

The Current State of Peritoneal Dialysis

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ABSTRACT

Technical innovations in peritoneal dialysis (PD), now used widely for the long-term treatment of ESRD, have significantly reduced therapy-related complications, allowing patients to be maintained on PD for longer periods. Indeed, the survival rate for patients treated with PD is now equivalent to that with in-center hemodialysis. In parallel, changes in public policy have spurred an unprecedented expansion in the use of PD in many parts of the world. Meanwhile, our improved understanding of the molecular mechanisms involved in solute and water transport across the peritoneum and of the pathobiology of structural and functional changes in the peritoneum with long-term PD has provided new targets for improving efficiency and for intervention. As with hemodialysis, almost half of all deaths on PD occur because of cardiovascular events, and there is great interest in identifying modality-specific factors contributing to these events. Notably, tremendous progress has been made in developing interventions that substantially reduce the risk of PD-related peritonitis. Yet the gains have been unequal among individual centers, primarily because of unequal clinical application of knowledge gained from research. The work to date has further highlighted the areas in need of innovation as we continue to strive to improve the health and outcomes of patients treated with PD.

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The first attempt to use the human peritoneum to dialyze uremic retention solutes was made almost 100 years ago.¹ Over the next five decades, the therapy gradually evolved with an expansion in our understanding of solute and water kinetics that allowed for successful application of this mode of dialysis to AKI and ESRD.^{2–10} This, in addition to the development of the indwelling catheter that provided access to the peritoneal cavity at will and standardization of the composition of dextrose-based dialysate culminated in the introduction of continuous ambulatory peritoneal dialysis in 1976 (Figure 1).^{11–13} This was followed by changes in connectology to

reduce the risk of infections, the introduction of volumetric cyclers, and several alternatives to conventional glucose-based peritoneal dialysis (PD) solutions.^{13–16} In this review, we highlight the major developments in the application of PD for the treatment of ESRD.

UTILIZATION AND OUTCOMES WITH PD

The early experience with PD raised numerous concerns about whether the therapy was a viable alternative to in-center hemodialysis (HD) for the long-term treatment of ESRD. These included

but were not limited to high risk of infections, inadequate clearance of small solutes, and deterioration of peritoneal health resulting in ultrafiltration failure, which together led to shorter time on therapy and higher risk for death compared with in-center HD.^{13,17–19} This led a leading nephrologist to retort in the 1980s that PD is a “second-class therapy for second-class patients by second-class doctors.” In part driven by these concerns, starting from the mid-1990s the proportion of patients with ESRD treated with PD progressively declined in many parts of the world.^{20,21}

Yet, the greatest improvements in the clinical application of PD occurred at the same time as a progressively smaller proportion of patients were utilizing the therapy. In the decade starting from the mid-1990s, there was a significantly larger reduction in risk of death for patients starting with PD around the world than for those undergoing in-center HD (Table 1).^{22–29} As a result, virtually all studies indicate PD and in-center HD now provide similar short- (1- or 2-year) or long-term (up to 5 years) survival (Table 1).^{23–25,29–31} Furthermore,

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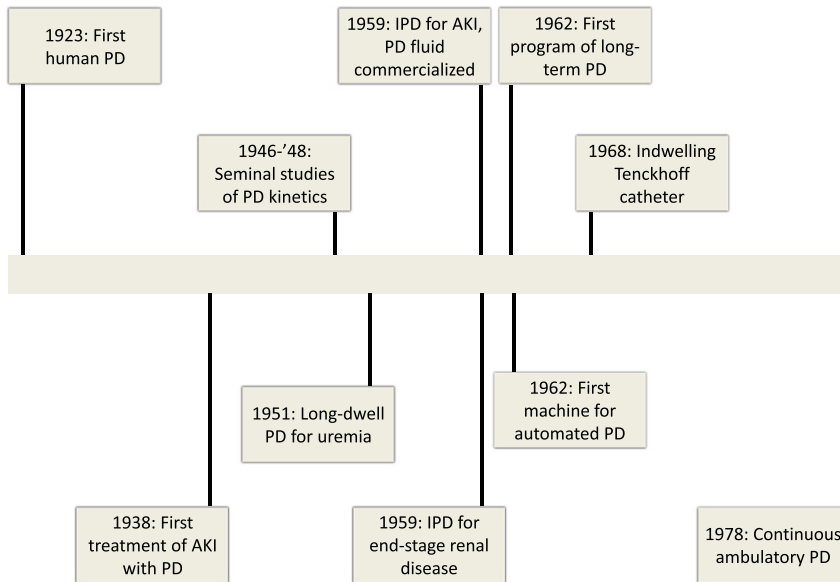


Figure 1. Major landmarks in the development of PD as a treatment for ESRD (1923–1978).

there has been a significant reduction in risk of patients treated with PD transferring to in-center HD in the United States, indicating a lower risk of therapy-related complications.³² These improvements have significant implications as they allow patients to receive treatment with an RRT best suited to their values, expectations, and lifestyles, and allow nations the flexibility to incentivize dialysis modalities that allow them to offer cost-effective treatment given increasing budgetary constraints.

