Prevention of peritoneal dialysis-related infections

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ABSTRACT

The use of peritoneal dialysis (PD) varies widely from country to country, with the main limitation being infectious complications, particularly peritonitis, which leads to technique failure, hospitalization and increased mortality. A large number of prophylactic strategies have been employed to reduce the occurrence of peritonitis, including the use of oral, nasal and topical antibiotics, disinfection of the exit site, modification of the transfer set used in continuous ambulatory PD exchanges, changes to the design of the PD catheter implanted, the surgical method by which the PD catheter is inserted, the type and length of training given to patients, the occurrence of home visits by trained PD nurses, the use of antibiotic prophylaxis in patients undergoing certain invasive procedures and the administration of antifungal prophylaxis to PD patients whenever they are given an antibiotic treatment course. This review summarizes the existing evidence evaluating these interventions to prevent exit-site/tunnel infections and peritonitis.

Keywords: catheter-related infections, exit site, peritoneal dialysis, peritonitis, randomized controlled trial

INTRODUCTION

Peritoneal dialysis (PD)-related infection, including peritonitis, exit-site infection (ESI) and tunnel infection, is a common complication that results in considerable morbidity and even death in up to 3.5–10.0% of patients [1]. Furthermore, peritonitis is a leading cause of patient transfer to haemodialysis [2, 3], which in turn leads to reduced quality of life for patients [4] and increased costs to the health system [5]. Peritonitis can also lead to loss of residual renal function and reduced dialysis adequacy, deteriorating ultrafiltration and, in some cases, encapsulating peritoneal sclerosis [6].

In this review, we discuss current evidence underpinning strategies for the prevention of PD-related infections, looking primarily at clinical practice guidelines, systematic reviews and randomized controlled trials (RCTs). Preference has been given to the inclusion of results from systematic reviews because explicit methods are used in their conduct, which aim to minimize bias and produce more reliable findings that can be used to inform clinical decision-making.

The searches were conducted in Medline (1946 to November, week 3, 2013) and Embase (1980–2013 week 50). The Cochrane Library was also searched for relevant systematic reviews using the term ‘peritoneal dialysis’.

USE OF PROPHYLACTIC ANTIBIOTICS AT CATHETER INSERTION

A number of randomized trials have examined whether intravenous antibiotic administration prior to or at the time of PD catheter insertion helps to reduce the infections that can occur with PD. The Cochrane systematic review by Strippoli et al. [7] included four trials (355 patients) which gave various antibiotics at catheter placement versus none and concluded that the use of perioperative intravenous antibiotic prophylaxis versus no treatment significantly decreased the risk of early peritonitis [relative risk (RR) 0.35, 95% CI: 0.15–0.80] but not the risk of ESI and tunnel infection (RR 0.32, 95% CI: 0.02–4.81). The International Society for Peritoneal Dialysis (ISPD) guidelines published in 2011 suggest that each PD programme should consider using vancomycin as prophylaxis at catheter placement but needs to carefully weigh the potential benefit against the risk of vancomycin use promoting the emergence of
resistant organisms [8]. The UK guidelines recommend that antibiotic prophylaxis be used perioperatively but do not stipulate which antibiotic should be used. The Kidney Health Australia Caring for Australians with Renal Impairment (KHA-CARI) guidelines also recommend that intravenous antibiotic prophylaxis be used at catheter insertion and suggest that vancomycin, cephalosporins or gentamicin are suitable. To summarize, a single dose of intravenous antibiotic given at the time of catheter insertion has been shown to decrease the risk of early peritonitis [9, 10] (Table 1).

THE ROLE OF PD CATHETER DESIGN

The systematic review by Strippoli et al. [11] assessed eight RCTs (405 patients), which compared the use of straight versus coiled catheters and found no significant difference in the risk of peritonitis (RR: 1.14, 95% CI: 0.73–1.79), peritonitis rate (RR: 0.89, 95% CI: 0.63–1.26), exit-site/tunnel infection (RR: 1.26, 95% CI: 0.91–1.73) and exit-site/tunnel infection rate (RR: 1.04, 95% CI: 0.73–1.47). More recently, a systematic review by Hagen et al. [12] found no statistically significant differences between coiled and straight catheters (6 studies, 454 patients) with respect to rates of ESI [risk difference (RD): 0.04, 95% CI: −0.02 to 0.11; P = 0.22], peritonitis (RD: 0.01, 95% CI: −0.05 to 0.06; P = 0.83) or wound/tunnel infection (RD = −0.00, 95% CI: −0.04 to 0.04; P = 0.81). Hagen et al. also assessed five studies (313 patients) that compared straight versus Swan neck catheters and found no statistically significant difference between the two regarding the risk of developing an exit-site/tunnel infection (RD: 0.04, 95% CI: −0.06 to 0.15; P = 0.42) or peritonitis (RD: 0.05, 95% CI: −0.06 to 0.16; P = 0.34) (Table 2).

Only one RCT [13] has evaluated whether double-cuff catheters are superior to single-cuff catheters for the prevention of peritonitis. No significant differences were observed between the two groups with respect to the number of peritonitis episodes (21 versus 24, RD: −0.10, 95% CI: −0.35 to 0.15; P = 0.44) or the mean interval between episodes (23.8 versus 21.6 months). However, the trial only included 60 patients and had limited statistical power.

