REVIEW

The truth on current peritoneal dialysis: state of the art

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ABSTRACT

The share of peritoneal dialysis (PD) in the spectrum of chronic dialysis has decreased markedly in the Netherlands in the last 15 years. Consequently, the knowledge of nephrologists and nursing staff on PD has declined leading to a negative spiral in which loss of experience resulted in loss of enthusiasm to offer PD to patients and also in less interest in the new PD developments. All these changes took place while the results of PD improved and patient survival was at least similar to that on haemodialysis.

The aim of this review is first to give a summary of the principles and practice of patient and staff education and to describe the role of the medical contribution in decision-making. On this basis, the second aim is to update internist-nephrologists on a number of issues that have been underexposed in the past.

Recent patient and technique survival data of PD patients is reviewed, and also the new insights into dialysis adequacy. The presence of residual renal function is the main determinant of patient survival together with prevention of overhydration. Urea and creatinine removal are not important at all when patients are still passing urine. Many early problems with PD are due to the peritoneal catheter and suggestions are made for improvement of its function. The prevention and management of infections is reviewed, and also the regular assessment of peritoneal function. Free water transport is a predictor of encapsulating peritoneal sclerosis (EPS), which should be assessed regularly. The pathogenesis of EPS, treatment and the decreasing incidence are discussed.

KEYWORDS

Assessment of peritoneal dialysis, education in peritoneal dialysis, encapsulating peritoneal sclerosis, infections in peritoneal dialysis, peritoneal dialysis

INTRODUCTION

Peritoneal dialysis (PD) is a modality for chronic renal replacement therapy which was introduced in the Netherlands in 1979. This form of home dialysis developed well and 31% of all dialysis patients were treated with PD in 2002, while the number of home haemodialysis patients was very small (< 5%) and the remaining 69% of patients received in-centre haemodialysis (ICHD).[1] The 'Planningsbesluit Dialyse' was abolished by the Dutch government in 2002, making it relatively easy to increase the number of ICHD facilities. This was associated with a progressive rise in the number of ICHD patients since 2003 and a concomitant decrease in the contribution of PD to 15% in 2015, but with a wide variation among centres.[2] The contribution of ICHD in 2015 was 82%, while home haemodialysis accounted for only 3%. This increase in ICHD was initially tolerated by health insurance companies, who considered dialysis costs a minor fraction of their total budget and had no objection to the most expensive treatment. The current emphasis of these companies on home dialysis mainly concerns haemodialysis, but health managers often lack the necessary insight into the type of patients that can be treated with either home haemodialysis or PD.

The declining share of PD in the spectrum of renal replacement therapy in the Netherlands, despite similar or even better patient survival[3] and other advantages such as longer preservation of residual renal function,[4,5] caused a negative spiral. In this spiral, loss or absence of knowledge on PD leads to an unwarranted pessimistic view of this form of renal replacement therapy and thus has an impact on predialysis patient education. On the other hand, use of PD is increasing worldwide, especially in South East Asia and South America. The aim of the current review is to update nephrologists on the state of the art of PD, thereby also improving the knowledge of the nursing staff, and to ensure access to this mode of renal replacement therapy for all well-informed patients.

Patient education

The impact of dialysis on all aspects of quality of life for patients and their families makes patient-centred and shared decision-making of utmost importance.[6] In the absence of medical contraindications, the choice of dialysis modality should be based on the preference of a well-informed and well-prepared patient. Balanced and unbiased information about haemodialysis and PD, including their relative benefits and drawbacks, should be given early in the disease process. Being confronted with end-stage renal failure, many patients do not feel the urge to choose between renal replacement modalities. This can be due to fear, non-acceptance or being overwhelmed by information. Patient engagement by a dedicated multidisciplinary team may identify possible barriers and overcome these by providing timely patient-tailored care, education and support. Such multidisciplinary teams should consist of a physician, nurse, dietician, social worker and include family members or support persons. The team should address health literacy, and psychosocial and cultural values related to the choice. Indeed, several studies indicate that patients who are educated about their treatment options will choose PD in 50 to 60% of the cases.[7-9] This is not surprising, since important themes from a patient's perspective such as keeping as much independence as possible, quality and quantity of life, flexibility of the daily treatment schedule[6] are all met by PD. Have patient preferences changed over time, explaining the generally observed decrease in PD utilisation? In the past, a randomised controlled trial (RCT) comparing PD with haemodialysis, which was included in the observational Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), had to be stopped early due to poor patient recruitment; ~50% of patients exhibited a strong preference for PD and refused to be randomly assigned to either haemodialysis or PD.[8] A more recent Dutch study on a structured multidisciplinary predialysis education program with a home-focused approach, showed that with this program the uptake of home dialysis increased.[10] The use of dialysis decision tools in patient education appears to be effective and also influences the choice and uptake of PD.[6-8,10-12] All studies show that predialysis patient education and training is a key target for more widespread utilisation of PD.[13] It can therefore be concluded that the decrease in the number of PD patients is not the result of changed patient preferences.