Public Policy Changes to Increase PD Utilization

The relative costs of HD and PD vary around the world.³³ In most developed countries and many developing countries societal costs with PD are lower providing impetus to these jurisdictions to enact public policy that promotes the use of a cheaper therapy.³³ This is important as it has long been recognized that nonmedical factors, including reimbursement, are the primary determinants of the proportion of ESRD patients treated with PD in any region of the world.^{34,35} With a backdrop provided by recent studies that PD provides equivalent survival to in-center HD, several countries around the world have introduced

changes to increase PD utilization to leverage its lower costs to the health system.³⁶ In the United States, an expanded prospective payment system became effective in 2011, which includes the cost of parenteral dialysis-related medications in capitated payments made for each dialysis treatment.^{37,38} Because PD patients require a significantly lower dose of erythropoiesis stimulating agents to achieve any given hemoglobin level, this policy change offers a significant financial incentive to a greater use of PD.³⁹ In Thailand, the government adopted a “PD-First” approach in 2008 as part of its universal health coverage scheme, as in Hong Kong, under the aegis of which dialysis services will be paid for only if the patient is treated with PD, given its lower cost.⁴⁰ Finally, China has been rapidly expanding access to RRT for its population and has a policy that encourages the use of PD without mandating it.³⁶ Each of these three countries has seen an unprecedented expansion in the use of PD. The growth in the United States has been so rapid (Figures 2, and 3) that the dominant manufacturer was not able to increase the supply of dialysate to meet the increasing demand leading to rationing of solutions in 2014.⁴¹ The

shortage has abated but has not been completely eliminated. With increasing use of PD, it is likely that the patient census of individual facilities in such countries will become larger which in turn is associated with longer time for patients on PD because of reduced transfer to in-center HD.

Rethinking Care Delivery to Increase Dialysis Treatment Options for Patients

An important barrier to a greater use of PD is that many patients with ESRD are unaware that dialysis can be done at home.^{42,43} Conversely, educating patients about treatment options is associated with a significantly higher use of PD even among patients who start dialysis without prior care with a nephrologist.^{44–46} Even when practices make comprehensive modality education programs available, many patients start RRT with little or no prior care by a nephrologist. These late-referred patients invariably start treatment with in-center HD with a central venous catheter.^{47,48} Even though “urgent-start” PD has been performed for decades, a growing number of centers around the world have now developed these programs both to increase the use of PD and reduce the proportion of patients that start dialysis with a central venous catheter.^{49–57} Successful implementation of urgent-start PD requires the ability to (1) educate late-referred patients on short notice about treatment options; (2) place PD catheters in a timely manner; and (3) offer intermittent PD in a hospital or dialysis facility up until the patient can be trained to perform treatments safely at home.⁵⁸ A large number of case-series have reported successful implementation of urgent-start PD without an increase in incidence of leaks or other therapy-related mechanical complications.^{49–57}

The elderly or the disabled is another group of patients that have significantly lower use of PD, even though many such patients would prefer treatment at home.⁵⁹ Many programs have long used family members to help patients with PD.⁶⁰ Several countries

Table 1. Summary of studies from around the world demonstrating greater reductions in risk for death in patients treated with PD compared with in-center HD

Author, Year	Country/Region	Periods	Mortality Trends by Modality	Trends in Comparative Survival
Mehrotra et al., 2007 ²²	United States	1996–1997 1998–1999 2000–2001 2002–2003	Compared with 1998–1999, the adjusted hazards for patients starting PD to die or transfer to HD within 12 mo was 17% lower; no significant difference over time for patients starting HD	The adjusted hazards ratio for death (PD, HD) were 1.07 (1.04, 1.11), 1.08 (1.06, 1.11), and 1.03 (0.99, 1.06), respectively
Mehrotra et al., 2011 ²³	United States	1996–1998 1999–2001 2002–2004		The adjusted hazards ratio for death (PD, HD) were 1.33 (1.21, 1.46), and 0.99 (0.87, 1.14), respectively
Chang et al., 2012 ²⁴	Taiwan	1997–2001 2002–2006		
Yeates et al., 2012 ²⁵	Canada	1991–1995 1996–2000 2001–2004		The adjusted hazards ratio for death (PD, HD) were 1.08 (1.02, 1.15), 1.13 (1.07, 1.20), and 0.99 (0.92, 1.06), respectively
Heaf and Wehberg, 2014 ²⁶	Denmark	1990–1994 1995–1999 2000–2004 2005–2010	Adjusted death risk for patients starting HD and PD in 2005–2010 was 30% (95% confidence interval, 13% to 37%) and 46% (95% confidence interval, 37% to 51%) lower compared with patients who started HD in 1990–1994	The adjusted hazards ratio for death (PD, HD) were 0.95 (0.85, 1.06), 0.90 (0.82, 1.00), 0.84 (0.77, 0.92), and 0.80 (0.71, 0.89), respectively
Marshall et al., 2015 ²⁷	Australia and New Zealand	1998–2002 2003–2007 2008–2012	Compared with 1998–2002, adjusted death risk for patients starting HD in 2008–2012 was 21% lower (95% confidence interval, 15% to 26%); for patients starting PD, 27% lower (95% confidence interval, 11% to 23%)	
Ryu et al., 2015 ²⁸	South Korea	Each year, from 2005 through 2008	Compared with 2005, in 2008 adjusted death risk for patients starting HD was 15% lower (95% confidence interval, 9% to 20%) and starting PD 25% lower (95% confidence interval, 16% to 34%)	Among patients who started dialysis in 2008, no significant difference in risk for death for patients treated with HD, compared with those treated with PD (adjusted hazards ratio, 0.91 [0.82, 1.00])
van de Luitjgaarden et al., 2015 ²⁹	Europe (ERA-EDTA Registry)	1993–1997 1998–2002 2003–2007	Compared with 1993–1997, adjusted death risk for patients starting HD in 2003–2007 was 18% lower (95% confidence interval, 16% to 20%) and starting PD was 36% lower (95% confidence interval, 33% to 39%)	The adjusted hazards ratio for death (PD, HD) were 1.02 (0.98, 1.06), 1.00 (0.96, 1.03), and 0.91 (0.88, 0.95), respectively