The latest ISPD guidelines on PD-related infections state that no particular catheter has been shown to be better than the standard silicone Tenckhoff catheter for the prevention of peritonitis [8]. The UK guidelines make a similar statement, saying that no particular catheter type has been proven to be better than another [9]. Overall, no one catheter type has been found to be associated with reduced PD-related infection outcomes.

It should be emphasized that the centre variations in infection rates are greater than the differences seen between catheter types. For example, two large studies, which audited practice and peritonitis outcomes at a number of PD units, found considerable variation in the peritonitis rates at the different PD units [14, 15]. Both studies could find no single factor that could account for the different peritonitis rates seen at the units.

In summary, the different catheter types are associated with similar PD-related infection outcomes.

METHOD AND LOCATION OF PD CATHETER INSERTION

Three RCTs comparing laparoscopic versus standard laparotomy PD catheter insertion have reported no significant difference in peritonitis rates after the initial post-surgery period [16–18]. The laparoscopic technique, however, had a lower incidence of early exit-site leak, fluid leakage and catheter tip migration. Moreover, a recent meta-analysis by Hagen et al. concluded that the laparoscopic insertion technique resulted in higher 1-year catheter survival (OR: 3.93, 95% CI: 1.80–8.57; P = 0.0006) and less frequent catheter migration (OR: 0.21, 95% CI: 0.07–0.63; P = 0.006), although there was no statistically significant difference in the occurrence of peritonitis (OR: 0.83, 95% CI: 0.48–1.42; P = 0.49) or exit-site/tunnel infection (OR: 0.80, 95% CI: 0.47–1.37; P = 0.41) [12].

Another method that has been employed involves the burying of the entire PD catheter subcutaneously at the time of insertion, with subsequent exteriorization of the tip of the catheter at a later date (Moncrieff–Popovich technique) [19]. A Cochrane systematic review found that burying the catheter did not significantly affect exit-site/tunnel infection rates (RR: 1.15, 95% CI: 0.39–3.42) or peritonitis rates (RR: 1.16, 95% CI: 0.37–3.60) compared with standard insertion techniques [11].

The technique of inserting the PD catheter in a midline versus lateral position has also been investigated. It was theorized that lateral insertion of the catheter might reduce the incidence of leakage and obstruction after insertion [20]. However, the Cochrane systematic review by Strippoli et al. [11] found that midline versus lateral insertion of the PD catheter was not associated with a statistically significant difference for the risk of peritonitis (RR: 0.65, 95% CI: 0.32–1.33) or exit-site/tunnel infection (RR: 0.56, 95% CI: 0.12–2.58).

The UK guidelines suggest that the method of PD catheter insertion should depend on the local expertise available at each unit [9]. While none of the different methods of catheter insertion have been found to be associated with a reduction in PD-related infection, the laparoscopic technique was associated with better catheter survival at 1 year and less instances of catheter migration.

PD PATIENT TRAINING

The safe practice of PD requires that a patient be taught how to perform good hand hygiene while carrying out a bag exchange. The aim of this is to reduce the occurrence of touch contamination, which is the commonest cause of peritonitis [21] (Table 3). There are no RCTs comparing different initial training regimens for PD patients. There are, however, a number of prospective and retrospective observational studies that have looked at the features of training programmes for new patients and the characteristics of those doing the training and have assessed these in relation to key patient outcomes. A non-randomized prospective multicentre study was conducted by Hall et al. [22] in which 620 new patients starting PD were trained...
# Table 1. Characteristics of included studies—prophylactic use of antibiotic/antibacterial

