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# **SPECIAL ARTICLE**

# ISPD POSITION STATEMENT ON REDUCING THE RISKS OF PERITONEAL DIALYSIS-RELATED INFECTIONS

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For a peritoneal dialysis (PD) program to be successful, close attention must be paid to preventing PD-related infections (defined as exit-site infections, tunnel infections, and peritonitis). The variation in peritonitis rates in recently published studies (1–20) is astonishing: from a low of 0.06 episodes per year in a Taiwanese program to a high of 1.66 episodes per year at risk in an Israeli pediatric program (Table 1). Those rates mean that an individual patient, on average, may expect to have peritonitis as rarely as once every 17 years in one center, or as frequently as once every 7 months in another. Even at centers within a single country, there is often a marked variation in the peritonitis rate. For example, the Scottish registry has centers with rates that range from

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0.43 episodes to 0.89 episodes per year (1), the London Thames centers vary from 0.14 episodes to 1.0 episodes per year (9), and the Austrian Study Group centers range from 0.07 episodes to 0.60 episodes per year (10). Explanations for such marked variations are lacking, but are likely related at least in part to differences in patient training and in infection-prevention protocols. Variations in the accuracy with which peritonitis episodes are recorded may also contribute in part to the differences in reported rates.

Studies on preventing PD-related infections are limited both in number and in quality, and guidelines are therefore not yet appropriate. The present position paper is a compilation of the opinions of experts in the field, combined with the available evidence. It is intended to provide support to PD programs developing approaches to reduce PD-related infections to very low levels at all centers. Suggestions for which there is published research are labeled "evidence"; suggestions for which only case reports, limited observational studies, or the experience of the work group are available are labeled "opinion." We hope that this review of the problems will stimulate further research into this important topic. Specific guidelines for treating peritonitis were updated and published in 2010 (21), as were guidelines for PD

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Country	Reference	Year	Patient population ( <i>n</i> )		Episodes per	
			Adults	Children	Centers	year at risk (n)
Scotland	Kavanaugh (1)	2004	1205ª			0.62
Japan	Hoshii (2)	2006		130		0.17
Canada	Mujais (3)	2006			26	0.43
United States	Mujais (3)	2006			35 <sup>a</sup>	0.37
Japan	Nakamoto (4)	2006	139			0.22
Portugal	Rodrigues (5)	2006	312			0.39
Canada	Fang (6)	2008	312			0.33
China	Fang (6)	2008	496			0.20
Taiwan	Tzen-Wen (7)	2008	100			0.06
Turkey	Akman (8)	2009		132		0.77
United Kingdom	Davenport (9)	2009			1904 pt–yrs <sup>a</sup>	0.82 CAPD
						0.66 APD
Austria	Kipriva–Altfart (10)	2009	332			0.24
Brazil	Mores (11)	2009	680 <sup>a</sup>			0.74
Canada	Nessim (12)	2009	4247 <sup>a</sup>			0.36
Spain	Perez Fontan (13)	2009	641			0.38
United States	Qamar (14)	2009	137 <sup>a</sup>			0.24
Netherlands	Ruger (15)	2009	205 <sup>a</sup>			0.60
France	Castrale (16)	2010	1631 <sup>b</sup>			0.36
Israel	Cleper (17)	2010		29		1.66
Australia/New Zealand	Fahim (18)	2010	4675 <sup>a</sup>			0.62
Australia	Jarvis (19)	2010	4675 <sup>a</sup>			0.60
Qatar	Shiqidi (20)	2010	241			0.24

TABLE 1 Peritonitis Rates Around the World

CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis.

<sup>a</sup> Registry data.

<sup>b</sup> Elderly patients.

catheter insertion and management (22). The present position paper is directed specifically at the prevention of PD-related infections, and it is intended primarily for adult programs; however, many of the principles are likely to be applicable to pediatric programs as well.

# MONITORING PERITONITIS

- Every program should monitor infection rates at least quarterly (23–26). (Opinion)
- A team approach for continuous quality improvement (CQI) is the key to a successful PD program (25–26). (Opinion)

The PD CQI team generally includes nephrologists, nurses, social workers, and dietitians. Regular meetings of the team should be held to examine all PD-related infections, identifying the root cause of each episode. If a pattern of infections develops, the team needs to investigate and to plan interventions such as retraining, equipment changes, application of new protocols for exit-site care, or management of contamination (to mention just a few examples). Tracking not only the overall rates of each type of PD-related infection, but also the rates by organism will aid the team in identifying problems and trends. The organisms causing the peritonitis episodes can provide important clues to the possible causality (Table 2). Peritonitis episodes caused by Staphylococcus aureus and Pseudomonas aeruginosa are often secondary to exit-site and tunnel infections with the same organisms; peritonitis episodes caused by coagulase-negative staphylococci are generally related to contamination at the time of connection or to contamination of tubing (27), and they indicate a need to re-examine training methods. The CQI team identifies problems, develops solutions, and evaluates results in an iterative fashion.

