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Dear All,

In this issue, we are delighted to have Professor Yu's group from China discuss the problems when treating elderly PD patients, and Dr. Katavetin from Thailand, share their experiences of PD treatment failure. In addition, Professor Johnson's group from Australia summarizes their recent trial on the use of antibacterial honey for the prevention of catheter infection.

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Sincerely,
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Prevention of Peritoneal Dialysis-Related Infections – Lessons learned from HONEYPOT: a randomized trial

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Peritoneal dialysis (PD) is used to treat end-stage kidney disease in more than 200,000 patients worldwide, accounting for 11% of the global dialysis population¹. PD-related infections, such as peritonitis and exit-site infections, are major barriers to successful uptake of PD². In order to mitigate the risks of developing these infections, there is evidence supporting the use of antimicrobial prophylaxis strategies, including nasal^{3,4} and exit-site mupirocin prophylaxis⁵, and exit-site gentamicin prophylaxis⁶. However, there have been growing concerns with regards to their limited microbiologic spectrum coverage and the risk of treatment failures from resistant organisms^{7,8}.

In contrast to these antimicrobial agents, antibacterial honey possesses a number of desirable features including its relatively low cost (AUD \$9.95-

\$13.95 for 25g), safety, efficacy against a broad range of microorganisms (including multi-resistant bacteria and fungi), and a lack of risk of developing resistance with its use^{9,10}. In light of these clear theoretical advantages, an application of antibacterial honey to PD exit-sites was evaluated by our group in the HONEYPOT trial as an alternative infection control strategy¹¹.

The HONEYPOT multicenter, open-label randomized controlled trial involved 371 PD patients from Australia and New Zealand who were randomized to either daily topical exit-site application of antibacterial honey ($n=186$) or standard intranasal mupirocin prophylaxis in those who were identified as nasal *S aureus* carriers (control, $n=185$). The primary endpoint was time to first infection related to PD (exit-site infection, tunnel infection, or peritonitis). The study participants and their exit-sites were reviewed every 2 months with the minimum and maximum follow-up durations of 12 months and 24 months, respectively. The key findings observed from this trial included:

1. Comparable PD-related infection-free survival times between the honey and control groups (16 months vs. 17.7 months; unadjusted hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.83-1.51, $p=0.47$).
2. Increased risks of both the primary endpoint (HR 1.85, 95% CI 1.05-3.24, $p=0.03$) and peritonitis (HR 2.25, 95% CI 1.16-4.36, $p=0.002$) in honey group patients with diabetes mellitus (a pre-specified subgroup analysis).
3. Comparable incidences of serious adverse events (298 vs. 327, $p=0.1$) and deaths (14 vs. 18, $p=0.9$) between the honey and control groups.
4. Higher incidence of treatment withdrawal in the honey group participants (29% vs. 9%, $p<0.001$). Eleven (20%) participants in the honey group discontinued honey because of a skin reaction.
5. Mupirocin-resistant *S aureus* was detected in only two participants in the control group (7%) and none in the honey group ($p=0.1$).

The results of the HONEYPOT trial have clearly demonstrated a lack of therapeutic superiority in using a topical antibacterial honey over standard nasal mupirocin prophylaxis in preventing PD-related infections. Furthermore, the use of honey was associated with a higher incidence of treatment withdrawal, including localized skin reaction rates.

Intolerance to honey was not detected in the previous antibacterial honey trial when applied thrice-weekly at the exit-sites of tunneled, cuffed central venous catheters in patients receiving haemodialysis (local skin reaction rates 2%, no treatment withdrawal)¹². It is biologically plausible that perhaps the relatively frequent (i.e. daily) application of the honey to the exit-site, which would have involved increased manipulation and potentially resulted in microtrauma to the skin, could have counterbalanced the potential benefit from its use¹³.

Furthermore, microtrauma to the skin from frequent manipulation at the exit-site could have contributed towards the observed increased risks of PD-related infections and peritonitis in diabetic patients who received antibacterial honey. Although this result was for a pre-specified sub-group analysis, it should be interpreted with caution. For instance, this analysis included only 115 patients, and the presence of diabetes mellitus *per se* was not associated with an increased risk of infection in additional analyses. Therefore, the observed results could have been a consequence of a type I statistical error and should be considered as hypothesis generating and not definitive evidence. Lastly, although not statistically significant, it is important

to note that mupirocin resistant *S aureus* isolates were only identified in the patients in the control group and were not observed in those who received antibacterial honey.

