Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial

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Summary

Background There is a paucity of evidence to guide the best strategy for prevention of peritoneal-dialysis-related infections. Antibacterial honey has shown promise as a novel, cheap, effective, topical prophylactic agent without inducing microbial resistance. We therefore assessed whether daily application of honey at the exit site would increase the time to peritoneal-dialysis-related infections compared with standard exit-site care plus intranasal mupirocin prophylaxis for nasal carriers of *Staphylococcus aureus*.

Methods In this open-label trial undertaken in 26 centres in Australia and New Zealand, participants undergoing peritoneal dialysis were randomly assigned in a 1:1 ratio with an adaptive allocation algorithm to daily topical exit-site application of antibacterial honey plus standard exit-site care or intranasal mupirocin prophylaxis (only in carriers of nasal *S aureus*) plus standard exit-site care (control group). The primary endpoint was time to first infection related to peritoneal dialysis (exit-site infection, tunnel infection, or peritonitis). The trial is registered with the Australian New Zealand Clinical Trials Registry, number 12607000537459.

Findings Of 371 participants, 186 were assigned to the honey group and 185 to the control group. The median peritoneal-dialysis-related infection-free survival times were not significantly different in the honey (16·0 months [IQR not estimable]) and control groups (17·7 months [not estimable]; unadjusted hazard ratio 1·12, 95% CI 0·83–1·51; p=0·47). In the subgroup analyses, honey increased the risks of both the primary endpoint (1·85, 1·05–3·24; p=0·03) and peritonitis (2·25, 1·16–4·36) in participants with diabetes. The incidences of serious adverse events (298 *vs* 327, respectively; p=0·1) and deaths (14 *vs* 18, respectively; p=0·9) were not significantly different in the honey and control groups. 11 (6%) participants in the honey group had local skin reactions.

Interpretation The findings of this trial show that honey cannot be recommended routinely for the prevention of peritoneal-dialysis-related infections.

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Introduction

Peritoneal dialysis is an important treatment for individuals needing renal replacement and is used in more than 200 000 patients with end-stage kidney failure worldwide.[1] An important barrier to further uptake and sustained use of peritoneal dialysis is infection, including peritonitis and exit-site and tunnel infections.[2] These infections frequently complicate peritoneal dialysis and are associated with greatly increased risks of all-cause and cardiovascular mortality, catheter removal, transfer to haemodialysis, loss of residual renal function, prolonged hospital admission, and further episodes of peritoneal-dialysis-related infections.[3–5]

Evidence for the use of topical nasal mupirocin (particularly in individuals who are carriers of nasal *Staphylococcus aureus*),[6–8] and exit-site mupirocin[9,10] or exit-site gentamicin application[11] to prevent peritoneal-dialysis-related infections has been obtained from only a few randomised controlled trials. The guidelines of Caring for Australasians with Renal Impairment (CARI), therefore, recommend intranasal mupirocin prophylaxis for participants with nasal *S aureus* carriage undergoing peritoneal dialysis,[12] whereas those of the International Society for Peritoneal Dialysis (ISPD) recommend use of topical antibiotics either at the catheter exit site or intranasally, or both, in all participants undergoing peritoneal dialysis.[13] However, these antibiotics are only active against a narrow range of microorganisms and an increasing number of reports suggest that these agents result in the selection of resistant microorganisms and subsequent treatment failures.[14,15]

Over the past decade, honey has been shown to be an inexpensive, safe, and effective antimicrobial agent, which is active against a broad range of fungi and bacteria (including multiresistant microorganisms),[16,17] prevents and disrupts formation of biofilm,[18] and does not result in antimicrobial resistance even under conditions that rapidly induce resistance to antibiotics.[19] The results of a meta-analysis of seven randomised controlled trials showed that honey was superior to antiseptics or systemic antibiotics, or both, for wound healing, maintenance of sterility, and eradication of infection.[20] In a randomised controlled trial of participants undergoing haemodialysis, topical application of standardised antibacterial honey to haemodialysis-catheter exit sites resulted in infection

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rates similar to mupirocin, without the problems associated with mupirocin resistance.[21] So far, there have been no other trials of honey to prevent peritoneal-dialysis-related infections.

The main objective in this trial was to assess whether daily application of honey at the exit site would increase the time to peritoneal-dialysis-related infections compared with standard exit-site care plus intranasal mupirocin prophylaxis for the carriers of nasal *S aureus*.

