Review

Customization of Peritoneal Dialysis in Cardiorenal Syndrome by Optimization of Sodium Extraction

Amir Kazory^a Abhilash Koratala^a Claudio Ronco^{b, c}

^aDivision of Nephrology, Hypertension, and Renal Transplantation, University of Florida, Gainesville, FL, USA; ^bDepartment of Nephrology, San Bortolo Hospital, Vicenza, Italy; ^cInternational Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy

Keywords

Cardiorenal syndrome · Heart failure · Peritoneal dialysis · Sodium · Congestion

Abstract

Background: Peritoneal dialysis (PD) has emerged as a mechanistically relevant therapeutic option for patients with heart failure (HF), volume overload, and varying degrees of renal dysfunction (i.e., chronic cardiorenal syndrome). Congestion has been identified as a potent ominous prognostic factor in this patient population, outperforming a number of established risk factors. As such, excess fluid removal is recognized as a relevant therapeutic target in this setting. **Methods:** Accumulating evidence points to the importance of sodium removal as part of any decongestive strategy because extraction of sodium-free water has little or no impact on the outcomes of these patients. Hence, optimization of sodium removal by PD should be the primary focus in the setting of HF and cardiorenal syndrome, especially if PD is started when the patient still has adequate residual renal function for clearance of waste products. **Results:** Herein, we provide an overview of approaches that can tailor PD treatment to the patients' characteristics and clinical needs (e.g., choice of PD modality) to fully exploit its decongestive properties. Other methods that could prove helpful in the future will also be briefly discussed. **Conclusion:** While these strategies could help with efficient sodium extraction and volume optimization, future studies are needed to evaluate their impact on the outcomes of this specific patient population.

© 2019 S. Karger AG, Basel

Amir Kazory, MD, FASN
Division of Nephrology, Hypertension and Renal Transplantation
College of Medicine, University of Florida
1600 SW Archer Road, Gainesville, FL 32610-0224 (USA)
E-Mail Amir.Kazory@medicine.ufl.edu

Background

The untoward impact of fluid overload on the outcomes has increasingly been recognized in a variety of complex clinical settings such as kidney disease and heart failure (HF). Once considered merely a marker of impaired water and solute excretion, recent data have identified congestion as a pro-oxidant and pro-inflammatory stimulus with consequent adverse effects such as endothelial activation [1]. Specifically in HF population, congestion has been recognized as a potent ominous prognostic factor, outperforming a number of established risk factors such as renal dysfunction [2]. As such, excess fluid removal has emerged as a relevant therapeutic target.

Peritoneal Dialysis and HF

Several investigators have advocated the use of peritoneal dialysis (PD) for management of lingering congestion in patients with refractory HF and varying degrees of renal dysfunction (i.e., cardiorenal syndrome [CRS]) [3]. PD therapy for refractory HF represents a collaborative opportunity for cardiologists and nephrologists to fight against a common, costly, and deadly disease state. The results of the studies have in general been very encouraging in terms of HF-related outcomes such as improvement in HF functional class and left ventricular ejection fraction as well as reduction in the rate and length of hospital admissions [4]. In this population, volume control is of utmost importance; not only is it the main reason HF patients are admitted to the hospital, but it is also an established determinant of PD adequacy. Nevertheless, PD regimens that were used to treat fluid overload have largely been similar to those conventionally used for patients with end-stage renal disease and were neither protocolized nor designed to specifically target congestion [5].

Sodium and PD

Impairment in sodium excretion starts in early subclinical stages of HF [6]. Sodium is the major determinant of extracellular volume, and its key role in retention of fluid and development of congestion has widely been recognized. Hence, optimization of sodium removal (SR) with PD should be the primary focus in the setting of HF and CRS, especially if PD is started when the patient still has adequate residual renal function for clearance of waste products. It is of note that overall PD is considered an efficient modality with regard to SR; while loop diuretics tend to generate hypotonic urine that contains about 60 mmol/L of sodium, the concentration of sodium in PD ultrafiltrate has been reported to be as high as 126–134 mmol/L [7, 8].

