ISPD Asia-Pacific Chapter Newsletter, December 2020

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Chapter News

New deputy editors of the Newsletter

From this issue, Dr. Chia-Te Liao from Taipei Medical University and Professor Talerngsak Kanjanabuch from the Chulalongkorn University will join as deputy editors of The Asia Pacific Chapter newsletter. We believe they can bring new ideas to the newsletter and facilitate the communication and information dissemination in the Asia Pacific Chapter.

Core Group and Executive Committee meeting

The Asia Pacific Chapter had a Core Group and Executive Committee meeting via Zoom on 12 November 2020 (Thursday). Items discussed in the meeting include:

- Cancellation ISPD APC 2021 meeting
- Bids for ISPD-APC 2023 meeting
- ISPD APC newsletter: new deputy editors and updates
- Revised criteria for the ISPD Asia Pacific Chapter scholarship
- Financial report of previous APC-ISPD meetings
- Composition and terms of reference of the core group and executives

Meeting and conference

In view of the COVID-19 pandemic, the 10th Asia Pacific Chapter Meeting of the International Society of Peritoneal Dialysis (APCM-ISPD 2021), originally planned to be hosted by the Indonesian Society of Nephrology on 21 to 23 October 2021, is cancelled.

The ISPD Asia Pacific Chapter has announced the call for bidding for hosting the 11th Asia Pacific Chapter Meeting of the International Society of Peritoneal Dialysis, which is expected in 2023. The Peritoneal Dialysis society of India has expressed interest and submitted the bid documents. Their application will be further considered.

Scholarship

There was one application for the ISPD Asia Pacific Chapter scholarship in the most recent round. In essence Dr. Varun Gosain from India applied to receive training at the Princess Alexandra Hospital,

Queensland, Australia for 3 months, and the application has been approved by the Asia Pacific Chapter core group. We have also take this opportunity and further refined the criteria for the ISPD Asia-Pacific Chapter Scholarship.

Prepared by: CC Szeto, Coordinator, ISPD Asia Pacific Chapter

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News from the ISPD

Join the ISPD !

Visit https://ispd.org/memberships/ to join the ISPD or renew your membership.

Membership benefits of the International Society for Peritoneal Dialysis include:

- print and/or online subscription to Peritoneal Dialysis International
- Receipt of PD News
- Online access to ISPD Guidelines
- Special registration fees at ISPD Chapter Meetings and the Annual Dialysis Conference
- Application for ISPD Scholarships and Grants

Membership for developing countries can be done at advantageous rates, by grouping members by institution or region geographical area. Write to admin@ispd.org for more information.

Asia-Pacific Chapter Scholarship

This is a scholarship to support up to 3 months training in clinical PD for doctors and nurses from Asia-Pacific region. Deadline for application for each round: twice a year at 30 June or 31 December. **The next deadline is 31 December 2020.** Details and application procedures can be found under the Regional Chapters – Asia-Pacific Chapter, at the ISPD website.

Upcoming Meetings

ISPD / EuroPD Joint Congress (fully virtual)

28 February – 2 March 2021
Scottish Event Campus (SEC), Glasgow, Scotland
Abstract Submission Deadline: 6 January 2021
Online Registration Deadline: 26 February 2021
Website: http://ispd-europd2020.com/

ISN World Congress of Nephrology (fully virtual)

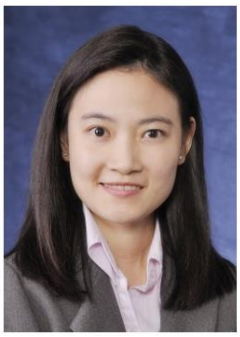
15-18 April 2021
Montreal, Canada
Eary bird registration deadline: 17 February 2021
Website: https://www.theisn.org/wcn21

19th Asian Pacific Congress of Nephrology
18-22 August 2021
Pattaya, Thailand

ISPD Congress 2022
14-17 May 2020
Suntec, Singapore
Website: https://ispd2022.com/

Guideline Update

International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis

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Since peritoneal dialysis (PD) treatment was first introduced two centuries ago by George Ganter, significant progress in PD technologies and effectively delivering this home-based therapy have evolved considerably. In the special issue of *Peritoneal Dialysis International* released in May 2020, the International Society for Peritoneal Dialysis (ISPD) has published the new practice recommendations: "Prescribing high-quality, goal-directed PD guidelines."[1] Stemming from discussions in the KDIGO Controversies Conference on Dialysis Initiation, Modality Choices, and Prescription in 2018 [2], and survey results from the Standardized Outcomes in Nephrology-PD (SONG-PD) initiative [3], the ISPD committee had invited a group of nephrologists to review relevant and update literature to develop new guidelines specifically addressing core outcomes in patients on PD based on the shared priorities of all stakeholders. Supporting evidence has been graded using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system. Any statements graded as 2C or 2D were labeled as practice points. A paradigm shift from disease-centered to person-centered care is clearly emphasized in the current set of guidelines. Consequently, all critical recommendations in these ISPD 2020 guidelines aim to deliver high-quality PD treatment that enables the patients to achieve their real-life goals on the one hand, but on the other hand, it also considers the burden created by unnecessary prescriptions. Herein, we summarize the main critical points drawn from each publication in this series as follows.

Key recommendation 1

"PD should be prescribed using shared decision-making between the person doing PD and the care team."

Instead of focusing on meeting a specific numerical number on small solute clearances, “high-quality, goal-direct” PD prescription should enable the patients to maintain quality of life and minimize symptoms, and any inherent burden from treatment, while continuing high-quality care. Patients should be educated and informed about their disease, prognosis, and options. Healthcare professions should encourage patients and caregivers to define their life or treatment goals through the shared-decision process.

Key recommendation 2

“The PD prescription should take into account the local country resources, the wishes and lifestyle considerations of people needing treatment, including those of their families/caregivers', especially if assisting in their care.”

PD Outcomes and Practice Patterns Study (PDOPPS)[4] demonstrated wide variations in patient characteristics, PD modality use, and prescription patterns among participants in the study. Significant differences in practice patterns might reflect variations in patient factors, physician’s preferences, cultural beliefs, and reimbursement policies. Healthcare providers should embrace patients’ and caregivers’ perspectives before prescribing or adjusting PD prescription.

Key recommendation 3

“Several assessments should be used to help ensure the delivery of high-quality care by focusing on Patient-reported outcomes, Fluid status, Nutritional status, and Removal of toxins."