<table>
<thead>
<tr>
<th>Study author and year</th>
<th>Study design</th>
<th>Intervention category</th>
<th>Intervention (experimental group)</th>
<th>Intervention (control group)</th>
<th>N</th>
<th>Duration of follow-up (months)</th>
<th>Effect of intervention on ESI</th>
<th>Effect of intervention on tunnel infection</th>
<th>Effect of intervention on peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strippoli et al. (2004)</td>
<td>Systematic review</td>
<td>Prophylactic intravenous antibiotics at catheter insertion</td>
<td>Various antibiotics</td>
<td>No antibiotic</td>
<td>355</td>
<td>N/A</td>
<td>Decreased early peritonitis RR: 0.35 (0.15–0.80) P = 0.013</td>
<td></td>
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</tr>
<tr>
<td>Zimmerman et al. (1991)</td>
<td>RCT</td>
<td>Prophylactic antibiotic to prevent PD-related infections</td>
<td>Oral rifampin 2x day for 5 days every 3 months</td>
<td>No antibiotic</td>
<td>64</td>
<td>20</td>
<td>No effect Rate ratio 0.61 (0.32–1.2) (NS) Reduced RR 0.59 (0.46–0.76) P &lt; 0.0001 Reduced with G 0.34/year versus 0.52/year P = 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al. (2010)</td>
<td>Systematic review</td>
<td>Prophylactic antibiotic to prevent PD-related infections</td>
<td>Topical application of mupirocin intranasally or at the exit site</td>
<td>No antibiotic</td>
<td>2450</td>
<td>N/A</td>
<td>Reduced RR 0.43 (0.34–0.54) P &lt; 0.00001 Reduced with G 0.23/year versus 0.54/year P = 0.005 Increased with G OR: 1.55 (1.05–2.28) P = 0.024</td>
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<tr>
<td>Bernardini et al. (2005)</td>
<td>RCT</td>
<td>Prophylactic antibiotic to prevent PD-related infections</td>
<td>Topical application of gentamicin at the exit site</td>
<td>Topical application of mupirocin at the exit site</td>
<td>133</td>
<td>8</td>
<td>Reduced with G 0.23/year versus 0.54/year P = 0.005 Reduced with M 0.28 versus 0.12 per patient-year P = 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pierce et al. (2012)</td>
<td>Observational</td>
<td>Prophylactic antibiotic to prevent PD-related infections</td>
<td>Topical application of gentamicin at the exit site</td>
<td>Topical application of mupirocin at the exit site</td>
<td>377</td>
<td>30</td>
<td>Reduced with G 0.23/year versus 0.54/year P = 0.005 Reduced with M 0.28 versus 0.12 per patient-year P = 0.02</td>
<td></td>
<td></td>
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<tr>
<td>McQuillan et al. (2012)</td>
<td>RCT</td>
<td>Prophylactic antibiotic to prevent PD-related infection</td>
<td>Topical application of P3 at the exit site</td>
<td>Topical application of mupirocin at the exit site</td>
<td>201</td>
<td>18</td>
<td>Reduced with M 0.28 versus 0.12 per patient-year P = 0.02 Equivalent 0.37 versus 0.40 per patient-year P = 0.39 Reduced 1 versus 3 peritonitis episodes P = 0.036 Equivalent 0.35 versus 0.35 episodes per patient-year Adjusted HR: 0.95 (0.66–1.38)</td>
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<tr>
<td>Nunez-Moral et al. (2014)</td>
<td>RCT</td>
<td>Prophylactic antibiotic to prevent PD-related infections</td>
<td>Topical application of polyhexanide solution at the exit site</td>
<td>Standard care of the exit site</td>
<td>60</td>
<td>12</td>
<td>Reduced 2 versus 6 ESI episodes P = 0.032 Equivalent 0.31 versus 0.24 episodes per patient-year Adjusted HR: 1.37 (0.89–2.12)</td>
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<td></td>
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<tr>
<td>Johnson et al. (2013)</td>
<td>RCT</td>
<td>Antibacterial honey to prevent PD-related infections</td>
<td>Topical application of antibacterial honey at the exit site</td>
<td>Standard care of the exit site</td>
<td>371</td>
<td>12–24</td>
<td>Reduced 2 versus 6 ESI episodes P = 0.032 Equivalent 0.31 versus 0.24 episodes per patient-year Adjusted HR: 1.37 (0.89–2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strippoli et al. (2004)</td>
<td>Systematic review</td>
<td>Prophylactic nasal antibiotic to prevent PD-related infections</td>
<td>Nasal application of antibiotic</td>
<td>No antibiotic</td>
<td>282</td>
<td>N/A</td>
<td>Reduced RR: 0.58 (0.40–0.85) Reduced RR: 0.58 (0.40–0.85) No effect RR: 0.94 (0.67–1.33) P = 0.74</td>
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<table>
<thead>
<tr>
<th>Study author</th>
<th>Study design</th>
<th>Intervention category</th>
<th>Intervention (experimental group)</th>
<th>Intervention (control group)</th>
<th>N</th>
<th>Duration of follow-up (months)</th>
<th>Effect of intervention on ESI</th>
<th>Effect of intervention on tunnel infection</th>
<th>Effect of intervention on peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mupirocin Study Group (1996)</td>
<td>RCT</td>
<td>Prophylactic nasal antibiotic to prevent PD-related infections</td>
<td>Nasal application of mupirocin</td>
<td>No antibiotic (placebo ointment)</td>
<td>267</td>
<td>18</td>
<td>No effect on overall ESI(^1) 33 versus 55 ESI episodes P = 0.17; Reduced ESI due to <em>S. aureus</em> 14 versus 44 ESI episodes P = 0.006</td>
<td>No effect 1 in 154.4 patient-months versus 1 in 123.6 patient-months</td>
<td>No effect 1 in 81.8 patient-months versus 1 in 53.8 patient-months (P = NS)</td>
</tr>
<tr>
<td>Davey <em>et al.</em> (1999)</td>
<td>RCT</td>
<td>Prophylactic nasal antibiotic to prevent PD-related infections</td>
<td>Nasal application of mupirocin</td>
<td>No antibiotic (placebo ointment)</td>
<td>267</td>
<td>18</td>
<td>No effect on overall ESI 1 in 42.1 patient-months versus 1 in 22.5 patient-months (P = 0.17) Reduced ESI due to <em>S. aureus</em> 1 in 99.3 patient-months versus 1 in 28.1 patient-months (P = 0.006)</td>
<td>No effect 192 versus 217 episodes</td>
<td>No effect on peritonitis due to <em>S. aureus</em> 1 in 81.8 patient-months versus 1 in 53.8 patient-months</td>
</tr>
</tbody>
</table>

N/A, not available; ESI, exit-site infection; G, gentamicin; M, mupirocin.
Table 2. Characteristics of included studies—catheter design, method of insertion and connection method