ERA-EDTA, European Renal Association - European Dialysis and Transplant Association.

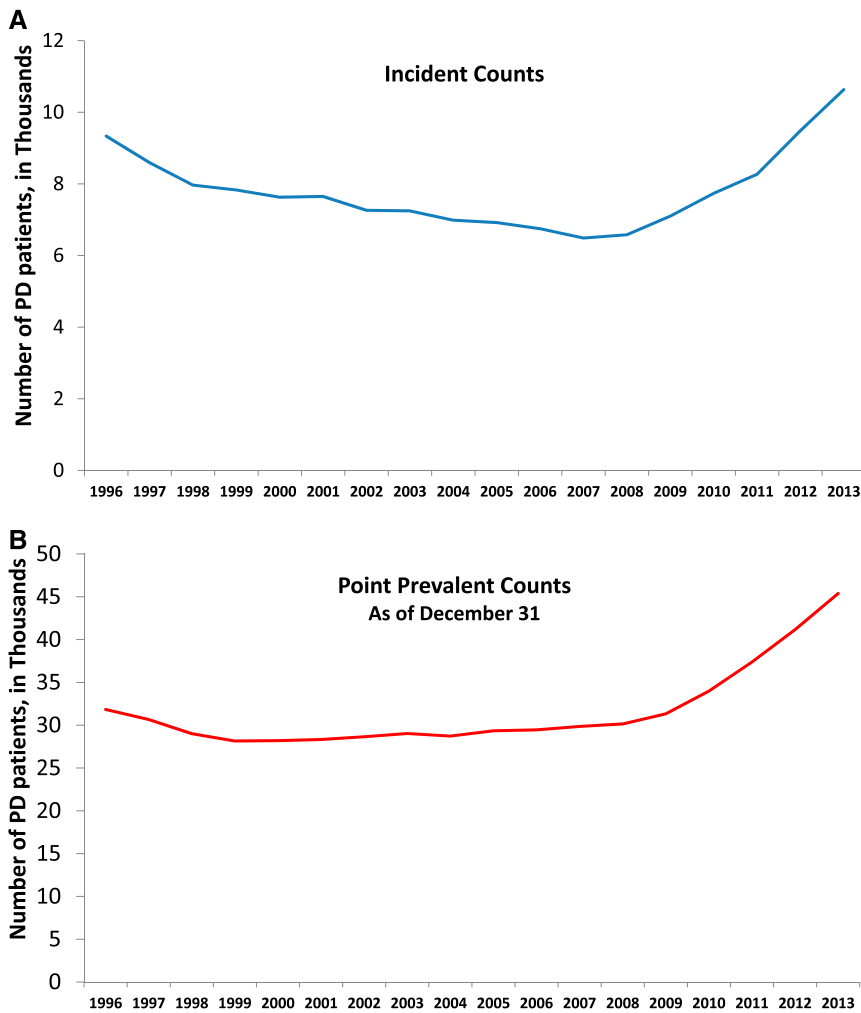


Figure 2. Secular trends in the number of patients treated with PD in the United States (1996–2013). (A) The number of patients treated with PD by 90 day of start of maintenance dialysis; (B) Point prevalent counts of the number of patients treated with PD as of December 31 of each calendar year.

have extended this concept to include a visiting nurse to help patients with PD at home.^{59,61–64} Some of these patients require assistance only for a short period of time.⁶³ Observational studies suggest that patients undergoing assisted PD have similar rates of bacterial peritonitis as with self-care PD and similar patient-reported outcomes and hospitalization as with in-center HD.^{61,64,65}

Finally, racial/ethnic minorities in the United States have a significantly lower use of home-based dialysis therapies.⁶⁶ It is imperative to further study this to ensure all patients have equal access to all dialysis modalities without regard to their race/ethnicity.