Patient-reported outcomes: PD infection, mortality, and life participation were the three top-ranked outcomes reported by patients, caregivers, and healthcare professionals in the SONG-PD study [3]. This list might not apply to every single PD patient. As a result, the healthcare team should identify core outcomes on each PD patient and use the patient-reported care experience as another crucial measure of how the patient-centered care concept is incorporated within the PD center. However, applying a patient-centered care approach in PD clinics with a shortage of PD nurses and physicians is challenging in real-world practice.

Fluid status: Achieving and maintaining clinical euvolemia remains the ultimate goal of volume management in PD patients. Clinical examination and blood pressure (BP) measurement are still the most common use to assess volume status. Attempts to find more objective tools for guiding volume management in PD patients, such as bioimpedance or serum biomarkers, are preferred more day by day but are still a need for further investigation. In the meantime, fluid restriction, a low salt diet, and diuretics should be encouraged to all patients. If these therapies are far from enough, such as UF failure type I or during peritonitis episode, icodextrin might have its role. Icodextrin has been proven to effectively manage hypervolemia and prolonged technique survival for an average of 11 months in the Australian study [5]. BP in PD patients may reflect volume status, cardiac function, nutritional condition, and comorbidities. Currently, no specific BP target in the PD population can be recommended. However, too high or too low systolic BP is associated with increased mortality.

Nutritional status: Maintaining normal nutritional status is a crucial dimension in delivering high-quality PD. Hypoalbuminemia and protein-energy wasting are not uncommon among PD patients and are associated with adverse outcomes. Potassium, bicarbonate, albumin, and phosphate should be included as part of nutritional assessment. Early dietary counseling at PD commencement should be considered on time.

Removal of toxins: Well-being in patients on dialysis depends on several factors, not only just achieving a specific quantity of small solute clearance. Admittedly, many physicians misinterpret the 2005 ISPD guideline on targets for solute and fluid removal recommendation and fixate with a notion of achieving Kt/Vurea > 1.7 at all times, regardless of residual kidney function (RKD). The 2020 guideline clearly

emphasizes that no specific small solute clearance target can guarantee adequate dialysis. RKF has been shown repeatedly to be associated with mortality in patients on PD [6,7]. On the contrary, peritoneal clearance has not. Based on high-quality studies, there is no mortality benefit observed from increasing total Kt/V above 1.7-1.8 [8,9]. The lower limit of Kt/V is still under debate. Unfortunately, there is no randomized controlled trial designed to answer this question yet. In anuric patients, however, maintaining a weekly Kt/V of at least 1.7 is recommended because, in cohort studies, Kt/V below 1.7 was associated with increased morbidity and mortality in anuric patients.

Though the impact of middle molecules removal on clinical outcomes in PD patients are still lacking, a trial of increasing PD intensity may be considered in patients who still experience from uremic symptoms, despite a Kt/Vurea > 1.7. Other non-dialysis factors contributing to unwell and failure to thrive should also be sought out and corrected.

Key recommendation 4

"The amount of kidney function that continues to remove waste products and the remaining urine volume should be known for all individuals doing PD. Management should focus on preserving this as long as possible."

The importance of RKF preservation to PD patients is well recognized, and therefore should be maintained. Residual urine volume assists in BP control and managing hydration status. Additionally, kidneys remove uremic, protein-bound toxins, and other inflammatory by-products excretion via glomerular filtration and through tubular excretion, which is not replaced by nowadays dialysis. Neutral pH, low glucose-degradation-product (GDP) solution demonstrated favorable outcomes on kidney function and urine volume preservations, but its uses may be limited in some countries due to financial constraints. Other adjunctive measures including but not limited to renin-angiotensin-aldosterone system (RAAS) blockade, diuretics, keeping euvolemic, and avoiding nephrotoxic medications should be applied in all PD patients who still have significant RKF.

Key recommendation 5

"For some people who require dialysis and who are old, frail, or have a poor prognosis, there may be a quality of life benefit from a reduced dialysis prescription to minimize the burden of treatment."

PD is a reasonable dialysis modality for patients who are frail and/or have multiple comorbidities. Quality of life is often their top priority in such individuals and even more important than small solute clearance or other biochemical parameters. PD prescriptions in that scenario should help the patient and family member attain their life goal while minimizing the burden from dialysis treatment as much as possible. Incremental and Decremental PD would be an exciting strategy and should be considered.

Key recommendation 6

"In low and lower-middle-income countries, every effort should be made to conform to the framework of these statements, taking into account resource limitations."

Prescribing good quality PD with a limited healthcare resource or financial constraint has been a challenge in low and low-middle income countries. Automated peritoneal dialysis, icodextrin, neutral pH low GDP solutions are relatively expensive, and some families/countries cannot afford those options. Incremental PD is a good option that is proved to use less PD solution than standard full-dose PD prescription and gave comparable results to those with a full-dose PD prescription. Applying low-cost adjunctive management strategies such as diet control, lifestyle modification, preservation of residual kidney function via RAAS blockade use are inexpensive and should be implemented to PD patients in all socioeconomic statuses.

Monitoring clinical well-being or obtaining only a few inexpensive biochemical parameters may be sufficient to assess treatment quality and adequacy in a resource-limited setting.

Key recommendation 7

"The principles of prescribing and assessing the delivery of high-quality PD to children are the same as for adults. In all cases, the PD prescription should be designed to meet the medical, mental health, social, and financial needs of the individual child and family."

In summary, the 2020 ISPD guidelines have nicely addressed evidence-based key recommendations and guided how to prescribe "high-quality, goal-directed" treatment to PD patients. The concept of individualized care and shared-decision making have been emphasized throughout the entire series. As we are all aware, PD treatment requires the patient's commitment and participation. Therefore, patients' wishes, lifestyles, and life goals should be considered when prescribing the treatment. Some recommendations may have to be adjusted in resource-limited countries, so it conforms to their local practice and limitation.

