Controversies in the Management of Infective Complications of Peritoneal Dialysis

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Abstract
Peritoneal dialysis is an effective form of renal replacement therapy. Despite improvements in connection technology, peritoneal infection is still the most important preventable cause of patient morbidity and mortality. There has been a shift in focus from treatment to prevention of infection, but wide variation in peritonitis incidence across and within peritoneal dialysis populations remains. This minireview aims to highlight current best practice, whilst discussing controversies in the diagnosis, prediction, prevention and management of peritonitis. Exit-site infection will not be discussed per se but only as it relates to peritonitis.

Key Words
Continuous ambulatory peritoneal dialysis · Peritoneal dialysis · Peritoneal effluent · Peritonitis · Exit-site infection · Tunnel infection · Antibiotic prophylaxis

Introduction
The use of continuous ambulatory peritoneal dialysis (CAPD) as an effective form of renal replacement therapy was first described by Popovich and Moncrief in 1978. Management and prevention of peritoneal dialysis (PD)-associated peritonitis (PDP) is the key factor in successful management of PD. PDP is the most common reason for patients to transfer to haemodialysis and causes significant morbidity with mortality in the region of 3.5–10% [1]. Even in those who do not immediately suffer technique failure, it can cause loss of residual renal function and dialysis adequacy, peritoneal membrane failure, decreases ultrafiltration and increases the risk of encapsulating peritoneal sclerosis [2].

Which Is the Best Diagnostic Technique?

PDP is defined by the International Society of Peritoneal Dialysis (ISPD) as 2 out of 3 of the following: (1) signs and symptoms; (2) white cell count (WCC) >100/ml of PD effluent (PDE) and >50% neutrophils after a dwell of at least 2 h, and (3) a positive culture of an organism from the PDE [3].

The correct culture of PDE is important to ensure appropriate antibiotics are used. ISPD guidelines recommend sampling 50 ml of PDE with aseptic technique. In automated PD (APD) the larger volumes and shorter dwell times mean the PDE may not appear cloudy and the WCC may be <100/ml. In this instance, a 1- to 2-hour or longer dwell is recommended before sampling. The PDE is centrifuged and the sediment resuspended in sterile...
saline and inoculated onto solid culture media. Alternatively, blood-culture bottles can be injected with 10 ml of PDE if centrifugation is not available. Although ISPD guidelines suggest that inoculation into blood cultures has a lower diagnostic accuracy, published comparisons between these two methods are scarce and the superior method is of relevance in healthcare systems which cannot afford to perform both [4]. Cloudy PDE with significant WCC but negative culture is referred to as culture-negative peritonitis. Szeto et al. [5] reviewed 212 such cases and found 25% were associated with prior use of antibiotics and were more likely when sampling was performed by a general compared to specialist nurse. Some data suggest culture-negative rates might be reduced by a longer dwell before sampling PDE as well as a larger sampled volume. Other causes of culture-negative peritonitis are beyond the scope of this article and have been extensively reviewed [6]. UK Renal Association guidelines define a standard of a culture-negative rate of <20% and ISPD guidelines suggest rates of <5% are possible and specialist centres should achieve <10% [3]. Despite this, a recent 800-patient UK audit demonstrated rates of 25% with wide variation between centres [7].

Table 1. Definition of peritonitis episodes [adapted from 3]

<table>
<thead>
<tr>
<th>Recurrent</th>
<th>An organism causes PDP within 28 days of therapy for a different causative organism</th>
</tr>
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<tbody>
<tr>
<td>Relapse</td>
<td>The same organism or a sterile episode of PDP within 28 days of completing therapy</td>
</tr>
<tr>
<td>Repeat</td>
<td>The same organism occurs after 28 days of completing therapy</td>
</tr>
<tr>
<td>Refractory</td>
<td>Failure of appropriate antimicrobial therapy response within 5 days</td>
</tr>
<tr>
<td>Catheter-related</td>
<td>PDP preceded by or coexisting with an exit-site or tunnel infection by the same organism or with one site sterile</td>
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to CAPD or APD demonstrating a significantly lower peritonitis rate of 0.51 episodes per patient-year in the APD group. Subsequent observational study and registry data have consistently failed to replicate this benefit outside of a clinical trial.

