Topical Honey in the Management of Pediatric Peritoneal Dialysis Exit Sites

International guidelines in peritoneal dialysis (PD) advocate for regular application of topical mupirocin in chronic PD exit-site care. A strong evidence base links this treatment to reduced rates of exit-site infections and peritonitis. However, emerging reports of increasing mupirocin resistance and gram-negative infections are threatening the long-term viability of topical antibiotic ointments as a prophylactic treatment. Medical grade honey has multiple proven antibacterial and wound healing properties. High-quality randomized controlled trial evidence (the HONEYPOT trial), however, does not support the use of topical medical-grade honey over antibiotic ointments for the prevention of exit-site infection and peritonitis in adults. Pediatric representation in these studies is low, and these findings may not extrapolate to the pediatric context, which has a higher incidence of PD-related infection and a lower prevalence of diabetes.

We present a series of 8 pediatric patients treated with topical Medihoney (Comvita, Paengaroa, New Zealand) in the context of poor exit-site condition, persistent infection, and recurrent granuloma where the addition of honey was felt to produce remarkable improvement in exit-site status.

Medihoney is the first-line prophylactic exit-site ointment in PD exit sites at our institution and has been implicated in the salvage of peritoneal access in some patients. No exclusively pediatric studies have been performed; however, existing literature suggests a beneficial effect in promoting healing of infected wounds with a lower risk of developing antimicrobial resistance.

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Peritonitis and exit-site infections (ESIs) represent a major threat to the viability of peritoneal dialysis (PD), are a leading cause of unplanned transfer to hemodialysis, and can lead to inpatient hospitalization and altered peritoneal function. Exit-site infection is a risk factor for the development of peritonitis, and ESI prevention is therefore a vital part of peritonitis prevention (1).

International guidelines advocate for prophylactic use of topical antibacterial ointments as part of primary preventive exit-site care (2). In the era of evolving antimicrobial-resistant nosocomial organisms there has been a resurgence of interest in the use of honey for its antibiotic and wound-healing properties. Recent randomized controlled trial evidence does not support a role for antibacterial honey for preventing PD-related infections over standard of care (3). We present a case series of 8 pediatric patients with unhealthy exit sites at commencement of Medihoney (Comvita, Paengaroa, New Zealand)

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who demonstrated improvement in their exit-site appearance. We formulate the hypothesis that honey may be of benefit to exit-site care in children.

CASE DESCRIPTIONS

Case 1 (Figure 1) commenced PD on day 10 of life, complicated by multiple ESIs and episodes of peritonitis, including fungal peritonitis, resulting in 2 months of hemodialysis prior to recommencement of PD. At 1 year of age, the exit site was indurated and erythematous with exudate and granulation. Repeated exit-site swabs and peritoneal-fluid cultures were negative. Despite transient improvement with the use of antimicrobial silver dressings, it seemed likely the catheter would need another replacement. Topical, medical-grade honey (Medihoney Antibacterial Wound Gel, Comvita, Paengaroa, New Zealand) was commenced with rapid improvement in exit-site appearance. With continued use of Medihoney over the following 12 months the exit site remained healthy and the patient was clear of peritonitis. Following this case and in the context of concerning peritonitis rates in our unit (2.39 episodes per patient year in 2010) we commenced using topical Medihoney as part of standard exit-site care.

In our protocol, patients are advised to perform dressing changes after bathing using an aseptic technique. The exit site is cleaned with sterile saline solution in babies and young children or with antibacterial soap in the shower for older children. A pea-sized amount of Medihoney is applied to the exit site using a sterile cotton tip. A sterile dressing (Opsite or Primapore, Smith and Nephew, North Ryde, New South Wales, Australia) is then applied. Patients perform dressing changes every 1 to 5 days depending on age-appropriate frequency of bathing. Both patients and parents/caregivers are empirically

treated with intranasal mupirocin for 5 days of every month without methicillin-resistant *Staphylococcus aureus* (MRSA) screening. Nasal swabs are not sent for culture.

