

ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment

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ISPD GUIDELINES/RECOMMENDATIONS

ISPD PERITONITIS RECOMMENDATIONS: 2016 UPDATE ON PREVENTION AND TREATMENT

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Peritonitis is a common and serious complication of peritoneal dialysis (PD). Although less than 5% of peritonitis episodes result in death, peritonitis is the direct or major contributing cause of death in around 16% of PD patients (1–6). In addition, severe or prolonged peritonitis leads to structural and functional alterations of the peritoneal membrane, eventually leading to membrane failure. Peritonitis is a major cause of PD technique failure and conversion to long-term hemodialysis (1,5,7,8).

Recommendations under the auspices of the International Society for Peritoneal Dialysis (ISPD) were first published in 1983 and revised in 1993, 1996, 2000, 2005, and 2010 (9–14). The present recommendations are organized into 5 sections:

1. Peritonitis rate

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2. Prevention of peritonitis
3. Initial presentation and management of peritonitis
4. Subsequent management of peritonitis
5. Future research

These recommendations are evidence-based where such evidence exists. Publications in or before December 2015 were reviewed. The bibliography is not intended to be comprehensive. When there were many similar publications on the same area, the committee included articles that were recently published. In general, these recommendations follow the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system for classification of the level of evidence and grade of recommendations in clinical guideline reports (15). Within each recommendation, the strength of the recommendation is indicated as Level 1 (We recommend), Level 2 (We suggest), or not graded, and the quality of the supporting evidence is shown as A (high quality), B (moderate quality), C (low quality), or D (very low quality). The recommendations are not meant to be implemented in every

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situation indiscriminately. Each PD unit should examine its own pattern of infection, causative organisms, and sensitivities, and adapt the protocols according to local conditions as necessary. Although many of the general principles presented here could be applied to pediatric patients, we focus on peritonitis in adult patients. Clinicians who take care of pediatric PD patients should refer to the latest consensus guideline from our pediatric colleagues for detailed treatment regimens and dosages (16).

PERITONITIS RATE

- We recommend that every program should monitor, at least on a yearly basis, the incidence of peritonitis **(1C)**.
- We recommend that the parameters monitored should include the overall peritonitis rate, peritonitis rates of specific organisms, the percentage of patients per year who are peritonitis-free, and the antimicrobial susceptibilities of the infecting organisms **(1C)**.
- We suggest that peritonitis rate should be standardly reported as number of episodes per patient-year **(not graded)**.
- We suggest that organism-specific peritonitis rates should be reported as absolute rates, i.e. as number of episodes per year **(not graded)**.

As part of a continuous quality improvement (CQI) program, all PD programs should monitor the incidence of peritonitis on a regular basis (17–19). During the computation, only peritonitis episodes that developed from the first day of PD training should be counted, while relapsing episodes should only be counted once. However, it may also be useful to monitor any peritonitis episode that develops after catheter insertion and before PD training is started. Peritonitis episodes that develop while the patient is hospitalized and PD performed by nurses should also be counted. In addition to the overall peritonitis rate, monitoring should include the peritonitis rate of specific organisms and drug susceptibilities of the infecting organisms (20), which may help to design center-specific empirical antibiotic regimens. With this information, interventions can be implemented when peritonitis rates are rising or unacceptably high.

There is a substantial variation in the peritonitis rate reported by different countries, as well as a great deal of variation within countries that is not well explained (1,3,14,19,21–26). Nonetheless, the overall peritonitis rate should be no more than 0.5 episodes per year at risk, although the rate achieved depends considerably on the patient population. In some outstanding centers, an overall peritonitis rate as low as 0.18 to 0.20 episode per year has been reported (27,28). All centers should work to continuously improve their peritonitis rates. There are several methods of reporting peritonitis rates (Table 1) (13,29), and expressing as number of patient-month per episode has been commonly used. However, the committee favors reporting peritonitis rates as number of episodes per year as data are presented

TABLE 1
Methods for Reporting Peritonitis

- As rates (calculated for all infections and each organism): Number of infections by organism for a time period, divided by dialysis-years' time at risk, and expressed as episodes per year.
- As percentage of patients per period of time who are peritonitis free.
- As median peritonitis rate for the program (calculate peritonitis rate for each patient, and then obtain the median of these rates).

N.B. Relapsing peritonitis (see Table 6 for the definition) should be counted as a single episode.

in a linear scale. Some centers also monitor the incidence of death associated with peritonitis, which is typically defined as death with active peritonitis or within 4 weeks of a peritonitis episode, or any death during hospitalization for a peritonitis episode (6,12,30).

PREVENTION OF PERITONITIS

Exit-site and catheter-tunnel infections are major predisposing factors to PD-related peritonitis (31). Many prevention strategies aim to reduce the incidence of exit-site and catheter-tunnel infections, and clinical trials in this area often report peritonitis rates as a secondary outcome. In this guideline, we focus on the prevention of peritonitis. The prevention of exit-site and catheter-tunnel infections will be covered in a separate guideline.

CATHETER PLACEMENT

- We recommend that systemic prophylactic antibiotics be administered immediately prior to catheter insertion **(1A)**.