References

1. Brown EA, Blake PG, Boudville N, Davies S, de Arteaga J, Dong J, et al. International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis. Perit Dial Int. 2020;40(3):244-53.
2. Chan CT, Blankestijn PJ, Dember LM, Gallieni M, Harris DCH, Lok CE, et al. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;96(1):37-47.
3. Manera KE, Johnson DW, Craig JC, Shen JI, Gutman T, Cho Y, et al. Establishing a Core Outcome Set for Peritoneal Dialysis: Report of the SONG-PD (Standardized Outcomes in Nephrology–Peritoneal Dialysis) Consensus Workshop. Am J Kidney Dis. 2020;75(3):404-12.
4. Wang AY-M, Zhao J, Bieber B, Kanjanabuch T, Wilkie M, Marshall MR, et al. International comparison of peritoneal dialysis prescriptions from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). Perit Dial Int. 2020:0896860819895356.
5. Johnson DW, Arndt M, O'Shea A, Watt R, Hamilton J, Vincent K. Icodextrin as salvage therapy in peritoneal dialysis patients with refractory fluid overload. BMC Nephrol. 2001;2:2.
6. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001;12(10):2158-62.
7. Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang SH, Zhu X, Lazarus JM. Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. Am J Kidney Dis. 1999;33(3):523-34.
8. Lo W-K, Ho Y-W, Li C-S, Wong K-S, Chan T-M, Yu AW-Y, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int. 2003;64(2):649-56.
9. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13(5):1307-20.

Innovation and Technology in PD

Urease-fixed silk fibroin-based filtering membrane with spherical carbonaceous adsorbent: a technological innovation for regeneration of peritoneal dialysate

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Peritoneal dialysis (PD) as a home-based kidney replacement therapy (KRT) has been constrained by its daily usage of large volumes of dialysate, causing inconvenience (time-consuming exchanges), discomfort (increased intra-abdominal pressure), and eco-unfriendly (waste fluids generated). Hence, the idea of a wearable artificial kidney (WAK) with integration of innovative "recirculating PD fluid system" is considerably attractive [1]. The Vincenza Wearable Artificial Kidney for PD (ViWAK PD) proposed by Ronco in 2007 is a good example of the miniatured dialysis devices for PD [2]. Despite its practical design and dialysis efficacy shown by *in vitro* studies, it remains several obstacles to overcome before the WAK can be routinely used in the real-world practice.

Within the WAK, **the filtering membrane** and **the sorbent system** are two key elements, together playing a crucial role in efficiently removing uremic toxins and regenerating the "clean dialysates" for recirculation. Recently, a group led by Dr. C.H. Park from South Korea, has developed a novel silk fibroin-based PD filtering membrane [3]. Silk fibroin, FDA-approved nature bioproduct, so far has been extensively applied into the development of biomedicine devices, i.e., serving as biomaterials for drug delivery (hydrogel), tissue engineering and regeneration. In their first paper, Park and colleagues have demonstrated that silk fibroin has a superior water-binding ability (more hydrophilic) and biocompatibility (based on *in vitro* cytotoxicity assay), compared to the conventional polyvinylidene fluoride (PVDF) membrane. Another key feature of this new membrane is immobilisation of the urease on to the silk fibroin scaffold. Urea is widely acknowledged as one of the major uremic toxins, which is difficult to be removed by activated carbon granule, ion-exchanging media, or reverse osmosis system. It is therefore utilizing the immobilized urease to catalyse the hydrolysis of urea to ammonia and carbon dioxide. Ammonia was then absorbed by the zirconium phosphate sorbent. Overall, they proved that the urease-immobilized silk fibroin filtering membrane could efficiently remove urea (90% removal after 24-hour filtration) and successfully regenerate peritoneal dialysate.

In a subsequent study, the group then incorporated the silk fibroin membrane with polymer-based spherical carbonaceous adsorbent (PSCA) into the WAK system [4]. PSCA is generated by means of carbonization process followed by and activation step of a polymeric precursor, resulting in a well-defined, adjustable pore size distribution system. To investigate the dialysis clearance efficacy, Park and colleagues first immersed the PSCA (or activated carbon/AC, acetic acid-activated carbon/AAC) into the peritoneal dialysate from the ESRD patients under PD, then continue stirring for achieving time-dependent absorption. The results showed that PSCA has a superior efficiency in removing uremic toxins including

urea, creatinine, uric acid, phosphorous and β2-microglobulin, compared to AC or AAC. They further filtered the peritoneal dialysate derived from PD patients, which again demonstrated its excellent efficacy on clearance of uremic toxins. Finally, they performed actual PD therapy on the rats receiving 5/6 nephrectomy (uremic model) through the inserted PD catheter connecting to the new WAK. The data showed that the new WAK system exhibited a superior performance in removing uremic toxins: > 90% removal of urea, creatinine, and uric acid after 6 hours of WAK treatment; >50% removal of phosphorous and β2-microglobulin after 24 hours, respectively), in general, more effective than conventional dialysis exchange group (every 6 hours, four exchanges a day).

Given the success with *in vitro* and *in vivo* testing, the next thing would be interesting to know how this new filter membrane/sorbent system work on PD patients in the future. Issues such as patient safety, dialysis adequacy and more importantly, patient outcomes, should be rigorously examined. From the viewpoint of basic and translational science, one would be very keen to understand to what extent this dialysate regeneration system would alter the cellular activity (mainly peritoneal resident immune cells and mesothelial cells) and the biomolecular constituents within the PD fluids, which potentially influence the host peritoneal defence system against diverse pathogens as well as peritoneal membrane longevity.

Reference

1. Roberts M and Lee DBN. A proposed peritoneal-based wearable artificial kidney. *Home Hemodialysis International* 1999; 3:65-67
2. Ronco C and Fecondini L. The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD). *Blood Purification* 2007; 25:383–388
3. Moon BM, Choi MJ, Sultan MT, et al. Novel fabrication method of the peritoneal dialysis filter using silk fibroin with urease fixation system. *J Biomed Mater Res Part B* 2017:105B:2136–2144
4. Sultan MT, Moon BM, Yang JW, et al. Recirculating peritoneal dialysis system using urease-fixed silk fibroin membrane filter with spherical carbonaceous adsorbent. *Materials Science & Engineering C* 2019; 97:55–66

Research News from Asia-Pacific Region

Peritoneal Dialysis: A Treatment for Patients with Heart Failure

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Background – Why Peritoneal Dialysis for Heart Failure?

Heart failure (HF) is a major cause of morbidity and mortality which places a heavy burden on patients, their loves ones and the healthcare system. Diuretics are the primary treatment but a significant

proportion of patients develop diuretic resistance(1). For such patients, extracorporeal therapies such as ultrafiltration may be useful.

Clinical studies comparing ultrafiltration against diuretics gave conflicting results. In the UNLOAD trial(2), patients on ultrafiltration had more fluid loss and less hospitalisations than those on diuretics, but the diuretic regimen was suboptimal. Other studies found less hospitalisations with ultrafiltration(3). However, when an enhanced diuretic regimen was pitted against ultrafiltration in the CARESS HF study(4), no differences in weight loss but instead a higher serum creatinine was seen with ultrafiltration.