The trial was strengthened by adequate sample size recruited from 26 PD centres, which increased the external validity of the observed outcomes. However, the study was also limited by high withdrawal rates in the honey group participants (29%) and by its open-label design, which could have introduced observer and performance biases.

In conclusion, the results from the HONEYPOT trial indicate that daily application of antibacterial honey to exit-site cannot be routinely recommended for prevention of PD-related infections.

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Treatment Failure in Peritoneal Dialysis Patients

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Technique failure is a disastrous event for those who have been on peritoneal dialysis. They have to abandon their familiar home-based peritoneal dialysis for in-center hemodialysis. The rate of technique failure has been widely used as an endpoint in studies of peritoneal dialysis outcomes, usually by treated death and transplantation as censored cases. Because death is, in a sense, also a failure of renal replacement therapy, focusing on death-censored technique failure might be misleading. A subgroup of peritoneal dialysis patients with low death-censored technique failure but high mortality rate is obviously unsatisfactory. Therefore, the combination of death and technique failure, collectively called "treatment failure", should be used as an endpoint in studies of peritoneal dialysis outcomes. We recently reported our single center experience of treatment failure in peritoneal dialysis patients over the past decade¹.

Among 121 peritoneal dialysis patients, 92 patients had treatment failure during the study period (74 deaths and 18 technique failures). The most common cause of treatment failure was infection (caused 30 deaths, 11 technique failures). Using multivariate Cox regression analysis, we found that patients with automated peritoneal dialysis (APD) had a lower risk of treatment failure than those with double-bag continuous ambulatory peritoneal dialysis (CAPD), adjusted HR 0.58 (95%CI 0.37-0.91). The relative benefit of APD was more pronounced on reducing technique failure, adjusted HR 0.30 (95%CI 0.10-0.93), while the effect on mortality did not reach statistical significance, adjusted HR 0.69 (95%CI 0.42-1.12).

Although APD has been reported to have many advantages over CAPD, such as lower peritonitis rate^{2, 3, 4} and more flexible dialysis regimens⁵, its disadvantages, such as faster loss of residual renal function^{6, 7} and peritoneal function⁸ have also been suggested. Therefore, the relative benefit of APD compared to CAPD depends on a patient's characteristics. Based on the potential advantages and disadvantages of APD mentioned above, patients who have a high risk of peritonitis and low life expectancy are likely to benefit most from APD. This might explain the better outcomes of APD in our study because infection is a major cause of treatment failure in our patients and patients in our centre are elderly with a mean age around 70 years.

On the other hand, certain subgroups of PD patients might be better off with CAPD. For example, the young educated patients with the ability to keep performing the non-contaminated PD exchange, have a relatively intact gastrointestinal tract, and are expected to have a long life expectancy would benefit from the potential advantage of CAPD on preserving residual renal function and peritoneal membrane.

Our findings that APD had a lower risk of treatment failure while having a similar (if not lower) mortality rate compared to double-bag CAPD would further support the widespread preference of APD over CAPD. It may also justify the use of APD despite its higher cost. The payers of the health care system should consider APD as a viable option in their long-term renal

replacement therapy treatment plan.

Older age, being dependent, non-hypertension and lower baseline albumin were also associated with higher risk of treatment failure in our peritoneal dialysis cohort. The associations of higher mortality rate with older age, being dependent and lower baseline albumin found in this study are somewhat straightforward. However, the association of hypertension co-morbidity with lower mortality is somewhat surprising. This finding might be comparable to the reverse epidemiology of cardiovascular risk factors in haemodialysis patients⁹. A possible explanation is that the lower blood pressure in PD patients reflects the impaired cardiac function. Furthermore, the use of antihypertensive drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers might also provide protective effects in hypertensive cases. Unfortunately, we could not investigate these hypotheses due to our limited data. Further studies are needed to be done to explore this issue.

We would like to encourage the use of treatment failure, the combination of death and technique failure, as an endpoint in studies assessing peritoneal dialysis outcomes. This endpoint would provide an overall impression of peritoneal dialysis outcome.