Calculation of peritonitis rates should be standardized and should be clearly defined in any publication on peritonitis. Most observers would start to calculate the time at risk for peritonitis as the first day of training;

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# TABLE 2 Causes of Peritonitis

1 Contamination, most likely skin or environmental organisms

Contamination at the time of connection Contamination from tubing Hole in exchange tubing or catheter Loss of cap on end of tubing or failure to close clamp with leaking Product defects

- 2 Catheter related, most often staphylococcal species or *Pseudomonas aeruginosa* Biofilm on internal portion of the catheter (relapsing, repeat peritonitis) Exit-site and tunnel infection
- 3 Bowel-source enteric organisms including gram-negative rods, *Candida*, and anaerobes
  - Diverticulitis Cholecystitis Ischemic bowel Colitis Perforated stomach or intestine Colonoscopy, especially with polypectomy Constipation with transmural migration of organisms into peritoneum
- 4 Bacteremia, often Streptococcus or Staphylococcus Transient from dental procedures Infection of intravascular device
- 5 Gynecologic source, often Streptococcus, Candida, some gram-negative rods Peritoneal vaginal leak Vaginal delivery Hysteroscopy

some might consider the date of catheter insertion to be the starting point. The former is probably preferable, because the latter might lead to falsely low rates, especially in centers that place the catheter many weeks or even months before the start of training.

The rate is calculated by totaling all the peritonitis episodes that occurred during the entire time on PD ("at risk") for all patients in the program during the period in question. That total is then divided by the time at risk in years. "Time at risk" is the sum of all days that each patient was on PD during the time in question. The days at risk are then converted to years at risk.

Peritonitis episodes that occur while the patient is hospitalized and not doing self-dialysis might be excluded, but the work group feels that including all episodes while the patient is on PD is the best approach. The stop points for time at risk are generally successful transplantation (even though the catheter may be left in place for a period of time) and transfer to hemodialysis. Time spent during a period of temporary transfer to hemodialysis should not be included in the time at risk.

As shown in Table 1, low peritonitis rates are achievable. We believe that a rate of 0.36 episodes per patient per year can be reached by most programs. However, overall rates as low as 0.06 - 0.24 episodes per year at risk or 1 episode every 50 - 200 months have been reported, and so those are the goals that dialysis programs should strive to achieve (2,4,6,7,10,14,20).

Yearly, each program should also examine the proportion of patients who are peritonitis-free. A minimum of 80% of patients should be peritonitis-free in any given year. Often, a small number of patients experience most of the peritonitis episodes. Those patients require close scrutiny, with the development of approaches to lower the infection risk in such patients. That effort may require more intensive training, home visits, or the training of a family member. The dialysis center personnel should closely examine the organisms causing the peritonitis and determine whether the peritonitis is relapsing, repeat, or recurrent (as discussed later in this position paper). A program may also find it helpful to calculate a median rate for all the individual patient rates. In a successful program, the median rate will be zero, with most patients having no peritonitis episodes in a given year.

It is very important to examine organisms not just as a percentage of the total but also as an absolute rate (episodes per year). Only in this way can the results of a center be compared, organism-by-organism, with the results in the literature. To evaluate problem areas in a program, the rates of infection by organism should be examined and followed on a regular basis because of the important information provided.

For example, at one center, 30% of all peritonitis is caused by *S. aureus*, similar to the proportion reported at another center. However, if the first center has an overall peritonitis rate of 0.2 episodes per year, the *S. aureus* rate is then 0.06 episodes per year. That rate can then be compared to the rate at the second center whose overall peritonitis rate is 0.60 episodes per year, for a *S. aureus* peritonitis rate of 0.18 episodes per year. The second center therefore has a rate of *S. aureus* peritonitis that is 3 times the rate at the first center, despite a similar proportion of *S. aureus* episodes at the two centers.

In addition to examining rates by organism at multiple centers, publications on PD-related infections should also present the organism-specific data as rates, and not just as proportions or percentages of the total peritonitis rate. Table 3 shows an example of rates by organism.

TABLE 3 Example of Rates by Organism

Organism	Episodes per year at risk	
Peritonitis		
Coagulase negative Staphylococcus	0.05	
S. aureus peritonitis	0.03	
Other gram-positive organisms	0.04	
Pseudomonas aeruginosa	0.03	
Other gram-negative organisms	0.10	
Multiple organisms	0.02	
Fungal	0.01	
No growth/no culture	0.06	
TOTAL	0.34	
Catheter infections (exit site, tunnel)		
S. aureus	0.05	
P. aeruginosa	0.03	
All others	0.12	
TOTAL	0.20	

#### CATHETER PLACEMENT TO PREVENT CATHETER INFECTIONS AND THE RELATED PERITONITIS EPISODES

- No particular catheter has been definitively shown to be better than the standard silicone Tenckhoff catheter for the prevention of peritonitis (28–30). (Evidence)
- Prophylactic antibiotics administered at the time of insertion decrease the infection risk (31). (Evidence)

The topic of peritoneal access has been covered in a recent position paper (22) from the International Society for Peritoneal Dialysis (ISPD). Ideally, the patient should see the surgeon or training nurse (or both) before catheter placement, with the ideal location for the exit site being determined. In addition, the patient should be free from constipation. Proper skin preparation and careful cleansing of the area where the catheter is to be placed is essential, and if there is an excess of hair, it may need to be removed. A single dose of intravenous (IV) antibiotic given at the time of catheter placement decreases the risk of subsequent infection. A firstgeneration cephalosporin has been most frequently used in that context. However, a randomized trial found that vancomycin (1 g IV, single dose) at the time of catheter placement is superior to cephalosporin (1 g IV, single dose) in preventing early peritonitis (31). The odds ratio of peritonitis without any antibiotic was 11.6, and for cefazolin (compared with vancomycin), it was 6.45. Each program must therefore consider using vancomycin for prophylaxis for catheter placement, carefully weighing the potential benefit against the risk of vancomycin use hastening the emergence of resistant organisms.

