFIC PERITONITIS RATES

Eighty-two episodes of peritonitis occurred in 52 patients in the honey group and 102 episodes occurred in 63 patients in the control group. The mean peritonitis rates in the honey and control groups were 0.41 (95% CI: 0.32 – 0.50) and 0.41 (95% CI: 0.33 – 0.49) episodes per patient-year, respectively (IRR 1.01, 95% CI: 0.75 – 1.35; p = 0.95). No significant differences were observed between the groups for gram-positive, gram-negative, culture-negative, or polymicrobial peritonitis (Table 1, Figure 1).

ORGANISM-SPECIFIC ESI RATES

Seventy-three episodes of ESI occurred in 43 patients in the honey group and 82 episodes occurred in 40 patients in the control group. The mean ESI rates in the honey and control groups were 0.37 (95% CI: 0.28 – 0.45) and 0.33 (95% CI: 0.26 – 0.40) episodes per patient-year, respectively (IRR 1.12, 95% CI: 0.81 – 1.53; p = 0.49). No significant differences were observed between the groups for gram-positive, gram-negative, culture-negative, or polymicrobial ESI (Table 2, Figure 2).

TABLE 1
Organism-Specific Peritonitis Rates in the Honey and Control Groups

Organism	Peritonitis Rates (95% CI) (episodes per patient-year) Honey (197.8 patient-years)	Control (248.2 patient-years)	IRR (95% CI)
Gram-positive	0.21 (0.15–0.28)	0.21 (0.16–0.27)	0.99 (0.66–1.49)
Coagulase-negative staphylococcus	0.08 (0.04–0.11)	0.09 (0.05–0.13)	0.82 (0.43–1.57)
Staphylococcus aureus	0.07 (0.03–0.10)	0.03 (0.01–0.05)	2.04 (0.85–4.92)
Streptococcus	0.03 (0.00–0.05)	0.04 (0.02–0.07)	0.57 (0.20–1.64)
Other gram-positive	0.05 (0.02–0.08)	0.04 (0.02–0.07)	1.03 (0.43–2.48)
Gram-negative	0.09 (0.05–0.13)	0.12 (0.08–0.16)	0.71 (0.39–1.29)
Pseudomonas	0.01 (0.00– 0.01)	0.01 (0.00– 0.03)	0.42 (0.04–4.02)
Non-*Pseudomonas*	0.08 (0.04–0.12)	0.11 (0.07–0.15)	0.74 (0.40–1.38)
Culture-negative	0.08 (0.04–0.12)	0.04 (0.02–0.07)	2.01 (0.91–4.42)
Polymicrobial	0.03 (0.01–0.05)	0.03 (0.01–0.05)	1.08 (0.36–3.20)
TOTAL	0.41 (0.32–0.50)	0.41 (0.33–0.49)	1.01 (0.75–1.35)

CI = confidence interval; IRR = incidence rate ratio.