IMPROVED UNDERSTANDING OF PERITONEAL PHYSIOLOGY AND PATHOPHYSIOLOGY

The primary goal of dialysis is to remove water and uremic solutes, and the effectiveness of their removal is an important determinant of outcomes of patients treated with PD.^{67,68} Recent studies have expanded our understanding of solute and water transport processes across the peritoneum some of which could be leveraged for increasing the efficiency of PD.

Aquaporins in the Peritoneum

The water channel aquaporin-1 (AQP1) is constitutively expressed in endothelial

cells lining peritoneal capillaries.⁶⁹ It is a member of a highly conserved family of water channels that are organized as homotetramers, with each monomer containing a central pore that facilitates the movement of water across the lipidic membranes.⁷⁰ The deletion of AQP1 in mice results in 50% decrease in net cumulative ultrafiltration, and abolition of sodium sieving.^{71,72} Indeed, glucose is effective as an osmotic agent because of the presence of the ultrasmall pore materialized by AQP1 in peritoneal endothelial cells.⁷³ Investigators are currently examining AQP1 as a therapeutic target to increase ultrafiltration with PD. High-dose dexamethasone increases AQP1 expression in peritoneal capillaries of rodents resulting in enhanced free-water transport and ultrafiltration.⁷⁴ Steroids may be efficacious in humans as illustrated by comparing ultrafiltration in patients before and after kidney transplantation.⁷⁵ Another potential agent is an arylsulfonamide, AqF026, the first pharmacologic agonist of AQP1 that interacts with an intracellular loop involved in the gating of the channel.⁷⁶ It enhances AQP1-mediated water transport and net ultrafiltration in rodents. These two examples give hope for the possibility of developing pharmacologic therapies targeting AQP1 to enhance ultrafiltration with PD.

Intraperitoneal Inflammation

There is increasing evidence that differences in chronic intraperitoneal inflammation, particularly IL-6 production by mesothelial and resident cells in the peritoneum, are primarily associated with differences in peritoneal solute transfer rate, which are in turn strongly associated with PD clinical outcomes.^{67,68,77–80} Consistent with this, genetic variants associated with higher IL-6 production are associated with higher peritoneal solute transfer rate.^{81,82}

In addition to chronic inflammation, episodes of peritonitis are associated with acute increases in intraperitoneal inflammation resulting in higher peritoneal solute transfer rates and lower ultrafiltration.⁸³ Studies in rodents suggest that

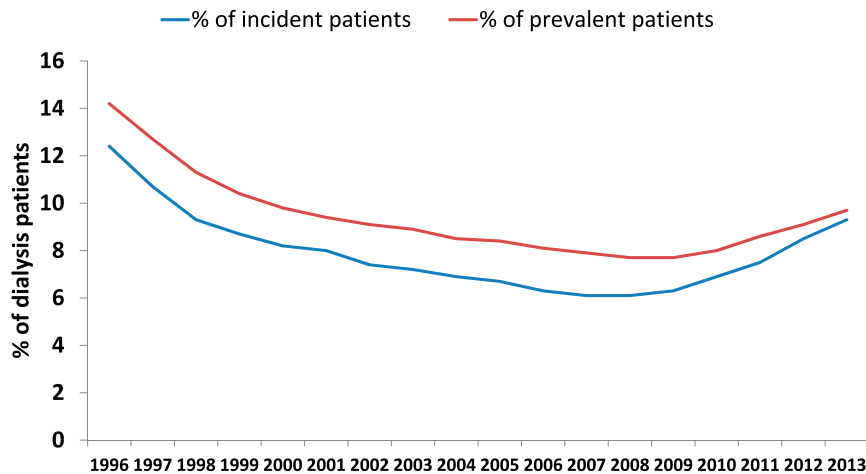


Figure 3. Secular trends in the proportion of patients undergoing maintenance dialysis treated with PD in the United States (1996–2013). The blue line represents the proportion of all patients undergoing maintenance dialysis treated with PD 90 days from the date of first dialysis and the red line represents the proportion of all patients undergoing maintenance dialysis on December 31 of any calendar year.

locally released vasoactive substances, particularly nitric oxide, may mediate the increase in peritoneal solute transfer rate.^{84–86} Pharmacologic inhibition or genetic deletion of the endothelial nitric oxide synthase significantly attenuates intraperitoneal inflammation in animals with peritonitis and the associated change in peritoneal solute transfer rate and ultrafiltration.⁸⁵

These findings point to potential therapeutic targets to be explored in the future to improve PD efficiency.