The wide range in penetration of PD among dialysis centres in the Netherlands raises a number of questions.[1] Have nephrologists and nurses in the Netherlands developed a somewhat biased view of PD over time by judging several factors as being relative contraindications for PD,[14] not confident with the fact that some of these can be overcome by more intense and individualised training?[2] Is it seen as a treatment in the short run because of previous overemphasis on the required dialysis dose and/or fear of encapsulating peritoneal sclerosis?[3] Did the low penetration of PD in the past decade already decrease experience with and thereby confidence in this modality? Clinician preference plays a major role in the multidisciplinary team.[15] To offset the concerns about nephrologists not being comfortable with PD, training programs must provide young doctors adequate exposure to PD, for instance by offering elective rotation in centres with larger PD populations.[13] Other team members may also have similar views on contraindications. Decision-making tools may help the team think differently about the treatment they recommend for individual patients. A continuing nursing education initiative was able to modify the opinions of in-centre haemodialysis nurses towards home modalities.[16] Most of the perceived barriers to PD in the elderly, such as dexterity, and visual and cognitive impairments, can be overcome with appropriate care, education and support, including social help, psychological counselling and assisted PD.[17,18] Also, limited health literacy is common in patients on chronic peritoneal dialysis, but is not associated with key adverse infectious complications or hospitalisations.[19] The importance of a dedicated team and the need for individualised support and training is even more true for elderly patients. Training that encompasses self-efficacy can enhance self-management skills.[20]

Modality education programs mainly direct their efforts to patients with advanced chronic kidney disease prior to initiation of dialysis therapy, but ~50% of patients will start dialysis urgently in the hospital.[21] This subset of patients typically start renal replacement therapy with haemodialysis by a catheter, although some centres offer acute PD. In these cases targeted modality education specifically addressing modality choice appears to be effective, since high-performing centres convert a significant number of such patients to PD in the first six months of therapy.[7-9] Alternatively, an acute start with PD only requires a dedicated surgeon, nephrologist or

radiologist for catheter placement. It can be regarded as a safe and feasible alternative to acute haemodialysis through a central-venous catheter, also in older patients and with ~10% incidence of minor peri-catheter leaks without a detrimental effect on patient outcome or PD technique survival (i.e. survival on PD after censoring for death and transplantation).[22,23]

Beyond patients preferences and nephrologists choices, other clinical, social, macro-economic and macro-organisational factors might explain why PD is underused. To turn the tide, a number of issues need to be addressed. These include patient-tailored education and training, investigation of perceived barriers, and the creation of a collaborating network to share experience, confidence and expertise with centres that are more supportive of PD use. Hopefully the recent initiative to follow patients prospectively by patient-reported outcome measures (PROMs, results of healthcare reported from patients points of view), will shine light on some of these issues. The same holds true for the recent initiative by the DOMESTICO group (Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes), which aims to assess whether home dialysis is associated with better quality of life, at least comparable clinical outcomes and reduced costs compared with in-centre haemodialysis. In addition, implementation of 'Best Practices' for home dialysis may lead to a change in treatment modality choices for end-stage renal disease patients and their doctors.

Patient and technique survival

Despite the initial poor results of PD, already in 1997 the Canadian Organ Replacement Register reported a better 2-year survival in almost 12,000 patients who started PD between 1990 and 1994, compared with haemodialysis.[24] These results were later confirmed in other parts of the world, including the Netherlands.[25] Recently a study from the European Renal Association Registry showed slightly higher adjusted five-year survival with haemodialysis and PD for patients who started dialysis between 2003 and 2007, with a hazard ratio for mortality on PD of 0.91 (confidence interval: 0.88-0.95) compared with haemodialysis.[3] Technique survival with PD has always been lower than with haemodialysis. This is partly related to the experience of the attendant, as was shown by Huisman et al.[26] A more detailed analysis of reasons for drop-out in the NECOSAD cohort, including about 2000 patients on haemodialysis and PD, showed that catheter-related and abdominal complications were the most important reasons for early PD discontinuation. Analysis of the 709 patients who started PD between 1997 and 2007 showed that after four years, 22% had been transplanted, 19% died and 24% were transferred to haemodialysis.[27] Ignorance on the part of the nephrology community in the Netherlands regarding survival data may be an important reason for the decreased penetration of PD.