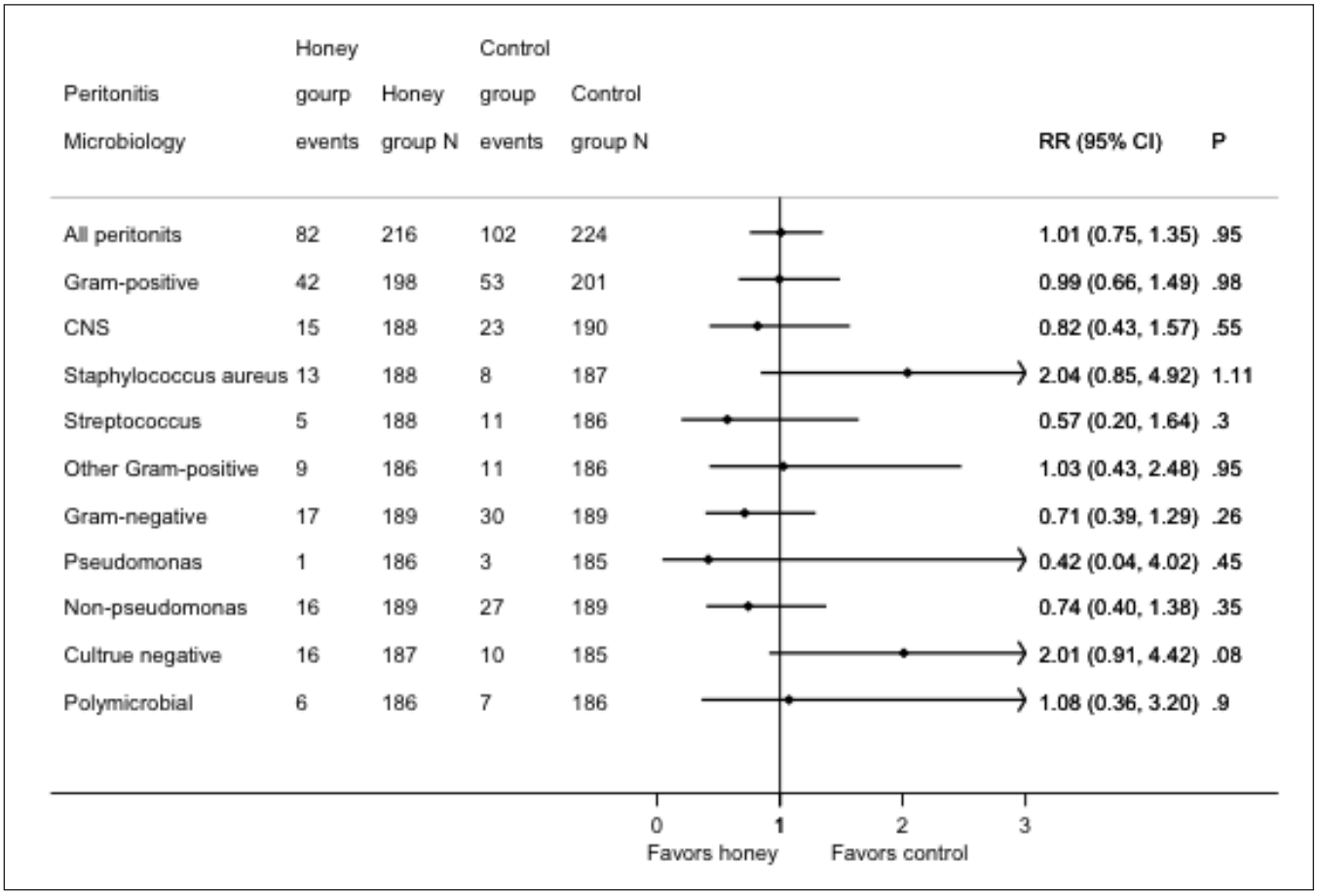

Figure 1 — Forest plot of organisms responsible for peritonitis episodes in the honey and control groups. RR = rate ratio; CI = confidence interval; CNS = coagulase-negative staphylococcus.

TABLE 2
Organism-Specific ESI Rates in the Honey and Control Groups

Organism	ESI Rates (95% CI) (episodes per patient-year) Honey (197.8 patient-years)	Control (248.2 patient-years)	IRR (95% CI)
Gram-positive	0.18 (0.12– 0.24)	0.17 (0.11–0.22)	1.10 (0.70–1.72)
Coagulase-negative *Staphylococcus*	0.03 (0.01–0.05)	0.03 (0.01–0.05)	0.94 (0.33–2.71)
Staphylococcus aureus	0.11 (0.06–0.15)	0.10 (0.06–0.14)	1.05 (0.59–1.88)
Streptococcus	0.02 (0.00–0.04)	0.00 (0.00–0.01)	5.02 (0.56–44.90)
Other gram-positive	0.03 (0.00–0.05)	0.03 (0.01–0.05)	0.90 (0.28–2.82)
Gram-negative	0.09 (0.05–0.13)	0.10 (0.06–0.14)	0.85 (0.46–1.58)
Pseudomonas	0.04 (0.01–0.06)	0.05 (0.02–0.08)	0.68 (0.27–1.69)
Non-*Pseudomonas*	0.05 (0.02–0.08)	0.05 (0.02–0.08)	1.05 (0.45–2.42)
Culture-negative	0.05 (0.02–0.08)	0.02 (0.00–0.04)	1.88 (0.67–5.29)
Polymicrobial	0.04 (0.01–0.07)	0.04 (0.02–0.07)	1.00 (0.40–2.54)
TOTAL	0.37 (0.28–0.45)	0.33 (0.26–0.40)	1.12 (0.81–1.53)

ESI = exit-site infection; CI = confidence interval; IRR = incidence rate ratio.