<table>
<thead>
<tr>
<th>Study author (year)</th>
<th>Study design</th>
<th>Intervention category</th>
<th>Intervention (experimental group)</th>
<th>Intervention (control group)</th>
<th>N</th>
<th>Duration of follow-up (months)</th>
<th>Effect of intervention on ESI</th>
<th>Effect of intervention on tunnel infection</th>
<th>Effect of intervention on peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strippoli et al. (2004)</td>
<td>Systematic review</td>
<td>PD catheter design</td>
<td>Straight catheter</td>
<td>Coiled catheter</td>
<td>324</td>
<td>N/A</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Hagen et al. (2013)</td>
<td>Systematic review</td>
<td>PD catheter design</td>
<td>Straight catheter</td>
<td>Coiled catheter</td>
<td>454</td>
<td>N/A</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Eklund et al. (1997)</td>
<td>RCT</td>
<td>PD catheter design</td>
<td>Double-cuff catheter</td>
<td>Single-cuff catheter</td>
<td>60</td>
<td>16.66 (double-cuff), 18.07 (single-cuff)</td>
<td>Equivalent 14/30 versus 11/30</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Tsimoyiannis et al. (2000)</td>
<td>RCT</td>
<td>Method of PD catheter insertion</td>
<td>Laparoscopic surgery</td>
<td>Standard laparotomy</td>
<td>50</td>
<td>21</td>
<td>Equivalent 14/30 versus 11/30</td>
<td>No stated</td>
<td>No stated</td>
</tr>
<tr>
<td>Gadallah et al. (1999)</td>
<td>RCT</td>
<td>Method of PD catheter insertion</td>
<td>Laparoscopic surgery</td>
<td>Standard laparotomy</td>
<td>148</td>
<td>36</td>
<td>No effect on ‘late’ ESI 33/76 versus 28/72</td>
<td>No stated</td>
<td>No stated</td>
</tr>
<tr>
<td>Wright et al. (1999)</td>
<td>RCT</td>
<td>Method of PD catheter insertion</td>
<td>Laparoscopic surgery</td>
<td>Standard laparotomy</td>
<td>50</td>
<td>Laparoscopic = 265 months; standard = 361 months</td>
<td>No effect on ‘late’ ESI 6/21 versus 4/24</td>
<td>No stated</td>
<td>No stated</td>
</tr>
<tr>
<td>Hagen et al. (2013)</td>
<td>Systematic review</td>
<td>Method of PD catheter insertion</td>
<td>Laparoscopic surgery</td>
<td>Standard laparotomy</td>
<td>474 (ESI/tunnel); 541 (peritonitis)</td>
<td>N/A</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Daly et al. (2000)</td>
<td>Systematic review</td>
<td>PD connection method</td>
<td>Y-set or twin-bag disconnect system</td>
<td>Standard spike connection system</td>
<td>485</td>
<td>N/A</td>
<td>No effect</td>
<td>No effect</td>
<td>Reducated RR: 0.55 (0.42–0.73) P = 0.000025</td>
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</table>

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on the PD technique and diet with an adult learning theory-based course or a conventional training programme. Compared with the control group, the adult learning group took significantly longer to train (29 versus 22.6 h, P < 0.0001), had comparable peritonitis rates (28.2 versus 36.7 per 1000 patient-months, P = 0.09783) and had significantly lower ESI rates (0.22 versus 0.38/patient-year, P < 0.004). A retrospective study conducted by Gadola et al. over a 28-month period evaluated the practical skills of patients who started PD during this time, following the use of a new multidisciplinary education programme. They found that the overall peritonitis rates fell significantly (0.28 versus 0.55/patient-year, P < 0.05) [23].

A survey of 150 Italian PD centres found that lower peritonitis rates were associated with pre-dialysis education, home visits and retraining, but not with the presence of specialized personnel, the ratio of nurses to patients or training time [24]. Kavanagh et al. also found no link between the peritonitis rate and the nurse-to-patient ratio or the average continuous ambulatory peritoneal dialysis training time [15]. Other studies have reported conflicting results regarding the association between training time and PD-related infections [25–27].

It is also unclear if there is a correlation between home visits and peritonitis rates [25, 28]. Nevertheless, home visits may highlight when retraining is necessary, with one study finding that 23% of the centre’s patients were not following exchange protocol procedures and 11% were non-compliant with the exit-site protocol procedures [29].

Dialysis centre size may have an effect on peritonitis rate, with one survey of paediatric patients reporting a rate of 1 episode/19.9 patient-months for large centres and 1 episode/13.5 patient-months for small centres (P < 0.05) [25].

In addition to patient training, the training given to the nurses teaching the patient is important. Although it seems counter-intuitive, one study found that the training nurses with ≥3 years of experience had a more than twofold increased likelihood of subsequent Gram-positive peritonitis in the patients they trained compared with the trainers with less training experience [30]. As explanation, it was suggested that more experienced nurses may be less familiar with the concept of using adult learning principles to train PD patients, nurses with more experience may be providing lower quality care and that nursing knowledge and skills are different to the skills needed to teach. It is also possible that the more experienced nurses were given the more challenging patients to train. There is also a study by Yang et al. which found that when nurses with more general medicine experience (≥15 years) trained PD patients, the time to first-episode Gram-positive peritonitis was significantly better than when patients were trained by nurses with less experience [31].