Peritoneal dialysis (PD) can provide fluid removal similar to ultrafiltration and at the same time, potentially mitigate the ill effects of poor renal function as observed in the CARESS HF study. To review the clinical outcomes of PD in patients with diuretic-resistant heart failure, we conducted a systematic review of studies from 1966-2017 utilising PD in heart failure. Studies on patients with end-stage kidney disease were excluded. From an initial 3195 citations, 31 articles (902 patients) were identified for inclusion in the review.(5)

Symptom Relief After PD in Heart Failure is Evident

Three studies had mortality data on patients assigned to PD or extracorporeal interventions (haemodialysis or ultrafiltration). Pooled patient survival was 42.1% for PD and 45.0% for extracorporeal therapy and this was not statistically different (OR 0.80, 95% CI 0.24 2.69; P=0.71) (Figure 1).

Fifteen studies with 361 patients reported the New York Heart Association (NYHA) Functional Classification before and after PD was initiated. All but one study reported symptomatic improvement in patients after PD was instituted. Between 40% to 100% of patients saw an improvement in NYHA status by ≥1. Eight studies reported that 40% to 90% of patients improved by 2 or more NYHA classes.

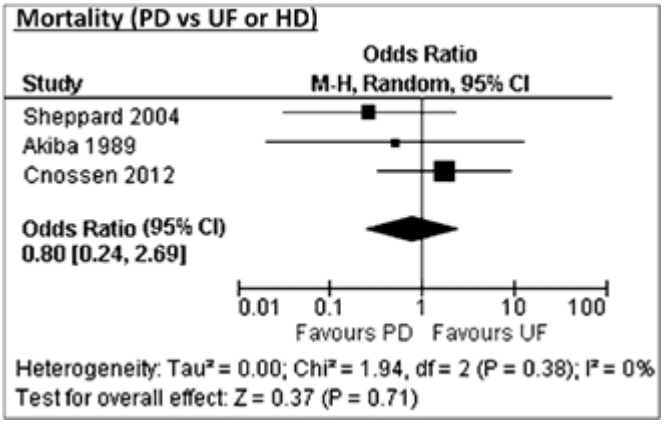

Figure 1. Pooled analysis of mortality outcomes when patients with heart failure were treated with peritoneal dialysis (PD) vs ultrafiltration (UF) or haemodialysis (HD).

Another interesting observation was the general improvement in left ventricular ejection fraction (LVEF) after PD was instituted (P<0.001), as shown in Figure 2. Seven studies saw an increase in LVEF by >10% from baseline.

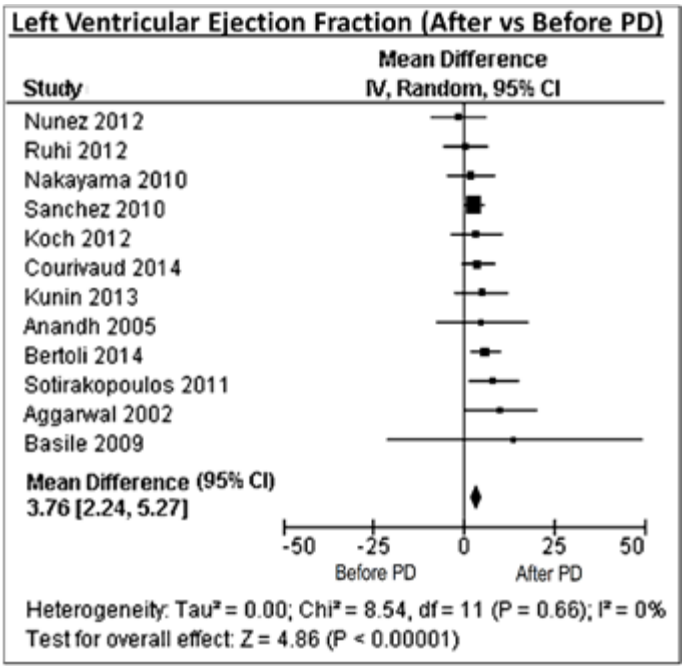

Figure 2. Pooled analysis of left ventricular ejection fraction before and after patients with heart failure were treated with peritoneal dialysis (PD).

All studies reported a favourable reduction in the frequency of hospitalisation or length of stay after PD was introduced. For reduction in length of stay in hospitals, the pooled estimate demonstrated a clear benefit of using PD over diuretic therapy in heart failure for the reduction of length of stay over diuretics only (OR -26.9, 95% CI -36.9 to -16.83; P<0.001) (Figure 3).

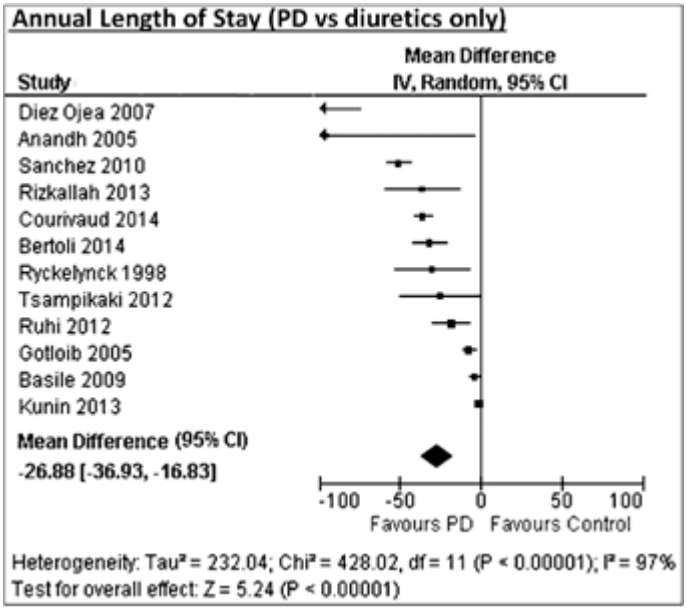

Figure 3. Pooled analysis of length of stay (per year) for patients with heart failure who were treated with peritoneal dialysis (PD) vs diuretics only.

Symptom relief may be a more important therapeutic goal for a patient suffering from severe heart failure and studies do find significant symptom relief following initiation of PD. Quality of life may improve with less hospitalisations, although any negative impact from PD treatments itself is not known.

When compared to extracorporeal therapy, there was no significant difference in the mortality rates. However, PD may be easier to institute in terms of dialysis access and complexity of care.