Detailed description of the recommended practice of PD catheter insertion has been covered in another ISPD position paper (32). There are 4 randomized, controlled trials on the use of perioperative intravenous (IV) cefuroxime (33), gentamicin (34,35), vancomycin (36), and cefazolin (35,36) as compared to no treatment. Three of them showed that perioperative antibiotic reduces the incidence of early peritonitis (34–36), while 1 that used cefazolin and gentamicin found no benefit (35). Vancomycin and cefazolin were compared head-to-head in 1 study (36), which showed that vancomycin is more effective than cefazolin. The overall benefit of prophylactic perioperative IV antibiotics was confirmed by a systematic review of these 4 trials (37). Although first-generation cephalosporin may be slightly less effective than vancomycin, the former is still commonly used because of the concern regarding vancomycin resistance. Each PD program should determine its own choice of antibiotic for prophylaxis after considering the local spectrum of antibiotic resistance. No data exist on the effectiveness of routine screening and eradication of *Staphylococcus aureus* nasal carriage before catheter insertion (e.g. by intranasal mupirocin).

Besides prophylactic antibiotics, various techniques of catheter placement have been tested. Four randomized trials have compared laparoscopic or peritoneoscopic catheter placement with standard laparotomy (38–41). One study showed that peritoneoscopic insertion led to significantly less early peritonitis (38), but the other 3 were negative (39–41). A systematic review concluded that there is no significant difference in peritonitis rate between these techniques (42). Two studies compared midline with lateral incision (43,44), but neither found any difference in peritonitis rate. Several studies examined the technique of burying the PD catheter in subcutaneous tissue for 4 to 6 weeks after implantation (45–47). The first prospective study with historic control found a decrease in rate of peritonitis (45). In the 2 subsequent randomized studies, one showed a decrease in peritonitis rate with a buried catheter (46), while the other showed no difference (47). One retrospective study found no difference in peritonitis rate between pre-sternal and abdominal swan-neck catheters (48). In summary, there are no convincing data that the buried catheter technique lowers peritonitis rates.

CATHETER DESIGN

- The committee has no specific recommendation on catheter design for prevention of peritonitis.

There are no convincing data regarding the effect of PD catheter design and configuration on peritonitis risk. Eight randomized trials have compared straight and coiled PD catheters (49–55) and found no difference in peritonitis rate. Two systemic reviews of these trials had the same conclusion (42,56). Two randomized controlled trials found no difference in peritonitis rate between a swan-neck design and the traditional Tenckhoff catheter (57,58). Several retrospective studies suggested that double-cuffed catheters are associated with a lower peritonitis rate than single-cuffed ones (59–62). However, the only randomized trial on this topic showed no difference in peritonitis risk between the two catheter types (63). Downward direction of the tunnel and exit site has theoretical benefits and is often advocated for the prevention of catheter-related peritonitis, but the data supporting this are weak (64).

CONNECTION METHODS

- We recommend that disconnect systems with a “flush before fill” design be used for continuous ambulatory PD (CAPD) **(1A)**.

For CAPD, several prospective studies confirm that the use of Y connection systems with the “flush before fill” design results in a lower peritonitis rate than the traditional spike systems (65–80). Two systematic reviews concluded that the risk of developing peritonitis was reduced by about one-third with the use of Y systems (42,81). Among all disconnect systems, 1 previous systematic review showed a significantly lower risk

of peritonitis with double bag compared with the standard Y systems (82). On the other hand, 2 updated systematic reviews did not find any difference (42,81). It was suggested that the use of conservative statistical techniques might have partly accounted for the lack of difference observed (42).

Published studies that compared the peritonitis rate of machine-assisted automated PD (APD) and CAPD showed conflicting results (83–91). However, most of these studies were observational rather than randomized trials, and the analysis of these studies is handicapped by failure to report on the connection type in the cyclers used. At present, the choice of APD versus CAPD should not be based on the risk of peritonitis.

TRAINING PROGRAMS

- We recommend that the latest ISPD recommendations for teaching PD patients and their caregivers be followed (92).
- We recommend that PD training be conducted by nursing staff with the appropriate qualifications and experience **(1C)**.

The method of training has an important influence on the risk of PD infections (92–103). Much research is needed on the best approach to train patients on the technique of PD to minimize PD-related infections. Unfortunately, high-level evidence guiding how, where, when, and by whom PD training should be performed is lacking (103). Detailed description of the recommended practice of PD training has been covered in another ISPD guideline (92,93), which each PD program should consult while preparing the trainer and developing a specific curriculum for PD training. In essence, all PD training nurses should receive adequate education to perform training and subsequent further education to update and hone their teaching skills. Each program should have an established curriculum that is followed in teaching the patient the procedure and theory of PD. Testing the patient practical skills at the end of training is essential.

After PD training is completed and patients are started on home PD, a home visit by the PD nurse is often useful in detecting problems with exchange technique, adherence to protocols, and other environmental and behavior issues which increase the risk of peritonitis (104–109). However, the effect of home visits on peritonitis risk has not been tested in a prospective study. One retrospective observational study in 22 pediatric patients reported a non-significant reduction in peritonitis rates following the introduction of home visits (110).