The solute and water transport in PD is dynamic and varies significantly within each dwell. With regard to sodium transport, each cycle can be divided into two segments; an early phase where aquaporin activation by crystalloid osmotic gradient results in transcellular removal of sodium-free water, hence a “dip” in the sodium concentration of dialysate as the water leaves vascular space to enter peritoneal cavity (i.e., sodium sieving). It is only after this initial period (i.e., 60–90 min) that sodium transport (convection, diffusion, and sometimes back-diffusion) takes place in the second phase through small pores of the peritoneal membrane. In order to optimize volume management, attempts should focus on modifying the proportion of these two segments in a dwell either by eliminating the early phase, or to make the cycles long enough to allow efficient SR after the early phase (but not too long to facilitate back diffusion). Conversely, in HF patients with hyponatremia, using frequent short

dwells would help increase serum sodium levels by enhancement of peritoneal free water clearance in the early phase of the dwell.

PD is a highly flexible therapeutic modality, and the choice of techniques, regimens, and solutions can affect its ability for optimization of fluid status. Herein, we discuss a number of methods, based on simple physiologic concepts of solute transport, that can be used (simultaneously or sequentially) to increase SR in patients with HF for whom PD is used as a decongestive strategy.

Icodextrin

Serious consideration should be given to icodextrin use in this clinical context where the primary goal is extraction of sodium-rich fluid. Icodextrin optimizes SR by elimination of the initial sodium-sieving phase because it does not activate aquaporins. Several studies have reported significant increase in SR with use of icodextrin-based solutions [9, 10]. Moreover, due to it being a glucose polymer with minimal absorption, sustained colloid osmotic gradient results in maximal convective SR during long dwells making it an appealing option for single use in a subset of patients with HF and CRS for whom clearance might not be the primary concern. In a recent simulation study, single daily icodextrin exchanges of 8–16 h resulted in SR of up to 87 mmol [11]. In an HF patient with low-sodium intake (e.g., 100 mmol/day), this would readily translate into a desirable negative daily sodium balance. Accordingly, it has been shown that one single nocturnal icodextrin exchange can successfully manage volume overload in patients with refractory HF [12]. Residual renal function should periodically be monitored in these patients; with progression of CRS over time, PD regimen can be gradually intensified by adding glucose-based solutions to provide more clearance and further enhance SR. In a recent study on more than 5,000 newly diagnosed end-stage renal disease patients undergoing PD, icodextrin users had an overall 26% lower incidence of HF compared to nonusers (13.7 vs. 18.6 per 1,000 person-years, hazard ratio 0.67, $p < 0.01$) [13].

One consideration is the recent reports on association of icodextrin use with hyponatremia that has been proposed to be translocational (i.e., due to presence of osmotically active metabolites in serum) [14, 15]. Hyponatremia, a surrogate for maladaptive pathophysiological mechanisms, is an ominous prognostic factor in both PD and HF populations. It remains to be explored whether icodextrin-associated hyponatremia (which generally tends to be mild) would portend similar prognostic value. By comparison, hyponatremia associated with extracorporeal ultrafiltration therapy in patients with acute decompensated HF has no impact on the outcomes.

PD Modalities

The distinct impact of PD modalities on SR has been a matter of debate. Continuous ambulatory PD (CAPD) is generally believed to result in higher SR than automated PD (APD) by virtue of typically having less frequent and longer cycles (and hence less sodium sieving) [16]. However, some authors have suggested that both modalities could result in similar sodium elimination with optimal PD prescription [17, 18]. In a study on 158 prevalent PD patients, Davison et al. [19] reported no difference between APD and CAPD with regard to the ratio of extracellular fluid volume to total body water using bioimpedance spectroscopy. Mean total daily removal of sodium was actually reported to be lower with CAPD than APD (109 and 130 mmol, respectively, $p = 0.23$). The results of this study can be in part explained by the fact that almost 80% of the APD patients received icodextrin for their long daytime

dwells, and the number of nocturnal exchanges were reduced (i.e., allowing for longer dwells and less sodium sieving). Nevertheless, a recent meta-analysis including 683 patients from 7 studies concluded that CAPD is associated with significantly higher SR compared with APD (141 vs. 86 mmol/day, respectively, $p = 0.015$) [20]. Since APD is the predominant modality in many countries, a number of investigators have explored methods (i.e., tidal APD and mid-day exchange) to enhance its SR capability rather than switching to CAPD.