Adequacy of dialysis

A high plasma concentration of urea is generally considered a representation of uraemic toxicity in non-dialysed patients with chronic renal failure, despite the fact that it is not toxic. Urea and creatinine are made up of small molecules and are therefore easily removed from the body by dialysis techniques, where diffusion is the main transport mechanism. The removal of unmeasured larger molecules and protein-bound toxins by dialysis is almost absent or much lower. This contrasts to native kidneys that remove solutes by glomerular filtration and tubular secretion, neither of which are influenced by their molecular weight. It follows from this reasoning that plasma urea is a poor marker of uraemic toxicity in patients treated with chronic dialysis. Yet, adequacy of dialysis is usually defined by the clearance of urea (Kt/V_{urea}), while in PD the clearance of creatinine is also used (weekly creatinine clearance/1.73 m^2 body surface area).

Targets for solute removal in PD were first formulated by the Dialysis Outcomes Quality Initiative (DOQI) in 1997 and were intended for use in the USA.[28] These consisted of the following targets: Kt/V_{urea} 2.0/week and weekly creatinine clearance 60 l/1.73 m^2. In comparison, an average continuous ambulatory peritoneal dialysis (CAPD) patient has a peritoneal Kt/V_{urea} of 1.5-1.7 and a peritoneal creatinine clearance of 40-45 litres/ week.

The above recommendations, based on results from the CANUSA study,[29] have been extremely harmful for the further development of PD. This study included 680 new PD patients from Canada and the USA and showed that higher solute clearances were associated with better survival. However, the mean follow-up was only 15 months, which makes confounding by residual renal function a likely explanation for the superior survival. This was confirmed in many other studies that found no effect of peritoneal solute clearances on mortality. A re-analysis of the CANUSA study indeed showed that mortality was not associated with peritoneal clearances, but only with urine production.[30] The importance of residual renal function was confirmed in the NECOSAD cohort, not only concerning patient survival, but also for patients' perceived quality of life.[31] Therefore a $Kt/V_{urea} < 1.7$ in the absence of uraemic symptoms is not a reason to transfer a PD patient to haemodialysis. The absence of evidence for the DOQI recommendations has been established firmly in two RCTs: from Mexico[32] and from Hong-Kong.[33] Both were unable to detect any effect of increasing peritoneal solute clearances to reach the DOQI targets on patient survival, not even in anuric patients. So, it is clear that pushing-up peritoneal Kt/V_{urea} from 1.6 to 2.0 per week in patients without signs of underdialysis has no effect on their survival: the effect of peritoneal solute clearance is overpowered by that of residual renal function. A number of studies have shown that the latter is better preserved in PD than in haemodialysis.[4,5]

Evidently a minimum dialysis dose is required in anuric patients. For ethical reasons this cannot be investigated in an RCT. A NECOSAD analysis showed that only Kt/V_{urea} < 1.5 and creatinine clearance <40 litres/week were associated with increased mortality.[34] Both targets are easily achieved with CAPD. Also a minimum target for ultrafiltration was investigated, but was impossible to establish. This is not really surprising, because the development of overhydration is not only dependent on fluid removal, but also on patients' fluid intake.

Only a few patients with a slow solute transport state who are treated with an automated peritoneal dialysis (APD) scheme consisting of many short (e.g. 30 min) exchanges, can have a discrepancy between a normal Kt/V and a creatinine clearance < 40 litres/week. These patients often have clinical signs of underdialysis. All discussed data reveal that the emphasis on peritoneal solute clearances is a misconception, based on guidelines that were not evidence-based and that considered residual renal function to be equal to a dialysis clearance, thereby neglecting the fact that kidney function consists of more than just glomerular filtration.

Catheter complications

It is frustrating for patients and dialysis staff when a carefully planned start of PD training is disturbed by catheter problems. These include leakage and catheter dysfunction, the latter usually presenting as outflow obstruction. Leakage generally responds well to temporary interruption of PD, but catheter dysfunction is a more serious problem that usually needs surgical intervention.[35] Attempts to salvage the catheter are often postponed, which regularly leads to the urgent start of haemodialysis using a central venous catheter. All in all, catheter problems are still amongst the leading causes of early PD technique failure.[25,36-38]

Fortunately, this situation can be improved, but nephrologists will have to adopt an important role by investing in a local, multidisciplinary peritoneal access team. According to the International Society for Peritoneal Dialysis (ISPD) guideline for Peritoneal Access, this team should consist of surgeons, nurses and nephrologists.[39] However, as fluoroscopic wire catheter manipulation may also be used to rescue a non-functioning PD catheter (see below), it may be advisable to include an interventional radiologist. The goals of such a team would be to reduce the incidence of primary PD catheter failures, and to develop and maintain the skills and infrastructure needed to rescue a non-functioning PD catheter.