In addition to the initial training, retraining plays an important role in reducing mistakes according to learning specialists (98,100). Previous studies showed that compliance with exchange protocols was significantly associated with peritonitis rate (98,111). Another study found that 6 months after the initiation of PD, most patients took shortcuts, modified the standard exchange method, or did not follow aseptic technique (102). Re-training may reduce peritonitis risk but data are limited to 2 small-scale uncontrolled studies (98,101). A randomized controlled trial has been completed

on re-training and the results are pending (112). The indication, optimal time, and content of retraining have not been well defined. Home visits by PD nurses may be a good way to determine which patients require re-training (98). Other indications for re-training are listed in Table 2 (14,92). Certainly, all patients must be re-trained whenever the equipment to perform PD is changed.

DIALYSIS SOLUTION

- The committee has no specific recommendation on the choice of dialysis solution for prevention of peritonitis.

Early data suggested that the choice of PD solution may affect peritonitis rates, although the results of published trials are conflicting (113–120). The largest and methodologically most robust randomized trial of neutral-pH, low-glucose-degradation-product (GDP) PD solutions demonstrated that these fluids significantly reduced the occurrence and severity of peritonitis compared with conventional solutions (117,121). A subsequent meta-analysis of 6 randomized controlled trials concluded that the quality of many trials was poor and that trial heterogeneity was high (primarily due to risk of attrition bias), such that the use of neutral-pH PD solutions with reduced GDPs had an uncertain effect on the rate of peritonitis (122). The choice of PD solution should therefore currently not be based on the risk of peritonitis.

EXIT-SITE CARE

- We recommend daily topical application of antibiotic (mupirocin or gentamicin) cream or ointment to the catheter exit site **(1B)**.
- We recommend prompt treatment of exit-site or catheter tunnel infection to reduce subsequent peritonitis risk **(1C)**.

General measures concerning exit-site care and meticulous hand hygiene during the dialysis exchange have been recommended and should be emphasized during patient training (14). Wearing a face mask during dialysis exchange is optional. A systematic review of 3 trials found that topical disinfection of the exit site with povidone-iodine did not reduce the risk of peritonitis compared to simple soap and water cleansing or no treatment (123). A number of observational studies, randomized controlled trials, and meta-analyses confirm that prophylaxis with daily application of mupirocin cream or ointment to the skin around the exit site is effective in reducing *S. aureus* exit-site infection (ESI) and possibly peritonitis (37,42,124–131). This strategy is further shown in another study to be cost-effective (132). In a meta-analysis of 14 studies (only 3 of which were randomized whilst the remaining 11 were historical cohort studies), topical mupirocin reduced the overall risk of *S. aureus* infection by 72%, and *S. aureus* peritonitis by 40% (127). One retrospective study showed that once weekly topical mupirocin was less effective than more frequent administration (133). A previous prospective

TABLE 2
Indications for PD Re-Training

- Following prolonged hospitalization
- Following peritonitis and/or catheter infection
- Following change in dexterity, vision, or mental acuity
- Following change to another supplier or a different type of connection
- Following other interruption in PD (e.g. period of time on hemodialysis)

PD = peritoneal dialysis.

study showed that intranasal mupirocin reduced *S. aureus* ESI but not peritonitis (134), but this study has been criticized for excluding patients at highest risk for *S. aureus* PD-related infections. Intranasal mupirocin treatment is also less well accepted by patients (135). A recent study in pediatric patients suggested that the addition of sodium hypochlorite solution to topical mupirocin may further reduce the rate of peritonitis (136). Mupirocin resistance has been reported, particularly with intermittent use but not daily use (137–140). The long-term implication of mupirocin resistance, however, has not been studied in detail.

With the extensive use of prophylactic agents against *S. aureus* infections, *Pseudomonas* species have become a proportionally more common cause of catheter infection (141). A randomized controlled trial showed that daily application of gentamicin cream to the exit site was highly effective in reducing ESIs caused by *Pseudomonas* species, and was as effective as topical mupirocin in reducing *S. aureus* ESIs (125). However, 2 subsequent prospective studies found no significant difference in the rates of infection between patients treated with topical gentamicin and mupirocin ointment (126,142). Other observational studies suggested that the change of prophylactic topical antibiotic protocol from mupirocin to gentamicin cream was associated with an increase in ESI caused by *Enterobacteriaceae*, *Pseudomonas* species, and probably non-tuberculous mycobacteria (143,144). At present, topical gentamicin should be considered as an acceptable alternative to mupirocin for prophylactic application at the exit site. Unfortunately, the incidence and implications of gentamicin resistance are uncertain.

Other alternative topical antibacterial agents have been tested. A randomized controlled trial found that with standard exit-site care, the rates of catheter infection and peritonitis were similar between patients receiving daily topical application of antibacterial honey to catheter exit site and those treated with intranasal mupirocin ointment (145). Similarly, another randomized trial found that topical triple ointment (polymyxin, bacitracin, and neomycin) was not superior to topical mupirocin in the prophylaxis of PD-related infections (146).