The ISPD guidelines/recommendations published in 2006 [32] state that a nurse should provide PD training whenever possible (opinion based) and that one nurse should train one patient rather than one nurse train a group of patients (opinion). The principles of adult learning should be followed in the training sessions and a new PD trainer should be supervised for at least one patient training course before being considered an independent trainer (opinion). The fact that cognitive skills may be compromised in a CKD patient needs
to be understood; their training will require much patience and repetition and a formalized programme is needed. The UK guidelines state that education programmes for CKD patients starting therapy should be multidisciplinary, multifaceted, tailored to individual needs and based on the principles of adult learning. Different ways of delivering the education should be available, the information imparted should be relevant to the person and the method, amount and pace of the delivery should be suited to the person’s learning style, capacity and preferences [33]. Although there are no studies on the topic of retraining, the ISPD Nursing Liaison Committee recommends retraining after peritonitis, catheter infection, prolonged hospitalization or any other disruption to PD [32]. The Committee also recommends periodic retraining should be performed on a regular basis for all patients. The UK guidelines make similar recommendations, stating that patients should be retrained at least annually and more often, if events such as an episode of PD-related infection or major interruption to the patient performing PD occurs [34]. To summarize, an observational study has found that patients taught according to adult learning theory did not experience reduced peritonitis rates compared with the control group, but they did experience significantly lower ESI rates. Other studies found that a multidisciplinary education programme, pre-dialysis education and retraining were associated with lower peritonitis rates. It is not clear if the years of experience that the nurse doing the training has affects patient outcomes, as different studies have yielded different conclusions.

### PD Connection Methods

The standard connection system that used a ‘spike’ or a luer lock device has largely been replaced by the Y-set or twin-bag systems as spiking was shown many years ago to lead to more frequent peritonitis [8]. A systematic review has shown that peritonitis rates are reduced when disconnect systems (Y-set and twin-bag systems) are used rather than conventional spike systems in PD (7 trials, 485 patients, RR: 0.64, 95% CI: 0.53–0.77) [35]. The use of the Y-set compared with the conventional spike system was associated with a significantly lower risk of peritonitis (7 trials, 485 patients, RR: 0.64, 95% CI: 0.53–0.77) and peritonitis rate (8 trials, 7417 patient-months, RR: 0.49, 95% CI: 0.40–0.61), but no difference was found in the incidence of exit-site/tunnel infection (3 trials, 226 patients, RR: 1.46) or rate (2 trials, 2841 patient-months, RR: 1.24, 95% CI: 0.91–1.69). There was no significant difference in the risk of catheter removal (1 trial, 40 patients, RR: 0.33, 95% CI: 0.04–2.94), technique failure
(2 trials, 184 patients, RR: 0.45, 95% CI: 0.19–1.05) or the risk of all-cause mortality with the Y-set compared with the standard spike systems (5 trials, 355 patients, RR: 1.03, 95% CI: 0.48–2.21).

The double-bag (twin-bag) system was developed in the 1980s, and it was thought that this system would lead to reduced infection rates because there is one fewer connecting procedure [36]. There was a statistically significant difference found with use of the double-bag system versus the standard system for the risk of peritonitis (2 trials, 170 patients, RR: 0.43, 95% CI: 0.29–0.62) and the peritonitis rate (2 trials, 2110 patient-months, RR: 0.31, 95% CI: 0.20–0.47). No significant difference was found for technique failure (1 trial, 80 patients, RR: 1.00, 95% CI: 0.06–15.44), exit-site/tunnel infection (1 trial, 80 patients, RR 0.75, 95% CI 0.18–3.14) and all-cause mortality (1 trial, 80 patients, RR: 1.00, 95% CI: 0.21–4.66).

Comparison of the Y-set system with the double-bag system [35] found no significant difference between the two for the risk of peritonitis (3 trials, 292 patients, RR: 0.59, 95% CI: 0.35–1.01), peritonitis rate (4 trials, 4319 patient-months, RR: 0.90, 95% CI: 0.49–1.66) and exit-site/tunnel infection rate (2 trials, 2319 patient-months, RR: 1.04, 95% CI: 0.52–2.06). However, the double-bag system was associated with a trend towards fewer patients with peritonitis (RR: 0.59, 95% CI: 0.35–1.01, P = 0.05).

Both the UK and the ISPD guidelines recommend that flush-before-fill dialysis delivery systems be used because these reduce the risk of contamination [8, 34]. Use of the disconnect systems has been shown to be associated with a significantly reduced rate of peritonitis but not alter the occurrence of exit-site/tunnel infection, catheter removal, technique failure and all-cause mortality [37]. There is little difference between the different disconnect systems in terms of PD-related infection outcomes.

### EXIT-SITE CARE TO PREVENT PERITONITIS

One of the recognized ways for peritonitis to start is via the catheter tunnel in the presence of exit-site colonization and infection, most commonly with Staphylococcus aureus and Pseudomonas aeruginosa organisms. The cohort study by Luzar et al. [38] looked at S. aureus nasal carriage and infection in 140 patients starting PD and found that nasal carriage of S. aureus was common (45%), carriers had significantly more ESIs than non-carriers, and that the peritonitis episodes caused by S. aureus all occurred in carriers. They recommended that nasal cultures be performed before catheter surgery to identify patients at high risk for subsequent S. aureus infection.