**Heterogeneity in Definitions of Outcomes**

It is important to be aware of heterogeneity in studies of outcome definitions when evaluating the vast literature on PDP. Treatment success or failure can be measured subjectively by resolution of symptoms and signs such as clearing of dialysate, or objectively by fall in effluent WCC which is confirmed to be sterile. Although ISPD guidelines have helped in standardizing definitions of recurrence and relapse (table 1), there remains no universally accepted definition of primary cure or failure, rendering comparison difficult. The value of such standardisation is illustrated by a recent study identifying worse outcomes for relapsing and recurrent peritonitis which might support a more aggressive approach than for a primary infection [8].

**Choice of Modality**

There is considerable uncertainty about the effects of APD on peritonitis rate compared to CAPD. Theoretically, the lower number of disconnections in APD reduces risk of touch contamination and consequent Gram-positive PDP. De Fijter et al. [9] randomised 82 patients to CAPD or APD demonstrating a significantly lower peritonitis rate of 0.51 episodes per patient-year in the APD group. Subsequent observational study and registry data have consistently failed to replicate this benefit outside of a clinical trial.

**Catheter-Related Interventions to Prevent Infection**

A 2004 Cochrane group meta-analysis supported the use of preoperative prophylactic intravenous antibiotics at catheter insertion to reduce the risk of PDP within the first month [10]. The same review group concluded no particular catheter design was proven to decrease PDP [11].

**Exit-Site Cleaning**

Although exit-site cleansing with an antibacterial soap has been recommended, this has not been tested in a randomised controlled trial (RCT).

**Prophylactic Antibiotics**

*Staphylococcus aureus* (SA) carriage in the nose and skin increases the relative risk of both SA exit-site infection (ESI) and peritonitis by two- to sixfold. This risk is related to touch contamination or exit-site colonisation as proven by serotyping studies. Preventing ESI should reduce peritonitis but the optimal strategy to do this has not been established. A 1996 multicentre RCT in patients se-
lected by nasal SA carriage showed that use of nasal mupirocin for 5 days a month reduced rates of ESI but not peritonitis [12]. A 1996 single-centre RCT showed equivalent efficacy of cyclical oral rifampicin and exit-site mupirocin cream in preventing ESI but not PDP. A 2005 single-centre RCT demonstrated superior efficacy of exit-site gentamicin cream compared to mupirocin in reducing ESI due to both SA and *Pseudomonas* [13]. More recently, Chu et al. [14] reported a single-centre RCT demonstrating no difference between exit-site gentamicin and mupirocin with respect to ESI. Only one of these RCTs was placebo-controlled so the Hawthorne effect, referring to the possibility that participating in the trial alters behaviour in a way that reduces ESI, cannot be excluded. A 2007 meta-analysis concluded that SA prophylaxis leads to decreased rates of ESIs but not PDP [15]. This may have been because the studies were too small and too short to generate the number of peritonitis events needed to show a benefit whereas ESIs occur more frequently. Further study of antimicrobial prophylaxis is warranted and antibacterial honey and polysporin are the subject of current RCTs.

### Aetiology and Trends in Causative Organisms

Historically, Gram-positive infections, dominated by SA and coagulase-negative staphylococci accounted for the majority (25–80%) of PDP in the largest published case series [16]. Use of disconnect systems with flush-before-fill connection technology has significantly reduced touch contamination-associated PDP which are largely due to Gram-positive organisms (fig. 1). The use of antibiotic creams at the exit site has further impacted on reducing SA and coagulase-negative staphylococci infection. This underlies the recent shift in the proportion of causative organisms of PDP towards enterococci and Gram-negative bacteria such as *Pseudomonas*. There is some concern that the increasing use of exit-site prophylaxis may have led to increased SA and coagulase-negative staphylococci resistance to mupirocin as well as possible increase in fungal ESI with gentamicin.