Other prophylactic strategies have been tested. In a randomized controlled trial, peritonitis caused by *S. aureus* or *P. aeruginosa* ESI was markedly reduced with the use of ciprofloxacin otologic solution to the exit site, as compared to

simple soap and water cleansing only (147). Two randomized studies comparing oral rifampicin with no treatment both demonstrated significant reductions in peritonitis risk with rifampicin treatment (148,149). In another study, cyclic oral rifampicin and daily topical mupirocin to the exit site were equally effective in reducing the rate of *S. aureus* peritonitis (125). However, adverse effects of rifampicin were more common than those of topical mupirocin (124). Moreover, drug interactions involving rifampicin were a real concern, and rifampicin resistance developed in up to 18% of cases with repeated usage (150). The use of oral rifampicin for prophylactic purpose is therefore not routinely advocated. Other oral antibiotics, such as trimethoprim/sulfamethoxazole, cephalexin, and ofloxacin were not effective in reducing peritonitis rates (151–153).

There is a strong association between ESI and subsequent peritonitis (31,154,155). Early detection of ESI and prompt management with appropriate antibiotics are logical steps to minimize the risk of subsequent peritonitis (31,154).

BOWEL AND GYNECOLOGICAL SOURCE INFECTIONS

- We suggest antibiotic prophylaxis prior to colonoscopy (2C) and invasive gynecologic procedures (2D).

Peritoneal dialysis peritonitis commonly follows invasive interventional procedures (e.g. colonoscopy, hysteroscopy, cholecystectomy) in PD patients (156–160). In a single-center study of 97 colonoscopies performed in 77 CAPD patients, peritonitis occurred in 5 (6.3%) of 79 colonoscopies performed without antibiotic prophylaxis and none of 18 colonoscopies performed with antibiotic prophylaxis ($p = 0.58$) (157). Another small retrospective observational study reported that prophylactic antibiotics before most endoscopic interventions, colonoscopy, sigmoidoscopy, cystoscopy, hysteroscopy, and hysteroscopy-assisted intrauterine device implantation or removal, but not upper gastrointestinal endoscopy, were associated with a lower peritonitis rate (0/16 vs 7/23, $p < 0.05$) (161). A previous systematic review recommended the use of intravenous (IV) ampicillin plus an aminoglycoside, with or without metronidazole, for this purpose (37). However, the optimal antibiotic regimen has not been determined by any clinical study.

Gastrointestinal problems, such as constipation and enteritis, have been reported to be associated with peritonitis due to enteric organisms (162–164). Several studies also note that hypokalemia is associated with an increased risk of enteric peritonitis (165–168). Although there is no compelling evidence to date that treatment of hypokalemia, constipation, or gastroenteritis reduces the rate of peritonitis, such problems, which are common in the PD setting, merit treatment in their own right. Observational data suggest that regular lactulose use reduces peritonitis rate (169).

OTHER MODIFIABLE RISK FACTORS

A number of other modifiable risk factors for PD peritonitis have been described. Peritonitis has been reported to

follow hysteroscopy with biopsy (170) as well as in women with vaginal fistula and leakage (171–174). One retrospective study of 13 gynecological procedures reported a non-significant reduction in peritonitis rates associated with antibiotic prophylaxis (0/4 vs 5/9, $p = 0.10$) but had inadequate statistical power (161). Transient bacteremia is common after dental procedures and may lead to peritonitis (175,176). Prophylactic antibiotics (e.g. single oral dose of amoxicillin) before extensive dental procedures may be reasonable.

Prophylactic antibiotics are usually recommended after wet contamination, i.e. if the dialysis solution is infused after contamination, or if the catheter administration set was open for an extended period (14). Most nephrologists give a 2-day course of oral antibiotics after contamination in which dialysis has been infused, but there is no widely accepted standard regimen.

A number of other potentially modifiable risk factors for peritonitis have been reported (19) and are summarized in Table 3. Notably, hypoalbuminemia (177,178), depression (179), and loss of motivation (180) are repeatedly reported as important risk factors, although there are no published data to show that treatment of these problems would reduce peritonitis rate. Similarly, exposure to domestic animals is another risk factor (181,182). Animals should be excluded from the space where the PD is being performed (182). Two observational studies suggested that oral vitamin D therapy was associated with a significantly lower incidence of peritonitis (183,184), but prospective randomized studies are needed to confirm the result.

TABLE 3
Modifiable Risk Factors of Peritonitis*

Social / Environmental
• Smoking
• Living distantly from PD unit
• Pets
Medical
• Obesity
• Depression
• Hypokalemia
• Hypoalbuminemia
• Absence of vitamin D supplementation
• Invasive interventions (e.g. colonoscopy)
Dialysis-related
• Prior hemodialysis
• PD against patient's choice
• Training
• Bioincompatible fluids
• Wet contamination
Infection-related
• Nasal <i>Staphylococcus aureus</i> carrier status
• Previous exit-site infection

PD = peritoneal dialysis.

* Adapted from Cho Y, *et al.* (19).