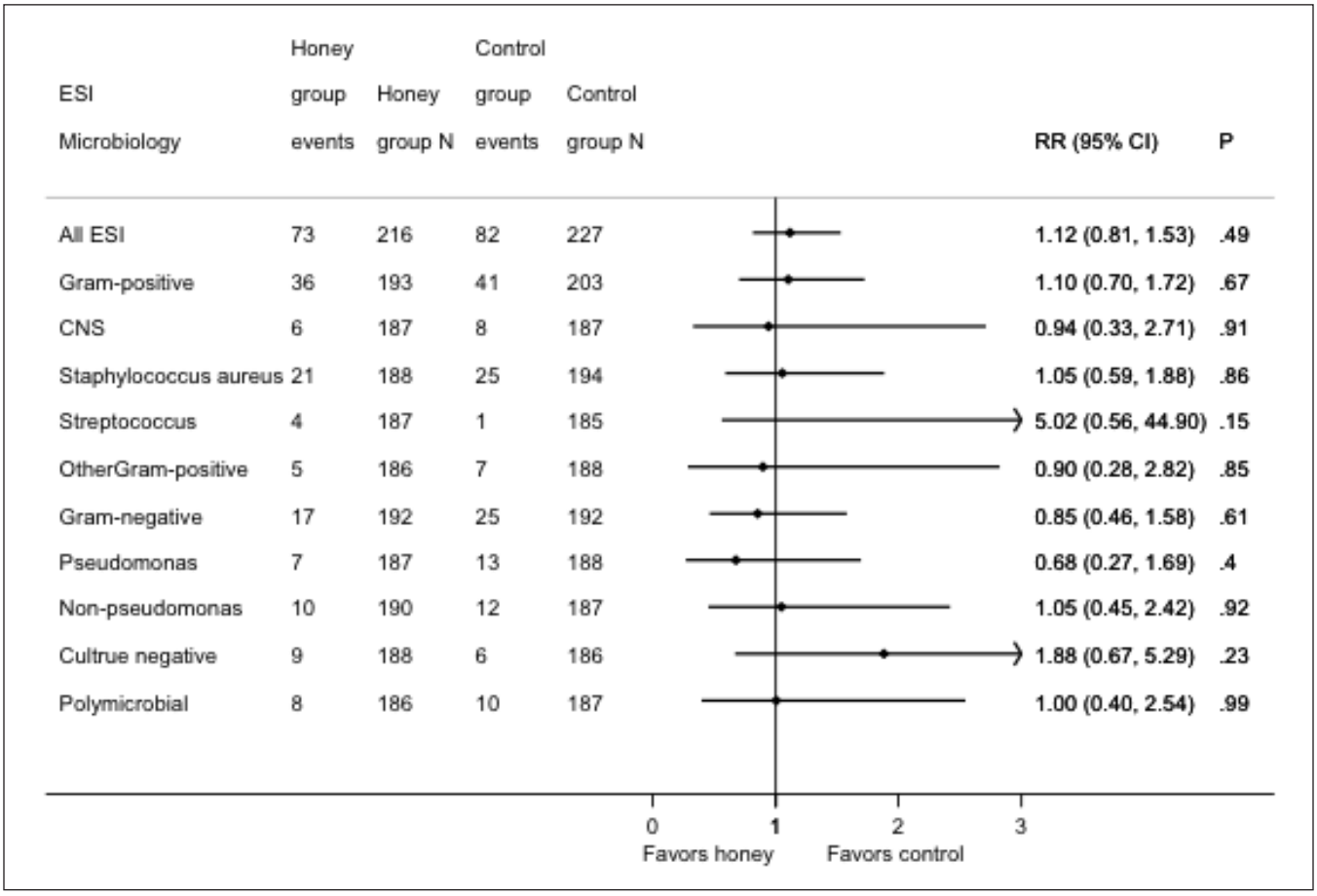

Figure 2 — Forest plot of organisms responsible for ESI episodes in the honey and control groups. ESI = exit-site infection; RR = rate ratio; CI = confidence interval; CNS = coagulase-negative staphylococcus.