	Control group (n=185)	Honey group (n=186)
Age (years)	62·1 (14·6)	61·2 (14·5)
Age (<18 years)	1 (<1%)	2 (1%)
Men	116 (63%)	108 (58%)
Ethnic origin*		
White	143 (78%)	148 (80%)
Aboriginal or Torres Strait Islander	3 (2%)	2 (1%)
Maori or Pacific Islander	10 (5%)	5 (3%)
Asian	24 (13%)	24 (13%)
Other	4 (2%)	6 (3%)
Primary cause of end-stage kidney disease†		
Diabetic nephropathy	41 (24%)	46 (27%)
Hypertensive nephrosclerosis	14 (8%)	8 (5%)
Chronic glomerulonephritis	36 (21%)	29 (17%)
Analgesic nephropathy	3 (2%)	5 (3%)
Polycystic kidney disease	14 (8%)	28 (16%)
Interstitial nephritis	6 (4%)	8 (5%)
Obstructive nephropathy	1 (<1%)	2 (1%)
Reflux nephropathy	7 (4%)	10 (6%)
Renovascular disease	15 (9%)	9 (5%)
Other or unknown	35 (20%)	28 (16%)
Kidney transplant failure	6 (3%)	8 (4%)
Body-mass index (kg/m²)	27·5 (4·9)	27·1 (5·6)
Obese (body-mass index ≥30 kg/m²)	55 (30%)	48 (26%)
Systolic blood pressure (mm Hg)	132 (21)	136 (22)
Diastolic blood pressure (mm Hg)	76 (12)	77 (12)
Smoker*		
Never	74 (40%)	77 (42%)
Former	91 (50%)	92 (50%)
Current	19 (10%)	16 (8%)
Diabetes mellitus	51 (28%)	64 (34%)
Ischaemic heart disease	47 (25%)	55 (30%)
Congestive heart failure	9 (5%)	13 (7%)
Cerebrovascular disease	21 (11%)	23 (12%)
Peripheral vascular disease	23 (12%)	29 (16%)
Haemoglobin (g/L)	114 (16)	115 (16)
Serum albumin (g/L)	35 (5)	35 (5)
Incident peritoneal dialysis‡	38 (21%)	37 (20%)
Peritoneal dialysis as first dialysis modality	138 (75%)	131 (70%)
Peritoneal dialysis modality*		
Continuous ambulatory peritoneal dialysis	92 (50%)	86 (47%)
Automated peritoneal dialysis	92 (50%)	99 (53%)

(Continues on next page)

Methods

Study design and participants

The trial was designed and supervised by the investigators in the management committee and coordinated by the Australasian Kidney Trials Network (University of Queensland, Brisbane, QLD, Australia). The trial design and the statistical analysis plan have been reported previously.[22,23]

Adults and children of all ages with end-stage kidney disease who were undergoing peritoneal dialysis were eligible for inclusion in the trial. The exclusion criteria were exit-site infection, 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. All potential participants were screened for nasal carriage of *S aureus* with standard microbiological methods.[24]

The trial was undertaken in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice guidelines. The study protocol was approved by the ethics committees at all participating centres and all participants provided written informed consent before participation in the trial.

Participants were recruited from 26 centres in Australia and New Zealand between Sept 17, 2008, and June 17, 2011. Results from two interim analyses were assessed by an independent data and safety monitoring board after a third and two-thirds of the total number of participants had been recruited and followed up for at least 2 months. The Haybittle-Peto[25] stopping rule for efficacy was not met, and the study was completed as per protocol. The data were analysed by trial statisticians (EMP and AS).

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio by use of an adaptive allocation algorithm designed to minimise imbalance in treatment groups for the three variables: study site, incident versus prevalent peritoneal dialysis status, and nasal carriage of *S aureus*.[26,27] To ensure adequate concealment of allocation, the randomisation was done with a password-protected internet-based system. The trial was open label, but microbiology staff at the local laboratories were not informed of the treatment allocation. Participants in the experimental group received daily topical exit-site application of 10 mg of antibacterial honey (Medihoney Antibacterial Wound Gel, Comvita, Paengaroa, New Zealand; AUD9·95–13·95 for 25 g) plus standard exit-site care. This high viscosity gel is a combination of 80% Medihoney Antibacterial Honey

(an ultrafiltered, irradiated medical grade honey with standardised antibacterial activity obtained from *Leptospermum* sp mainly) and natural waxes and oils. In the control group, participants without nasal carriage of *S aureus* at baseline received standard exit-site care and underwent nasal swab screening every 6 months thereafter. Participants with nasal carriage of *S aureus* at initial or subsequent screens received 2% mupirocin ointment (Bactroban, GlaxoSmithKline, Melbourne, VIC, Australia) for self-application twice daily to both anterior nares for 5 consecutive days each month plus standard exit-site care for the duration of the trial.