Subsequent to this, a number of antibiotics were trialled with the aim of preventing ESI and peritonitis. An early RCT used intermittent oral rifampin, which was effective at reducing the catheter-related infection rate but not peritonitis, and was associated with patient withdrawal due to adverse effects [39]. Rifampin has not been further used to eliminate nasal carriage because it can cause allergic reactions, has drug interactions and results in the rapid development of resistance [40].

The antibiotic mupirocin was first trialled in the 1990s and has excellent activity against Gram-positive organisms but does not affect Gram-negative organisms. A systematic review published in 2010 investigated whether the application of mupirocin (at the exit site or intranasally) was effective in the prevention of ESI and peritonitis in PD patients [41]. A total of 14 studies with 1233 enrolled patients and 1217 controls were included in the review. Mupirocin was associated with a significantly lower risk of ESI (0.57, 95% CI: 0.46–0.66, P < 0.0001) and peritonitis (0.41, 95% CI: 0.24–0.54, P < 0.0001) due to all organisms. When only ESI and peritonitis due to S. aureus were considered, a bigger reduction in risk was seen for both outcomes (0.72, 95% CI: 0.60–0.81, P < 0.0001; 0.70, 95% CI: 0.52–0.81, P < 0.00001).

There are no published RCTs that have looked at the effectiveness of applying mupirocin to the catheter exit site as routine practice.

Gentamicin antibiotic cream can be applied topically to prevent ESI and is considered an alternative choice to mupirocin. The main study to support its use is a prospective RCT of 133 patients, which compared the topical application of mupirocin cream (2%) or gentamicin sulphate cream (0.1%) to the exit site [42]. Application was daily and follow-up was for a median of 8 months per patient. Use of gentamicin was associated with a lower catheter infection rate (0.23/year versus 0.54/year, P = 0.005), a longer time to first catheter infection (proportion without catheter infection 0.82/year versus 0.65/year, P = 0.03) and a decrease in the peritonitis rate (0.34/year versus 0.52/year, P = 0.03). The possibility of gentamicin resistance developing is potentially a major problem as gentamicin is used to treat PD-related peritonitis. The study by Pierce et al. [43] found a significant increase in episodes of ESI (0.098 versus 0.153/year, P = 0.024) and a decrease in gentamicin susceptibility for Enterobacteriaceae of 12% and for Pseudomonas of 14%, after their unit switched from routinely using mupirocin 2% cream to gentamicin 0.1% cream at the exit site.

A potential alternative agent is medical-grade honey. Honey has long been known to possess antimicrobial properties and is thought to potentially be less likely to lead to the development of drug-resistant microorganisms compared with antibiotics. Medical-grade honey has been shown to be as efficacious as topical mupirocin in the prevention of catheter-associated sepsis in haemodialysis patients but without the problem of antibiotic resistance [44]. An RCT of its use in adult and paediatric PD patients in Australia and New Zealand has been completed, but the findings do not support a role for antibacterial honey in the prevention of PD-associated infections [45]. The intervention involved daily application of honey to the PD catheter exit site in one group and standard prophylactic care in the other group (application of mupirocin intranasally for 5 days each month for the duration of the study in S. aureus carriers only).

A multicentre RCT of mupirocin versus Polysporin Triple (P³) antibiotic ointment (containing bacitracin, gramicidin and polymyxin B) randomized 201 adult PD patients to apply one or other of the ointments to the exit site with each dressing change [46]. Patients were followed for 18 months or until death or catheter removal. The primary study outcome was a composite endpoint of ESI, tunnel infection or peritonitis.
The study found no difference between the two groups in the time to first event (13.2 months for P^2, 95% CI: 11.9–14.5; 14.0 months for mupirocin, 95% CI: 12.7–15.4; P = 0.41). However, a higher rate of fungal ESI was seen in patients using P^3 (0.07 versus 0.01, P = 0.02) and there was a corresponding increase in fungal peritonitis (0.04 versus 0.00, P < 0.05). Consequently, the use of P^3 over mupirocin as a prophylactic agent cannot be advocated.

A single-centre RCT compared the antibiotic polyhexanide (solution) versus standard care at the exit site (saline solution and povidone-iodine) [47]. Patients were followed for 12 months. Thirty patients were randomized to each group but only 46 completed the 12-month follow-up. Both incident and prevalent patients were enrolled. The primary study outcome was ESI rate. The study found a significant difference between the ESI rate for the polyhexanide group compared with the standard care group (0.117 per year versus 0.328 per year, P = 0.017). The authors suggest polyhexanide is efficient in the prevention of ESI and should be considered a prophylactic agent that can be routinely used at the exit site.

The ISPD guidelines recommend that all PD patients use topical antibiotic either at the catheter exit site or intranasally or both [8]. The UK guidelines also recommend this [34]. The KHA-CARI guidelines are more specific, recommending the use of mupirocin ointment topically (intranasally or at the exit site) [10]. Patients who are nasal carriers of S. aureus have been shown to be at increased risk for ESI and peritonitis [38]. Of the antibiotics/agents that have been trialled to prevent ESI, mupirocin has been found to be the best choice because it significantly reduces ESI and peritonitis without unwelcome effects such as those seen with P^3.