Structural and Functional Changes over Time

Prolonged treatment with PD is associated with structural (fibrosis, angiogenesis, hyalinizing vasculopathy) and functional (increased peritoneal solute transfer rate, ultrafiltration failure) changes.⁸⁷ One of the most serious complications of long-term PD is encapsulating peritoneal sclerosis, a rare complication characterized by an exaggerated fibrogenic response of the peritoneum.^{88,89} Studies suggest that peritoneal ultrafiltration capacity decreases before the clinical manifestation of encapsulating peritoneal sclerosis and that the primary mechanism is reduction in osmotic conductance (ultrafiltration volume for a given osmotic gradient) that is related to the

increased collagen fiber density in the interstitium.^{88,90,91}

The mechanisms of peritoneal fibrosis remain debated. Progressive fibrosis is characterized by the release of growth factors such as TGF- β 1, resulting in the accumulation of α -smooth muscle actin myofibroblasts in the peritoneum.^{87,92} Several *in vitro* and *in vivo* studies indicated that myofibroblasts are derived from mesothelial cells through epithelial-mesenchymal transition,^{93–96} in which epithelial cells lose their polarity and differentiation, gain migratory and invasive properties, and become pluripotent mesenchymal stem cells that differentiate into fibroblasts. Consistent with studies questioning the role of epithelial-mesenchymal transition in renal fibrosis,^{97–99} Chen *et al.*¹⁰⁰ recently applied lineage-tracing technology in several models of peritoneal fibrosis and showed that submesothelial fibroblasts – and not mesothelial cells *via* epithelial-mesenchymal transition – are the major precursors of myofibroblasts.

These improvements in our understanding of the mechanisms involved in changes in the peritoneum with long-term PD hold hope that future therapies may allow us to ameliorate them. As an example, *post hoc* analysis of a recent randomized controlled trial suggests

that patients treated with biocompatible PD solutions may not have the increase in peritoneal solute transfer rate after the first month of therapy, as seen with conventional PD solutions.^{101,102} Observational studies have also raised the possibility that inhibitors of the renin-angiotensin-aldosterone system may ameliorate change in peritoneal solute transfer capacity over time¹⁰³; the beneficial effect of these drug classes, however, has not been tested in clinical trials.

CARDIOVASCULAR RISK MODIFICATION IN PD PATIENTS

About 40%–60% of deaths in PD patients are associated with cardiovascular events¹⁰⁴; even more can be considered indirectly related if the link between cardiovascular disease, inflammation and frailty leading to debilitation, transfer to HD, and treatment withdrawal are considered.^{79,105–107} Registry analyses suggest that PD patients may have a higher risk of myocardial infarction compared with HD.^{104,108} This section is focused on nonconventional cardiovascular risk factors, with emphasis on modification by treatment with PD (Figure 4). A more comprehensive evaluation of evidence of cardiovascular risk factors is included in recently published clinical practice guidelines.^{109,110}

Importance of Metabolic Risk Factors and the Role of Glucose-Sparing Regimens

The most obvious risk factors exacerbated by PD are metabolic, related to systemic glucose absorption from the dialysate. They include worsening dyslipidemia, insulin resistance and metabolic syndrome, and weight gain.^{111–117} Yet, the evidence that they translate into significantly worse outcomes for PD patients is variable. For example, the greater weight gain with PD compared with HD is unclear. Patients gain weight after starting PD, and this is closely mirrored by an increase in total cholesterol and fat mass. However, in many circumstances this weight gain reflects catch-up

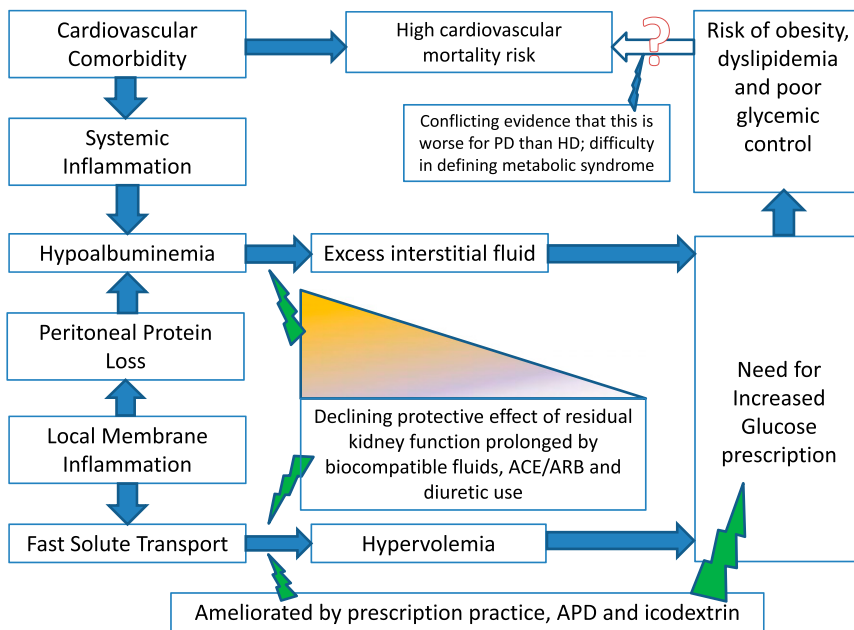


Figure 4. Overview of interrelationships between modality-specific factors that may contribute to the cardiovascular risk of patients undergoing PD.