One study suggested that larger centre size is associated with less catheter dysfunction.[40] Unfortunately, the almost 45% reduction in the number of patients on PD in the Netherlands since 2002[1] has been accompanied by an increasing number of dialysis centres to 112 at present, many of these being small. The resulting reduction in the number of catheter insertions per centre must have reduced the surgical experience in catheter placement and salvage techniques, inducing a vicious circle of poor catheter outcomes, a defeatist attitude towards PD and low PD prescription. In the current situation, therefore, providing additional training in PD catheter insertion and salvage techniques seems mandatory. This need has been recognised in North America by the institution of a Peritoneal Dialysis University for Surgeons,[41] an initiative that was recently also introduced in Europe by the International Society for Peritoneal Dialysis (ISPD). Interestingly, a post-course analysis of this theoretical program revealed that it resulted in a considerable increase in the use of techniques that may improve catheter outcomes.[41] In the Netherlands, a PD catheter workshop for surgeons has been held in Maastricht for many years, and continuation of such a program would obviously be very helpful in the current situation. However, providing training in surgical PD catheter management will need time to become effective. For the short term, therefore, it may also be necessary to cluster PD catheter surgery in dedicated regional centres that have maintained relatively large PD patient populations. Such institutions could also serve as practical training centres for surgeons wishing to improve their PD catheter management skills.

The present ISPD guideline, which dates from 2010, recommends that '... local expertise at individual centres should govern the choice of method of PD catheter insertion' and does not recommend a specific catheter insertion method.[39] A more recent guideline approved by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) in 2014 contains a similar statement.[42] Nevertheless, a balanced and comprehensive literature review included in the latter guideline shows that dedicated surgical teams applying advanced forms of laparoscopy, including adhesiolysis, catheter tip suture fixation, preperitoneal tunnelling or omentopexy during insertion or combinations of the above, can obtain very low catheter dysfunction rates being in the region of only 0-10%. In accordance with this, a recent meta-analysis showed that laparoscopic PD catheter insertion is associated with a clinically relevant reduction in migration rate and a higher one-year catheter survival.[43] Interestingly, it has recently been suggested that, despite higher initial costs, laparoscopic PD catheter insertion may reduce the total costs due to fewer postoperative complications.[44] All in all, the literature clearly supports the view that advanced laparoscopic PD catheter insertion by dedicated surgical teams can help PD units struggling with high PD catheter dysfunction and failure rates. The guidelines mentioned earlier do not express a preference for a particular type of

PD catheter.[39,42] However, a recent meta-analysis showed that PD catheters with a straight intraperitoneal segment had a significantly better survival than those with a coiled tip, suggesting preferential use of straight catheters.[45]
Another promising method is the use of the self-locating catheter, featuring a tip with a 12-gram tungsten weight. A large non-randomised multicentre trial reported a marked reduction in the percentage of dislocations when comparing the self-locating catheter with Tenckhoff catheters, and superior two-year survival of the self-locating catheter.[46] A subsequent RCT comparing insertion of the straight Tenckhoff catheters with the self-locating catheter in 61 patients showed that reoperations for obstruction had to be performed in 22% of the Tenckhoff catheter insertions, but in none of the procedures involving the self-locating catheter.[47] In a larger RCT in 78 patients, the self-locating catheter had a significantly longer malposition-free survival rate than the straight Tenckhoff catheter.[48] The Tenckhoff catheter had a 4.5-fold increased probability of malfunction.[48] In these two studies, a surgical technique under local anaesthesia and sedation was used, but laparoscopic insertion with its additional advantages is also feasible.[49]
Finally a robust program has to be available to salvage malfunctioning PD catheters. An often neglected procedure that can be performed timely without general anaesthesia is wire manipulation under fluoroscopic control, which is quite often successful without major complications.[50-52] If this approach fails, the usefulness of laparoscopy, which allows repositioning of the catheter under direct vision and performing interventions, including adhesiolysis, relief of omental wrapping, catheter tip fixation, omentopexy or partial omentectomy, has been documented extensively.[53-55] In a recent study from the Netherlands, malfunction of PD catheters could be corrected by laparoscopy in almost 80% of cases.[56]
Improving catheter outcomes in PD patients in the Netherlands is possible, but this requires close cooperation between enthusiastic and optimistic nephrologists and surgeons who are willing to apply advanced laparoscopy for PD catheter insertion and salvage. Other methods to prevent catheter dysfunction may include the preferential use of catheters with a straight intraperitoneal segment or application of the self-locating catheter.