Tidal PD and Mid-Day Exchange

The concept of tidal PD involves draining only part of the initial fill volume and replacing it by fresh dialysate during each cycle. At the end of the tidal session, the whole dialysate volume is drained from the peritoneal cavity. It has been proposed that tidal PD could increase the contact time between peritoneum and larger amounts of dialysate (hence improving the clearance of the solutes) because only part of the PD solution is drained and immediately replaced by fresh dialysate [21]. As such, the less efficient and slower part of the dialysate outflow/drainage is excluded. However, there have been conflicting data regarding the impact of tidal PD on SR. While tidal prescription does not appear to significantly increase sodium extraction in fast transporters, a potential benefit is possible in slow transporters as it diminishes sodium sieving [21, 22]. More studies are needed to elucidate the precise impact of tidal PD on SR. Another proposed approach to augment SR by APD is addition of a manual daytime exchange to the regimen. In a randomized controlled crossover trial, Demetriou et al. [23] showed that compared to high dialysate flow, a manual daily exchange added to low flow APD significantly increases SR (128 vs. 176 mmol/day, respectively, $p = 0.01$). However, it is to be noted that daily exchanges generally impair quality of life (hence could be considered counterintuitive in this specific population) and could increase the risk of PD-associated infections.

Peritoneal Dialysate Volume

Larger dialysate volumes can recruit more peritoneal membrane (i.e., “wetted” membrane) and result in further enhancement of SR by virtue of involving higher number of small pores in the exchange process [11]. However, it should be noted that progressively higher intraperitoneal pressures induced by larger dialysate volumes (i.e., $>1,400$ mL/m² body surface area) could hamper or offset this salutary effect at some point by facilitating back-ultrafiltration and back-diffusion of sodium [24]. Of special consideration for HF population, the larger volumes can also portend untoward impact on cardiac function (see below).

Ultrafiltration Volume and Posture

Since sodium transport in PD is largely through convection, increasing ultrafiltration volume through conventional methods is expected to potentiate SR [8]. The correlation between ultrafiltration volume and sodium extraction could be more pronounced in patients treated with CAPD than APD (possibly due to a higher proportion of the ultrafiltrate volume being from the sodium-free water in APD) [20].

Fischbach and Haraldsson [25] have also proposed that supine position is associated with a 30% increase in the proportion of the peritoneal surface area that is recruited for solute exchange when compared to upright position. Although lower intraperitoneal pressure in the supine position could have a salutary impact on the ultrafiltration volume with conse-

quent enhanced SR, that study was performed in children; future studies are needed to confirm the results in adults. In a randomized controlled trial, increasing fill volumes from 2 to 3 L in the supine position was followed by an impairment in cardiac performance (i.e., reduction in cardiac output and stroke volume coupled with rise in peripheral systemic resistance) [26]. The impaired cardiac function was already present after a 2-L fill in the upright position and did not change further by increasing volumes. While the adverse impact of increased intra-abdominal pressure on cardiorenal interplay has long been recognized, future studies are needed to determine its precise role in this setting.

Potential Future Approaches

In addition to the above-mentioned methods for optimization of sodium extraction in PD, there are a number of potential options that need to be given special consideration in HF population. These approaches could prove useful in the future but are not yet part of the standard of care primarily due to lack of enough evidence.

Low-Sodium Peritoneal Dialysate

Low-sodium PD solutions containing variable concentrations of sodium (e.g., 115–126 mmol/L) have been used to enhance its diffusive removal. The glucose concentration can be increased in these solutions to maintain osmotic pressure and prevent decline in ultrafiltration (i.e., compensated low-sodium PD solutions). In a randomized controlled trial on 108 patients treated with CAPD, use of a modestly low-sodium solution (i.e., 125 mmol/L) in all dwells resulted in a marked increase in SR by 50 mmol/day [27]. The authors observed a trend towards decreased thirst in the low-sodium group. This is of special interest for the HF population because these patients typically present with inappropriately high levels of angiotensin, a potent trigger of thirst.

A clinical concern relevant to these patients is that low-sodium PD solutions could potentially induce or worsen hyponatremia. However, it does not seem that the change in serum sodium levels is clinically significant (it was 0.8–2 mmol/L in the above-mentioned study), and it could possibly be prevented by alternating these dialysates with standard-sodium solutions. Moreover, similar to icodextrin, the prognostic impact of the intervention-induced hyponatremia remains elusive. Although the studies on low-sodium PD solutions have been performed for decades, these solutions are not yet widely available for routine clinical practice.

Bimodal Peritoneal Dialysate

There have been suggestions for use of combined solutions with icodextrin and glucose (i.e., “bimodal solution”). These solutions are indeed a form of compensated low-sodium solution with enhanced ultrafiltration and SR capacity due to the combined effect of crystalloid and colloid osmosis during the same exchange while significantly limiting exposure to glucose. Several studies have reported significant increase in ultrafiltration volume and SR with bimodal solutions. For example, in a study by Freida et al. [28], the authors reported an impressive increase in the estimated ultrafiltration volume and SR of 150 and 147%, respectively, for their bimodal solution (sodium 121 mmol/L) compared to icodextrin alone.

