

The Current State of Peritoneal Dialysis

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Abstract

It took almost 60 years for peritoneal dialysis (PD) to be used widely for the long-term treatment of end-stage renal disease. Technical innovations resulted in a significant reduction in therapy-related complications, allowing patients to be maintained on PD for longer periods of time. More recently, there has also been a greater decrease in mortality for patients treated with PD compared to in-center hemodialysis such that the two modalities now provide equivalent patient survival. In parallel, changes in public policy have spurred an unprecedented expansion in the use of PD in several parts of the world. Our understanding of the molecular mechanisms involved in solute and water transport across the peritoneum has expanded leading to the identification of potential therapeutic targets for improving efficiency of PD. The pathobiology of structural and functional changes in the peritoneum with long-term PD has also been clarified providing new targets 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 the high risk for cardiovascular events. Tremendous progress has been made in developing interventions that substantially reduce the risk of PD-related peritonitis. Yet, the gains have been unequal primarily because of unequal application of knowledge from research into clinical practice. The work to date has further highlighted the areas in need for innovation as we continue to strive to improve the health and outcomes of patients treated with PD.

Key Words: peritoneum; end-stage renal disease; peritoneal solute transfer rate; fibrosis; ultrafiltration failure; cardiovascular disease; metabolic; peritonitis; mortality

The first attempt to use the human peritoneum to dialyze uremic retention solutes was made almost one hundred years ago¹. 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 acute kidney injury and end-stage renal disease (ESRD)²⁻¹⁰. This, in addition to the development of indwelling catheter that provided access to peritoneal cavity at will and standardization of the composition of dextrose-based dialysate culminated in the introduction of continuous ambulatory PD 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 PD solutions¹³⁻¹⁶. In this review, we highlight the major developments in the application of PD for the treatment of ESRD.

Utilization and Outcomes with Peritoneal Dialysis

The early experience with PD raised numerous concerns whether the therapy was a viable alternative to in-center hemodialysis for the long-term treatment of ESRD. These included but were not limited to high risks 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 to in-center hemodialysis^{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 for

death for patients starting with PD around the world than for those undergoing in-center hemodialysis (Table 1)²²⁻²⁹. As a result, virtually all studies indicate PD and in-center hemodialysis now provide similar short (1- or 2-year) or long-term (up to 5 years) survival (Table 1)^{23-25, 29-31}. Furthermore, there has been a significant reduction in risk of patients treated with PD transferring to in-center hemodialysis in the United States indicating a lower risk of therapy-related complications³². These improvements have significant implications as they allow patients to receive treatment with a renal replacement therapy best suited to their values, expectations, and lifestyles, and 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 hemodialysis and PD vary around the world{Karopadi, 2013 #1}. In most developing 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{Karopadi, 2013 #1}. This is important as it has long been recognized that non-medical factors, including reimbursement, are the primary determinants of the proportion of ESRD patients treated with PD in any region of the world^{33, 34}. With a backdrop provided by recent studies that PD provides equivalent survival to in-center hemodialysis, several countries around the world have introduced changes to increase PD utilization to leverage its lower costs to the health-system³⁵. 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^{36, 37}. Since 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 PD³⁸. 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 cost³⁹. Finally, China has been rapidly expanding access to renal replacement therapy to its population and has a policy that encourages the use of PD without mandating it³⁵. 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 1 and 2) that the dominant manufacturer was not able to increase the supply of dialysate to meet the increasing demand leading to rationing of solutions in 2014⁴⁰. The shortage has abated but has not been completely eliminated.

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^{41, 42}. 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^{43, 44} {Rioux, 2011 #2}. Even when practices make comprehensive modality education programs available, many patients start renal replacement therapy with little or no prior care by a nephrologist. These late-referred patients invariably start treatment with in-center hemodialysis with a central venous catheter^{45, 46}. Even though “urgent-start” PD has been performed for decades, a growing number of centers around the world have developed these programs both to increase the use of PD and reduce the proportion of patients that start dialysis with a central venous catheter⁴⁷⁻⁵⁵. Successful implementation of “urgent-start” PD requires (1) the ability to 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 home⁵⁶. 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 complications⁴⁷⁻⁵⁵.

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 home⁵⁷. Many programs have long used family members to help patients with PD⁵⁸. Several countries have extended this concept to include a visiting nurse to help patients with PD at home^{57, 59-62}. Some of these patients require assistance only for a short-period of time⁶¹. 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 hemodialysis^{59, 62, 63}.

Finally, racial/ethnic minorities in the United States have a significantly lower use of home-based dialysis therapies⁶⁴. 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^{65, 66}. Recent studies have expanded our understanding of solute and water transfer across the peritoneum some of which could be leveraged for increasing the efficiency of PD.