Follow-up

Participants underwent a medical review and inspection of the exit-site in accordance with the Twardowski classification system every 2 months.[28] The minimum and maximum follow-up durations were 12 months and 24 months, respectively. The participants were followed up until either completion of peritoneal dialysis, completion of 24 months of follow-up, or the end of the study (June 16, 2012—ie, 12 months after the recruitment of the last participant), whichever came first.

Statistical analysis

The primary efficacy endpoint was time to first peritoneal-dialysis-related infection (exit-site infection, tunnel infection, or peritonitis, whichever came first). Exit-site infection was defined as a purulent discharge at the catheter exit site or presence of at least two of the following: erythema greater than 13 mm, induration, or tenderness. Peritonitis was defined as a cloudy effluent with a white cell count greater than 100 per mm^3 (1×10^8 per L) with at least 50% polymorphonuclear cells. Tunnel infection was defined as the presence of at least two of the following: induration, tenderness, or radiographic evidence of a collection along the subcutaneous pathway of the catheter.

The secondary efficacy endpoints were time to the individual components of the primary composite endpoint (exit-site infection, peritonitis, or tunnel infection), time to infection-associated catheter removal, death, and serious adverse events. The exploratory endpoints were the frequencies of the type of infective microorganisms and mupirocin-resistant *S aureus*.

Results are expressed as percentages for categorical variables, mean and SD for continuous normally distributed variables, and median and IQR for continuous non-normally distributed variables. The primary and secondary efficacy endpoints were analysed in accordance with the intention-to-treat principle. Kaplan-Meier survival curves by intervention group were generated for the primary and secondary efficacy outcomes. Survival curves were compared statistically using the log-rank test. Unadjusted hazard ratios (HRs) were estimated from Cox proportional-hazards regression models. The robustness of these estimates was assessed with prespecified multivariable analyses adjusted for six baseline characteristics (incident or prevalent peritoneal dialysis, nasal carriage of *S aureus*, continuous ambulatory peritoneal dialysis or automated peritoneal dialysis, age

	Control group (n=185)	Honey group (n=186)
(Continued from previous page)		
Carrier of nasal *Staphylococcus aureus*	41 (22%)§	40 (22%)
Dialysate Kt/V per week	1·6 (0·6)	1·7 (0·6)
Residual renal Kt/V per week	0·8 (0·3–1·3)	0·8 (0·2–1·4)
Dialysate-to-plasma creatinine ratio at 4 h	0·69 (0·10)	0·68 (0·10)
Peritoneal membrane transport category¶		
High	22 (14%)	11 (7%)
High average	78 (50%)	84 (55%)
Low average	52 (33%)	53 (35%)
Low	4 (3%)	5 (3%)
Neutral pH, low glucose degradation product solution	13 (7%)	9 (5%)
Exit site as per Twardowski classification*		
Perfect	92 (50%)	90 (49%)
Good	77 (42%)	77 (42%)
Equivocal	14 (8%)	16 (9%)
Acute infection	1 (<1%)	0

Data are number (%), mean SD, or median (IQR). Kt/ V=fractional urea clearance per week. *Data were missing for one to three participants per group. †Data were missing for 13 participants per group. ‡Commenced peritoneal dialysis for the first time within 12 weeks of randomisation. §25 (17%) of 144 participants who were not carriers of nasal *Staphylococcus aureus* at baseline in the control group became carriers during follow-up. ¶Data were missing for 29 participants in the control group and 33 in the honey group.

Table 1: **Baseline characteristics of participants in the control and honey groups**