Infections

Dialysis procedure-related infections occur more often in PD patients than systemic infections.[57] These include exit-site infections, tunnel infections and peritonitis, and are an important reason for dropout from PD.[25] To reduce the incidence of PD-related infections, a number of prophylactic measures should be employed.
First, a single dose of an intravenous antibiotic should be administered prior to or at the time of PD catheter insertion or repositioning to reduce the risk of subsequent peritonitis.[58] A randomised controlled trial found that 1000 mg vancomycin intravenously before catheter insertion was superior to 1000 mg intravenous cefazolin.[59] However, this study was performed before 2000 and in the USA, where there is a different spectrum of antibiotic resistance. In addition, vancomycin has to be administered slowly to avoid the 'red man syndrome'. Furthermore, there is a risk of development of vancomycin-resistant microorganisms. In daily clinical practice a first-generation cephalosporin is most frequently used as prophylactic agent and is probably a good choice.
Second, patients must be trained to perform good hand hygiene while carrying out an exchange, to prevent touch contamination. Indeed, a multidisciplinary education program including retraining was associated with a lower peritonitis rate.[60] Home visits may be useful for detecting problems. Furthermore, each centre should have an appropriate protocol to deal with contamination to prevent the development of peritonitis.[61] Cultures of the PD effluent should be taken and prophylactic antibiotics should be prescribed if a PD solution is infused after contamination or if the catheter administration set is open and exposed to bacteria. Although there is no standard regimen for this situation, a single dose of intraperitoneal antibiotic could be given, for instance vancomycin with or without Gram-negative coverage. Positive culture results are helpful in the determination of subsequent therapy.
Third, all PD patients should use a topical antibiotic either at the exit site, intranasally, or both.[61] A systematic review showed that application of mupirocin at the exit site or intranasally reduced the risk of exit-site infections by 57% and of peritonitis due to all microorganisms by 41%. The risk reduction was even 70% for infections with *S. aureus*.[62] Topical application of mupirocin cream (2%) and gentamicin cream (0.1%) at the exit site were compared in an RCT in 133 patients.[63] The use of gentamicin was associated with lower rates of catheter infection and peritonitis. Gentamicin was as effective as mupirocin in preventing *S. aureus* infections but more effective in preventing Gram-negative peritonitis and *P. aaeruginosa* catheter infections. Unfortunately, the availability of gentamicin is limited in the Netherlands. In patients with a history of *P. aeruginosa* exit-site infection or in carriers of mupirocin-resistant *S. aureus*, prophylaxis with gentamicin cream may be warranted. Studies of other solutes than antibiotics are attractive to prevent the development of resistance. Regrettably, a recent RCT concluded that there is no role for medihoney in the prevention of PD-related infections.[64]
Fourth, prophylaxis to prevent fungal peritonitis should be considered in PD patients who are treated with a course of antibiotics for longer than a week. This was investigated in two RCTs. In the first RCT[65] 199 PD patients received

oral nystatin (500,000 units 4 times a day) whenever a course of antibiotics was prescribed, regardless of the indication for the antibiotic therapy. In the control group, no nystatin was routinely co-prescribed. Patients in the nystatin-treated group had a significantly higher *Candida* peritonitis-free survival after two years. A more recent RCT in 420 patients with bacterial peritonitis showed that administration of oral fluconazole 200 mg every 48 hours throughout the time they received antibiotics significantly prevented fungal peritonitis.[66] Given the mild side effect profile, nystatin may be a good choice.

Fifth, intravenous antibiotic prophylaxis is recommended to prevent peritonitis in PD patients undergoing invasive gastrointestinal and gynaecological procedures, including colonoscopy.[67] The optimal antibiotic regimen is unknown. A single dose of 1000 mg cefazolin intravenously combined with 500 mg metronidazole intravenously prior to the procedure is possibly a good choice. In all cases, the abdomen should be emptied of PD fluid before the procedure. Furthermore, oral antibiotic prophylaxis two hours prior to extensive dental intervention, for example 2000 mg amoxicillin, is also suggested to prevent peritonitis.[67]