### PROPHYLACTIC NASAL ANTIBIOTIC USE

A systematic review found that nasal mupirocin compared with placebo significantly reduced the exit-site and tunnel infection rates and the presence of S. aureus nasally but had no significant effect on peritonitis rates [48]. The Mupirocin Study Group ran a large multicentre RCT with 267 PD patients who were identified S. aureus nasal carriers randomized to receive intranasal mupirocin (2%) or placebo ointment [49]. Patients applied the nasal ointment twice daily for five consecutive days, every 4 weeks. The results did not show any significant difference between the two groups in terms of overall ESIs, but it did show a significant reduction in the number of episodes of ESI due to S. aureus in the mupirocin group. The regular use of mupirocin reduced nasal carriage of S. aureus to between 10 and 18%; however, the rates of tunnel infection and peritonitis showed no significant difference.

The authors of the MediHoney® trial also performed a systematic review of topical antimicrobial prophylaxis for preventing infections in PD and found nine relevant trials (954 participants). They concluded that the results provide inconclusive evidence for nasal mupirocin, exit-site mupirocin and exit-site gentamicin prophylaxis.

There is concern that the routine use of mupirocin will lead to the emergence of resistant bacteria. The evidence to date suggests minimal development of resistance in the Mupirocin Study Group trial (nasal application), although it has been argued that a follow-up period of only 18 months was insufficient to adequately assess the development of resistance [50]. A study that examined mupirocin use in PD patients over a decade observed concerning increases in high-degree mupirocin-resistant S. aureus rates in PD patients and their dialysis partners (from 0% to 12.4%) [51]. Nearly one-third of patients with S. aureus ESI were colonized with mupirocin-resistant strains.

This development raises concerns about the ability to continue using mupirocin in the future to prevent S. aureus colonization in PD patients. Antibiotic resistance is a growing problem and has also been seen with the development of vancomycin intermediate-susceptible S. aureus which shows reduced responsiveness to vancomycin, which is commonly used to treat methicillin-resistant S. aureus infections [52]. Studies that looked at the use of nasal mupirocin in identified carriers yielded conflicting results as to whether or not ESI was reduced. Rates of tunnel infection and peritonitis were unaffected.

### PRE-PROCEDURAL PROPHYLAXIS

Although there are no RCTs in this area, intravenous antibiotic prophylaxis is recommended to prevent early peritonitis in PD patients undergoing invasive gastrointestinal and gynaecological procedures, such as colonoscopy with or without polypectomy, barium enema, laparoscopic cholecystectomy, uterine biopsy and hysteroscopy as these procedures have been shown to sometimes cause peritonitis in PD patients [8]. Peritonitis is thought to occur as a result of transient bacteraemia, from the transmural migration of organisms from the gut into the peritoneal cavity and via the gynaecological tract [53]. Oral antibiotic prophylaxis 2 h before extensive dental work is also suggested because transient bacteraemia resulting from the dental work can lead to peritonitis [8].

The UK guidelines recommend that invasive procedures are accompanied by antibiotic prophylaxis and emptying the abdomen of dialysis fluid for the period of time that the procedure takes [34].

### PROPHYLAXIS TO PREVENT FUNGAL PERITONITIS

Fungi account for 1–15% of PD peritonitis episodes and are associated with significant morbidity and mortality and high rates of permanent haemodialysis transfer [54]. Patients who receive prolonged or repeated antibiotics courses are at increased risk of developing fungal peritonitis. A number of studies have looked at the use of antifungal prophylaxis but only two of these studies have been RCTs. The first of these by Lo et al. [55] randomly allocated PD patients to treatment with oral nystatin tablets (500,000 units four times a day) whenever a course of antibiotics was prescribed or to no co-prescribed antifungal treatment (control). The proportion of
patients who did not experience *Candida* peritonitis by the end of 2 years was higher in the group given Nystatin compared with controls (0.974 versus 0.913, *P* < 0.05). This finding may be limited because the control arm had a relatively high incidence of *Candida* peritonitis [56] such that the results may not necessarily be generalizable to PD units with lower PD peritonitis rates (Table 4).

A more recent RCT used oral fluconazole as the prophylactic agent and randomized 420 patients with any PD-related infection to receive or not receive fluconazole (200 mg every 48 h) for the period that they were receiving therapeutic antibiotics [57]. Of patients with bacterial peritonitis, those receiving fluconazole during all courses of antibiotics had significantly fewer fungal peritonitis episodes than did controls (3 versus 15, *P* = 0.0051).

The ISPD work group recommends that each PD programme should look at their history of fungal peritonitis and decide if an antifungal with antibiotic protocol would be beneficial, particularly for patients taking prolonged or frequent courses of antibiotics [8]. The KHA-CARI guidelines state that oral antifungal prophylaxis should be considered when PD patients are given antibiotics to reduce their risk of developing fungal peritonitis [10].

In summary, two RCTs co-prescribed an antifungal agent to PD patients whenever they were administered a course of antibiotics. The control group did not receive the antifungal treatment. The intervention group had significantly fewer episodes of fungal peritonitis than did the control group. This is a prophylactic measure that those caring for PD patients need to consider.