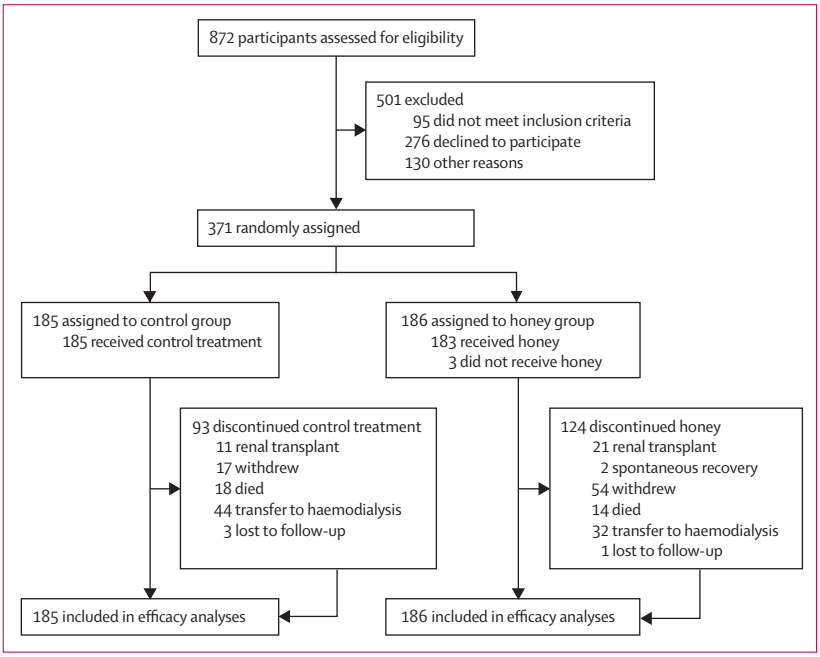

Figure 1: **Trial profile**

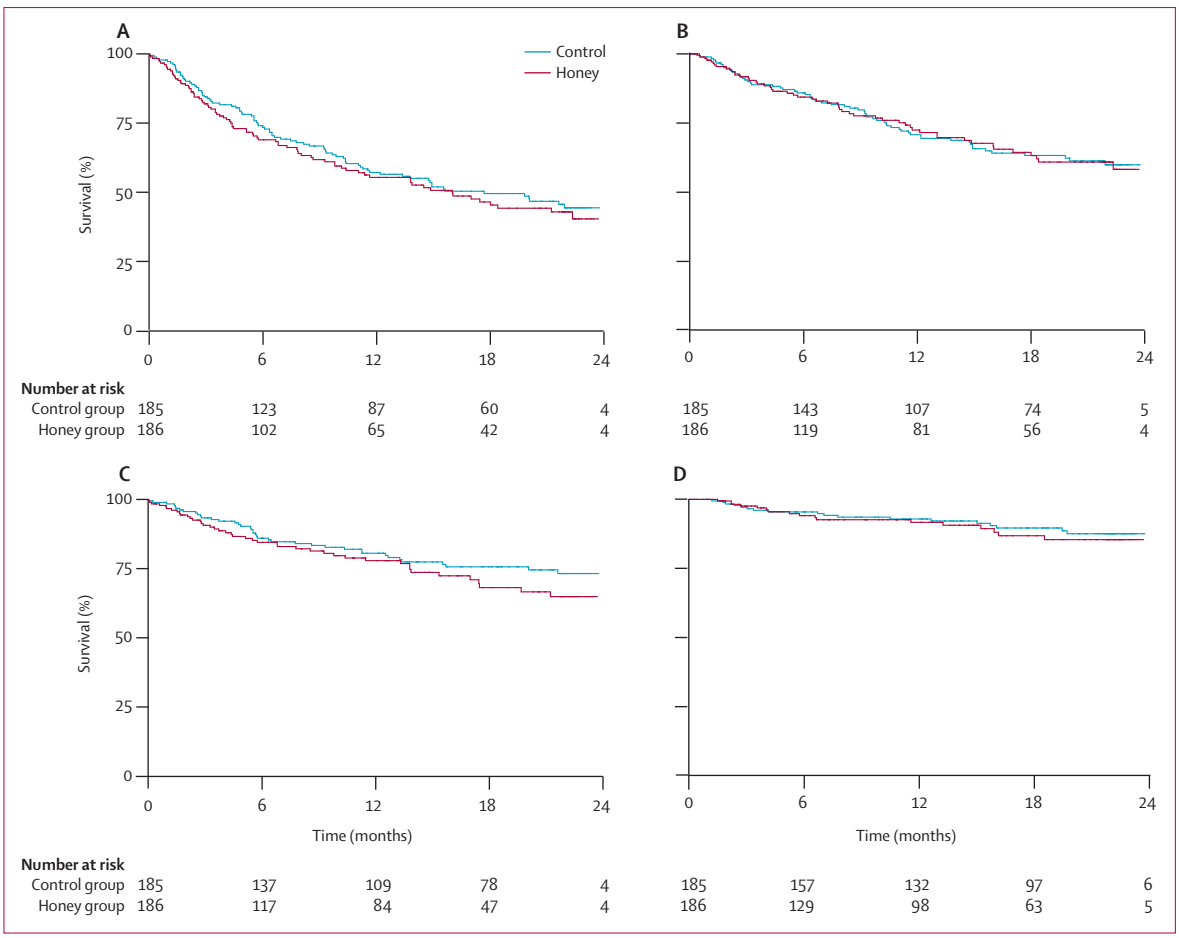

Figure 2: **Kaplan-Meier survival curves for the control and honey groups**
(A) Primary efficacy endpoint (composite of exit-site infection, tunnel infection, and peritonitis). (B) Peritonitis. (C) Exit-site infection. (D) Infection-associated catheter removal.