From 2012 to 2014, 34 patients (representing all our incident PD patients over this time) have used Medihoney as part of standard exit-site care. Eight patients had sub-optimal exit sites when we commenced using Medihoney in our center. There have been no adverse effects. These patients had photographs taken of their exit sites before and after treatment with Medihoney. These photos were used to retrospectively

Figure 2 — Case 2 before and after treatment with topical honey.

Figure 1 — Case 1 before and after treatment with topical honey.

Figure 3 — Case 3 before and after treatment with topical honey.

assign a score to the exit site before and after treatment using the Twardowski classification system (4). A selection of these patients is presented photographically, with consent (Case 1, described previously, and Cases 2 and 3, as follows).

Case 2 (Figure 2) commenced acute PD at 4 months of age for 2 weeks and was subsequently recommenced on PD at 8 months of age. He developed *Aspergillus* peritonitis after 9 days, necessitating immediate removal of his PD catheter. At

TABLE 1
Clinical Summary of Patients Improving with Topical Exit-Site Medihoney

Case	Age (time on PD)	Description of exit site at commencement (Twardowski Score ^a)	Follow-up period	Description of exit site at follow-up (Twardowski Score ^a)	Other treatments	Positive microbiology
1	15 months (13 months)	Erythematous, indurated, swollen mild external granulation, mild exudate (4, Figure 1)	6 months	Clean, dry exit site (0, Figure 1)	PO flucloxacillin (5 days) PO amoxicillin (5 days)	No results available
2	11 months (2 months)	Swollen, erythematous, indurated and crusting (4, Figure 2)	2 months	Clean, dry exit site; swelling resolved (0, Figure 2)	IP ceftazidime (16 days), IP vancomycin (11 days) PO vancomycin (9 days), PO metronidazole (8/7)	PD fluid <i>Enterococcus</i> (acellular) Stool: <i>Clostridium diff</i>
3	11 years (2 years)	Significant protrusion of friable granulation tissue (1, Figure 3)	1 month	Clean, dry exit site (0, Figure 3)	Nil Fortnightly silver nitrate	No microbiology performed
4	15 years (15 days)	Deep red opening with exposed, black, necrosed, tissue crusting away (2)	7 months	Clean, dry exit site; minor crust (1)	Amoxicillin and clavulanic acid chest prophylaxis	No results available
5	6 months (10 days)	Localized erythema with some epidermal breakdown and granulation (1)	1 month	Clean, dry exit site; some crust (1)	IP vancomycin (2 days) IP ceftazidime (17 days) IV ceftriaxone (5 days)	Swab: <i>Enterococcus faecalis</i> PD Fluid: WCC 7250 – <i>Klebsiella oxytoca</i> and <i>Pseudomonas putida</i> Blood culture: CONS, alpha hemolytic strep
6	14 years (10 months)	Internal and external granulation with mild erythema and serious exudate (3)	1 month	Clean, dry exit site; some crust (1)	Nil	No microbiology performed
7	6 months (2 months)	No erythema; moderate crust and exudate (2)	2 weeks	Minor erythema, crust resolved, no exudate (1)	IV vancomycin (1 dose) IP gentamicin (2 days) IP ceftazidime (3 wks) IV fluconazole (1 dose) IV ceftriaxone (3 doses) IV amphotericin (7 days) PO miconazole 2% gel	PD Fluid: Yeast, GNB, <i>Pseudomonas</i> (1,000 WCC)
8	16 months (13 months)	Severe erythema, induration, exudate and granulation (4)	3 months	Mild erythema and induration; some crust (3)	IP vancomycin, IP clindamycin Ciprofloxacin ear drops to exit site with dressing changes; PO ciprofloxacin; PO Nilstat Mupirocin ointment	Swab: <i>Enterobacter cloacae</i> PD Fluid – gram-negative cocci and mixed growth Swab: <i>S. aureus</i> and <i>Candida albicans</i>

PD = peritoneal dialysis; PO = oral; IP = intraperitoneal; IV = intravenous; CONS = coagulase-negative staphylococcus; GNB = gram-negative bacilli; WCC = white cell count.