of the predialysis loss.^{111,118} This also happens with HD and a large study found that the risk of significant weight gain is lower with PD.¹¹⁸ For patients undergoing maintenance dialysis, the greater nutritional risk is being underweight and in this context additional calories from the dialysate could be advantageous^{119,120}; what is less clear is whether the lower death risk with larger body size consistently observed among patients undergoing HD is seen with PD.¹²¹ This may be influenced by other regional factors as the risk or benefit of being obese in PD varies between national registries, being harmful in Australasia and neutral or advantageous in the United States and Brazil.^{118,122–124}

One potential shortcoming of the registry analyses is the use of body mass index as surrogate for obesity which may underestimate fat gain in PD patients; the preferred use of waist circumference in defining metabolic syndrome is also hard to validate in PD patients in whom abdominal girth measurements are influenced by intra-abdominal fluid. Equally, measuring insulin resistance in a patient who is never fasting because of continuous glucose absorption presents problems. This may explain the incon-

sistencies between studies linking metabolic syndrome in PD to worse outcomes.^{114,125,126} Again the role of treatment modality varies, as new-onset diabetes is less common in Chinese patients treated with PD than HD, and in either dialysis modality much less than for newly transplanted patients.^{127,128} What at first sight may be an obvious modality-specific risk factor for cardiovascular disease, *i.e.*, systemic glucose absorption, turns out to be much less clear.

Regardless of these inconsistencies, there are now several studies showing that these risk factors are modifiable, although none of the trials are sufficiently powered to address hard endpoints. Glucose sparing solutions have been developed, such as amino acid and icodextrin. In nonpatients with diabetes, the colloid agent icodextrin used in the long exchange prevents nonfluid (presumed fat) weight gain and improves insulin resistance.^{129–131} In patients with diabetes, including when in combination with amino acid solutions, icodextrin improves glycemic control and lipid profiles.^{132–134} Poor glycemic control is associated with worse outcomes in diabetic PD patients.^{135,136}

Given the concern of increased risk of myocardial infarction in patients receiving PD the lack of evidence that statins can reduce this is disappointing.¹³⁷ Interestingly, a prespecified subgroup analysis of the Study of Heart and Renal Protection study, the only trial to include PD patients, found a nonsignificant but potentially important risk reduction suggesting that these patients may be different and worthy of further investigation.¹³⁸

Residual Kidney Function

Residual kidney function is strongly associated with better survival in studies of both PD and HD.^{139,140} In the Canada-USA study every 250 ml higher urine volume per day translated into a 36% lower 2-year mortality.¹³⁹ Evidence suggests that PD is associated with better preservation of residual kidney function compared with HD, typical reported rates of loss in clearance per month being 0.25–0.28 and 0.30–0.40 ml/min per 1.73 m², respectively^{141–146}; the mechanism is still debated but is likely to be in part the avoidance of intravascular volume depletion which occurs more frequently with HD.¹⁴⁷ Cohort studies and controlled trials find that in patients undergoing PD the rate of loss of kidney function could be slowed with avoidance of volume depletion, use of blockers of renin-angiotensin-aldosterone system, and the use of diuretics (urine volume and sodium loss).^{145,146,148,149}

The most studied intervention to maintain residual kidney function is the use of biocompatible solutions. Biocompatible solutions avoid the need for sterilizing glucose at higher pH so limiting the formation of glucose degradation products and thus avoiding their associated toxicity. The Balance, Australia and New Zealand study demonstrated that these solutions delay the time to anuria, and slow the rate of loss of clearance from 0.28 to 0.22 ml/min per 1.73 m² per month.¹⁵⁰ Subsequent meta-analyses have confirmed this observation.^{143,151}

Volume Management

As already alluded to, volume depletion puts residual kidney function at risk but equally volume excess is detrimental.

Hypertension in patients healthy enough to be wait-listed for transplant is associated with worse survival and there is a growing body of evidence from bioimpedance data that over-hydration predicts worse survival.^{152,153} In anuric patients the ultrafiltration performance of the peritoneum becomes critical and daily net fluid removal of <750–1000 ml is associated with higher mortality.^{154,155} There is evidence that automated PD and icodextrin use can improve the risks associated with fast peritoneal solute transfer rate.^{68,156,157}

The fluid status of PD patients is no worse on average than for HD patients predialysis, but that the distribution of fluid is likely different.¹⁴⁷ Hypoalbuminaemia is more common with PD due to the additional peritoneal protein losses and is a reflection of their largely independent systemic and intraperitoneal inflammatory states.^{79,158} Intravascular plasma volume is typically normal in PD, even when excess fluid associated with hypoalbuminemia is present, indicating it being in the interstitial compartment.¹⁵⁹ This means that normalizing fluid status runs the risk of plasma volume depletion, hypotension, and faster loss of residual kidney function. A recent trial using bioimpedance to support clinical decision making found that fluid status was very stable in PD patients with residual kidney function whereas the challenge in anuric patients was how to reduce volume status so that extracellular fluid was reduced in parallel with the loss in lean body tissue.¹⁶⁰ The only intervention that achieved this was an increase in glucose prescription. As things stand, clinicians need to exercise caution and clinical judgment in setting target weights.