### SUMMARY OF THE EVIDENCE

Overall, there is a lack of RCTs for many interventions and so data from less rigorous study designs such as cohort studies are our current best available evidence. It also means that systematic reviews have few RCTs that can be included in the analysis. In addition, the quality of the RCTs is variable with some having small patient numbers, short follow-up times and an increased risk of bias because of poor or unclear randomization and blinding processes. In summary, the quality of the evidence is strong for some aspects such as the PD connection method and the use of antibiotic to prevent ESI but is weak for other areas such as the method for training patients.

### CONCLUSION

Intravenous antibiotic administration prior to PD catheter insertion is well proven to prevent the occurrence of early postoperative peritonitis. The elimination of *S. aureus* nasal carriage using topical mupirocin reduces the risk of exit-site/tunnel infections but not peritonitis. The routine application of mupirocin at the exit site is recommended for all PD patients at increased risk for *S. aureus* infection. The daily use of gentamicin cream at the exit site reduces both the catheter-associated infection and peritonitis rates. The prescribing of oral nystatin with an antibiotic course reduces the development of *Candida* peritonitis.

While improvements in connection technology have reduced peritonitis rates in the past decade, PD-related infection remains a serious problem for PD patients. The disconnect systems are better than the standard spike system in terms of preventing peritonitis. No advantage can be found for using different catheter designs, surgical implantation techniques, catheter placement or automated peritoneal dialysis (APD) versus chronic peritoneal dialysis (CPD). Adoption of a team-based, multifaceted approach to continuous quality improvement with regular audit of infection rates and outcomes is considered essential to improving peritonitis rates.

The training of patients is recognized as a modifiable risk factor for PD peritonitis and it is known that the training given to patients varies considerably between different centres. Patient training and retraining should become a major clinical and research focus for all units striving to improve their peritonitis rates. Future studies should specifically examine the roles of use of pretraining assessment tools, home-based versus centre-based training, group versus single patient training, training programmes using adult learning principles versus an alternative approach and routine (pre-emptive) versus reactive retraining. The training of staff is also important, and active continued learning and retraining is required to achieve good outcomes. In addition, evidence-based national and international guidelines exist in regard to optimal antimicrobial practice and PD units should review their protocols/policies to ensure that they accord with guideline recommendations.

### Table 4. Characteristics of included studies—prophylactic use of antifungal

<table>
<thead>
<tr>
<th>Study author (year)</th>
<th>Study design</th>
<th>Intervention category</th>
<th>Intervention (experimental group)</th>
<th>Intervention (control group)</th>
<th>N</th>
<th>Duration of follow-up (months)</th>
<th>Effect of intervention on ESI</th>
<th>Effect of intervention on tunnel infection</th>
<th>Effect of intervention on peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo <em>et al.</em> (1996)</td>
<td>RCT</td>
<td>Prophylaxis to prevent fungal peritonitis</td>
<td>Oral nystatin with antibiotic course</td>
<td>No antifungal treatment with antibiotic course</td>
<td>397</td>
<td>18 (N), 16.6 (C)</td>
<td>N/A</td>
<td>N/A</td>
<td>Reduced <em>Candida</em> peritonitis episodes 4/199 versus 12/198 <em>P</em> &lt; 0.05 Reduced RR: 0.20 (0.06–0.68) <em>P</em> &lt; 0.05</td>
</tr>
<tr>
<td>Restrepo <em>et al.</em> (2010)</td>
<td>RCT</td>
<td>Prophylaxis to prevent fungal peritonitis</td>
<td>Oral fluconazole with antibiotic course</td>
<td>No antifungal treatment with antibiotic course</td>
<td>420</td>
<td>1–5</td>
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11. Strippoli GFM, Tong A, Johnson D

16. Tsimoyiannis EC, Siakas P, Glantzounis G

13. Eklund B, Honkanen E, Kyllonen L


19. Wright MJ, Bel

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18. Wright MJ, Bel

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Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury

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ABSTRACT

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury that has experienced significant epidemiological and clinical changes in the last years. The classical presentation, mostly induced by antibiotics and accompanied by evident hypersensitivity manifestations (skin rash, eosinophilia, fever) has been largely replaced by oligosymptomatic presentations that require a higher index of suspicion and are increasingly recognized in the elderly, having non-steroidal anti-inflammatory agents and proton pump inhibitors as frequent offending drugs. Drug-induced AIN continues to be the commonest type, but it requires a careful differential diagnosis with other entities (tubulointerstitial nephritis with uveitis syndrome, IgG4-related disease, drug reaction with eosinophilia and systemic symptom syndrome, sarcoidosis and other systemic diseases) that can also induce AIN. Cortico-dependant, relapsing AIN is a recently recognized entity that poses an important therapeutic challenge. Although corticosteroids are widely used in drug-induced AIN to speed kidney function recovery and avoid chronic kidney disease, their efficacy has not been tested by randomized controlled trials. New diagnostic tests and biomarkers, as well as prospective therapeutic studies are needed to improve AIN diagnosis and management.

Keywords: acute interstitial nephritis, AKI in the elderly, corticosteroids, proton pump inhibitors

INTRODUCTION

Acute kidney injury (AKI) is a growing worldwide problem with huge untoward economic and medical consequences [1]. Whereas