In patients participating in the U.S. National CAPD Registry, catheter survival was superior for double-cuff catheters compared with single-cuff catheters; doublecuff catheters were also less likely to result in catheter removal for exit-site infection (32). This benefit was not confirmed in a single-center randomized trial with a much smaller number of patients (33); however, a recent study from Canada found that double-cuff catheters were associated with lower rates of *S. aureus* peritonitis (12). A large multicenter randomized controlled trial (RCT) would be helpful to resolve this question.

A downward-directed tunnel may decrease the risk of catheter-related peritonitis (34); however, randomized trials have not confirmed a benefit for the swan-neck configuration in reducing PD-related infections (29,30), nor has burying the catheter proved effective in reducing the risk of infection (35). Outcomes for infectious and mechanical complications are equivalent in catheter types using downward and lateral tunnel-tract and exitsite configurations (30).

Every effort should be made to avoid trauma and hematoma during catheter placement. The exit site should be round, and the tissue should fit snugly around the catheter. Sutures at the exit site increase the risk of infection and are contraindicated. Some programs obtain nose cultures before placement of the catheter, and they treat positive *S. aureus* nasal carriage with a 5-day course of intranasal mupirocin. No data on the effectiveness of that approach are available. Once the catheter is placed, and until healing is complete, dressing changes should be done by a dialysis nurse using sterile technique. The exit site should be kept dry until well healed, which precludes showers or tub baths for that period, which can take up to 2 weeks or more.

#### TRAINING PROGRAMS

- Training methods influence the risk of PD infections (36-46). (Evidence)
- Whenever possible, a nurse should provide the training, according to the 2006 ISPD guidelines/ recommendations for PD patient training (Figure 1, Table 4), using the principles of adult education (38). (Opinion)
- Each PD program should consult the ISPD guidelines/ recommendations to prepare the trainer and to develop a specific curriculum for PD training. (Opinion)

Each PD program should ensure that the trainer of the PD patients is well prepared and has the specific theoretical and clinical skills to present a well-planned PIRAINO et al.

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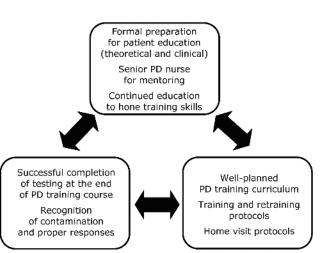


Figure 1 — Center approach to peritoneal dialysis (PD) training.



After hospitalization After peritonitis or catheter infection After change in dexterity, vision, or mental acuity Three months after initial training and routinely thereafter (once yearly at minimum)

curriculum for the patient. The center should not assume that a nurse who knows how to do PD is prepared to train patients to do PD. When the learner is a patient with a chronic disease such as end-stage renal disease, that learner has special needs that require specific teaching techniques (42). Nurse education should include theories of adult education and the specifics for teaching adult patients on PD. A full discussion of adult learning is beyond the scope of this position paper, but is described in some detail in the ISPD guidelines/recommendations for PD patient training at http://www.ispd.org (38).

Ideally, a senior mentor should train new PD nurses. That approach may require that new nurses be sent to train at a more experienced center. The old adage of "see one, do one, teach one" is not an appropriate foundation for the education of nurses in the principles of teaching PD. A structured nurse training program with subsequent continuing education is important to enhance the skills and the knowledge base of the trainers. A structured approach can translate into high-quality patient training and good outcomes.

Unfortunately, few if any studies have considered the nurse:patient ratio that leads to the best outcomes. Overburdening the nurse with excessive numbers of patients will result in shortened training times and difficulty in scheduling retraining as needed. Ideally the PD nurse should be focused solely on home dialysis and should have no in-center hemodialysis responsibilities. The work group feels that, although the practice has not been adequately studied, the assignment of one nurse to fully train a particular patient rather than a different nurse on different days should be adhered to, if possible. One-on-one training is ideal, although it may not always be feasible.

Interestingly, the experience of the PD nurse may be less important than the training protocol (40). A retrospective study paradoxically found that, compared with patients trained by newer, less experienced nurses, the patients trained by nurses with more experience had a shorter time to peritonitis. The authors speculated that nurses who had practiced PD for many years may have been more resistant to the institution of a protocol using adult learning techniques that the center had implemented. Another explanation might be that the nurses with more experience had been assigned to train patients who were perceived to be more difficult to train. The work group members feel that all nurses need continuous education to update and hone teaching skills.

The center should have a clearly developed curriculum for PD training modeled after the ISPD guidelines/ recommendations for PD patient training (38). This curriculum should include a daily plan for training content and handouts such as those that can be downloaded from the relevant article posted on the ISPD website. Hand hygiene must be emphasized. Training in the proper washing and drying of the hands, and use of hand disinfectant, especially where the water supply is not to be trusted, are critical parts of the training (further detail provided later in this paper). At the end of training, the patient should be tested to ensure that learning of the objectives has occurred.

Very few randomized trials have compared training protocols and curricula for PD patients. The length of patient training for PD is variable around the world (47). The length of training has never been shown to correlate with peritonitis rates. A trial that randomized centers to an enhanced training program using adult learning principles or to the center's standard approach found that peritonitis rates were lower with the enhanced training: 0.33 episodes per year (1 episode in 36.7 months) compared with 0.43 episodes per year (1 episode in 28.2 months) respectively (37). However, the details of the training curricula were not described, and the baseline peritonitis rates differed in the two groups. In children, peritonitis rates were lower in programs with longer training dedicated to theory and technical skills (39). No randomized trials have compared different training schedules that cover the same content and curriculum.