FIRST PERITONITIS-ASSOCIATED AND FIRST INFECTION-ASSOCIATED HOSPITALIZATION

Forty-six participants (25%) in the honey group and 49 participants (26%) in the control group experienced a first peritonitis-associated hospitalization ($p = 0.70$). The rates of first peritonitis-associated hospitalization were similar in the honey and control groups (HR 1.17, 95% CI: 0.78 – 1.75; $p = 0.45$) (Figure 3).

Sixty-four participants (34%) in the honey group and 71 participants (38%) in the control group experienced a first infection-associated hospitalization ($p = 0.43$). No significant differences in time to first infection-associated hospitalization were observed between the honey and control groups (HR 1.11, 95% CI: 0.79 – 1.56; $p = 0.55$) (Figure 4).

TECHNIQUE SURVIVAL

The causes of withdrawal from PD are shown in Table 3. Thirteen (18%) patients in the honey group and 22 (29%) in the control group had their catheters removed and were converted to hemodialysis due to PD-related infection, respectively ($p = 0.11$). One death related to infection (intra-abdominal sepsis) occurred in a patient in the control group.

The rates of PD withdrawal due to PD-related infection were similar in the honey and control groups (HR 0.73, 95% CI: 0.37 – 1.45; $p = 0.37$) (Figure 5). We noted similar findings with the competing-risks survival analysis (HR 0.68, 95% CI: 0.34 – 1.35; $p = 0.27$).

DISCUSSION

This pre-specified sub-study of the HONEYPOT trial showed that, compared with standard nasal mupirocin prophylaxis targeting nasal carriage of *S. aureus*, daily exit-site application of antibacterial honey resulted in similar organism-specific rates of peritonitis and ESI among PD patients. The risks of first peritonitis-associated hospitalization, first infection-associated hospitalization and hemodialysis conversion due to infection were also comparable between the groups. These observations extend the main findings of the HONEYPOT trial by demonstrating that antibacterial honey does not provide any organism-specific infection control advantage over mupirocin, despite the fact that honey has a broader antimicrobial spectrum.

Honey has been reported to be effective against a large variety of microorganisms in *in vitro* studies, including gram-positive organisms, *Staphylococcus aureus* (29), methicillin-resistant *Staphylococcus aureus* (MRSA) (30), coagulase-negative *Straphylococci* (31), *Streptococcus pyogenes* (32,33), *Escherichia coli* (34), *Pseudomonas aeruginosa* (34–37), fungi (38), and vancomycin-resistant enterococci (39). In contrast to mupirocin, honey has a greater inhibitory effect on gram-negative bacteria than gram-positive bacteria (40) and a much more potent effect on multiple antibiotic-resistant microorganisms (22). Moreover, there are currently no known microorganisms resistant to honey (41,42). Honey has also been reported to reduce inflammation, debride necrotic tissue, reduce edema, and promote angiogenesis, granulation, and epithelialization of wounds (43). In spite of these

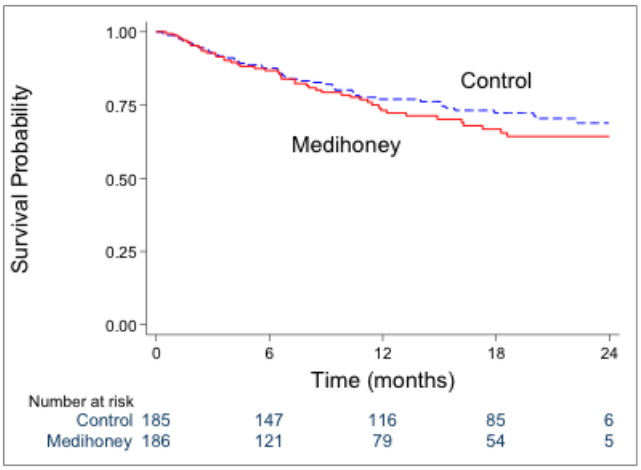

Figure 3 — Survival analysis of first peritonitis-associated hospitalization in the honey and control groups [HR 1.17 (95% CI 0.78–1.75); p=0.45]. HR = hazard ratio; CI = confidence interval.