Aquaporins in the Peritoneum

The water channel aquaporin-1 is constitutively expressed in endothelial cells lining peritoneal capillaries⁶⁷. 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 facilitate the movement of water across the lipidic membranes⁶⁸. The deletion of *Aqp1* in

mice results in 70% decrease in solute-free ultrafiltration, 50% decrease in cumulative ultrafiltration, and abolition of sodium sieving^{69, 70}. Indeed, glucose is effective as an osmotic agent because of the presence of aquaporin-1 in peritoneal endothelial cells⁷¹. Investigators are currently examining aquaporin-1 as a therapeutic target to increase ultrafiltration with PD. High-dose dexamethasone increases aquaporin-1 expression in peritoneal capillaries of rodents resulting in enhanced free-water transport and ultrafiltration⁷². Steroids may be efficacious in humans as illustrated by comparing ultrafiltration in patients before and after kidney transplantation⁷³. Another potential agent is an arylsulfonamide, AqF026, the first pharmacological agonist of aquaporin-1 that interacts with an intracellular loop involved in the gating of the channel⁷⁴. It enhances aquaporin-mediated water transport and net ultrafiltration in rodents. These two examples give hope for the possibility of developing pharmacologic therapies targeting aquaporin-1 to enhance ultrafiltration with PD.

Intra-peritoneal inflammation

There is increasing evidence that differences in chronic intraperitoneal inflammation, particularly interleukin-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^{65, 66, 75-78}. Consistent with this, genetic variants associated with higher interleukin-6 production are associated with higher peritoneal solute transfer rate^{79, 80}.

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 ultrafiltration⁸¹. Studies in rodents suggest that locally released vasoactive substances, particularly nitric oxide, may mediate the increase in peritoneal solute transfer

rate⁸²⁻⁸⁴. Pharmacological 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 ultrafiltration⁸³.

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) changes⁸⁵. 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^{86, 87}. Studies suggest that peritoneal ultrafiltration capacity decreases prior to the clinical manifestation of encapsulating peritoneal sclerosis^{88, 89} 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 interstitium⁸⁶.

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^{85, 90}. Several *in vitro* and *in vivo* studies indicated that myofibroblasts are derived from mesothelial cells through epithelial-mesenchymal-transition⁹¹⁻⁹⁴, 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 fibrosis⁹⁵⁻⁹⁷, Chen *et al*⁹⁸ 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^{99, 100}. Observational studies have also raised the possibility that inhibitors of renin-angiotensin-aldosterone system may ameliorate change in peritoneal solute transfer capacity over time{Kolesnyk, 2009 #3}; 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 events¹⁰¹; even more can be considered indirectly related if the link between cardiovascular disease, inflammation and frailty leading to debilitation, transfer to hemodialysis, and treatment withdrawal are considered^{77, 102-104}. Registry analyses suggest that PD patients may have a higher risk of myocardial infarction compared to hemodialysis^{101, 105}. This section is focused on non-conventional 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^{106, 107}.

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 gain¹⁰⁸⁻¹¹⁴. Yet, the evidence that they

translate into significantly worse outcomes for PD patients is variable. For example, the greater weight gain with PD compared to hemodialysis 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 of the pre-dialysis loss^{108, 115}. This also happens with hemodialysis and a large study found that the risk of significant weight gain is lower with PD¹¹⁵. For patients undergoing maintenance dialysis, the greater nutritional risk is being underweight and in this context additional calories from the dialysate could be advantageous^{116, 117}; what is less clear is whether the lower death risk with larger body size consistently observed among patients undergoing hemodialysis is seen with PD¹¹⁸. 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^{115, 119-121}.

One potential shortcoming of the registry analyses is the use of body mass index as surrogate for obesity which may under-estimate 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 inconsistencies between studies linking metabolic syndrome in PD to worse outcomes^{111, 122, 123}. Again the role of treatment modality varies, as new-onset diabetes is less common in Chinese patients treated with PD than hemodialysis, and in either dialysis modality much less than for newly transplanted patients^{124, 125}. 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 non-diabetics icodextrin used in the long exchange prevents non-fluid (presumed fat) weight gain and improves insulin resistance¹²⁶⁻¹²⁸. In diabetics, including when in combination with amino-acid solutions, icodextrin improves glycemic control and lipid profiles¹²⁹⁻¹³¹. Poor glycemic control is associated with worse outcomes in diabetic PD patients^{132, 133}.

Given the concern of increased risk of myocardial infarction in PD patients the lack of evidence that statins can reduce this is disappointing¹³⁴. Interestingly a pre-specified subgroup analysis of the SHARP study, the only trial to include PD patients, found a non-significant but potentially important risk reduction suggesting that these patients may be different and worthy of further investigation¹³⁵.