Catheter infections can lead to subsequent peritonitis.[68] Therefore, early detection and prompt treatment with appropriate antibiotics is recommended.[67] Empirical antibiotic therapy should be based on patient history and centre-specific sensitivity pattern. In most cases, an oral agent can be given. Intraperitoneal vancomycin could be necessary if a *Corynebacterium* species is cultured that is resistant to oral antibiotics. This treatment should also be considered in case of refractory culture-negative exit-site infections, because *Corynebacterium* is sometimes difficult to isolate and not always recognised as a pathogen. Treatment must be continued until the exit site appears normal, but for at least two weeks.[67]

The very high incidence of peritonitis in the past has been reduced to less than one episode/patient year.[69] A target of 0.5 has been included in the ISPD guideline.[67] Abdominal pain and/or cloudy effluent are the presenting symptoms of peritonitis, but it should always be considered in PD patients with gastrointestinal symptoms. The diagnosis is confirmed by a PD effluent white blood cell count > 0.1 x 10^9/l or 100/µl after a dwell time of at least two hours with > 50% polymorphonuclear cells and/or a positive PD effluent culture.[67] In case of a short dwell time, a proportion of > 50% polymorphonuclear cells is highly suggestive for peritonitis, even if the white blood cell count is < 0.1 x 10^9/l. Although Gram's staining of the PD effluent is often negative, presence of yeast cells or pseudohyphae allows prompt initiation of antifungal therapy.

Empirical antibiotic therapy should start immediately and cover both Gram-positive and Gram-negative microorganisms. Intraperitoneal administration is generally preferred.[67] No antibiotic regimen has been proved to be superior to others as empirical therapy.[70] Gram-positive microorganisms can be treated with vancomycin or a first-generation cephalosporin and Gram-negative microorganisms by a third-generation cephalosporin or an aminoglycoside.

Culture reveals a Gram-positive, non-enterococcal microorganism in more than 50% of peritonitis episodes, with coagulase-negative staphylococci being the most common species.[69,71,72] Such episodes are mostly due to touch contamination. While most coagulase-negative staphylococci peritonitis episodes respond well to intraperitoneal antibiotic treatment and catheter removal is required in only 4% of cases,[69] relapsing peritonitis can occur suggesting biofilm formation. Intracatheter urokinase in combination with oral rifampicin could be considered in those cases to prevent catheter removal.[73] *S. aureus* peritonitis is frequently due to catheter infection, resulting in catheter removal.[74-76] This underscores the need for topical prophylaxis. *Corynebacterium* species should be treated with effective intraperitoneal antibiotics for three weeks to prevent a relapse.[77]

Gram-negative microorganisms are cultured in 20-30% of all PD-related infections. *Pseudomonas* species and *Enterobacteriaceae* are the most relevant pathogens.[69,71,72] While *Pseudomonas* species are considered to be 'water' bacteria, especially known for causing pulmonary infections, *Enterobacteriaceae* are labelled as enteric microorganisms with *E. coli*, *Klebsiella*, *Serratia*, and *Enterobacter* species as typical representatives. Peritonitis caused by these Gram-negative microorganisms is associated with a high catheter removal rate, approaching 40%[69] and therefore a high technique failure rate. Therefore, the ISPD advises to treat *Pseudomonas* peritonitis with two antibiotics with different modes of action for which the microorganism is sensitive, for instance intraperitoneal gentamicin or oral ciprofloxacin combined with intraperitoneal ceftazidime.[67] Recently, a study from the Netherlands showed that the poor outcome of peritonitis caused by enteric microorganisms in PD patients aged > 50 years could be improved by applying a treatment protocol involving temporary discontinuation of PD without catheter removal (peritoneal rest) and intravenous and intracatheter meropenem.[72] This Mero-PerRest protocol resulted in a cure rate of 90%, a lower catheter removal rate of 4%, and a better technique survival of 90%. These figures are far superior to the results of a more traditional intraperitoneal gentamicin-rifampicin based regimen. The Mero-PerRest protocol was most effective in patients with polymicrobial enteric peritonitis and also in peritonitis episodes caused by non-enteric microorganisms.

In case of fungal peritonitis the ISPD recommends immediate catheter removal, resulting in a high technique failure rate.[67] Therefore, antifungal prophylaxis is recommended. In case of *Candida albicans*, catheter removal can sometimes be prevented by treatment with intraperitoneal administration of amphotericin B and 5-flucytosine.[78] Similar results have been reported more recently with intracatheter instillation of amphotericin B as a catheter lock after each CAPD exchange combined with intraperitoneal fluconazole and oral flucytosine.[79]

In summary, PD-related infections are still encountered, but are usually a manageable problem. Unconventional treatment strategies such as peritoneal rest and antibiotic catheter locks could contribute to improving technique survival.