Twice-Daily Icodextrin

Since ultrafiltration does not increase substantially with icodextrin after 8–10 h, it is conceivable that two 8-h icodextrin exchanges could provide higher ultrafiltration volume than one exchange over 16 h. As such, twice-daily icodextrin exchanges could be a promising

Table 1. Proposed approaches for enhancement of sodium extraction in peritoneal dialysis for heart failure

Icodextrin use rather than glucose-based solutions
Continuous ambulatory peritoneal dialysis rather than automated peritoneal dialysis
Addition of mid-day exchange
Increase in dialysate volume
Optimization of dwell time (sodium sieving vs. back diffusion)
Increase in ultrafiltrate volume (e.g., use of higher concentrations of glucose)
Supine position
Consideration of tidal volume
Low-sodium dialysate
Bimodal dialysate
Consideration of twice-daily icodextrin
Adapted automated peritoneal dialysis

approach for efficient decongestion with PD. A number of relatively small studies have reported favorable results with regard to increase in ultrafiltration volume and ejection fraction as well as reduction in weight, blood pressure, serum B-type natriuretic peptide, and left ventricular mass [29–31]. However, whether long-term use of large volumes of icodextrin could potentially lead to accumulation of its metabolites remains unexplored. As previously mentioned, there have been reports on the association of icodextrin and hyponatremia. The clinicians should be aware that the risk could be further increased with twice-daily use of icodextrin; close monitoring of serum sodium levels would be warranted. Larger studies are needed to ascertain the safety of twice-daily icodextrin before it can be widely recommended.

Adapted APD

In contrast to hemodialysis where ultrafiltration and solute clearance can take place independent of each other, these two processes are coupled in PD and take place simultaneously in every exchange. With the advent of new generation of cyclers that permit individualization of PD exchanges, the concept of adapted APD (A-APD) has recently been introduced to enhance water and solute transport. Conventional PD regimens include a series of exchanges with fixed dwell time and identical dialysate volumes; A-APD consists of two different sequences of exchanges during a single PD session. The first phase includes cycles with short dwell time (e.g., 45 min) and small fill volumes (e.g., 1,500 mL) to primarily promote ultrafiltration, and the second phase consists of cycles with long dwell time (e.g., 150 min) and large dwell volumes (e.g., 3,000 mL) to facilitate solute (e.g., sodium) removal. The number of cycles, dwell time, and fill volume are determined based on the individual patient's membrane characteristics as well as clinical needs (e.g., degree of congestion and renal dysfunction). Interestingly, although A-APD is performed with standard-sodium solutions, it still benefits from the concept of low-sodium dialysate because the sodium-free water generated during the first phase is only partially drained due to small dwell volume and low intraperitoneal pressure. As such, the retained water in the peritoneum will dilute the infused dialysate of the second phase, forming a low-sodium solution. In a pilot randomized controlled trial, A-APD resulted in significantly higher SR than conventional APD (35 and 18 mmol per session, respectively, $p < 0.01$) [32]. However, a more recent computer simulation study reported that ultrafiltration and SR by A-APD are only marginally higher than APD [33]. The investigators found that the salutary impact of increased fill volumes on recruitment of small pores in the second phase of A-APD is largely countered by the increased intraperitoneal pressure that hinders sodium transport. Future clinical studies are needed to clarify the precise effect of A-APD on sodium and fluid removal and to explore its potential role in management of congestion in HF and CRS.

Conclusion

PD has been used for management of congestion in a subset of patients with HF and CRS who present with refractoriness to conventional diuretic-based therapies. PD can be the last resort for such patients, and the primary goal is in general to improve the quality of life and performance by efficient management of fluid overload, hence prevention of HF-related hospital admission. It is prudent to not only tailor the PD treatment to the specific patient's characteristics and clinical needs, as is done for patients with end-stage renal disease, but to also optimize the regimen to fully exploit its decongestive properties. Attention to the mechanistic details of PD therapy and applying the aforementioned approaches (summarized in Table 1), whenever indicated, is likely to improve the care of patients with HF and CRS. These measures would obviously be most helpful in conjunction with other nonspecific conventional strategies used to manage volume overload in patients with HF (e.g., low-salt intake and optimal use of diuretics).