PERITONITIS

Peritonitis continues to be a major cause of morbidity and mortality in PD patients globally.^{104,161,162} Depending on the underlying causative organism, PD-related peritonitis is complicated by relapse in 3%–20% (14% overall),

catheter removal in 10%–88% (22% overall), permanent HD transfer in 9%–74% (18% overall), and death in 0.9%–8.6% (2%–6% overall) of cases.^{163–174} After a single episode of peritonitis, the risks of death due to infection, cardiovascular disease, and dialysis withdrawal are markedly increased in the first month and continue to remain significantly elevated for up to 6 months afterward.¹⁰⁶ Severe and/or repeated peritonitis episodes may also culminate in sufficient damage that precludes successful PD and, rarely, encapsulating peritoneal sclerosis.^{175,176} The complication imposes a heavy financial burden on the health care system with one health economics analysis estimating the average cost of peritonitis-related hospitalization to be of the order of \$3100.¹⁷⁷ Finally, concern about the risk of PD peritonitis represents one of the most important patient-related barriers to the greater uptake of PD.¹⁷⁸

Nevertheless, peritonitis is a preventable condition and there is abundant evidence that infection rates around the world have decreased considerably over time.¹⁷⁹ Single center observational studies from different parts of the world, as well as multinational national

registry studies have reported that the rates of PD-related infections have steadily decreased over the last 10–20 years.^{161,180–185} Although this reduction has been most apparent for Gram-positive infections, significant reductions have also been reported for Gram-negative peritonitis.^{161,180–185} These reductions have been variously attributed to the use of twin bag disconnection systems, implementation of mupirocin chemoprophylaxis protocols, topical exit site application of gentamicin, coprescription of nystatin or fluconazole with antibiotic therapy, improved training of PD patients and/or staff, and better identification and targeting of peritonitis risk factors.^{180,186–193} Within Australia, country-wide PD-related peritonitis rates fell significantly by 37% over a 5-year period from 0.62 episodes per patient-year in 2008 to 0.39 episodes per patient-year in 2013 after a concerted, multidisciplinary and multipronged national peritonitis reduction campaign involving quarterly audit and feedback of individual unit peritonitis rates, prioritization of peritonitis prevention trials by the Australasian Kidney Trials Network, updating national clinical practice guidelines on peritonitis, launching peritonitis

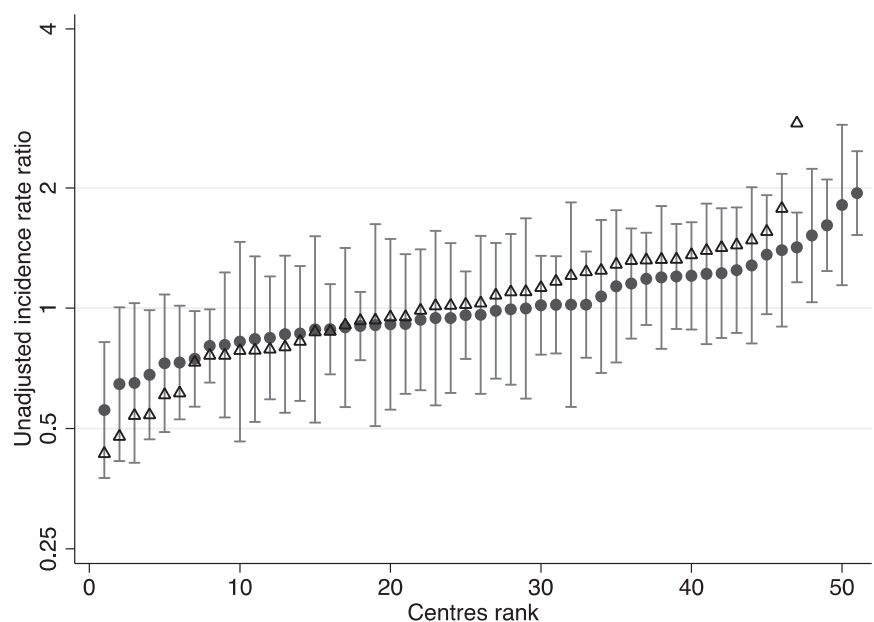


Figure 5. Center-specific PD-related peritonitis rates (incidence rate ratios) in Australia during the periods 2004–2008 (open triangles) and 2009–2013 (solid circles).

guideline implementation projects, publishing of a call to action paper, establishment of a PD Academy to provide PD training to junior nephrologists and nursing staff, and development of a Home Dialysis Network to support home dialysis patients (<http://homedialysis.org.au/>).^{194–199}

Despite these improvements, there remains a wide and unacceptable variation in reported rates from different countries, ranging from 0.06 episodes/year in Taiwan to 1.66 episodes/year in Israel.²⁰⁰ Furthermore, up to 20-fold variation in peritonitis rates has been reported between centers within individual countries, such as Australia (Figure