CONTINUOUS QUALITY IMPROVEMENT

- We recommend each PD center have a continuous quality improvement (CQI) program in place to reduce peritonitis rates **(1C)**.
- We suggest that multidisciplinary teams running CQI programs in PD centers meet and review their units' performance metrics regularly **(2C)**.

A team approach for CQI is the key to a successful PD program (19). The CQI team generally includes nephrologists, nurses, social workers, and dietitians. Regular meetings of the team should be held to examine all PD-related infections and identify the root cause of each episode. The CQI team identifies problems, develops solutions, and evaluates results in an iterative fashion. In essence, if a pattern of infections develops, the team needs to investigate and plan interventions such as retraining, changing equipment, applying new protocols for exit-site care, or managing contamination. Preliminary data suggest that CQI programs reduce peritonitis rates (17,185,186).

SECONDARY PREVENTION

- We recommend anti-fungal prophylaxis when PD patients receive antibiotic courses to prevent fungal peritonitis **(1B)**.

The majority of fungal peritonitis episodes are preceded by courses of antibiotics (187–189). A number of observational studies and randomized trials have examined the use of either oral nystatin or fluconazole as prophylaxis during antibiotic therapy (190–197). In essence, 2 randomized controlled trials (192,197) and a systematic review (37) showed a significant benefit. Most of the other reports on the prophylactic use of antifungals during antibiotic administration were non-randomized studies and have yielded a mixed result. Unfortunately, nystatin is not available in some countries. Observational data and 1 randomized controlled trial showed that prophylactic fluconazole is effective (197–200). However, there are potential problems (e.g. drug interactions, emergence of resistant strains) with fluconazole prophylaxis that should also be considered.

The CQI program may also have a role in secondary prevention. For each peritonitis episode, a root-cause analysis should be done to determine the etiology, and, whenever possible, an intervention directed against any reversible risk factor should be made to prevent another episode. For example, peritonitis episodes caused by coagulase-negative *Staphylococcal* species are associated with touch contamination, while *Staphylococcus aureus* infections have been associated with touch contamination or catheter infections. Identification of etiology may involve review of the exchange technique. Retraining is sometimes necessary. Replacement of the catheter may be considered in patients with relapsing or repeat peritonitis (201,202) and has been reported to be more effective than

urokinase therapy (203). When PD effluent clears up after antibiotic treatment, catheter removal and re-insertion can be performed as a single procedure without the need for temporary hemodialysis (202,204,205).

INITIAL PRESENTATION AND MANAGEMENT OF PERITONITIS

The algorithm of initial management for PD patients presenting with a clinical diagnosis is summarized in Figure 1.

Clinical Presentation and Diagnosis of Peritonitis

- We recommend that peritonitis always be diagnosed when at least 2 of the following are present: (1) clinical features consistent with peritonitis, i.e. abdominal pain and/or cloudy dialysis effluent; (2) dialysis effluent white cell count $> 100/\mu\text{L}$ or $> 0.1 \times 10^9/\text{L}$ (after a dwell time of at least 2 hours), with $> 50\%$ polymorphonuclear; and (3) positive dialysis effluent culture **(1C)**.
- We recommend that PD patients presenting with cloudy effluent be presumed to have peritonitis and treated as such until the diagnosis can be confirmed or excluded **(1C)**.
- We recommend that PD effluent be tested for cell count, differential, Gram stain, and culture whenever peritonitis is suspected **(1C)**.

Patients with peritonitis usually present with cloudy PD effluent and abdominal pain. Cloudy effluent almost always represents infectious peritonitis, although there are other differential diagnoses (Table 4) (206). Some patients present with cloudy effluent but no or minimal abdominal pain. On the other hand, peritonitis should also be included in the differential diagnosis of the PD patient presenting with abdominal pain, even if the effluent is clear. In addition to the presenting symptoms, the patient should be questioned about any recent contamination, accidental disconnection, endoscopic or gynecologic procedure, as well as the presence of constipation or

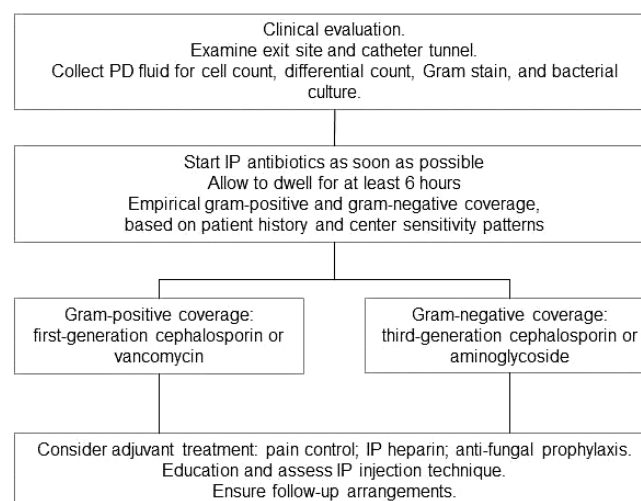


Figure 1 — Initial management of peritonitis. IP = intra-peritoneal.