Functional assessment of the peritoneum as dialysis membrane

Overhydration is probably the most important risk factor for death in peritoneal dialysis patients.[80] Yet, assessment of the transport function of the peritoneum used as a dialysis membrane, has mainly focused on small solute clearances. A standardised test for functional peritoneal assessment, the peritoneal equilibration test (PET), was published in 1987 and has been widely promoted ever since.[81] The PET consists of a four-hour dialysis exchange with a 2.27% glucose-based dialysis solution and a blood sample. Calculated parameters after drainage include the dialysate/plasma concentration ratio (D/P) of creatinine, the ratio of the dialysate glucose concentration before inflow (D0) and after drainage (Dt/D0), and net ultrafiltration being the difference between the drained and the instilled volume. D/P creatinine is dependent on the number of perfused peritoneal microvessels. Therefore it represents the effective peritoneal surface area. Ultrafiltration failure is an important, but not the only factor that can lead to overhydration. Mismatches between fluid intake, urine production and peritoneal fluid removal are common causes of overhydration. The 2.27% glucose may not be ideal for assessment of ultrafiltration capacity, because it only induces a limited quantity of ultrafiltrate. Consequently the arousal (incomplete drainage) may overwhelm the signal (ultrafiltered volume). The 3 x 4 rule is considered the best parameter for the presence of ultrafiltration failure.[82] According to this rule, ultrafiltration failure is present when net ultrafiltration is less than 400 ml after a four-hour dwell with a 3.86%/4.25% glucose dialysis solution. Longitudinal data from the Netherlands showed that ultrafiltration failure, as defined by the 3 x 4 definition, developed in <4% of patients within two years after starting PD, but in 21% at some time after more than two years.[83]

Investigations on net ultrafiltration assume that fluid transport occurs through a system of pores of uniform size within the vascular wall. Already in 1969 it became evident that the dialysate Na^+ concentration decreased in the initial phase of exchanges with very hypertonic dialysis solutions, i.e. 3.86% glucose or higher.[84] It took more than 30 years to demonstrate that this dilutional phenomenon was caused by the peritoneal water channel aquaporin-1 (AQP-1).[85] Glucose-induced crystalloid osmosis is required for free water transport (FWT) without transfer of solutes. Ultrafiltration during the first hour of a dwell usually consists of 40% FWT and 60% fluid transport through the so-called interendothelial small pores, which also allow transport of small solutes, such as urea, creatinine and glucose.[86] FWT is decreased in some long-term patients and extremely low in those with encapsulating peritoneal sclerosis (EPS).[83,87] The determination of FWT in long-term patients might identify those with extensive peritoneal fibrosis.[88] A simple calculation of FWT in patients is possible with the use of a one hour of 3.86% glucose exchange. Fluid transport together with Na+ transport is calculated as Na+ clearance. Subtraction of this from net ultrafiltration gives FWT.[89,90] However D/P and Dt/D0 ratios cannot be interpreted. This problem is solved with the modified (3.86% glucose instead of 2.27%) PET with temporary drainage after one hour for weighing and sampling, followed by reinfusion and final drainage after four hours (MoPET 1/4).[91] It follows from the abovementioned data that modern peritoneal dialysis should include regular measurement of peritoneal function, especially parameters of fluid transport. The MoPET 1/4 provides the best information that can be achieved in clinical practice.

Encapsulating peritoneal sclerosis

EPS is a clinical entity defined by signs and symptoms of (intermittent) bowel obstruction caused by excessive fibrosis of the visceral peritoneal membrane constricting the intestines. Although rare, it is a feared complication of PD as morbidity is high and mortality within the first year after diagnosis is on average 40%.[92] The number of patients who developed EPS has varied in time and between countries from 0.7-3.3%.[92] Duration of PD is by far the major determinant of the risk for the development of EPS.[93] For instance, in most case series and registries the occurrence of EPS in patients treated with PD for three years was almost absent. However, the incidence has been reported to rise with increasing time on PD to values of more than 10% in patients treated with PD for > 8 years.[94] Relatively recently, EPS was also documented as a complication in former PD patients relatively shortly after kidney transplantation. This has been coined