### Antimicrobial Therapy for PDP

The more recent ISPD guidelines of 2005 and 2010 have been less prescriptive about specific antimicrobial therapy than previous versions emphasising that empirical antimicrobial choice must be determined by local microbiological history aiming to cover the most likely pathogens [3]. There are benefits and disadvantages to use of all antibiotics and many disadvantages are focussed on the emergence of resistance and a residual of organisms associated with worse outcomes. Quinolone use is declining in some centres as they have been shown to promote selection of organisms including methicillin-resistant SA. The historic rationale for cephalosporins and quinolones were as alternatives to aminoglycosides and glycopeptides based on their more adverse side-effect profile. In particular, observational studies suggested gentamicin caused more rapid loss of residual renal func-

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**Fig. 1.** Annual incidence of peritonitis episodes from 1980 to 2002 according to the causative organism expressed as episodes per patient-years treatment. Taken from Brown et al. [16], with permission of Multimed Inc. Copyright © 2007 International Society for Peritoneal Dialysis.
tion [17]. More recent observational data suggested otherwise and there has been no randomised study directed at this question [18]. A Cochrane group review found no universally superior combination of antibiotics but concluded that the intraperitoneal route led to a superior primary cure rate than the intravenous route [19]. Controversies remain in establishing the optimal dosing regimens. Continuous dosing of cephalosporin has been shown to achieve bacteriocidal concentrations for longer than intermittent regimens but this has not translated into improved primary cure rates [20]. Most CAPD-based pharmacokinetic studies show that long dwells are needed to achieve sustained therapeutic antibiotic levels and at least 4 hours are recommended. The evidence base supporting the comprehensive dosing regimens of the ISPD guidelines apply almost exclusively to CAPD and there has been less study of dosing in APD where shorter dwells with increased antibiotic clearance require higher intermittent doses [21]. Some centres work around this by switching patients from APD to CAPD whilst treating PDP or adding antibiotics to a daytime dwell. It is recommended to compensate for renal clearance by increasing dosage by 25% in those with significant residual renal function (>100 ml urine/day), though there has yet to be a rigorous evaluation of cure rates using this approach [3]. Adjustment of empirical doses to target therapeutic serum levels of glycopeptides or aminoglycosides allows for fine bacteriocidal activity of antimicrobials by the minimum inhibitory concentration of bacteria in the planktonic phase. On a PD catheter, bacteria exist in the more resistant biofilm phase and study of rarely performed assays of minimum biofilm eliminating concentrations have shown these to be much greater, particularly for Gram-negative organisms [24]. This may in part explain the higher rates of relapse associated with these organisms [1, 7]. Several centres have advocated the use of urokinase or heparin both to prevent catheter occlusion and break up the biofilm as an adjunctive therapy to antibiotics. An 88-patient RCT of intraperitoneal urokinase failed to demonstrate any improved outcomes in this respect [25].

Length of Course

Expert opinion supports that minimum length of course of antimicrobial therapy for PDP should be 2 weeks for most infections and 3 weeks or more in severe infections such as fungal PDP [3]. As yet there is no evidence to direct clinicians as to whether longer or shorter courses might be beneficial for some causative organisms and whether serial microscopy and culture of dialysate would be necessary for such a strategy. Although seemingly counter-intuitive, longer courses might impair host defences and increase the risk of a subsequent episode of fungal PDP [26].

When Should a PD Catheter Be Removed?

A closely related issue is indication for catheter removal. This is recommended if the infection has not resolved (dialysate fluid is clear and WCC <100/ml) within 3 days. Some researchers have explored determinants of outcomes that can inform a decision to remove a catheter or consider additional antimicrobial agents. Chow et al. [27] validated a WCC of ≥1,090/ml on day 3 of peritonitis as being predictive of a ninefold increased risk of treatment failure whilst the WCC on day 1 was not. ISPD guidelines recommend to remove the catheter in refractory and relapsing PDP as well as consideration in episodes caused by multiple, fungal and mycobacterial organisms [3]. These recommendations are based on the consistent association of these organisms with the worst outcomes.