TABLE 4
Differential Diagnosis of Cloudy Effluent

- Culture-positive infectious peritonitis
- Infectious peritonitis with sterile cultures
- Chemical peritonitis
- Calcium channel blockers
- Eosinophilia of the effluent
- Hemoperitoneum
- Malignancy (rare)
- Chylous effluent (rare)
- Specimen taken from "dry" abdomen

diarrhea. In addition, the patient should be questioned about past history of peritonitis and ESI.

On physical examination, abdominal tenderness is typically generalized and is occasionally associated with rebound. Localized pain or tenderness should raise the suspicion of an underlying surgical pathology. Physical examination should also include a careful inspection of the catheter tunnel and exit site. Any discharge from the exit site should be cultured. The degree of abdominal pain and tenderness are important factors in deciding whether a patient requires hospital admission. In general, patients with minimal pain could be treated on an outpatient basis with intraperitoneal (IP) antibiotic therapy if this can be arranged. Follow-up within 3 days is advisable to confirm resolution and appropriateness of the antibiotic choice.

When peritonitis is suspected, dialysis effluent should be drained, carefully inspected, and sent for cell count with differential, Gram stain, and culture (207). An effluent cell count with white blood cells (WBC) $> 100/\mu\text{L}$ (after a dwell time of at least 2 hours), with $> 50\%$ PMN, is highly suggestive of peritonitis (208). Abdominal X ray is generally not necessary. Peripheral blood culture is usually not necessary but should be obtained if the patient is clinically septic. To prevent delay in treatment, antibiotic therapy (see below) should be initiated once the appropriate dialysis effluent specimens have been collected, without waiting for the results of laboratory testing.

The WBC count in the effluent depends in part on the length of the dwell. For patients on APD with rapid cycle treatment, the clinician should use the percentage of PMN rather than the absolute WBC count to diagnose peritonitis, and a proportion above 50% PMN is strong evidence of peritonitis, even if the absolute WBC count is less than $100/\mu\text{L}$ (208). On the other hand, APD patients without a daytime exchange who present with abdominal pain during the daytime may have no effluent to drain. In this case, 1 L of dialysis solution should be infused, dwelled for 1 to 2 hours, and then drained for inspection and laboratory testing.

Some PD patients live far away from medical facilities and cannot be seen expeditiously after the onset of symptoms. Since prompt initiation of therapy for peritonitis is critical, this necessitates reliance on immediate patient reporting of symptoms to the center, and then initiating IP antibiotics in

the home setting. Such an approach requires that the patients be trained in this technique and that antibiotics be kept at home. Whenever possible, cultures should be obtained either at a local facility or by having blood culture bottles kept at home for use. However, it is important that no one accesses the PD catheter without the appropriate training or equipment, which is often the case in smaller emergency departments. In this case the patient can drain his/her abdomen and provide the cloudy effluent for culture. Alternatively, the patient may place the cloudy effluent bag in the refrigerator until they can bring the sample to their PD center. The benefit of self-initiated treatment, however, should be carefully balanced against the potential problems of over-diagnosis and habitual misuse of antibiotics.

Identification of Causative Organism

- We recommend that the blood-culture bottle be the preferred technique for bacterial culture of PD effluent **(1C)**.
- We suggest that sampling and culture methods be reviewed and improved if more than 15% of peritonitis episodes are culture-negative **(2C)**.

Gram stain of the PD effluent should be performed even though the result is often negative (209). The yield on the Gram stain is increased if it is performed on centrifuged specimens. An appropriate method of culturing PD effluent is the most important step in establishing the causative organism. In some specialized centers, one could achieve less than 10% rate of culture negative peritonitis. Identification of the organism and subsequent antibiotic sensitivities help to guide the choice of antibiotic, and the type of organism often indicates the possible source of infection. Bedside inoculation of 5 – 10 mL effluent in 2 (aerobic and anaerobic) blood-culture bottles has a reasonable sensitivity, and the culture-negative rate is typically around 10 – 20%. (210,211). The yield of peritoneal fluid culture is enhanced by inoculating the fluid directly into rapid blood-culture bottle kits (e.g. BACTEC, Kent, UK; Septi-Chek, Roche Diagnostics, Basel, Switzerland; BacT/Alert, Biorimieux, Inc., Basingstoke, UK), centrifuging PD fluid and culturing the pellet, or the lysis centrifugation technique compared to inoculation into standard blood-culture bottles. Specifically, centrifugation of 50 mL PD effluent at 3,000 g for 15 minutes, followed by resuspension of the sediment in 3 – 5 mL supernatant and inoculation on solid culture media or standard blood-culture media, increases the yield by 5 to 10 times but is more cumbersome (212,213). The combination of water lysis, Tween-80 blood agar and Triton-X treatment of the PD effluent is also a sensitive culture method (214). The specimens should arrive at the laboratory within 6 hours. If immediate delivery to the laboratory is not possible, the inoculated culture bottles should ideally be incubated at 37°C. The solid media should be incubated in aerobic, microaerophilic, and anaerobic environments.

The speed with which bacteriological diagnosis can be established is very important. Concentration methods do not

only facilitate microbial identification, but also reduce the time needed for a positive culture. In over 75% of cases, microbiologic diagnosis can be established in less than 3 days. When the causative microorganism has been identified, subsequent cultures for monitoring may be performed by only inoculating the effluent in blood-culture bottles.