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No specific funding was used for preparation of this article.

Author Contributions

A. Kazory: literature search and writing the draft; *A. Koratala*: literature search and revising; *C. Ronco*: overseeing and revising.

References

- Colombo PC, Doran AC, Onat D, Wong KY, Ahmad M, Sabbah HN, et al. Venous congestion, endothelial and neurohormonal activation in acute decompensated heart failure: cause or effect? *Curr Heart Fail Rep*. 2015 Jun;12(3):215–22.
- Palazzuoli A, Lombardi C, Ruocco G, Padeletti M, Nuti R, Metra M, et al. Chronic kidney disease and worsening renal function in acute heart failure: different phenotypes with similar prognostic impact? *Eur Heart J Acute Cardiovasc Care*. 2016 Dec;5(8):534–48.
- Kazory A. Peritoneal dialysis for chronic cardiorenal syndrome: lessons learned from ultrafiltration trials. *World J Cardiol*. 2015 Jul;7(7):392–6.
- Lu R, Muciño-Bermejo MJ, Ribeiro LC, Tonini E, Estremadoyro C, Samoni S, et al. Peritoneal dialysis in patients with refractory congestive heart failure: a systematic review. *Cardiorenal Med*. 2015 Apr;5(2):145–56.
- Kazory A. Fluid overload as a major target in management of cardiorenal syndrome: implications for the practice of peritoneal dialysis. *World J Nephrol*. 2017 Jul;6(4):168–75.
- Volpe M, Tritto C, DeLuca N, Rubattu S, Rao MA, Lamenza F, et al. Abnormalities of sodium handling and of cardiovascular adaptations during high salt diet in patients with mild heart failure. *Circulation*. 1993 Oct;88(4 Pt 1):1620–7.
- Ali SS, Olinger CC, Sobotka PA, Dahle TG, Bunte MC, Blake D, et al. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. *Congest Heart Fail*. 2009 Jan-Feb;15(1):1–4.