What were the complications experienced?

Similar to reported experience when PD is used for AKI(6), the commonest reported complication of PD therapy was peritonitis. One outlier had a the highest peritonitis rate of 0.46 episodes per patient year(7) but other studies reported rates ranging from 0.02 to 0.27 episodes per patient year(8, 9). When compared to international standards for chronic PD, these peritonitis rates appear to be acceptable.

How was PD prescribed for Heart Failure?

The technique of PD in heart failure was variable. It appears that the most common technique employed was intermittent PD with 1-4 manual exchanges in each session. Most utilised dextrose-based solutions and/or icodextrin. Ultrafiltrative volume ranged from 0.5-3L per day.

The dose of PD was not well described but the focus of the studies was on achieving adequate ultrafiltration rather than solute clearance.

The need for more research

The quality of most studies was poor. All were observational studies and there were no randomised controlled trials (RCT). It would be good to see a future study similar to the CARESS HF study(4), pitting PD against an enhanced diuretic regimen. Quality of life measures should be included to determine if PD itself has an impact on the general well-being of the patients.

Conclusions

The option of a home-based therapy with family/community support may be an attractive option for patients especially if it results in lower readmission rates and duration of hospitalisation. PD can be performed intermittently based on weight gain or symptoms, empowering the patient to provide self-care. There is inadequate evidence comparing PD to extracorporeal therapy but limited data suggests similar mortality rates for either forms of therapy.

As compared to other forms of therapy, implementation of a PD programme for heart failure is very simple. Many institutions would already have an established PD programme for patients with kidney failure, supported by counsellors, nurses and allied health professionals. Techniques of PD prescription are also well described.(10) Extending the PD programme to patients with heart failure would entail simple changes to prescribing protocols and treatment aims without any major investment required in new machines which may be unfamiliar.

References

1. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P*, et al.* The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21:137-155.
2. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR*, et al.* Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007; 49:675-83.
3. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V*, et al.* Continuous ultrafiltration for congestive heart failure: the CUORE trial. J Card Fail. 2014; 20:378.e1-9.
4. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA*, et al.* Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012; 367:2296-304.
5. Chionh CY, Clementi A, Poh CB, Finkelstein FO, Cruz DN. The use of peritoneal dialysis in heart failure: A systematic review. Perit Dial Int. 2020:896860819895198.

6. Chionh CY, Soni SS, Finkelstein FO, Ronco C, Cruz DN. Use of peritoneal dialysis in AKI: a systematic review. Clin J Am Soc Nephrol. 2013; 8:1649-60.
7. Courivaud C, Kazory A, Crepin T, Azar R, Bresson-Vautrin C, Chalopin JM, *et al.* Peritoneal dialysis reduces the number of hospitalization days in heart failure patients refractory to diuretics. Perit Dial Int. 2014; 34:100-8.
8. Sanchez JE, Ortega T, Rodriguez C, Diaz-Molina B, Martin M, Garcia-Cueto C, *et al.* Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure. Nephrol Dial Transplant. 2010; 25:605-10.
9. Bertoli SV, Musetti C, Ciurlino D, Basile C, Galli E, Gambaro G, *et al.* Peritoneal ultrafiltration in refractory heart failure: a cohort study. Perit Dial Int. 2014; 34:64-70.
10. Chionh CY, Soni S, Cruz DN, Ronco C. Peritoneal dialysis for acute kidney injury: techniques and dose. Contrib Nephrol. 2009; 163:278-284.

Peritoneal dialysis for COVID-19-associated acute kidney injury

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Coronavirus disease 2019 (COVID-19) has remained a major threat to public health since the World Health Organization reported the global health crisis in March 2020. This virus has put lives in danger and affected social and economic activities worldwide. Unfortunately, many experts anticipate that this crisis will not end soon. Thus, we need to look for ways to coexist with COVID-19 and to prepare continuously for the next wave of the pandemic.

Acute kidney injury (AKI) is one of the significant complications of COVID-19 as well as acute respiratory distress syndrome [1]. Recent studies have demonstrated that AKI may be a poor prognostic factor in patients with severe COVID-19 [2,3]. The greater the severity of COVID-19, the greater the need for renal replacement therapy (RRT). If the number of patients with COVID-19 spikes dramatically, clinicians may be forced to provide appropriate RRT with limited medical resources. Here, we report the successful treatment of a patient with COVID-19 who received peritoneal dialysis (PD) as emergency RRT [4].

Our case was a 62-year-old male with a polymerase chain reaction (PCR) test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). After admission to the depressurized room in our intensive care unit (ICU), the patient's oxygenation and hemodynamics deteriorated rapidly. We started mechanical ventilation and administered vasopressors, favipiravir, and ciclesonide.

The patient's serum creatinine levels became elevated (day 1: 0.77 mg/dL→day5: 5.19 mg/dL) and his urine volume dropped to 0.1 ml/kg/day. Urine analysis revealed no significant abnormalities such as hematuria or proteinuria. Sonography did not show hydronephrosis. Thus, we diagnosed this patient with COVID-19-associated AKI. As he progressed to anuria, it became difficult to control his serum potassium and maintain the hemodynamics due to acidemia.

Generally, for hemodynamically unstable patients with anuria, continuous renal replacement therapy (CRRT) is the first choice among RRT modalities. In this case, however, there were some concerns regarding the application of CRRT. The first concern was related to the large amount of personal protective equipment (PPE) employed. CRRT requires frequent bedside care by a health provider (e.g., responding to alarms, correcting abrupt poor blood drainage, and changing anticoagulants). Providing this care utilizes a very large amount of PPE, and at the time there was a serious risk of running out of PPE. The second concern relates to the sharing of hemodialysis machines with compromised host patients. In our hospital, patients from all over Japan receive transplant operations. In particular, postoperative transplant patients usually receive a high starting dose of immunosuppression drugs such as corticosteroid, tacrolimus, and mycophenolic acid. If SARS-CoV-2 particles spread to such patients through dialysis instruments, the consequences would be fatal.

To remove uremic solute, PD only requires the periodic exchange of peritoneal dialysate, and does not demand specialized instruments. Thus, PD does not necessitate additional precautions to prevent the spread of SARS-Cov-2 through dialysis instruments. Additionally, as dialysate exchange does not need to be punctual, it is possible to perform infusion bottle exchanges or postural changes at the same time. This practice would limit the waste of precious PPE.