When cultures remain negative after 3–5 days of incubation, PD effluent should be sent for repeat cell count, differential count, fungal, and mycobacterial culture. In addition, subculture on media with aerobic, anaerobic, and microaerophilic incubation conditions for a further 3–4 days may help to identify slow-growing fastidious bacteria and yeasts that are undetectable in some automated culture systems.

Other Novel Diagnostic Techniques

- We suggest that there is insufficient evidence to currently support the use of novel techniques for the diagnosis of peritonitis **(2D)**.

A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis, including leukocyte esterase reagent strips, biomarker assays (matrix metalloproteinase-8 and -9, neutrophil gelatinase-associated lipocalin and procalcitonin), polymerase chain reaction (PCR) for bacterial-derived DNA fragments, 16S rRNA gene sequencing, matrix-assisted laser desorption ionization-time of flight (MALDI-TOF), and pathogen-specific “immune fingerprints” (215–226). However, none of them has been proved to be superior to conventional techniques. Other novel techniques have also been developed for rapid species identification and the determination of resistant organisms (e.g. methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci, *Klebsiella pneumoniae* carbapenemase), which may allow more rapid initiation of focused antimicrobial therapy of resistant pathogens, but their role in the management of PD-related peritonitis remain unclear. Further studies in this area are necessary.

Empiric Antibiotic Selection

- We recommend that empirical antibiotic therapy be initiated as soon as possible after appropriate microbiological specimens have been obtained **(1C)**.
- We recommend that empirical antibiotic regimens be center-specific and cover both gram-positive and gram-negative organisms **(1C)**.
- We recommend that gram-positive organisms be covered by vancomycin or a first generation cephalosporin and gram-negative organisms by a third-generation cephalosporin or an aminoglycoside **(1B)**.

Antibiotic treatment should aim for rapid resolution of inflammation and preservation of the peritoneal membrane function. No antibiotic regimen has been proved to be superior to others as empirical treatment (203), although the combination of a glycopeptide (vancomycin or teicoplanin) plus

ceftazidime was considered to be superior to other regimens in a proportional meta-analysis (227).

For gram-positive coverage, several studies compared a first-generation cephalosporin with a glycopeptide-based regimen (228–231). When analyzed as a whole, glycopeptide-based regimens result in a higher complete cure rate, but there is no difference in the rate of primary treatment failure, relapse, or catheter removal (203). A systematic review noted that the result was largely influenced by 1 study, in which the dosage of cefazolin was substantially lower than current recommendations (228). Other studies found no difference in cure rates for vancomycin and cefazolin when an appropriate cephalosporin dose was used (228,230,231). Nonetheless, some PD units have a high rate of methicillin-resistant organisms and vancomycin may be preferable for empirical gram-positive coverage (232), although it remains controversial what threshold prevalence of methicillin resistance would justify the routine empirical use of vancomycin as gram-positive coverage.

For the coverage of gram-negative organisms, previous studies have shown that aminoglycosides (e.g. gentamicin or netilmicin) (233), ceftazidime (233), cefepime (234), or a carbapenem (235,236) are all effective. Cefepime *per se* has reasonable activity against gram-positive bacteria and monotherapy may be feasible (234). Fluoroquinolones could also be used if supported by the local antimicrobial susceptibilities of antibiotic sensitivities (237–241). For patients allergic to cephalosporins, aztreonam is also a possible alternative (242–244). In a randomized controlled study, IP netilmicin and ceftazidime had similar efficacy to empirical gram-negative coverage (233). Short-term aminoglycoside treatment is inexpensive, safe, and provides good gram-negative coverage. There is no evidence that short courses of aminoglycosides accelerate the loss of residual renal function (233,245–247). However, repeated or prolonged aminoglycoside treatment (more than 3 weeks) was associated with a high incidence of vestibular toxicity or oto-toxicity and should be avoided (248,249).

In addition to the above combinations, a variety of regimens have been shown by prospective trials to have acceptable results (250). For example, imipenem/cilastatin monotherapy was as effective as cefazolin plus ceftazidime (236), and cefepime was as effective as vancomycin plus netilmicin (234). In another study, oral ofloxacin alone was not inferior to cephalothin plus tobramycin (241), but the effectiveness of ciprofloxacin monotherapy has declined markedly in the past decade (251).

It is important to note that antibiotic resistance may develop with extensive empiric use of broad-spectrum cephalosporins or fluoroquinolones. The prevalence of resistant pathogens in each program should be regularly monitored and the choice of empirical antibiotic may need to be changed accordingly.

Dosage of Antibiotics

- We recommend that IP antibiotics be the preferred route of administration unless the patient has features of systemic sepsis **(1B)**.

- We suggest that IP aminoglycoside be administered as daily intermittent dosing **(2B)**.
- We recommend that prolonged courses of IP aminoglycoside be avoided **(1C)**.
- We suggest that IP vancomycin be administered intermittently and the serum vancomycin level be kept above 15 µg/mL **(2C)**.
- We suggest that IP cephalosporin be administered either continuously (in each exchange) or on a daily intermittent basis **(2C)**.