≥65 years, diabetes mellitus, and obesity). Participants who were withdrawn from the trial without having a primary outcome event were censored in the survival analyses. Since the events of death, catheter removal, transfer to haemodialysis, renal transplant, and spontaneous recovery either prevent or alter the probability of occurrence of the three infections in the composite outcome, competing-risks survival analyses were done to test the sensitivity of results to the presence of these informative events, also known as competing risks.[29] Results for serious adverse events and infecting microorganisms are presented as incidence rates to adjust for unanticipated differences in follow-up in the two intervention groups.

The study was designed to have 80% statistical power to detect an increase in median infection-free survival from 18 months to 30 months (HR 0·6), assuming α is 0·05, a recruitment period of 24 months, a minimum follow-up of 12 months, and an attrition rate of 2% per month (calculated with compounding, about 20% per year). Allowing for 10% of the individuals in the honey group to change to standard treatment by the end of the trial required an increase in study size by a factor of 1·23. The final sample size was estimated to be 185 individuals per group (370 in total).

The trial is registered with Australian New Zealand Clinical Trials Registry, number 12607000537459.

Role of the funding source

None of the funding sources had any role in the study design, gathering, analysis, and interpretation of data, writing of the report, or decision to submit the report for publication.

Results

186 of 371 participants were assigned to the honey group and 185 to the control group. Table 1 shows the two groups were well matched with respect to all baseline characteristics, including nasal carriage of *S aureus*. In the control group, 134 and 72 participants completed 12 months and 24 months of follow-up, respectively. At study termination, 20 participants who had not completed 24 months were censored. In the honey

group, 101 and 52 participants completed 12 months and 24 months of follow-up, respectively. At study termination, ten participants who had not completed 24 months were censored. In both groups, all participants who were censored at study termination had completed the minimum follow-up of 12 months. Median duration of follow-up was 18·7 months (IQR 11·2–22·2) in the control group and 13·1 months (4·6–21·8) in the honey group. More participants discontinued the intervention in the honey group than in the control group (124 [67%] of 186 *vs* 93 [50%] of 185; the main reason was withdrawal from the study (54 [29%] of 186 *vs* 17 [9%] of 185; figure 1; appendix p 5). The most common reason for withdrawal was participant's or physician's request (29 [54%] of 54 and 12 [71%] of 17 in the honey and control groups, respectively). 11 (20%) participants in the honey group discontinued the honey because of a skin reaction.

170 (46%) of 371 participants—82 in the honey group and 88 in the control group—experienced the primary endpoint during the study. The median peritoneal-dialysis-related infection-free survival times were not significantly different between the honey and control groups (16·0 months [IQR not estimable] *vs* 17·7 months [not estimable]; HR 1·12, 95% CI 0·83–1·51; p=0·47; figure 2A; appendix p 5). We noted similar findings with the competing-risks survival analysis (1·06, 0·78–1·43; p=0·71; appendix p 5).

A significant interaction was noted between treatment and diabetes mellitus in the prespecified subgroup analysis—participants with diabetes who had peritoneal dialysis and received antibacterial honey had significantly higher risks of the primary composite outcome (HR 1·85, 95% CI 1·05–3·24; $p_{interaction}$=0·03; figure 3) and peritonitis (2·25, 1·16–4·36; $p_{interaction}$=0·002; appendix p 2). The risk of the primary composite endpoint in participants without diabetes in the honey group was similar to the control group (0·88, 0·61–1·28; figure 3), whereas the risk of peritonitis was lower (0·62, 0·38–1·00; appendix p 2). No significant differences were noted in the primary composite endpoint between the honey and control groups in any of the other five prespecified subgroups (figure 3).

No differences were noted between the honey and control groups in the secondary efficacy endpoints time to first peritonitis (HR 0·99, 95% CI 0·69–1·43; p=0·97), time to first exit-site infection (1·30, 0·84–2·00; p=0·24), and time to infection-associated catheter removal (1·18, 0·61–2·30; p=0·62; figure 2B–D; appendix p 5). The four tunnel infections were too few to permit a meaningful analysis.

Rates of exit-site infection (incident rate ratio 1·25, 95% CI 0·88–1·79) and peritonitis (1·00, 0·73–1·37) were similar in the honey and control groups (appendix p 5).

The types of infecting organisms were similar in the two groups, although it was noted that culture-negative infections were more common in the honey group (appendix p 5). Mupirocin-resistant *S aureus* isolates were not detected in the 34 participants with infections in the antibacterial honey group, but were detected in two of 27 participants in the control group (p=0·1).