Considering the aforementioned advantages of PD, we inserted a PD catheter into the recto-vesical pouch at the bedside and then infused the peritoneal dialysate (Fig. 1). Although anuria persisted for a while, the increased amount of peritoneal dialysate easily normalized the acidemia and serum potassium level. Furthermore, the PD procedure did not influence the patient's hemodynamics or respiratory status. After the normalization of acidemia and electrolytes, the vasopressors were tapered off, and the inflammation status also improved. On day 14, the patient was discharged from our ICU with the PD catheter.

Figure 1. The insertion of the PD catheter to the recto-vesical pouch at the bedside.

As for the safety of PD waste, SARS-CoV-2 was undetectable in the peritoneum and the PD waste of our case although it was detectable in the sputum [4]. Indeed, although similar case reports and case series have reported the usefulness of PD following our previous reports, some have also indicated a low risk of virus transmission through PD effluent [5-8]. It might, however, be premature to conclude that PD is a safer RRT in terms of infection control compared with CRRT. In fact, one report on end-stage kidney disease patients showed SARS-CoV-2 positivity in PD waste [9]. Another report demonstrated the presence of SARS-CoV-2 in the peritoneal fluid of non-dialysis COVID-19 patients who underwent subtotal colectomy [10]. It thus remains controversial whether PD waste has a low risk of SARS-Cov-2 transmission.

On the other hand, PD has additional significant advantages over other RRT modalities. Specifically, the peritoneal dialysate exchange procedure is quite simple. Also, as seen in our case, PD catheter insertion is possible even at the bedside. PD may be applicable to various emergency treatment situations for anuria patients, such as natural disasters or developing countries. As PD meets more social and technical needs

than it did before the COVID-19 pandemic, clinicians should take it into consideration in case of emergency.

References

1. Fanelli V, Fiorentino M, Cantaluppi V, et al. Acute kidney injury in SARS-CoV-2 infected patients. Critical care (London, England) 2020;24:155.
2. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ (Clinical research ed) 2020;368:m1091.
3. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international 2020;97:829-38.
4. Nagatomo M, Yamada H, Shinozuka K, Shimoto M, Yunoki T, Ohtsuru S. Peritoneal dialysis for COVID-19-associated acute kidney injury. Critical care (London, England) 2020;24:309.
5. El Shamy O, Vassalotti JA, Sharma S, et al. Coronavirus disease 2019 (COVID-19) hospitalized patients with acute kidney injury treated with acute peritoneal dialysis do not have infectious peritoneal dialysis effluent. Kidney international 2020;98:782.
6. Shankaranarayanan D, Neupane SP, Varma E, et al. Peritoneal dialysis for acute kidney injury during the COVID-19 pandemic in New York City. Kidney international reports 2020;5:1532-4.
7. Sourial MY, Sourial MH, Dalsan R, et al. Urgent peritoneal dialysis in patients with COVID-19 and acute kidney injury: a single-center experience in a time of crisis in the United States. American journal of kidney diseases: the official journal of the National Kidney Foundation 2020;76:401-6.
8. Al-Hwiesh AK, Mohammed AM, Elnokeety M, et al. Successfully treating three patients with acute kidney injury secondary to COVID-19 by peritoneal dialysis: Case report and literature review. Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis 2020;40:496-8.
9. Vischini G, D'Alonzo S, Grandaliano G, D'Ascenzo FM. SARS-CoV-2 in the peritoneal waste in a patient treated with peritoneal dialysis. Kidney international 2020;98:237-8.
10. Barberis A, Rutigliani M, Belli F, Ciferri E, Mori M, Filauro M. SARS-Cov-2 in peritoneal fluid: an important finding in the Covid-19 pandemic. The British journal of surgery 2020.

Icodextrin use in the Asia-Pacific: Economic, Centre or Patient related considerations?

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Since Icodextrin was introduced as an alternative osmotic agent to glucose in peritoneal dialysis (PD) solutions in the 1990s, its use has been increasing globally with more than 30,000 patients in 55 or more countries using this solution in 2011 [1]. Icodextrin's use has translated into better volume control and

fewer episodes of fluid overload [2] and is attractive to prescribe in patients with high or high average peritoneal membrane transport status where osmotic gradient is difficult to maintain in longer dwells to achieve the desired ultrafiltration volume. Moreover, Icodextrin has no known deleterious effect on peritoneal membrane, whereas glucose degradation products associated with glucose containing peritoneal dialysis fluids (GCPDFs) contribute to peritoneal fibrosis, vasculopathy and altered membrane transport characteristics [3]. Use of GCPDFs is also known to be associated with hyperglycemia, hyperinsulinemia and hyperlipidemia, while Icodextrin usage can improve these parameters especially in patients with diabetes [4].

The growing uptake of Icodextrin has been mainly guided by the above clinical considerations, however, benefits related to hard outcomes such as technique and patient survival with Icodextrin have been difficult to prove [2,5]. The negative driver for increasing Icodextrin utilization is its higher cost as compared to GCPDFs, leading to the variability in Icodextrin uptake in the Asia-Pacific region, with the highest uptake in South Korea, Australia and New Zealand (ANZ) and Taiwan, constituting 75%, 48%-66% and 60% of their PD population respectively, as compared with 15% in India and 4% in Indonesia. The variability can be partly explained by individual country's GDP per capita, proportion of expenditure to GDP on healthcare and health-reimbursement policies. Wealthier countries in the Asia-Pacific region with higher GDP per capita and higher percentage of GDP expenditure on health appear to use more Icodextrin and vice versa (figure 1). Interestingly, Icodextrin penetration in China's PD population is nearly 0%, as majority of patients have to bear the costs of dialysis consumables, whereas in ANZ with publicly funded universal health insurance and Hong Kong with high government subsidy on PD, Icodextrin utilization is significantly higher.