Gram-Negative PDP

Gram-negative PDP is notable by its absence in these recommendations as it also consistently associates with more adverse outcomes including a lower primary cure rate and greater mortality compared to Gram-positive organisms [1, 7]. Historically, Gram-negative PDP is con-
sidered to be due to transmural migration of enteric pathogens and these are theoretically less amenable to advances in connection technology and exit-site prophylaxis. A trial comparing gentamicin cream to mupirocin cream at the exit site demonstrated a striking reduction in Gram-negative infection with gentamicin, suggesting the peri-catheter route may be more important than previously thought [13].

**Fungal PDP**

Fungal peritonitis is a serious complication of PD. The largest experience of fungal PDP from the ANZDATA registry examined 162 episodes showing a prevalence of 4.5% with *Candida* species implicated in 68% of cases and a mortality of 9% [28]. Outcomes were best when antifungal therapy was combined with catheter removal. The largest single-centre study reporting 94 episodes showed improved outcomes if the catheter was removed within 24 hours of diagnosis [29]. Such studies can never remove the problem of confounding by indication and few have explored whether the catheter must be removed if appropriate therapy is commenced. Studies advocating late catheter removal must be cautiously interpreted as they are based on less than 20 episodes and use historical controls. The most frequent risk factors for developing fungal PDP are a prolonged course of antibiotics or previous episode. Prophylaxis with oral nystatin during any antibiotic therapy has only been tested in one RCT demonstrating a significant reduction in the probability of fungal peritonitis-free survival (0.974 vs. 0.915; p < 0.05), though this benefit might not be replicated outside of centres with particularly high rates [30].

**Polymicrobial PDP**

Current ISPD guidelines recommend immediate catheter removal and a surgical opinion for polymicrobial PDP based on historic studies supporting an enteric source of infection [3]. This advice is contentious as in the modern era an enteric source is only identified in 7% of cases. Observational data suggest polymicrobial PDP complicates 10–16% of all episodes and is successfully treated by antibiotics without catheter removal in 57–64% of cases [31]. Proponents of early catheter removal will note that clinical outcomes are distinctly worse than single organism PDP with higher rates of hospitalisation and mortality. This is largely driven by the non-*Pseudo-

**Tuberculous PDP**

Tuberculous (TB) peritonitis is rare with less than 200 cases reported in the literature. This makes diagnostic accuracy of tests impossible to quantify but the largest case series show a prevalence less than 3% with the most common presentation mimicking bacterial PDP with abdominal pain, cloudy fluid and neutrophil-predominant leucocytosis [32]. Lymphocytes predominate in only 30% of cases. Other presenting features are non-specific making it difficult to diagnose. Ziehl-Neelsen staining allows an early diagnosis if the smear is positive and is enhanced by centrifuging larger volumes (100–150 ml) of dialysate, but smear-negative disease is most likely. Detection time can be enhanced by using lower incubation temperatures and fluid media. Most cases are identified by prolonged culture for acid-fast bacilli but some require histology and culture of a peritoneal biopsy specimen to diagnose. It should be considered in all episodes of culture-negative peritonitis but as 19% of cases are reported with concomitant bacteria or fungi it should also be considered in refractory peritonitis. It is a sobering thought that the average interval from presentation to diagnosis is 7 weeks and the only significant variable predicting an estimated 9-month mortality of 25% was the delay to treatment. Extraperitoneal disease is seen in less than 20% of cases. Treatment is as for extraperitoneal TB but dose adjustment is required for many drugs. Ethambutol is avoided as there is a greater risk of optic neuritis. Historically, ISPD guidelines recommended catheter removal in all cases and this approach remains contentious. By 2005 the approach had changed to ‘consider removal’ in recognition that some centres successfully treated TB with the catheter in situ including half of 47 patients in a recent case series [32]. The small numbers in such studies means we can only speculate the effect of catheter removal on outcomes.

**Recurrent/Relapsing PDP**

As alluded to earlier, a recent study from Hong Kong has highlighted that relapsing and recurrent PDP (defined in table 1) are likely to represent distinct disease entities being caused by different bacterial types and portending a worse prognosis than for a primary infection.
In particular, recurrent episodes had worse outcomes than relapsing [8]. This might support earlier catheter removal though such an approach remains untested.