Overall, there were no significant differences in serious adverse events and deaths between the honey and control groups (table 2). However, serious adverse events diabetes,

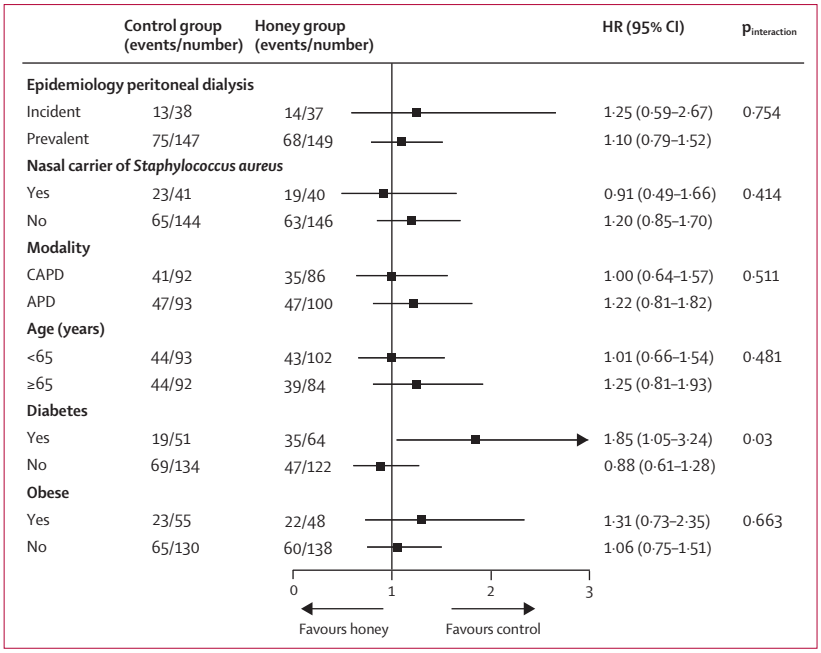

Figure 3: **Forest plot of the effect of honey on the primary efficacy endpoint by subgroups**
HR=hazard ratio. CAPD=continuous ambulatory peritoneal dialysis. APD=automated peritoneal dialysis.

	Control group (n=185)		Honey group (n=186)		p value
	Number of events	Exposure-adjusted rate (events per 100 patient-years)	Number of events	Exposure-adjusted rate (events per 100 patient-years)	
All serious adverse events	327	131·8	298	150·7	0·1
Death	18	7·3	14	7·1	0·9
Life-threatening event	5	2·0	4	2·0	0·9
Initial or prolonged hospital admission	279	112·4	265	134·0	0·04
Disability	1	0·4	1	0·5	0·9
Congenital abnormality	0	..	0	..	..
Important medical event	24	9·7	14	7·1	0·4
Serious adverse events by system					
Cardiovascular	50	20·1	27	13·7	0·1
Nervous	7	2·8	8	4·0	0·5
Diabetes, endocrine, reproductive	1	0·4	11	5·6	0·01
Gastrointestinal	31	12·5	20	10·1	0·5
Haematological	4	1·6	7	3·5	0·2
Hepatic	2	0·8	1	0·5	0·7
Musculoskeletal	14	5·6	6	3·0	0·2
Renal or dialysis complication	143	57·6	154	77·9	0·01
Respiratory	12	4·8	11	5·6	0·7
Other	29	11·7	32	16·2	0·2

Table 2: **Serious adverse events by treatment group**

See **Online** for appendix

and endocrine and reproductive systems were significantly more common in the honey group than the control group (table 2). These events included hospital admissions for parathyroidectomy (seven in the honey group *vs* zero in the control group), uterine bleeding (one *vs* zero, respectively), and hypoglycaemia (three *vs* one, respectively). 11 (6%) participants withdrew from the study in the honey group because of local reactions (appendix p 5).

Discussion

Our results show that compared with standard exit-site care with additional nasal mupirocin for nasal carriage of *S aureus*, daily exit-site application of antibacterial honey resulted in similar rates of peritoneal-dialysis-related infections in all participants, increased risks of both infection and peritonitis related to peritoneal dialysis in participants with diabetes, and higher rates of withdrawal from the study. 6% of participants in the honey group withdrew from the study because of local skin reactions. Mupirocin-resistant *S aureus* was only detected in only two participants in the control group and none in the honey group.