^a Twardowski Score: 0: perfect; 1: good; 2: equivocal; 3: acute infection; 4: chronic infection.

11 months of age he recommenced PD and developed *Enterococcus* peritonitis treated with IP ceftazidime and vancomycin. He developed *Clostridium difficile* enteritis and received oral vancomycin and metronidazole. Throughout this time he had a persistently erythematous and indurated exit site. Topical Medihoney was commenced and within 2 months the exit site remained clean, dry, and aseptic.

Case 3 (Figure 3) had recurrent, severe granulation tissue at the exit site necessitating regular silver nitrate therapy. Following commencement of topical Medihoney no further granulation tissue occurred.

This exit-site protocol was instituted as part of an overhaul of our PD practices, with a focus on increased education for ward-based nurses and parents, standardizing PD techniques, and root cause analysis for all peritonitis episodes. Following this we have noted an improvement in total peritonitis rates within our unit (2.39 to 0.24 episodes per patient year) between 2010 and 2014.

DISCUSSION

We present a case series of children for whom exit-site appearance improved with the addition of topical Medihoney (Comvita, Paengaroa, New Zealand) to the exit-site care regimen.

The HONEYPOT trial concludes that “honey cannot be recommended routinely [over standard of care] for the prevention of PD-related infection” (3). The treatment group had a high drop-out rate (29%) including a high rate of local skin reaction (11%) (3). None of our patients experienced local reaction and only 2 patients (additional to those presented in Table 1) self-discontinued therapy, believing their exit site was healthy. One developed increased erythema, granulation, and culture-negative exudate, which resolved on reinstitution of topical Medihoney. The second developed an aggressive *Pseudomonas* tunnel infection. The PD catheter was removed, and the patient was transitioned to hemodialysis. Active substances in honey are able to diffuse through an established biofilm matrix, rendering *P. aeruginosa* as vulnerable to honey within a biofilm matrix as in planktonic form (5).

Another finding of the HONEYPOT trial was the higher rate of PD-related infections in patients who suffered from comorbid diabetes. Given that only 1% of the study groups were pediatric, that PD-related infections are more common in pediatrics (6), and that diabetes is rare, the conclusions of the HONEYPOT trial may not translate to a pediatric cohort. A previous case series describes improvement in chronic wounds in hematology/oncology patients with use of topical honey (7).

Case 3 demonstrates the ability of topical honey to improve exit-site appearance through mechanisms other than antibacterial activity. Honey has multiple modes of action, and thus the risk for development of bacterial resistance may be decreased. Its antimicrobial properties are mediated by its high sugar content, low pH, hydrogen peroxide, methylglyoxal, and bee defensin-1. Honey also acts to remove slough, a rich source of bacteria, has anti-inflammatory effects which

reduce wound exudate, promotes the formation of healthy granulation tissue, and optimizes both epithelialization and angiogenesis (8).

The limitations of this case series include small sample size and the retrospective, non-randomized approach without a control group. Improvement in the appearance of the exit site may have been the result of concurrent antibiotic therapy and increased education in PD handling by parents and hospital nursing staff. However, our clinicians feel a clear temporal relationship exists between commencement of Medihoney and improvement in exit-site appearances.

Despite high-quality evidence suggesting honey is not superior to standard of care for prevention of PD-related infection in adults, we feel our experience alongside existing literature in children frames the hypothesis that pediatric patients may derive some benefit from its antibiotic and wound-maintenance effects over standard of care alone.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

Thomas A. Forbes
Loren Shaw
Catherine Quinlan*

Department of Nephrology
The Royal Children's Hospital
Parkville, Victoria, Australia

*email: Catherine.Quinlan@rch.org.au

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