All patients must be taught what contamination is and what the proper response to contamination is. Each center should have a appropriate protocol to handle contamination (48). The protocol should detail the responses to specific occurrences such as fluid infused after the contamination and open compared with closed clamping of exchange tubing (36). Patients need to come to the center for a tubing change if the end of the tubing is contaminated. Prophylactic antibiotics should be prescribed if dialysis solution was infused after contamination or if the catheter administration set was open and exposed to bacteria for an extended period of time. After a known break in technique, many nephrologists give a 2-day course of antibiotics; others provide a single dose of intraperitoneal antibiotic. There is no standard regimen. Generally, a culture of the effluent is not obtained after an episode of contamination. However, if culturing is done and is positive, consideration might be given to extending therapy. After contamination, a positive culture in the presence of clear fluid and no symptoms should not be considered peritonitis; however, if left untreated, the patient might develop peritonitis. The goal of managing contamination is always to prevent the development of peritonitis.

According to learning specialists, retraining plays an important role in reducing mistakes (41,43,44). Task repetition causes the brain to learn both the cognitive and the physical steps of the procedures. A psychological mechanism called "false memory" is readily illustrated by patients who perform an exchange in front of the nurse, but who are not aware of mistakes being made and who say that they were taught to perform the exchange that way (41). Memory is in a labile state after early exposure to new information; memory is enhanced by returning to the learning context and cues for correct performance (43,44).

After a period of time, patients may alter the procedure they were taught during training. A study of compliance with the exchange procedure done at 6 months after the start of PD found that most patients had begun to take shortcuts or had simply veered off the prescribed steps that they had been carefully taught at the start of PD (46). Half the patients did not wash their hands according to procedure, nearly half did not check the bag for leaks, and 10% forgot to wear their mask or cap. Not wearing a mask or cap was associated with subsequent peritonitis risk in that study. However, other studies have not shown that using a mask reduces peritonitis risk (49,50). An Italian study of patient knowledge about PD (assessed using a questionnaire and a review of patient behavior during a home visit) found that, after a mean of 33 months on PD, 34% of patients did not answer the questions accurately,

and 23% did not follow the correct exchange procedures (41). Noncompliance with exchange protocols was significantly associated with a higher peritonitis rate. These studies suggest a need for periodic retraining.

Retraining seems to be helpful in reducing peritonitis risk, but data are limited (41,45). Russo and colleagues (41) found retraining to be important for younger patients (<55 years of age), patients with a lower education level, and patients in the early or late phase of PD therapy (<18 or >36 months). An observational study of 120 dialysis centers in Italy found that retraining and home visits correlated with lower peritonitis rates (45). How often a patient should be retrained or how soon after initiation is unknown and requires study. Table 4 shows our suggestions.

A patient's learning about the signs of peritonitis in training may be long forgotten if the patient does not develop their first peritonitis for several years and if there is no reinforcement of information on peritonitis given earlier. Retraining therefore needs to include not just technique but also recognition of this important complication. The patient needs to be reminded that haziness of the effluent might be peritonitis even in the absence of pain, and that they should take that haziness as an indication to call the dialysis unit.

In the absence of definitive studies, each PD program must decide when and how often to routinely retrain patients. Retraining should include observation of dialysis exchange procedures, handwashing technique, recognition of signs and symptoms of peritonitis, recognition of contamination and the appropriate response to it, and exit-site care. Retraining is an opportunity to prevent future infections, with observation to identify the emergence of problems such as poor vision, forgetfulness, or shortcuts.

Home visits by the PD nurse may be very useful in detecting problems with exchange technique, adherence to protocols, and other environmental and behavioral issues that increase the risk of infection and are best dealt with proactively. It has long been accepted that the location for exchanges must be clean, with avoidance of animal hair, dust-laden air, and fans or drafts. Home visits indicated that retraining was necessary in approximately one half of a center's patients, who were not following protocols (41).

#### CONNECTION METHODS

 Spiking of dialysis bags is a procedure that poses a high risk for contamination of the system. "Flush before fill" reduces the risk of contamination (51–58). (Evidence)

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- Data on peritonitis rates in automated PD (APD) and continuous ambulatory PD (CAPD) are conflicting (12,59–62). (Evidence)
- The decision on modality (APD vs CAPD) should not be based on peritonitis risk. (Opinion)

Data to show that spiking leads to peritonitis are abundant. Furthermore, for both CAPD and APD, flushing with dialysate before filling the abdomen has been shown to decrease the risk of peritonitis from contamination. Therefore, for CAPD, a double-bag system should be used. Manual spiking should be avoided as much as possible; if spiking is required, assist devices may be used. A systematic review concluded that of all catheter-related interventions designed to prevent peritonitis in PD, only disconnect (twin-bag and Y-set) systems have been proved to be effective (compared with conventional spike systems) (58). Close attention must therefore be paid to the connection methodology. For programs that switch vendors and, therefore, connection method, careful attention should be paid to subsequent infection rates.

Peritonitis rates on APD and CAPD are probably similar (12,59,60). The literature describing the relative risks of peritonitis with continuous cycling PD (CCPD) and CAPD is conflicting, but the disparate results may reflect the fact that the cycler connection methodology varies from study to study and sometimes is not even mentioned in the paper (59). Several studies have shown that, compared with CAPD patients, CCPD patients have significantly lower peritonitis rates (61,62); however, use of a cycler that requires spiking may lead to high rates of peritonitis caused by contamination if an assist device is not used. The work group recommends either the use of an assist device, if available, for all spiking procedures or conversion to a system that does not require spiking. Some cyclers require a cassette; if the cassette is reused, the risk of peritonitis cause by water-borne organisms is high (63,64). Cassettes should not be reused. More research is needed comparing peritonitis risk in dry day, CCPD, and CAPD patients. Patients on nightly PD (cycler at night with a dry day) may have a decreased risk of infection compared with those on CCPD (cycler at night plus a day fill), perhaps because the empty abdomen for part of the day enhances immune function (65). This issue also requires further study.