Panel: Research in context

Systematic review

According to the results of a 2001 meta-analysis of seven randomised controlled trials, honey was superior to antiseptics or systemic antibiotics, or both, for wound healing, maintenance of sterility, and eradication of infection.[20] The results of a more recent systematic review of the effect of honey on the rate of healing of acute and chronic wounds was inconclusive.[30] We systematically reviewed topical antimicrobial prophylaxis for prevention of infections in peritoneal dialysis. Relevant studies were identified through electronic searches of Medline through Ovid and the Cochrane Central Register of Controlled Trials using a comprehensive search strategy. Nine trials of 954 participants were included in the systematic review (appendix pp 6–8). The trials were comparisons of nasal or exit-site mupirocin use with no treatment, oral rifampicin, placebo, topical neomycin, topical gentamicin, or topical polysporin triple ointment. Antibacterial use of honey was not assessed in any of the trials. Generally, the studies included had poor methodological quality. A quantitative meta-analysis could not be done because of substantial trial heterogeneity with respect to study treatment, nasal carriage of *Staphylococcus aureus*, follow-up duration, and risk of bias. Trial results are summarised in the appendix and provide inconclusive evidence for nasal mupirocin, exit-site mupirocin, and exit-site gentamicin prophylaxis. Harms, including antimicrobial resistance, have been studied poorly. Antibacterial honey, which has antimicrobial activity against a wide range of microorganisms (including those that are multiresistant) and has not been shown to induce antimicrobial resistance, has not been assessed in participants having peritoneal dialysis.

Interpretation

Despite increased risks of infections and infectious mortality in peritoneal dialysis, current guidelines for prevention of peritoneal-dialysis-related infections are limited by the findings of a small number of randomised controlled trials showing uncertain benefits. To the best of our knowledge, the HONEYPOT study is the first trial of antibacterial honey in peritoneal dialysis and the largest trial of topical antimicrobial prophylaxis for related infections. In this study, daily topical exit-site application of antibacterial honey was not superior to targeted nasal mupirocin prophylaxis in carriers of nasal *S aureus* and resulted in a high withdrawal rate. The findings of this study do not support a role for antibacterial honey for preventing peritoneal-dialysis-associated infections.

These results differ slightly from those of an open-label randomised controlled trial of thrice-weekly exit-site application of antibacterial honey versus mupirocin in 101 participants undergoing haemodialysis through tunnelled, cuffed central venous catheters.[21] Although honey was associated with similar rates of catheter-associated bacteraemia and avoidance of mupirocin resistance compared with controls, local skin reactions were low (2%) in both the treatment and control groups and no participants discontinued study treatment.[21] The differences in honey tolerability and discontinuation rates between Johnson and colleagues' and our trials might be explained by methodological differences pertaining to catheter type (tunnelled, cuffed central venous catheter *vs* peritoneal dialysis catheter, respectively), topical antibacterial honey administration frequency (thrice weekly *vs* daily), mupirocin use in the control group (all participants *vs* nasal carriers), intervention administration (nursing staff *vs* self) and median follow-up (3 months *vs* 15 months).

The results of our study also differ from those of a previously published meta-analysis of randomised controlled trials, showing that the use of topical honey was superior to other conventional and unconventional treatments for wound healing, maintenance of sterility, or eradication of infection in superficial burns and wounds.[20] The disparity in results between this systematic review[20] and our investigation most likely relates to key differences in trial design pertaining to application site (superficial wounds or burns *vs* peritoneal dialysis exit sites [non-wounds]), population (generally normal kidney function *vs* end-stage kidney disease), control treatment (polyurethane film or amniotic membrane or potato peel or sulfadiazine silver *vs* mupirocin in nasal carriers), and outcome measures (wound healing *vs* prevention of peritoneal dialysis-related infection). So far the effect of antibacterial honey on prevention of peritoneal-dialysis-related infections has not been assessed in any randomised controlled trial (panel).

Nasal application of mupirocin was chosen in preference to daily exit-site application in the current study because it was one of the key prophylactic strategies recommended by the ISPD guidelines;[13] it was preferentially recommended for prevention of peritoneal-dialysis-related infections by CARI;[12] it was used in most of the peritoneal dialysis units in Australia at the inception of the HONEYPOT trial and therefore was standard care in the Oceania region;[31] nasal carriage of *S aureus* is the major source of touch contamination of catheters in participants undergoing peritoneal dialysis;[32] and, when considering randomised trials of mupirocin versus no mupirocin prophylaxis in participants with peritoneal dialysis, there is at least similar evidence for the eradication of nasal carriage of *S aureus* with mupirocin.[6,9,33] Further reasoning was that restriction of mupirocin exposure by targeting nasal carriage of *S aureus* would reduce the risk of mupirocin resistance.