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Clinical Outcome in Elderly Patients on Continuous Ambulatory Peritoneal Dialysis in Southern China

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The proportion of elderly people is rising and the demand for renal replacement therapy (RRT) in those suffering from end-stage renal disease (ESRD) is increasing worldwide as a result of increasing longevity and changes in the demographics of renal disease¹. Most studies have shown the superiority of PD over HD for elderly ESRD patients. The problems occurred during HD (hypo- or hypertension, arrhythmia, angina pectoris, and variations in volume) can, especially in the elderly, lead to a marked deterioration in clinical condition that can be prevented by prescribing PD for elderly ESRD patients². When medical teams face the choice of dialysis therapy in elderly patients, PD is frequently considered because PD better preserves residual renal function, avoids large volume and electrolyte shifts, provides better cardiovascular stability, and avoids the need for vascular access³. However, findings concerning outcome in elderly patients on continuous ambulatory peritoneal dialysis (CAPD) are still discordant. We therefore retrospectively analyzed a cohort of elderly PD patients to address the questions of outcome in elderly patients undergoing CAPD and the clinical risk factors associated with their survival.

This retrospective cohort study included all incident CAPD patients treated at the PD center of The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China from 2006 to 2009. Of 805 patients on CAPD, the elderly group (>65years; mean: 71.3 ± 4.3 years) consisted of 148 patients, and the younger group (<65years; mean: 43.1 ± 12.2 years) consisted of 657 patients. Compared with the younger group, the elderly group had a higher prevalence of cardiovascular disease (CVD) (53.4% vs 26.0%, $p = 0.000$) and diabetes (49.3% vs 17.7%, $p = 0.000$) at PD start. Score on the Charlson comorbidity index was significantly higher in elderly patients than in younger patients ($p = 0.000$). The laboratory data showed significant differences in serum albumin ($p = 0.000$), serum prealbumin ($p = 0.000$), phosphate ($p = 0.017$), creatinine ($p = 0.000$), blood urea nitrogen ($p = 0.006$), intact parathyroid hormone ($p = 0.001$), and uric acid ($p = 0.000$), being significantly lower in the elderly patients. Values for C-reactive protein ($p = 0.000$), peritoneal Kt/V ($p = 0.006$), and estimated glomerular filtration rate ($p = 0.005$) were significantly higher in the elderly patients. Total urine output in 24 hours at the start of dialysis was significantly higher in younger patients ($p = 0.000$). The 1-, 2-, 3-, and 5-year patient survival rates were 97%, 92%, 88%, 73% for the younger group and 79%, 67%, 56%, 30% for elderly group. The patient survival rates were significantly lower for the elderly group than for the younger group ($p = 0.000$). Mortality in the elderly patients was associated with advanced age [relative risk (RR): 1.088; 95% confidence interval (CI): 1.027 to 1.153; $p = 0.004$], diabetes (RR: 2.064; 95% CI: 1.236 to 3.445; $p = 0.006$), and lower serum albumin (RR: 0.940; 95% CI: 0.897 to 0.985; $p = 0.010$). Our study demonstrated that most deaths in elderly patients were a result of comorbid conditions, either CVD (50.7%) or infection (25.4%). The higher rate of infections in elderly patients might be a result of a high prevalence of diabetes and poor nutrition status^{4,5}.

However, our study found no significant difference in technique survival between the younger and elderly patient groups. In the elderly CAPD patients, mean death-censored 1-, 2-, 3-, and 5-year technique survival rates were 97%, 96%, 91%, and 78%. For younger patients, the rates were 98%, 94%, 92%, and 87% respectively. It is well documented that older patients are vulnerable to the problems associated with aging, which may affect their level of independence and their long-term prognosis. Assistance from a family member or a caregiver may overcome this problem. In our study, the elderly group of patients had a significantly higher rate of assistance (47.7% vs 8.4% for younger patients, $p = 0.000$). Help or assistance with CAPD for elderly patients may contribute to the better technique survival in our group of elderly patients who were treated with PD at home^{6,7}.

Taken together, it was concluded that elderly ESRD patients undergoing CAPD have a death-censored technique survival comparable to that in a group of younger patients. As expected, the survival of the elderly patients was significantly shorter than that of the younger patients on CAPD. In elderly patients, advanced age, diabetes, and low serum albumin were strongly associated with patient survival. Our results indicate that chronic PD is a viable dialysis option for elderly patients with ESRD. Better management of hypoalbuminemia and comorbid conditions might improve survival in elderly PD patients.

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Madrid, Spain

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Important dates:

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Early bird registration deadline: June 14, 2014

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