#### EXIT-SITE CARE TO PREVENT PERITONITIS

Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care. Antibiotic protocols against *S. aureus* are effective in reducing the risk of *S. aureus* catheter infections (66–81). (Evidence)

- All PD patients should use topical antibiotic either at the catheter exit site or intranasally or both (66,70,71,73–76,78,82). (Evidence)
- Topical antibiotic ointments (as opposed to antibiotic creams) should not be used at the exit site of polyure-thane catheters (82). (Evidence)

Routine exit-site care by the patient begins when the exit site is well healed; such care is part of the patient's training. Water and antibacterial soap are recommended by many centers. Use of an antiseptic to clean the exit site is preferred in some programs, but the agent must be non-cytotoxic. The concentration of the cleansing agents must be carefully considered (83–87). For example, povidone iodine is cytotoxic at concentrations greater than 0.001%; hydrogen peroxide, at greater than 0.003%; sodium hypochlorite, at greater than 0.24%; and chlorhexidine, at greater than 0.005% (83,84).

Excellent hand hygiene is most important before any examination of the patient's exit site by the patient, family members, and members of the health care team. The U.S. Centers for Disease Control and Prevention recommends 70% alcohol-based hand rubs as the most effective hand cleansing agent (88). The quantity applied to the hands should take at least 15 seconds of hand rubbing to dry. Handwashing for 15 seconds with antimicrobial soap (4% chlorhexidine) is the next most effective method for hand cleansing. Visibly dirty hands require handwashing with soap. Polished nails double the risk of bacterial contamination on hands, and artificial nails create a risk of bacterial contamination that is increased by a factor of 7 (88). Patients, health care givers, and patient helpers should all be aware of proper hand hygiene protocols. If the water the patient uses is thought to have a high bacterial count, then the use of alcohol hand hygiene is preferred to simply using tap water.

A number of protocols for the prevention of S. aureus PD-related infections have been examined. Prophylaxis using daily application of mupirocin cream or ointment to the skin around the exit site has been effective in reducing S. aureus exit-site infection and peritonitis in a number of reports (70,75,76,78,80,89). An observational study in 740 incident PD patients showed that use of topical mupirocin was associated with a significant reduction in exit-site infection (0.168 vs 0.156 episodes per patient-year) and peritonitis (0.443 vs 0.339 episodes per patient-year) (80). In a meta-analysis of ten studies (three RCTs and seven historical cohort studies) of mupirocin prophylaxis to prevent S. aureus infection, PD patients using prophylaxis had a 63% reduction in the risk of S. aureus infection—peritonitis being reduced by 66% and exit-site infection by 62% (66). A more recent

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meta-analysis published in 2009 demonstrated that mupirocin reduced the overall risk of S. aureus infection by 72%—S. aureus exit-site infections by 72%, and S. aureus peritonitis by 40% (75).

Intranasal mupirocin is another possible approach to reduce S. aureus PD-related infections (73). A large multicentric trial of intranasal mupirocin compared with intranasal placebo in PD patients showed that prophylaxis reduced S aureus exit-site infections but not peritonitis (73). A head-to-head comparison of intranasal mupirocin and exit-site mupirocin has not yet been done. It is possible that some combination of both might be most effective. Intranasal mupirocin is expensive (if based on nose cultures) and difficult to implement (82). By contrast, exit-site mupirocin cream used in a protocol that is applied to all patients is simple, easy to implement, and cost effective (by avoiding the need to do costly nose cultures). Note that exit-site antibiotic ointments containing polyethylene glycol base (as opposed to antibiotic creams) should not be applied to polyure thane catheters because deformation leading to rupture of the catheter can occur (82). The work group recommends that each center determine which approach is best for their patients.

Without a protocol to prevent S. aureus PD-related infections, that organism will be the major cause of exitsite infection, which will often lead to peritonitis and catheter loss (80). Use of prophylaxis can dramatically lower the rate of PD-related S. aureus infections. The targeted rate for S. aureus catheter infection should be less than 0.05 episodes per patient per year—that is, 240 months (20 years) between episodes (82). The targeted rate for S. aureus peritonitis should be less than 0.06 episodes per patient per year—that is, 1 episode in 200 months (16.7 years) (48).

Mupirocin resistance has been reported (90–92). Resistance to mupirocin can be classified as "low" if the minimal inhibitory concentration is greater than or equal to 8  $\mu$ g/mL, or "high" if the minimal inhibitory concentration is greater than or equal to 512  $\mu$ g/mL. It is expected that high-level resistance will eventually result in clinical failure or a high relapse rate. Resistance to mupirocin does not yet appear to have eliminated the efficacy of that agent, but that consequence is likely with longer periods of individual exposure and with more patients being exposed. Pérez–Fontán *et al.* have observed a greater incidence of exit-site infections in patients colonized with mupirocin-resistant S. aureus than in those colonized with sensitive organisms, suggesting that the development of mupirocin resistance may have adverse clinical consequences and lead to treatment failures (91).