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Nevertheless, the incidence of mupirocin-resistant *S aureus* was low in the current study. Other investigators have reported similar incidence of mupirocin-resistant *S aureus* isolates and treatment failures associated with mupirocin prophylaxis.[14] By contrast, antimicrobial resistance to honey has not been reported despite substantial accumulated experience of honey use in wound infections, thereby making it a very attractive antimicrobial prophylaxis strategy.[19]

Although there was no significant difference in the incidence of peritoneal-dialysis-related infections between antibacterial honey and standard exit-site care with additional nasal prophylaxis with mupirocin for nasal carriage of *S aureus*, it is noteworthy that honey seemed to afford inferior protection against infection and peritonitis related to peritoneal dialysis in participants with diabetes. The explanation for this treatment interaction is uncertain, and cannot be attributed to other characteristics of participants, such as obesity or nasal carriage of *S aureus*. Because these findings are from a subgroup analysis (albeit prespecified), they should be viewed as hypothesis generating only and therefore warrant further investigation. In the multivariable Cox proportional hazards regression analyses, the presence of diabetes mellitus was not associated with increased risks of primary or secondary outcomes (data not shown). Therefore, it is unlikely that the open-label study design contributed to the interaction with diabetes mellitus. It is possible that the subgroup results are due to a type 1 statistical error. The finding of more diabetes, endocrine, and reproductive system serious adverse events in the honey group is judged too unreliable for statistical interpretation. Furthermore, since these events were predominantly associated with parathyroidectomy, they were not related to the study medication.

The other noteworthy finding in this trial was the fairly high rate of withdrawals of participants from the honey group (29%), which raises concerns about the feasibility of an infection prevention strategy of daily exit-site application of honey. Non-compliance and withdrawal of consent were the predominant causes of withdrawal listed as participant choice in both groups. All withdrawals listed as investigator choice were due to either recurrent infections or concurrent illness. Since detailed data for the causes of non-compliance or withdrawal of consent were not gathered, the ability to explain the unexpected high withdrawal rate in the honey group was severely hampered. The high rate might have been related partly to specific properties of the antibacterial honey gel (eg, moistness or stickiness). Although 20% of the participants withdrew due to local skin reactions, most withdrawals were the results of the participant's or investigator's desire to discontinue honey. 23 (43%) of 54 and seven (41%) of 17 participants from the honey and control groups, respectively, had a primary outcome before withdrawal (appendix p 5). The open-label study design might have contributed to the higher withdrawal rate in the honey group.

The strengths of this study include adequate sample size, involvement of several centres, and pragmatic study design similar to clinical practice. The main limitation of this study was its open-label design, which might have introduced observer and performance biases. Study withdrawal rate was higher in the honey group (29%), resulting in shorter follow-up.

In conclusion, the results of this trial indicate that honey cannot be routinely recommended for prevention of peritoneal-dialysis-related infections. The findings might also have implications for the use of honey for the prevention of device-associated infections in general. In future studies of interventions to prevent peritoneal-dialysis-related infections, randomisation should include stratification for diabetes mellitus and consideration of a head-to-head comparison of nasal versus exit-site application of mupirocin.

Contributors

DWJ was the principal investigator; he conceived the idea for the study, participated in design and coordination, data analysis and interpretation of the results, helped to draft the manuscript, and read and approved the final manuscript. SVB participated in design and coordination, data interpretation and analysis, drafting of the manuscript, and read and approved the final manuscript. All other authors were members of the HONEYPOT Trial Management Committee; they participated in study design, data analysis and interpretation of results, read and commented on interim drafts, and approved the final manuscript. The trial collaborators were lead investigators and study coordinators at local study sites. They participated in study design at the initial investigators' meeting, oversaw local data gathering, and read and approved the final manuscript.

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Conflicts of interest

DWJ is a consultant for Baxter Healthcare and has previously received research funds from the company; he has also received speakers' honoraria and research grants from Fresenius Medical Care; he has previously been a consultant to Gambro and was the recipient of a Gambro Research Grant that partly funded the HONEYPOT trial. NI, CC, and DWJ received a Baxter Healthcare Renal Discoveries Extramural Program Grant that partly funded the HONEYPOT trial. DWJ is an International Society of Peritoneal Dialysis Councillor and is a current recipient of a Queensland Government Health Research Fellowship. AC is a consultant for and has received research funds from Baxter Healthcare, has received speakers' honoraria from Fresenius Medical Care, and is a recipient of a National Health and Medical Research Council Principal Research Fellowship. CMH has received speakers' honoraria and research grants from Fresenius Medical Care and has been a consultant to Fresenius Medical Care, and she has received research funds from Gambro and was the recipient of a Queensland Health Smart Health Research grant. The other authors declare that they have no conflicts of interest.

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