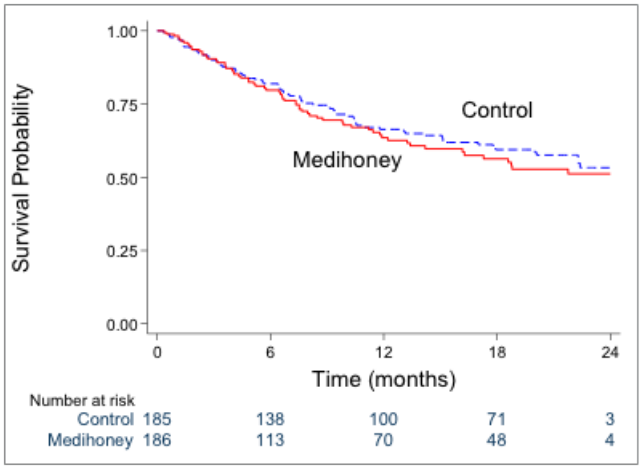

Figure 4 — Survival analysis of first infection-associated hospitalization in the honey and control groups [HR 1.11 (95% CI 0.79–1.56); p=0.55]. HR = hazard ratio; CI = confidence interval.

TABLE 3
Causes of Withdrawal from PD in the HONEYPOT Study Participants

Causes	Honey (*n* =71)	Control (*n* =76)
Hemodialysis transfer, *n* (%)	32 (45)	44 (58)
PD-related infection*	13 (18)	22 (29)
Catheter malfunction	4 (6)	3 (4)
Inadequate solute clearance	7 (10)	5 (7)
Hernia	0	2 (3)
Dialysate leak	0	4 (5)
Fluid overload	1 (1)	2 (3)
Other	7 (10)	6 (8)
Death, *n* (%)	14 (20)	18 (24)
Cardiovascular	5 (7)	5 (7)
Cerebrovascular	2 (3)	3 (4)
Infectious	0	1 (1)
Other	7 (10)	9 (12)
Transplant, *n* (%)	21 (30)	11 (14)
Spontaneous recovery of renal function, *n* (%)	2 (3)	0
Other, *n* (%)	2 (3)	3 (4)

PD = peritoneal dialysis.
* p=0.11.

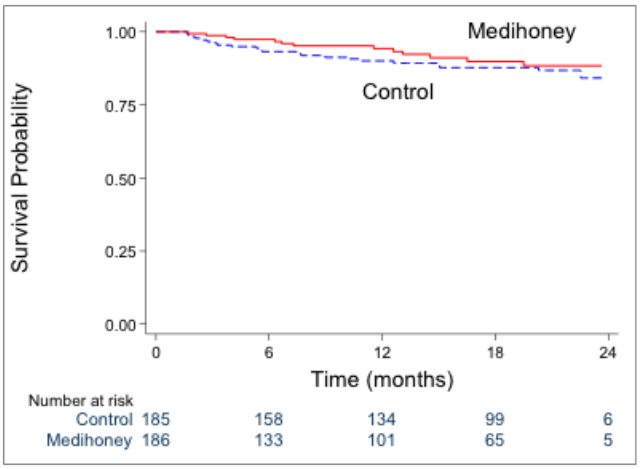

Figure 5 — Survival analysis of PD withdrawal due to PD-related infection in the honey and control groups [HR 0.73 (95% CI: 0.37–1.45); p=0.37]. PD = peritoneal dialysis; HR = hazard ratio; CI = confidence interval.

attractive properties, very few studies have compared the effect of honey with antibiotics for either therapeutic or prophylactic purposes.

One study in Egypt (44) compared the *in vitro* effects of honey versus a wide variety of commonly used antibiotics (ciprofloxacin, sulbactam/ampicillin, ceftriaxone, vancomycin, imipenem, amoxicillin/clavulinic acid, ceftriaxone, and methicillin) on organisms isolated from the infected wounds of 33 burn patients. The authors reported that honey exerted greater inhibitory effects on gram-negative bacteria and MRSA than these commonly used antibiotics. Adeleke and colleagues similarly reported that honey had higher *in vitro* antibacterial activities against *Pseudomonas aeruginosa* and *Escherichia coli* than gentamicin in organisms isolated from infected burn wounds (45), whilst Jenkins *et al.* noted that honey had a superior antimicrobial effect on *Staphylococcus aureus* compared with vancomycin (46). However, these studies were all *in vitro* investigations and therefore were not necessarily generalizable to the clinical setting.