With the use of mupirocin leading to a reduction in S. aureus infections, P. aeruginosa becomes the most troublesome organism at the exit site (76). In a multicentric double-blind randomized trial comparing daily exit-site mupirocin with daily exit-site gentamicin, gentamicin cream was shown to be as effective as mupirocin in reducing S. aureus exit-site infections and also highly effective in reducing P. aeruginosa exit-site infections (71). Compared with the mupirocin approach, the gentamicin protocol had the added advantage of reducing peritonitis risk. However, an increased risk of fungal exit-site infections accompanied the use of gentamicin at the exit site. In a nonrandomized study by Chu et al. in Hong Kong in 2008, exit-site mupirocin was compared with exit-site gentamicin in a 1:1 open assignment at a single center (74). No significance difference was found in the rates of infection for the two groups; but the study had several limitations, including small patient numbers, short follow-up, and no power calculations. Because gentamicin is a useful drug for treating infection, long-term use to prevent infection raises the question of whether such use in patients will eventually lead to gentamicin resistance, which is a concern.

Randomized trials currently under way are examining other approaches to exit-site care. One is a RCT comparing Medihoney antibacterial wound gel (Comvita New Zealand, Te Puke, New Zealand) to intranasal mupirocin (93). The MP3 Study, a multicentric randomized trial comparing exit-site mupirocin with Polysporin Triple (Johnson & Johnson, New Brunswick, NJ, USA) at the exit, has been presented in abstract form; the triple antibiotic ointment led to higher rates of fungal peritonitis and therefore cannot be recommended (94). Until further studies are available, each center must determine the best approach to prevent S. aureus PD-related infections.

#### PREVENTION OF BOWEL-SOURCE INFECTIONS

- Severe constipation and diarrhea can both be associated with peritonitis caused by enteric organisms (95,96). (Evidence)
- Hypokalemia is associated with an increased risk of enteric peritonitis (97-99). (Evidence) Hypokalemia should therefore be avoided and, if present, treated. (Opinion)
- Invasive gastrointestinal procedures may infrequently cause peritonitis in PD patients (100–102). (Evidence) Intravenous antibiotic prophylaxis reduces early peritonitis in these patients (67). (Evidence)

Peritonitis can result from transmigration of microorganisms across the bowel wall (95,103). Dialysis

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patients, especially those with diabetes, may have hypomotility disorders, may be more prone to gastrointestinal ulcerations, and often are taking drugs (such as oral iron, oral calcium, and certain analgesics) that contribute to constipation. Constipation is quite common and might sometimes not be recognized by the patient. All PD patients should be instructed during training on the importance of regular bowel movements and the avoidance of constipation.

Colitis and diarrhea may be followed by peritonitis (96). The mode by which the infecting organisms gain entry in such cases is unclear. Transmural migration of organisms is possible, as is touch contamination. Again, the importance of hand hygiene should be emphasized to the patient and, if need be, where the water is contaminated, the use of alcohol hand wash should be considered. Active inflammatory bowel disease is considered by many of the work group members to be a contraindication to PD.

Several observational studies have reported an increased risk of peritonitis, most commonly involving Enterobacteriaceae, in patients with hypokalemia (97–99). The authors speculate that the underlying cause is transmural migration from the intestinal mucosa to the peritoneum, and they further note that patients with hypokalemia often suffer from malnutrition, which may suppress immune response. In the absence of a RCT, it would seem reasonable to follow potassium levels carefully and to treat hypokalemia when present in PD patients.

Pathology of the intra-abdominal organs can present as peritonitis (104,105). Cholecystitis, gastric perforation, ischemic bowel, appendicitis, and diverticulitis or diverticulosis in a PD patient can cause enteric peritonitis (104–107). Underlying pathology of this kind should be suspected if 2 or more enteric organisms grow from the effluent and especially if the culture grows an anaerobe or fungus. Prevention of peritonitis from these causes is not straightforward, but if signs and symptoms indicate intra-abdominal pathology, consideration should be given to stopping PD at least temporarily, because lavaging of the peritoneal space with PD fluid obscures the underlying pathology and the effluent interferes with the normal antimicrobial functions of the peritoneal space. Diverticulosis may be a risk for enteric peritonitis (101). Methods to prevent infection from such a source are not clear, but it seems logical that constipation and a diet that might precipitate diverticulitis should be avoided.

Certain procedures—including colonoscopy, hysteroscopy, dental work, and cholecystectomy—can lead to peritonitis (100,105–108). A recent retrospective study found that the risk of peritonitis after colonoscopy without antibiotic prophylaxis was 6.3%; colonic biopsy or polypectomy did not appear to further increase the risk (101). In that study, no peritonitis was observed after colonoscopy in patients that were given prophylactic antibiotics, although the difference was not statistically significant. Antibiotics such as ampicillin (1 g) plus a single dose of aminoglycoside, with or without metronidazole, given intravenously just before the procedure may lower the risk of peritonitis (67). Alternatively, some might choose to administer prophylactic antibiotics by the intraperitoneal route the night before the procedure. The work group recommends that the abdomen be emptied of fluid before any procedure involving the abdomen or pelvis, including colonoscopy, renal transplantation, cholecystectomy, and endometrial biopsy.

# PREVENTING BACTEREMIC SOURCES OF PERITONITIS

Transient bacteremia—for example, from dental work or dental abscess, or even poor dentition—can lead to peritonitis (100). A single oral dose of amoxicillin (2 g) 2 hours before extensive dental procedures are used in some programs as prophylaxis. Currently, no studies have evaluated antibiotic prophylaxis for dental work to prevent peritonitis in PD patients. This is one area in which further research is needed. For the moment, each center will have to make a decision regarding use of prophylaxis in such cases.