5),^{174,194} Austria,²⁰¹ Scotland,²⁰² and the United Kingdom.²⁰³ The sources of these variations have not been adequately investigated but may relate to center-related factors, such as unit size, topical antibiotic prophylaxis, or PD training practices.^{161,192,201,202,204,205} A previous national survey found highly variable and generally poor compliance of centers with clinical practice guidelines for prevention of peritonitis.²⁰⁶ More recently, an Australia and New Zealand Dialysis and Transplantation Registry analysis found that the wide variation in peritonitis rates across Australian dialysis centers was decreased by 16% after adjustment for patient

characteristics (*e.g.*, demographics, comorbidities), and was reduced by a further 34% after accounting for a limited number of center-level characteristics, such as unit size, proportion of dialysis patients treated with PD, use of antifungal chemoprophylaxis, icodextrin use, performance of peritoneal equilibration tests, cyclor use, and propensity to admit patients with PD-related peritonitis to hospital.²⁰⁷ This observation suggests that center practices play a dominant role in mediating between-center variation in peritonitis rates. Similarly, unacceptable variations in the outcomes of peritonitis treatment have been significantly associated with observed

Table 2. Important thematic areas in need of further research

Thematic Areas	Details of Areas in Need of Further Research
Utilization and outcomes with PD	<p>Approaches to modality education that optimize decision support and reduce decisional conflict</p> <p>Clinical outcomes of late-referred patients starting treatment with PD (“urgent-start” PD) and in-center HD with central venous catheter</p> <p>Comparative effectiveness of home and in-center dialysis for end-of-life care for patients with ESRD</p> <p>Understanding reasons for the low utilization of PD by racial/ethnic minorities and tailored interventions to overcome barriers</p> <p>Adequately powered studies comparing a broad range of patient-reported outcomes with different dialysis modalities, including effect-modification by cultural differences</p>
Peritoneal physiology and pathobiology	<p>Mechanisms of osmosis, choice of solutions, new osmotic agents, combination of different types of osmotic agents</p> <p>Biomarkers of peritoneal solute and water transfer – at baseline and over time on PD: genetics, proteomics, metabolomics</p> <p>New indications for PD: intoxications (<i>e.g.</i>, liposome-supported PD for intoxication and metabolic disorders)</p> <p>Reversibility of the structural changes in the peritoneal membrane: fibrosis, angiogenesis</p> <p>Cellular mechanisms of peritoneal fibrosis and EPS</p> <p>Identification of molecular counterparts of additional transport structures, <i>e.g.</i>, the small pores</p>
Cardiovascular risk with PD	<p>Validation of more practical approach to defining metabolic syndrome for PD patients</p> <p>Better understanding of high risk cardiovascular risk phenotypes to include interactions with diabetes, gender, and ethnicity</p> <p>Adequately powered study to test the benefit of statins</p> <p>Trials to evaluate additional strategies for preserving residual kidney function</p> <p>Trials addressing the risk/benefit of preserving residual kidney function while optimizing volume status and BP management, including further evaluation of technologies to evaluate fluid status at the bedside</p>
Peritonitis	<p>Determining which PD training methods, curricula, and structured assessment methods lead to better peritonitis rates</p> <p>Determining whether structured periodic retraining after initial baseline training leads to a reduction in peritonitis rates</p> <p>Development and evaluation of rapid (within hours) organism identification methods in PD-related peritonitis</p> <p>Does use of continuous versus intermittent intraperitoneal antibiotics for peritonitis treatment lead to better peritonitis outcomes?</p> <p>Does temporary conversion of automated PD patients to CAPD during peritonitis treatment lead to better outcomes compared with leaving patients on automated PD?</p>

EPS, encapsulating peritoneal sclerosis; CAPD, continuous ambulatory peritoneal dialysis.

deviations in practice from clinical practice guidelines.²⁰⁸

The key message from these studies is that although peritonitis rates are generally improving globally over time, there have been marked and unacceptable variations in peritonitis rates and outcomes between centers in many countries. This variation is explained to a large extent by variation in center practices, with poorer results generally being observed in units that deviate from evidence-based best practice recommendations (and not infrequently from their own unit policies).¹⁹⁵ Key strategies for correcting this ubiquitous problem in PD include benchmarking of PD center peritonitis rates and outcomes through the establishment of national PD peritonitis registries within each country, alignment of PD practice in each center with clinical practice guidelines, strengthening of clinical governance within each unit, and adoption of a whole-of-unit approach to continuous quality improvement, including root cause analysis of all cases of peritonitis within each center to identify areas for improvement.^{200,208}

FUTURE DIRECTIONS

Despite tremendous progress on multiple fronts, patients with ESRD carry a heavy burden of disease and treatment. We owe to the patients to continue to reconfigure health care delivery to better match dialysis modality to patients' desires, improve the efficiency of therapy without putting a greater burden on patients, reduce cardiovascular risk, and better apply lessons learnt from research in clinical practice (Table 2).

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