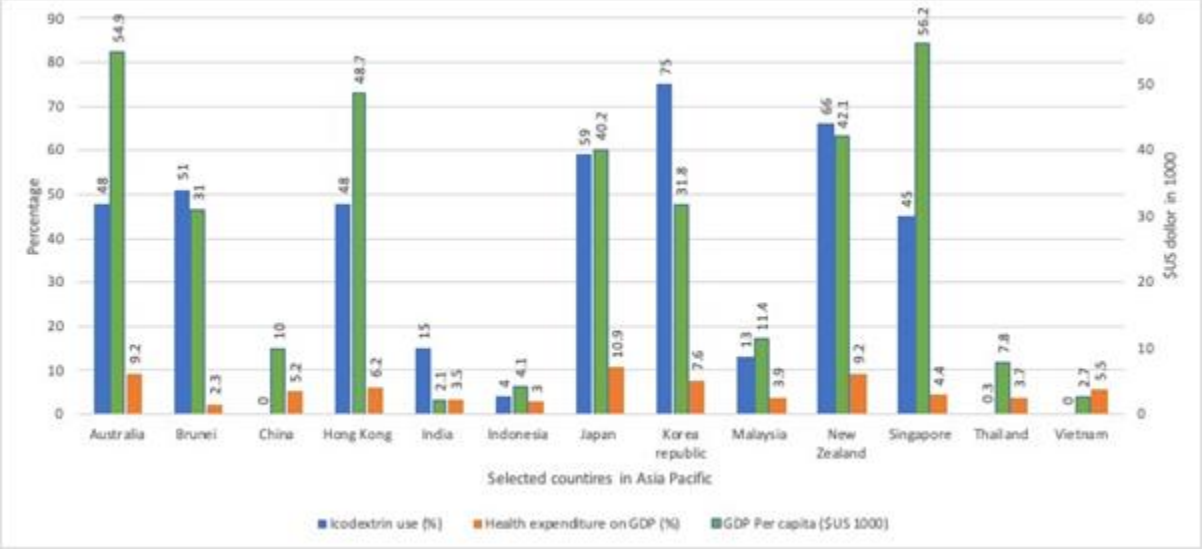

Figure 1. Icodextrin usage in peritoneal dialysis population in selected countries in Asia-Pacific region.

Notes: Data on Icodextrin usage in Asia-pacific region provided by Baxter healthcare ANZ (Personal communication)

Despite similar universal health insurance and patient demographics between Australia and New Zealand, significant variability of Icodextrin usage still occurs. In fact, large variability is also evident within the different states in Australia [6]. We therefore recently investigated patient and centre related factors that determine Icodextrin use at commencement of PD. In this study, we analysed data from Australia and New Zealand Dialysis and Transplant Registry and included all Australian adult patients commencing PD between January 2007 and December 2014 [7]. Of the 5948 patients commencing PD, 33.7% started PD

on Icodextrin and we found a 35% increase icodextrin uptake at PD initiation when comparing 2011–2014 era with 2007-2010 era. Patient level characteristics that were significantly associated with Icodextrin use were male sex, obesity, presence of diabetes and prior kidney replacement therapy (KRT) including transplant or haemodialysis. This would suggest that clinicians were more likely to prescribe Icodextrin for its reported metabolic benefits [8,9] in addition to its' ultrafiltration enhancement property, if we consider previous KRT being a surrogate marker of poor residual renal function. Furthermore, patients living in a wealthier postcode were more likely to initiate Icodextrin, potentially reflecting higher health literacy in this population, hence requesting its use. The only relevant centre-level characteristic associated with commencement of Icodextrin was centres routinely doing peritoneal equilibration test in their patients, while PD centre size did not have a significant association – suggesting that Icodextrin is more likely to be prescribed based on patients' peritoneal membrane transport characteristics. It was heartening to report that only 25% of the variability in Icodextrin utilization was related to centre level characteristics in Australia.

The enhanced ultrafiltration and avoidance of undesirable metabolic effects of Icodextrin usage appeared to have a number of benefits but until recently, there was insufficient data that these led to improvements in important hard outcomes. The recent meta-analysis by Goossen et al [10] confirmed that whilst Icodextrin increases ultrafiltration and reduces episodes of uncontrolled fluid overload, it does not have any significant effect on peritonitis rates, loss of residual kidney function or technique survival. In addition, the overall reduction in glucose exposure by using Icodextrin did not lead to sustained improvements in glycaemic or lipid control. More importantly, for the first time, it reported a possible signal that Icodextrin use could be associated with reduction in mortality (RR 0.49; 95% confidence interval, 0.24-1.00), this is of borderline significance since there were only 32 events in the 19 trials analysed and the confidence intervals are wide. Given that there were no differences in metabolic parameters, any reduction in mortality is likely only related to superior volume control in patients on Icodextrin.

A number of interventions can be useful to achieve and maintain euvolemia in patients on PD and Icodextrin is just one of them – the others being salt and fluid restriction; maintaining residual kidney functions with renin-angiotensin blockade and avoiding nephrotoxic insults including inappropriate use of aminoglycosides; using loop diuretics to enhance free water clearance and reducing PD dwell times in patients with high or high average membrane transport status by converting patients to automated PD or a dry night PD regimen. Unless the cost differential between Icodextrin and GCPDFs is reduced, in low resource settings where the Icodextrin usage depends on the paying capacity of users, its utilisation will unavoidably be low and variable as clinicians will continue to employ 'non-Icodextrin' measures to achieve volume control. However, in high income countries or where there is a third party payment or reimbursement of dialysis consumables, Icodextrin utilization will continue to be high and possibly increase further, given the new soft signal of reduced mortality and Icodextrin will be used as a 'peritoneal diuretic' of the rich.

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References

1. Mistry CD. The beginning of icodextrin. *Perit Dial Int.* 2011;31 Suppl 2:S49-52.
2. Htay H, Johnson DW, Wiggins KJ, et al. Biocompatible dialysis fluids for peritoneal dialysis. *Cochrane Database Syst Rev.* 2018;10:CD007554.

3. Davies SJ, Phillips L, Naish PF, Russell GI. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J Am Soc Nephrol.* 2001;12(5):1046-1051.
4. Li PK, Culleton BF, Ariza A, et al. Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J Am Soc Nephrol.* 2013;24(11):1889-1900.
5. Cho Y, Johnson DW, Badve S, Craig JC, Strippoli GF, Wiggins KJ. Impact of icodextrin on clinical outcomes in peritoneal dialysis: a systematic review of randomized controlled trials. *Nephrol Dial Transplant.* 2013;28(7):1899-1907.
6. ANZDATA. ANZDATA Annual Report 2019-chapter 5-peritoneal dialysis. https://www.anzdata.org.au/wp-content/uploads/2019/09/c05_peritoneal_2018_ar_2019_1.1_20200415-1.pdf. Published 2019. Accessed.
7. McDonald SP. Australia and New Zealand Dialysis and Transplant Registry. *Kidney Int Suppl (2011).* 2015;5(1):39-44.
8. Cho KH, Do JY, Park JW, Yoon KW. Effect of icodextrin dialysis solution on body weight and fat accumulation over time in CAPD patients. *Nephrol Dial Transplant.* 2010;25(2):593-599.
9. Paniagua R, Ventura MD, Avila-Diaz M, et al. Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. *Perit Dial Int.* 2009;29(4):422-432.
10. Goossen K, Becker M, Marshall MR, et al. Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials. *Am J Kidney Dis.* 2020;75(6):830-846.