# PREVENTING PERITONITIS FROM GYNECOLOGIC SOURCES

Gynecologic sources are unusual causes of peritonitis. Vaginal delivery was associated with peritonitis in a woman whose vaginal vault was colonized with Escherichia coli (109). Such a complication would seem to be preventable by giving prophylactic antibiotics before delivery. Hysteroscopy with biopsy can lead to severe peritonitis (100,110). Peritonitis has been reported secondary to a vaginal leak occurring after recurrent peritonitis, leading to formation of a subcompartment in the peritoneal cavity (111), or to a vaginal fistula presenting as a vaginal leak (112,113), and even to a vaginal leak in a prepubescent child on PD (114). Vaginal colonization with Streptococcus agalactiae can be the source of contamination for a female patient or for a male patient who is the partner of a colonized woman (115–117). Organisms are variable, but vaginal sources can lead to fungal peritonitis.

# PREVENTION OF FUNGAL PERITONITIS

• Most episodes of fungal peritonitis are preceded by courses of antibiotics (118–122). (Evidence)

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 Fungal prophylaxis during antibiotic therapy may prevent some cases of Candida peritonitis in programs that have high rates of fungal peritonitis (118,119,123–130). (Evidence)

Patients receiving prolonged or repeated courses of antibiotics are at increased risk of fungal peritonitis. A number of studies have examined the use of prophylaxiseither oral nystatin or a drug such as fluconazole—given during antibiotic therapy to prevent fungal peritonitis, with mixed results. Programs with high baseline rates of fungal peritonitis found such a prophylactic approach to be beneficial; those with low baseline rates did not detect a benefit. In a recent observational study, the fungal peritonitis rate of the nystatin group was slightly lower than that of the control group (0.011 vs 0.019 episodes per patient-year) but the difference did not reach statistical significance (123). There was, however, a significant decrease in the incidence and proportion of antibiotic-related fungal peritonitis in the nystatin group (123). A RCT by Lo et al. showed that antifungal prophylaxis during all courses of antibiotics prolonged time to *Candida* peritonitis (129). Another RCT recently demonstrated that, compared with a group not receiving fluconazole, the group receiving fluconazole 200 mg every 48 hours during all courses of antibiotics had significantly fewer (p = 0.0051) fungal peritonitis episodes (131). The work group feels that each PD program must examine their history of fungal peritonitis and decide whether such a protocol might be beneficial, particularly for patients taking prolonged or frequent courses of antibiotics (such as those with foot ulcer and osteomyelitis).

#### REDUCING THE RISK OF RELAPSE AND REPEAT PERITONITIS

Replacing the PD catheter in the setting of relapsing peritonitis will reduce the risk of subsequent relapse and repeat episodes (132,133). (Evidence)

The definition of "relapsing peritonitis" is a second episode with the same organism within 4 weeks of stopping antibiotics for the initial episode (21). A culturenegative episode of peritonitis within 4 weeks of stopping antibiotics might also be considered to be within the scope of relapsing peritonitis. "Repeat peritonitis" is another episode of peritonitis with the same organism more than 4 weeks after stopping antibiotics for the initial episode. That definition contrasts with the definition of "recurrent peritonitis," which is another episode of peritonitis with a different organism within 4 weeks of stopping antibiotics for an earlier episode. Although relapsing peritonitis is not counted as a new episode in calculating a center's peritonitis rate, the center must still carefully track relapsing episodes and repeat episodes (which should be counted as new episodes in calculating the total rate). Relapsing and recurrent peritonitis have been found to be caused by different spectra of bacteria and may therefore represent distinct clinical entities (98). Recurrent peritonitis appears to have the poorer prognosis (98). A careful examination of the exit site may reveal an occult infection as the cause. S. aureus is a common organism causing peritonitis by that mechanism. Alternatively, bacteria living within the biofilm lining the intra-abdominal portion of the catheter may possibly be seeding the peritoneal space and causing relapsing or repeat peritonitis. Seeding from biofilm is particularly common with coagulasenegative staphylococci, but can also occur with S. aureus, P. aeruginosa, and other organisms. Inadequate treatment of peritonitis—particularly through low trough levels of antibiotics in the effluent, which may not be adequate to reach the biofilm-predisposes to this complication (134).

Replacement of the catheter when the patient presents with relapsing or repeat peritonitis will lower the risk of further peritonitis episodes from the same organism and may protect the peritoneal membrane (132,133). Provided that antibiotic treatment clears the effluent, catheter replacement can safely be done as a simultaneous procedure (135). That approach may minimize time on hemodialysis and the risk of receiving a hemodialysis catheter.

One peritonitis episode appears to increase the risk of another episode (98,133). It is unclear whether that risk is a result of a depressed intraperitoneal immune response or of inadequate exchange technique, or both. The approach to preventing peritonitis from different organisms after a first episode is unclear, but retraining would appear to be an acceptable way to attempt to lower the risk of another episode of peritonitis (Table 5).

#### PD SOLUTION

• No recommendation can be made on the specific choice of PD solution to reduce peritonitis risk.