**Patient Training/Continuous Quality Improvement**

There has been a shift in the paradigm from treatment to prevention of infection. Several observational studies and one randomised study have proven the benefit of patient training and retraining in reducing the risk of ESI or PDP [33]. Patient training is usually performed one-to-one by a specialist PD nurse. Whether training can be delivered to a group without adversely affecting peritonitis rate has not been explored. ISPD guidelines recommend a root-cause analysis of each episode of PDP [3]. This includes non-judgementally enquiring with the patient about factors known to increase the risk of PDP, reassessing technique and home visits. Although depression has been identified as a risk factor for subsequent PDP, it is not known whether modifying this will reduce the risk. The best PDP outcomes are reported by centres which have adopted a continuous cycle of incremental quality improvement. Although we have focused on evidence-based methods, some practices, such as hand washing, are good practice and it would be unrealistic to expect every observational association to be tested through the rigor of the RCT, and these are summarised in table 2. However, important questions remain and the ISPD guidelines include an exhaustive list [3].

**Conclusion**

The variability in peritonitis rates both between different centres and between patients within a single centre is complex and largely unexplained. There is an opportunity to improve PDP outcomes by learning from the practice of those centres with the best case-mix-adjusted outcomes. Adoption of a team-based, multifaceted commitment to continuous quality improvement will involve patients, surgeons, nephrologists, microbiologists, nursing staff and administrators. Patient and staff education needs supporting by regular audit of outcomes and further research is required.

**Disclosure Statement**

Dr. Odudu declares that there is no conflict of interest. Dr. Wilkie has received speaker’s honoraria from Gambro, Baxter and Fresenius and has participated in clinical trials with Baxter and Fresenius.

**Table 2. Summary of evidence-based methods to reduce PD catheter associated infections**

- Catheter insertion by an experienced operator in a sterile environment in a position which avoids pressure from daily activities
- Dressings performed by a trained dialysis nurse until the exit site is healed
- Avoid removing dressing and keep dry for 5 days post-insertion
- Avoid using the catheter if possible until well healed
- Regular patient education on exit-site care once it is well healed. Use antibacterial soap and water or antiseptic wash
- Prophylactic use of mupirocin cream or gentamicin cream at the exit site applied daily after cleansing – some centres reserve mupirocin use for those with nasal SA carriage
- Alternatively nasal mupirocin for those who have nasal SA carriage; this strategy may be more expensive than exit-site mupirocin as it requires more testing
- Avoid mupirocin ointment as polyethylene glycol in the ointment can damage the polyurethane in some PD catheters increasing the infection risk

**References**

The review by Odudu and Wilkie is timely as far as it addresses a range of issues, controversies and practices related to CAPD/APD. It focuses on the management of peritonitis, a common complication of this form of renal replacement therapy, known to impact on the technique survival. This is all the more relevant since the percentage of ESRD patients treated by CAPD has decreased recently. Data from the USA shows that the current prevalent CAPD population is down to 7% compared to 15% in the 1980s, with the great majority being treated by HD or transplantation. This, in spite of comparable survival on HD and CAPD at least during the first few years when some residual renal function is preserved. So why are ESRD patients and nephrologists abandoning CAPD? It
has been argued that the ageing of the ESRD population and its dependency favours in-centre HD. Also, physician comfort with the modality, perceived superiority of HD, and reimbursement incentives in some countries have all contributed to the underutilization of PD. Another important reason for the low PD prevalence is the transfer to HD. Recurrent peritonitis and the subsequent loss of ultrafiltration are major causes of transfer. The review by Odudu and Wilkie addresses ways to minimise infections and its complications. The authors, like many practicing nephrologists (e.g., Chaudhary K, Sangha H, Khan-na R: Peritoneal dialysis first: rationale. Clin J Am Soc Nephrol 2010, Nov 29 [Epub ahead of print]), believe that CAPD is a very efficient first dialysis modality that retains an important place in the range and scope of renal replacement therapies. As mentioned by Chaudhary and colleagues, PD should be seen as a viable renal replacement therapy option, complementing and not competing with HD or transplantation.