- 8 Rodríguez-Carmona A, Fontán MP. Sodium removal in patients undergoing CAPD and automated peritoneal dialysis. *Perit Dial Int*. 2002 Nov-Dec;22(6):705–13.
- 9 Qi H, Xu C, Yan H, Ma J. Comparison of icodextrin and glucose solutions for long dwell exchange in peritoneal dialysis: a meta-analysis of randomized controlled trials. *Perit Dial Int*. 2011 Mar-Apr;31(2):179–88.
- 10 Fourtounas C, Hardalias A, Dousdampanis P, Papachristopoulos B, Savidaki E, Vlachojannis JG. Sodium removal in peritoneal dialysis: the role of icodextrin and peritoneal dialysis modalities. *Adv Perit Dial*. 2008;24:27–31.
- 11 Agar BU, Sloand JA. Single Daily Icodextrin Exchange as Initial and Solitary Therapy. *Perit Dial Int*. 2018 Mar-Apr;38(2):119–24.
- 12 Sánchez JE, Ortega T, Rodríguez C, Díaz-Molina B, Martín M, García-Cueto C, et al. Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure. *Nephrol Dial Transplant*. 2010 Feb;25(2):605–10.
- 13 Wang IK, Lin CL, Yen TH, Lin SY, Yao-Lung L, Sung FC. Icodextrin reduces the risk of congestive heart failure in peritoneal dialysis patients. *Pharmacoepidemiol Drug Saf*. 2018 Apr;27(4):447–52.
- 14 Kunin M, Ganon L, Holtzman EJ, Dinour D. Hyponatremia in refractory congestive heart failure patients treated with icodextrin-based peritoneal dialysis: A case series. *Nefrologia*. 2018 Jan - Feb;38(1):87–91.
- 15 Viglino G, Neri L, Feola M. Peritoneal ultrafiltration in congestive heart failure-findings reported from its application in clinical practice: a systematic review. *J Nephrol*. 2015 Feb;28(1):29–38.
- 16 Ortega O, Gallar P, Carreño A, Gutierrez M, Rodriguez I, Olié A, et al. Peritoneal sodium mass removal in continuous ambulatory peritoneal dialysis and automated peritoneal dialysis: influence on blood pressure control. *Am J Nephrol*. 2001 May-Jun;21(3):189–93.
- 17 Moor V, Wagner R, Sayer M, Petsch M, Rueb S, Häring HU, et al. Routine Monitoring of Sodium and Phosphorus Removal in Peritoneal Dialysis (PD) Patients Treated with Continuous Ambulatory PD (CAPD), Automated PD (APD) or Combined CAPD+APD. *Kidney Blood Press Res*. 2017;42(2):257–66.
- 18 Fourtounas C, Dousdampanis P, Hardalias A, Vlachojannis JG. Sodium removal and peritoneal dialysis modalities: no differences with optimal prescription of icodextrin. *Artif Organs*. 2013 Jul;37(7):E107–13.
- 19 Davison SN, Jhangri GS, Jindal K, Pannu N. Comparison of volume overload with cyclo-assisted versus continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol*. 2009 Jun;4(6):1044–50.
- 20 Borrelli S, La Milia V, De Nicola L, Cabiddu G, Russo R, Provenzano M, et al.; Study group Peritoneal Dialysis of Italian Society of Nephrology. Sodium removal by peritoneal dialysis: a systematic review and meta-analysis. *J Nephrol*. 2018 Jul 5. doi: 10.1007/s40620-018-0507-1.
- 21 Vychytil A, Hörl WH. The role of tidal peritoneal dialysis in modern practice: A European perspective. *Kidney Int Suppl*. 2006 Nov;70(103):S96–103.
- 22 Perez RA, Blake PG, McMurray S, Mupas L, Oreopoulos DG. What is the optimal frequency of cycling in automated peritoneal dialysis? *Perit Dial Int*. 2000 Sep-Oct;20(5):548–56.
- 23 Demetriou D, Habicht A, Schillinger M, Hörl WH, Vychytil A. Adequacy of automated peritoneal dialysis with and without manual daytime exchange: A randomized controlled trial. *Kidney Int*. 2006 Nov;70(9):1649–55.
- 24 Fischbach M, Zaloszyk A, Schaefer B, Schmitt CP. Optimizing peritoneal dialysis prescription for volume control: the importance of varying dwell time and dwell volume. *Pediatr Nephrol*. 2014 Aug;29(8):1321–7.
- 25 Fischbach M, Haraldsson B. Dynamic changes of the total pore area available for peritoneal exchange in children. *J Am Soc Nephrol*. 2001 Jul;12(7):1524–9.
- 26 Ivarsen P, Povlsen JV, Jensen JD. Increasing fill volume reduces cardiac performance in peritoneal dialysis. *Nephrol Dial Transplant*. 2007 Oct;22(10):2999–3004.
- 27 Rutkowski B, Tam P, van der Sande FM, Vychytil A, Schwenger V, Himmele R, et al.; Low Sodium Balance Study Group. Low-Sodium Versus Standard-Sodium Peritoneal Dialysis Solution in Hypertensive Patients: A Randomized Controlled Trial. *Am J Kidney Dis*. 2016 May;67(5):753–61.
- 28 Freida P, Issad B, Dratwa M, Lobbedez T, Wu L, Leypoldt JK, et al. A combined crystalloid and colloid pd solution as a glucose-sparing strategy for volume control in high-transport apd patients: a prospective multi-center study. *Perit Dial Int*. 2009 Jul-Aug;29(4):433–42.
- 29 Sav T, Inanc MT, Dogan A, Oymak O, Utaş C. Two daytime icodextrin exchanges decrease brain natriuretic peptide levels and improve cardiac functions in continuous ambulatory peritoneal dialysis patients. *Nephrology (Carlton)*. 2010 Apr;15(3):307–12.
- 30 Dousdampanis P, Trigka K, Chu M, Khan S, Venturoli D, Oreopoulos DG, et al. Two icodextrin exchanges per day in peritoneal dialysis patients with ultrafiltration failure: one center's experience and review of the literature. *Int Urol Nephrol*. 2011 Mar;43(1):203–9.
- 31 Ballout A, García-López E, Struyven J, Maréchal C, Goffin E. Double-dose icodextrin to increase ultrafiltration in PD patients with inadequate ultrafiltration. *Perit Dial Int*. 2011 Jan-Feb;31(1):91–4.
- 32 Fischbach M, Issad B, Dubois V, Taamma R. The beneficial influence on the effectiveness of automated peritoneal dialysis of varying the dwell time (short/long) and fill volume (small/large): a randomized controlled trial. *Perit Dial Int*. 2011 Jul-Aug;31(4):450–8.
- 33 Öberg CM, Rippe B. Is Adapted APD Theoretically More Efficient than Conventional APD? *Perit Dial Int*. 2017 Mar-Apr;37(2):212–7.