Residual Kidney Function

Residual kidney function is strongly associated with better survival in studies of both PD and hemodialysis^{136, 137}. In the CANUSA study every 250 ml higher urine volume per day translated into a 36% lower 2-year mortality¹³⁶. Evidence suggests that PD is associated with better preservation of residual kidney function compared to hemodialysis, typical reported rates of loss in clearance per month being 0.25-0.28 and 0.30-0.40 ml/min/1.73m², respectively¹³⁸⁻¹⁴³; the mechanism is still debated but is likely in part the avoidance of intravascular volume depletion which occurs more frequently with hemodialysis¹⁴⁴. 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)^{142, 143, 145, 146}.

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 balANZ 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/1.73m²/month¹⁴⁷. Subsequent meta-analyses have confirmed this observation^{140, 148}.

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^{149, 150}. 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^{151, 152}. There is evidence that automated PD and icodextrin use can improve the risks associated with fast peritoneal solute transfer rate^{66, 153, 154}.

The fluid status of PD patients is no worse on average than for hemodialysis patients pre-dialysis, but that the distribution of fluid is likely different¹⁴⁴. 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^{77, 155}. Intravascular plasma volume is typically normal in PD, even when excess fluid associated with hypoalbuminemia is present, indicating it being in the interstitial compartment¹⁵⁶. 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 tissue¹⁵⁷. 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^{101, 158, 159}. 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 hemodialysis transfer in 9-74% (18% overall), and death in 0.9-8.6% of cases (2-6% overall)¹⁶⁰⁻¹⁷¹. Following 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 afterwards¹⁰³. Severe and/or repeated peritonitis episodes may also culminate in sufficient damage that precludes successful PD and, rarely, encapsulating peritoneal sclerosis^{172, 173}. The complication imposes a heavy financial burden on the healthcare system with one health economics analysis estimating the average cost of peritonitis-related hospitalization to be of the order of \$3100¹⁷⁴. Finally, concern about the risk of PD peritonitis represents one of the most important patient-related barriers to the greater uptake of PD¹⁷⁵.

Nevertheless, peritonitis is a preventable condition and there is abundant evidence that infection rates around the world have decreased considerably over time¹⁷⁶. Single center observational studies from different parts of the world, as well as a multi-national national registry studies have reported that the rates of PD-related infections have steadily

decreased over the last 10-20 years^{158, 177-182}. Although this reduction has been most apparent for Gram-positive infections, significant reductions have also been reported for Gram-negative peritonitis^{158, 177-182}. 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, co-prescription of nystatin or fluconazole with antibiotic therapy, improved training of PD patients and/or staff, and better identification and targeting of peritonitis risk factors^{177, 183-190}. 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 following a concerted, multi-disciplinary and multi-pronged 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 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/>)¹⁹¹⁻¹⁹⁶.

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 Israel¹⁹⁷. Furthermore, up to 20-fold variation in peritonitis rates has been reported between centers within individual countries, such as Australia (Figure 5)^{171, 191}, Austria¹⁹⁸, Scotland¹⁹⁹, and the United Kingdom²⁰⁰. 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^{158, 189, 198, 199, 201, 202}. A previous national survey found highly variable and generally poor compliance of centers with clinical practice

guidelines for prevention of peritonitis²⁰³. More recently, an ANZDATA 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 anti-fungal chemoprophylaxis, icodextrin use, performance of peritoneal equilibration tests, cyclor use and propensity to admit patients with PD-related peritonitis to hospital²⁰⁴. 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 deviations in practice from clinical practice guidelines²⁰⁵.

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)²⁰⁵. 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^{197, 206}.

Future Directions

Despite tremendous progress on multiple fronts, patients with end-stage renal disease 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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Potential Conflicts of Interest

Simon Davies has received research funding, speakers honoraria and participated in occasional advisory boards for Baxter Healthcare and Fresenius Medical Care.

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Figure Legends

- Figure 1:** Major landmarks in the development of peritoneal dialysis as a treatment for end-stage renal disease (1923-'78). Abbreviations, AKI: acute kidney injury; PD, peritoneal dialysis.
- Figure 2:** Secular trends in the number of patients treated with peritoneal dialysis in the United States (1996-2013). (1A) The number of patients treated with peritoneal dialysis by 90 of start of maintenance dialysis; (1B) Point prevalent counts of the number of patients treated with peritoneal dialysis as of December 31 of each calendar year.
- Figure 3:** Secular trends in the proportion of patients undergoing maintenance dialysis treated with peritoneal dialysis in the United States (1996-2013). The blue line represents the proportion of all patients undergoing maintenance dialysis treated with peritoneal dialysis 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.
- Figure 4:** Overview of interrelationships between modality-specific factors that may contribute to the cardiovascular risk of patients undergoing peritoneal dialysis
- 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)

Table 1: Summary of studies from around the world demonstrating greater reductions in risk for death in patients treated with peritoneal dialysis compared to in-center hemodialysis