Only 1 previously published randomized controlled trial, by Johnson and colleagues, has examined the effect of topical exit-site application of honey compared with antibiotics on preventing clinical infections (24). In this study of 101 hemodialysis patients with dialysis catheters, the exit-site application of honey was not significantly associated with catheter-associated bacteremia-free survival compared with mupirocin (unadjusted HR 0.94, 95% CI 0.27 – 3.24; p = 0.92), similar to the main findings of the HONEYPOT trial in PD patients. However, organism-specific infection rates were not examined in that study due to the low number of observed infectious events (n = 11). The present sub-study of the HONEYPOT trial is therefore the first randomized controlled trial to report the clinical impact of honey on infections due to specific organisms, compared with antibiotic prophylaxis (mupirocin). Although high levels of mupirocin resistance have been reported (47,48), a low incidence of mupirocin-resistant microorganisms was found in the present study, which may have been due to the short duration of follow-up.

Apart from a neutral effect of antibacterial honey on PD-related infection rates compared with mupirocin, the current study also found that honey did not attenuate the severity of PD-related infections, as evidenced by comparable rates of first peritonitis-associated hospitalization, first infection-associated hospitalization and infection-related technique failure. These findings contrast with those of a previous meta-analysis of 7 randomized controlled trials, which demonstrated that the use of honey as a wound dressing was superior to antiseptics and/or systemic antibiotics for wound healing, maintenance of sterility, and eradication of infection (49). Some of the apparent disparity in findings with those of the present study may be explained by differences in indications for honey administration (prevention of catheter-association infection versus

treatment of infected burns or post-operative wounds) and in the interventions used in the control group (mupirocin vs polyurethane film, amniotic membrane, potato peel, or silver sulphadiazine). Moreover, the systematic review examined small sample size, single-center trials of short duration and suboptimal methodological quality, 6 of which were performed by the same investigator.

Another randomized controlled trial of dressings soaked in honey vs Edinburgh University Solution of Limes (UESOL) in 32 children with 43 pyomyositis abscesses reported that honey-treated wounds demonstrated quicker healing and a shorter length of hospital stay compared with EUSOL-treated wounds ($p = 0.019$) (50). These results may also have differed from those of the present study as a result of the different indications for honey use and the different interventions used as a comparator.

The strengths of this study include its large sample size and involvement of many centers from 2 different countries, thereby enhancing the generalizability of the trial's findings. The pragmatic study design also closely mirrored 'real-world' clinical practice. Balanced against these strengths, the principal limitation of this sub-study was that analysis of PD-related infections due to some individual peritonitis organisms was limited by low event rates and therefore inadequate statistical power. For example, only 4 episodes of pseudomonas peritonitis occurred during the study (1 in the honey group and 3 in the control group). These organisms were therefore grouped into larger categories, such as gram-positive, gram-negative, and polymicrobial peritonitis or ESI, to increase event numbers and analytic power. The open-label design of the trial also potentially introduced observer and performance biases, whilst the higher withdrawal rate in the honey group (29%) potentially resulted in attrition bias. The findings of the trial may also not be generalizable to exit-site mupirocin application, which is commonly practiced in some PD centers.

In conclusion, daily topical exit-site application of antibacterial honey was not superior to nasal mupirocin prophylaxis for the prevention of catheter-associated infection, hospitalization, and technique failure in PD patients and there were no differences in the microbiological profiles of either ESI or peritonitis between the 2 treatment arms.

DISCLOSURES

David Johnson is a consultant for Baxter Healthcare Pty Ltd and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. He has previously been a consultant to Gambro Pty Ltd and was the recipient of a Gambro Research Grant which partly funded the HONEYPOT trial. Nikky Isbel, Carolyn Clark, and David Johnson received a Baxter Healthcare Renal Discoveries Extramural Program Grant which partly funded the HONEYPOT trial. David Johnson is an International Society for Peritoneal Dialysis Councillor and is a current recipient of a Queensland Government Health Research Fellowship. Alan Cass is a consultant for and has received research funds from Baxter Healthcare Pty Ltd. He has also received speakers' honoraria from Fresenius Medical Care. He is a recipient of a National Health and Medical Research Council Principal Research Fellowship. Carmel Hawley has received speakers' honoraria and research grants from Fresenius Medical Care and has been a consultant to Fresenius Medical Care. She has received research funds from Gambro Pty Ltd and was the recipient of a Queensland Health Smart Health Research Grant. All other authors have no financial conflicts of interest to declare.

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