Special Feature

Prescribing exercise in peritoneal dialysis patients: A challenging effort



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Inspired by Shad Ireland, a triathlete who had been on dialysis for 20 years before his first triathlon event. Starting from a 34-kg dialysis patient, he slowly built up his muscle strength and cardiovascular endurance from his hard work-out and sheer force of iron will. He completed the Ironman triathlon event in 2004

and became the first-ever dialysis patient Ironman finisher [1]. **So**…**Why don't we prescribe a regular exercise program for our peritoneal dialysis (PD) patients?**

It is no doubt that exercise is good for everyone's health, including a dialysis patient. If performed appropriately, exercise, regardless of modalities, generally improves patient-reported outcomes and physical function in dialysis patients [2]. Nevertheless, the evidence of exercise benefits in patients receiving PD is limited in numbers and quality of the studies [3,4]. A cross-sectional study demonstrated a strong relationship between aerobic capacity and patients-reported outcome measures (PROMs) in PD patients [5]. In 2020, the ISPD Guidelines incorporated exercise as one of the non-dialytic intervention for high-quality care [6].

Still, a few risk assessments are needed to ensure patients' safety before prescribing an exercise regimen, including risks of falling, traumatic injury, cardiovascular accidents (stroke, arrhythmia, myocardial infarction), and PD-related complications (infection, PD catheter damage). Some factors may limit exercise capacities, such as hypertension, anemia, and muscle atrophy, which should also be considered. Moreover, output indicators should be measured periodically to assess adherence and effectiveness of the intervention. According to a survey of barriers to and constraints of exercise in PD patients, patients preferred to exercise at home and reported improving energy, physical strength, and sleep quality as top-three desired aims of their exercise. However, multiple concerns had been raised, including limited physical function (feeling fatigue, tiredness, and weakness), fear of complications during exercise, and lack a well-established exercise program for PD [7].

The American College of Sports Medicine [8] issues general concepts for exercise, including a proper warm-up/cool down and gradual accelerating the intensity (from low to high) and duration (from short to long) of exercise. The programs should include aerobic and strength training, it should be personalized according to patient's needs, treatment burden, and health condition. Generally, cardiovascular exercise frequency should be 3–5 days per week at a moderate intensity for 20-60 minutes in duration, with up to multiple bouts daily. For strength training, it should be 2–3 days per week. Whether PD patients should exercise when they are "**wet**" or "**dry**" is still debatable. Although clinicians typically recommend draining dialysate ("**dry**") before vigorous exercise, there are not enough supporting evidences. Core strengthening exercise is likely beneficial as strong abdominal muscles could prevent leaks and hernias. If patients are too frail or weak for intense exercise, other exercises such as stationary cycling, Wu-style Tai Chi, light resistance with weights, and swimming are well tolerated and approved [3]. Particular attention should be taken to fluid balance during aerobic exercise, and sports drinks should be avoided because of containing high potassium supplements.

Figure 1: Exercise and Demonstration of strength training during PD visits

Photo credit: Ms. Ranu Yaibuaiam, R.N., Chao Phraya Yom Marat Hospital, Suphanburi and Ms. Niparat Pikul, Amnatcharoen Hospital, Amnatchareon, Thailand

In Thailand, many facilities have established home-based exercise programs, usually led and demonstrated during PD visits by PD nurses or physiologists. The program is composed of both aerobic and resistance exercises with a "**wet**" abdomen (Figure 1). Various outcomes evaluating the effectiveness

of the exercise program were periodically assessed, including ***(1) PROMs*** (e.g., quality of life, Global Physical Activity Questionnaire) ***(2) Physical functioning assessment*** [e.g., 6-minute walk distance, shuttle-walk distance, handgrip and quadriceps strength, stair climb repetitions, Rapid Assessment of Physical Activity(RAPA) test, 30'' Sit-to-Stand test, VO2max] ***(3) Nutritional status assessment*** (e.g., serum albumin, anthropometric measurement, malnutrition-inflammation score). In summary, PD patients are encouraged to increase their physical activities through exercise to improve physical function and PROMs. To date, exercise deems to be safe without serious adverse effects in PD patients. Yet, further studies are required to determine the practical and suitable exercise program for patient receiving PD.

References

1. Bell J. Dialysis patient is 20-time triathlon athlete [Internet]. The Courier. 2011 [cited 2020 Oct 27]. Available from: https://www.yourconroenews.com/neighborhood/moco/news/article/Dialysis-patient-is-20-time-triathlon-athlete-9260974.php
2. Clarkson MJ, Bennett PN, Fraser SF, Warmington SA. Exercise interventions for improving objective physical function in patients with end-stage kidney disease on dialysis: a systematic review and meta-analysis. Am J Physiol Renal Physiol. 2019 01;316(5):F856–72.
3. Isnard-Rouchon M, West M, Bennett PN. Exercise and physical activity for people receiving peritoneal dialysis: Why not? Semin Dial. 2019;32(4):303-7.
4. Thangarasa T, Imtiaz R, Hiremath S, Zimmerman D. Physical Activity in Patients Treated With Peritoneal Dialysis: A Systematic Review and Meta-analysis. Can J Kidney Health Dis. 2018;5:2054358118779821.
5. Uchiyama K, Washida N, Muraoka K, Morimoto K, Kasai T, Yamaki K, et al. Exercise Capacity and Association with Quality of Life in Peritoneal Dialysis Patients. Perit Dial Int. 2019;39(1):66-73.
6. Brown EA, Blake PG, Boudville N, Davies S, de Arteaga J, Dong J, et al. International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis. Perit Dial Int J Int Soc Perit Dial. 2020;40(3):244–53.
7. Moorman D, Suri R, Hiremath S, Jegatheswaran J, Kumar T, Bugeja A, et al. Benefits and Barriers to and Desired Outcomes with Exercise in Patients with ESKD. Clin J Am Soc Nephrol. 2019;14(2):268-76.
8. Riebe D, Ehrman JK, Liguori G, Magal M, editors. American College of Sports Medicine's: Guidelines for Exercise Testing and Prescription. 10 ed. Philadelphia: Wolters Kluwer; 2018.