Author, Publication Year	Country/Region	Eras	Mortality Trends by Modality	Trends in comparative survival
Mehrotra, '07 ²²	United States	1996-1997 1998-1999 2000-2001 2002-2003	Compared to 1998-1999, the adjusted hazards for patients starting peritoneal dialysis to die or transfer to hemodialysis within 12 months was 17% lower; no significant difference over time for patients starting hemodialysis	
Mehrotra, '11 ²³	United States	1996-1998 1999-2001 2002-2004		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
Chang, '12 ²⁴	Taiwan	1997-2001 2002-2006		The adjusted hazards ratio for death (PD/HD) were 1.33 (1.21, 1.46), and 0.99 (0.87, 1.14) respectively
Yeates, '12 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, '14 ²⁶	Denmark	1990-1994 1995-1999	Adjusted death risk for patients starting hemodialysis and peritoneal dialysis in 2005-2010	The adjusted hazards ratio for death (PD/HD) were 0.95 (0.85, 1.06), 0.90 (0.82, 1.00), 0.84

		2000-2004 2005-2010	was 30% (95% confidence interval, 13-37%) and 46% (95% confidence interval, 37-51%) lower compared to patients who started hemodialysis in 1990-1994	(0.77, 0.92), and 0.80 (0.71, 0.89), respectively
Marshall, '15 ²⁷	Australia and New Zealand	1998-2002 2003-2007 2008-2012	Compared to 1998-2002, adjusted death risk for patients starting hemodialysis in 2008-2012 was 21% lower (95% confidence interval, 15-26%) compared to 1998-2002; for patients starting PD, 27% lower (95% confidence interval, 11-23%)	
Ryu, '15 ²⁸	South Korea	Each year, from 2005 through 2008	Compared to 2005, in 2008 adjusted death risk for patients starting hemodialysis was 15% lower (95% confidence interval, 9-20%) and starting peritoneal dialysis 25% lower (95% confidence interval, 16-34%)	Among patients who started dialysis in 2008, no significant difference in risk for death for patients treated with HD, compared to those treated with PD (adjusted hazards ratio, 0.91 (0.82, 1.00))
van de Luitgaarden, '15 ²⁹	Europe (ERA-EDTA Registry)	1993-1997 1998-2002 2003-2007	Compared to 1993-1997, adjusted death risk for patients starting hemodialysis in 2003-2007 was 18% lower (95% confidence interval 16-20%) and starting peritoneal dialysis was 36% lower (95% confidence interval, 33-39%)	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

Table 2: Important thematic areas in need for further research**Utilization and Outcomes with Peritoneal Dialysis**

- Approaches to modality education that optimize decision support and reduce decisional conflict
- Clinical outcomes of late-referred patients starting treatment with PD (“urgent-start” PD) and in-center hemodialysis with central venous catheter
- Comparative effectiveness of home and in-center dialysis for end-of-life care for patients with end-stage renal disease
- Understanding reasons for the low utilization of PD by racial/ethnic minorities and tailored interventions to overcome barriers
- Adequately powered studies comparing a broad range of patient-reported outcomes with different dialysis modalities, including effect-modification by cultural differences

Peritoneal Physiology and Pathobiology

- Mechanisms of osmosis, choice of solutions, new osmotic agents, combination of different types of osmotic agents
- Biomarkers of peritoneal solute and water transfer - at baseline and over time on PD: genetics, proteomics, metabolomics
- Nanoparticles, new indications for PD: intoxications (liposome supported peritoneal dialysis for intoxication and metabolic disorders)
- Getting hematopoietic stem cells from patients on PD
- Identification of other molecular counterparts of additional transport structures, e.g. the small pores

Cardiovascular Risk with Peritoneal Dialysis

- Validation of more practical approach to defining metabolic syndrome for PD patients

- Better understanding of high risk cardiovascular risk phenotypes to include interactions with diabetes, gender and ethnicity
- Adequately powered study to test the benefit of statins
- Trials to evaluate additional strategies for preserving residual kidney function
- Trials addressing the risk/benefit of preserving residual kidney function while optimizing volume status and blood pressure management, including further evaluation of technologies to evaluate fluid status at the bedside.

Peritonitis

- Determining which PD training methods, curricula and structured assessment methods lead to better peritonitis rates
- Determining whether structured periodic retraining after initial baseline training leads to a reduction in peritonitis rates
- Development and evaluation of rapid (within hours) organism identification methods in PD-related peritonitis.
- Does use of continuous vs. intermittent intraperitoneal antibiotics for peritonitis treatment lead to better peritonitis outcomes?
- Does temporary conversion of automated PD patients to continuous ambulatory PD during peritonitis treatment lead to better outcomes compared with leaving patients on automated PD?

