FROM THE EDITORS

Confounding and Bias in Epidemiological Research: “Dirty Hands but a Clean Mind”

In this issue of *Peritoneal Dialysis International*, Pozdzik *et al.* describe a case of encapsulating peritoneal sclerosis (EPS) that occurred post-transplantation and speculate on whether a switch of immunosuppressive therapy from everolimus to tacrolimus had a role in unmasking the condition. An interesting observation, but difficult to substantiate, particularly as the patient had several other risk factors for EPS. Exploring the epidemiology of EPS is fearfully complicated, and, as a result, we are still not in a position to be able to recommend a robust risk-avoidance strategy. In their invited commentary, Nitsch and Davenport discuss some of the problems faced by those attempting to study this challenging condition, including case ascertainment and the identification of populations at risk. They conclude that the best study design required to minimize the risk of bias comprises adequately powered cohort studies that include prospective biomarker measurement. Despite best efforts, it is important to recognize that bias cannot be completely eliminated from epidemiological studies, and although adjustments are commonly made for measured variables, unmeasured influences present a problem. The quotation in the title has been described as “the epidemiologist’s motto” (1).

We include 3 metabolic studies led by Jie Dong from Peking University. The first is a 6-month randomized, unblinded, controlled trial of keto-acid supplementation in peritoneal dialysis (PD) (Dong, Li, Xu, Ikizler, and Wang) evaluating the impact on an indicator of insulin resistance (HOMA-IR). Although the primary outcome measure was not met, there were differences in secondary outcome measures—high sensitivity C-reactive protein (CRP) and the leptin/adiponectin ratio—between the groups by the end of the study. The potential effects of vitamin D on the immune system have stimulated considerable interest over the last decade or so, with associative studies linking deficiency to poorer patient outcomes. This provided the rationale for a study (Dong, Pi, *et al.*) that evaluated the impact of baseline 25 (OH) vitamin D levels on the subsequent development of peritonitis in 326 PD patients, divided according to tertile of vitamin D concentration. After adjustment for confounders including age, gender, dialysis duration, diabetes, albumin, residual renal function, and history of peritonitis, baseline 25 (OH) vitamin D level was an independent predictor for the subsequent occurrence of peritonitis with each increase of 1 nmol in the concentration being associated with a 6% reduction in risk. Our reviewer was keen to explore the question of whether patients with lower vitamin D levels

were just sicker, and, to address this, Charlson and Karnofsky indices were included in the statistical model. It is important to note that the mean vitamin D level in this study was low at 16 nmol/L. The use of active vitamin D supplementation was not associated with a lower risk of peritonitis.

The third study (Dong, Li, Xu, *et al.*) compared several different mechanisms to calculate lean body mass (LBM) using a validation cohort to test precision and accuracy. The methods investigated included dual energy X-ray absorptiometry (DEXA), anthropometry, handgrip strength, and creatinine kinetics. Each of these techniques is subject to a different range of confounders—e.g. methods that rely on anthropometry may overestimate LBM in obese patients or those with fluid retention. The newly developed equations that used anthropometrics and handgrip strength compared well with DEXA—importantly avoiding the requirement to use ionizing radiation.

Two papers report initiatives from Australia to tackle peritoneal infection. Readers will be aware that the HONEYPOT study reported in 2014 that daily antibacterial honey as part of exit-site care was not superior for the prevention of overall PD infections to standard exit-site care plus the intranasal application of mupirocin in *Staphylococcus aureus* carriers (2). Secondary outcome measures reported in this issue of *PDI* include organism-specific peritonitis rates and infection-related hospitalization—reporting no difference between the groups (Zhang *et al.*). Mean peritonitis rates were 0.41 episodes per year in both intervention and control groups, which is much lower than that reported at the start of a quality improvement initiative from Western Australia between 2008 and 2013 (Chakera *et al.*). This involved using a state-wide protocol for the management of PD-related peritonitis based on weight-adjusted doses of vancomycin and gentamicin as first-line therapy. Notably, peritonitis rates were 0.75 per year at the start of that period, falling to 0.41 by the end. Importantly, resistance rates to both antibiotics remained constant during the course of the study. This study provides some evidence that consistent application of evidence-based guidelines has the potential to reduce unwarranted variation, leading to improvements in clinical care.

We have updated the instructions for authors for *PDI*—and I acknowledge support in this from Laura Hope at Multimed, Professor Olivier Devuyst, and Dr. Ags Odudu. To improve the reporting of clinical studies, we have recommended that authors follow the CONSORT (3) and STROBE (4) statements for clinical trials and observational epidemiological studies. To enhance our governance processes, we will be routinely applying plagiarism software to new articles from 2016 onward.

Peritoneal Dialysis International is indeed indebted to our dedicated reviewers, who take time from their busy clinical

schedules to critically appraise and contribute to the quality of the work that we publish. Sometimes reviewers can feel undervalued and anonymous in their work—but I should like to emphasize that their critical appraisal underpins the confidence that we have in the quality of work presented to the PD community through this journal. In the last year, our most frequent reviewers were Peter Blake, John Crabtree, Andrew Davenport, Helen Hurst, Raymond Krediet, Mark Lambie, Matthew Oliver, Beth Piraino, Jeff Perl, Badri Shrestha, and Graham Woodrow. A full list of reviewers is included in the online supplemental material.

Martin Wilkie
Editor-in-Chief

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