post-transplantation EPS and is in general less severe and associated with a substantially better patient survival.[95,96]
The current view on the pathogenesis of EPS distinguishes this entity from simple sclerosis of the peritoneal membrane, which is a limited fibrotic response to the exposure to conventional peritoneal dialysis fluids that contain not only extremely high glucose concentrations, but also glucose degradation products, and are acidic. Instead, EPS is a condition with much more extensive and dense collagenous peritoneal interstitial tissue, sometimes characterised by infiltration with helper T lymphocytes and type 2 macrophages, merging into a severe and advanced fibrotic response.[97,98] The growth factors CCN2, TGFβ and VEGF are key players.[99] The presence of an inflammatory reaction is also evidenced by activation of T cells[100] and the description in some studies of elevated concentrations of several markers of inflammation in the blood, such as C-reactive protein and soluble CD25. Also an increased dialysate interleukin-6 has been reported before the clinical diagnosis of EPS.[101-103] At present, it is not known why the peritoneal membrane of some PD patients responds with increased chronic inflammation and excessive fibrosis to long-term exposure to PD fluids.
Ultrafiltration failure is present in all EPS patients, but only 20% of patients with late ultrafiltration failure develop EPS.[104] Therefore, the presence of late ultrafiltration failure is not a predictor of EPS. The most striking abnormality in and before the condition, is a marked reduction of FWT,[83,87] which is an early sign of imminent EPS, as judged from its high discriminative power of 0.82.[104] A cut-off value of FWT < 75 ml in the first 60 minutes of a 3.86% glucose dwell is the best predictor of EPS.[104] In contrast, signs of EPS on abdominal imaging are usually only found late in the disease process.[105,106]
An important notion of the last decade is that EPS is no longer a condition without potentially therapeutic options. Especially tamoxifen and steroids are now considered an important first step in medical treatment.[107] When patients remain dependent on parenteral feeding or have a bowel perforation, surgeons specialised in EPS may perform peritonectomy and enterolysis (PEEL) with impressively good results.[108] In particular, patients with localised EPS are amenable to surgery.[109]
The risk for EPS was seen by many nephrologists in the Netherlands as an important factor to take into account when deciding to offer PD instead of haemodialysis.[110] In fact, this may have been fuelled by an unexpected rise in EPS cases documented between 1998 and 2005.[111] For this reason, the Dutch EPS Registry was started in 2009 with the goal to register all EPS cases in the Netherlands.[110] A recent analysis showed a significant decline by at least six-fold in the yearly incidence of EPS from 0.85% in 2009 to 0.14% in 2014. A clear explanation for this observation was not identified. However, this trend is strikingly similar to the decline in EPS prevalence recently reported from Japan and Germany.[112,113] The prevalence of EPS after eight years of PD treatment in Japan has fallen to 2.3%.[112] This may have been the result of the increased use of biocompatible solutions and glucose-sparing dialysis schedules.[112,114] Indeed, a recent study from Spain showed that the use of biocompatible PD solutions was associated with better preservation of the mesothelial layer, less thickening of the submesothelial compact zone, and less hyalinising vasculopathy.[115] Also, the incidence of post-transplantation EPS seems currently low. In a recent Dutch prospective study, no cases of post-transplantation EPS were found in PD patients undergoing kidney transplantation between 2009 and 2013.[116] This is probably for the greatest part explained by the average PD duration of 31 months in this cohort, reflecting the current kidney transplantation policy in the Netherlands.
At present, EPS should be considered a rare complication of PD in the Netherlands for which therapeutic interventions exist, specifically tamoxifen and PEEL by experienced surgeons. Given the severity of the condition, a high awareness for EPS remains needed, for instance by the measurement of FWT in long-term patients, but the risk for EPS should not be a reason to refrain from starting PD or to avoid transplantation of PD patients.

CONCLUSIONS

The decline of PD in the Netherlands cannot be explained by medical reasons. Whatever the causes, it has resulted in a downward spiral where loss of experience and insufficient knowledge on important pathophysiological and other related pertinent issues of this home dialysis modality have resulted in an almost exclusive attention to haemodialysis. This happened while it is now evident that patient survival on PD is at least similar or even better than that on haemodialysis, also in the long-term. To change the tide, the quality of education of patients, nurses and doctors needs updating. The above review is an effort by a group of professionals involved in peritoneal dialysis to revitalise the interest of the Nephrology and Internal Medicine communities in up-to-date PD. Important conclusions are that patient education can be improved, that PD leads to better preservation of residual kidney function, that the value of small uraemic toxin removal is less important than good management of the hydration state of patients, that peritonitis is a manageable problem, that EPS is a lesser problem than it used to be, and that imminent EPS can be identified before the clinical signs and symptoms appear. Therefore it can be concluded that PD is an excellent chronic dialysis modality that deserves a larger penetration than is currently present.

DISCLOSURES

None of the authors has anything to disclose.

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