A few studies have found that the choice of PD solution may affect the peritonitis rate. Duranay et al. compared peritonitis rates for 147 patients treated with glucose, icodextrin, and amino-acid-based solutions and concluded that the type of PD solution does not appear to be a risk factor for development of peritonitis (136). Montenegro et al. studied 100 incident PD patients treated with either lactate- or pure bicarbonatebuffered solutions (137) and found peritonitis rates

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TABLE 5
Pattern of Peritonitis and Possible Action to Reduce the Risk of Further Episodes

Time since completion of antibiotic therapy	Organism			
for prior peritonitis episode	Same	Different		
≤4 Weeks	Relapse	Recurrence:		
	(including 2nd culture-negative episode): Consider catheter replacement	Retraining		
>4 Weeks	Repeat:	High-risk period for 6 months:		
	Consider catheter replacement	Retraining		

of 1 episode in 21 patient-months and in 36 patientmonths respectively (p = 0.017). Two other retrospective studies also found that, compared with the use of conventional lactate-based dialysate, the use of neutral bicarbonate/lactate dialysate appears to reduce the peritonitis rate (138,139). In the multicentric randomized crossover Euro-Balance trial, conventional acidic lactate-buffered dialysate was compared with pH-neutral lactate-buffered solution low in glucose degradation products. No difference was seen in the peritonitis rates for the two groups (140). Fan et al. randomized 118 incident PD patients to biocompatible or standard solution and found no difference in peritonitis risk (141). On the whole, current research does not support the use of biocompatible solutions as a method to reduce peritonitis risk.

#### POTENTIALLY MODIFIABLE RISK FACTORS

Table 6 lists the peritonitis risk factors that may be amenable to modification.

Hypoalbuminemia is a well-known risk factor for peritonitis (142,143). A small study in children in which serum albumin was increased saw a fall in peritonitis (144); however, data on this topic are very limited, and more study is required.

Depression has also been shown to be a risk factor for peritonitis (145). The mechanism is unclear. Theoretically, patients with depression might have an alteration in immune function, or they might be more likely to contaminate during the connection process. There is no study showing that treatment for depression lowers the subsequent peritonitis risk.

In a single-center study (146), oral active vitamin D therapy has been reported to significantly lower the risk of peritonitis in PD patients (80% reduced relative risk; hazard ratio: 0.20; 95% confidence interval: 0.06 to 0.64; p = 0.007). Vitamin D deficiency is extremely common in PD patients, in part because of losses of 25-OH vitamin D in effluent. Vitamin D deficiency is known to

#### TABLE 6 Potentially Modifiable Risk Factors for Peritonitis

Hypoalbuminemia Vitamin D insufficiency Depression Connection methodology Technique errors Hypokalemia Prolonged antibiotics Medical procedures Constipation Exit-site colonization and infection Exposure to pets

have a negative impact on the immune system. Further study in this important area is needed.

Peritonitis from cats (usually caused by *Pasturella multocida*) or other domestic animals has been reported in PD patients (147,148). Cats are likely to bite or claw cycler tubing and thus pets should always be excluded from the room in which dialysis exchanges are performed. A recent review emphasizes the importance of both an initial evaluation of pet ownership and ongoing patient education about the risk of infection related to pets in preventing peritonitis from this source (148).

#### FUTURE RESEARCH

Much additional research is needed in the area of preventing PD-related infections. In particular, properly conducted RCTs that are powered to investigate the question under study are needed. A recent review outlined some of the controversies in PD-related infections that require further study and emphasized the need for a team-based approach to lowering infection rates (149). Table 7 lists some suggested trials that might be carried out. The work group encourages programs with excellent peritonitis rates to publish descriptions of their training methods and protocols for peritonitis

# TABLE 7 Suggested Targets for Further Research

- Randomized controlled trial of retraining and reassessment of exchange technique at 1, 3, and 6 months (versus no additional training)—outcome: subsequent peritonitis
- Multicenter randomized controlled trial of providing antibiotic prophylaxis with dental work (versus no antibiotic prophylaxis)—outcome: subsequent peritonitis
- Randomized controlled trial of *Staphylococcus aureus* nasal carriage eradication at the time of peritoneal catheter insertion (versus no eradication)—outcome: time to *S. aureus* peritonitis
- Randomized controlled trial of repetitive courses of intranasal mupirocin (versus daily exit-site mupirocin) outcome: preventing peritonitis

prevention. Particular attention should be paid to successful programs that deal with patients of low socioeconomic status and limited education. One example is a report from southern China, where satellite programs supplying care to rural patients were established using the expertise of a knowledgeable center located at Sun Yat-sen University (150). In 2009, the expert center had an outstanding peritonitis rate of 0.194 episodes per year at risk (1 episode in 61.3 patient-months). The satellite centers had a total peritonitis rate of 0.26 episodes per year at risk, not quite as good, but still very low (150). That report demonstrates how a structured approach using centers of excellence as models can result in excellent outcomes in outreach programs.

# SUMMARY

Infection continues to be a serious complication for PD patients. Reducing the risk of PD-related infections should be a primary goal of every PD program. Quality improvement programs with continuous monitoring of infections and root-cause analysis of each infectious episode are critical to decrease PD-related infections (151). Very low rates of infection can be achieved if close attention is continuously paid to training and retraining, equipment, and protocols to prevent infections.

# DISCLOSURES

DWJ is a consultant for Baxter Healthcare Pty Ltd. and has previously received research funds from that company. He has also received speakers' honoraria and research grants from Fresenius Medical Care, and he is a recipient of a Queensland Government Health Research Fellowship. He is the lead investigator for a randomized controlled trial of Medihoney (Comvita New Zealand) compared with mupirocin prophylaxis of catheter-associated infections in PD. JB belongs to the speakers' bureau and is a consultant for Baxter Healthcare, Inc. EB belongs to the speakers' bureau for Baxter Healthcare, Inc. No other author has any conflict of interest to declare.

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