The recommended dosage of antibiotics for the treatment of PD-related peritonitis is summarized in Tables 5 and 6 (236–239,252–303). However, the recommended dosages of many antibiotics are based on published clinical experience rather than formal pharmacokinetic studies. It was recommended

previously that for patients with substantial residual renal function, the dose of antibiotics that have renal excretion needs to be adjusted (12,13). However, recent studies suggest that such adjustments are not necessary (284,304).

In general, IP dosing results in high IP drug levels and is preferable to IV administration. Moreover, IP dosing avoids venipuncture and could be done by the patient at home after appropriate training. Although IV vancomycin is reasonably successful as empirical gram-positive coverage (237), previous studies have shown that IV vancomycin resulted in a significantly higher rate of primary treatment failure than IP administration (203,305). Intraperitoneal antibiotics should be added using sterile technique, such as placing povidone iodine, rubbing with alcohol 70% strip, or chlorhexidine on the medication port for 5 minutes prior to insertion of the needle through the port.

TABLE 5
Intraperitoneal Antibiotic Dosing Recommendations for Treatment of Peritonitis

	Intermittent (1 exchange daily)	Continuous (all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg daily (252)	LD 25 mg/L, MD 12 mg/L (253)
Gentamicin	0.6 mg/kg daily (254)	LD 8 mg/L, MD 4 mg/L (255,256)
Netilmicin	0.6 mg/kg daily (233)	MD 10 mg/L (257)
Tobramycin	0.6 mg/kg daily (253)	LD 3 mg/kg, MD 0.3 mg/kg (258,259)
Cephalosporins		
Cefazolin	15–20 mg/kg daily (260,261)	LD 500 mg/L, MD 125 mg/L (254)
Cefepime	1,000 mg daily (262,263)	LD 250–500 mg/L, MD 100–125 mg/L (262,263)
Cefoperazone	no data	LD 500 mg/L, MD 62.5–125 mg/L (264,265)
Cefotaxime	500–1,000 mg daily (266)	no data
Ceftazidime	1,000–1,500 mg daily (267,268)	LD 500 mg/L, MD 125 mg/L (236)
Ceftriaxone	1,000 mg daily (269)	no data
Penicillins		
Penicillin G	no data	LD 50,000 unit/L, MD 25,000 unit/L (270)
Amoxicillin	no data	MD 150 mg/L (271)
Ampicillin	no data	MD 125 mg/L (272,273)
Ampicillin/Sulbactam	2 gm/1 gm every 12 hours (274)	LD 750–100 mg/L, MD 100 mg/L (253)
Piperacillin/Tazobactam	no data	LD 4 gm/0.5 gm, MD 1 gm/0.125 gm (275)
Others		
Aztreonam	2 gm daily (242)	LD 1,000 mg/L, MD 250 mg/L (243,244)
Ciprofloxacin	no data	MD 50 mg/L (276)
Clindamycin	no data	MD 600 mg/bag (277)
Daptomycin	no data	LD 100 mg/L, MD 20 mg/L (278)
Imipenem/Cilastatin	500 mg in alternate exchange (244)	LD 250 mg/L, MD 50 mg/L (236)
Ofloxacin	no data	LD 200 mg, MD 25 mg/L (279)
Polymyxin B	no data	MD 300,000 unit (30 mg)/bag (280)
Quinupristin/Dalfopristin	25 mg/L in alternate exchange ^a (281)	no data
Meropenem	1 gm daily (282)	no data
Teicoplanin	15 mg/kg every 5 days (283)	LD 400 mg/bag, MD 20 mg/bag (229)
Vancomycin	15–30 mg/kg every 5–7 days ^b (284)	LD 30 mg/kg, MD 1.5 mg/kg/bag (285)
Antifungals		
Fluconazole	IP 200 mg every 24 to 48 hours (286)	no data
Voriconazole	IP 2.5 mg/kg daily (287)	no data

LD = loading dose in mg; MD = maintenance dose in mg; IP = intraperitoneal; APD = automated peritoneal dialysis.

^a Given in conjunction with 500 mg intravenous twice daily (281).

^b Supplemental doses may be needed for APD patients.

TABLE 6
Systemic Antibiotic Dosing Recommendations for
Treatment of Peritonitis

Drug	Dosing
Anti-bacterials	
Ciprofloxacin (237)	oral 250 mg BD ^a
Colistin (288)	IV 300 mg loading, then 150–200 mg daily ^b
Ertapenem (289)	IV 500 mg daily
Levofloxacin (239)	oral 250 mg daily
Linezolid (290–292)	IV or oral 600 mg BD
Moxifloxacin (293)	oral 400 mg daily
Rifampicin (294,295)	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg
Trimethoprim/ Sulfamethoxazole (252)	oral 160 mg / 800 mg BD
Anti-fungals	
Amphotericin (296)	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 hours; increased to target dose 0.75–1.0 mg/kg/day over 4 days
Caspofungin (297,298)	IV 70 mg loading, then 50 mg daily
Fluconazole (299)	oral 200 mg loading, then 50–100 mg daily
Flucytosine (296)	oral 1 gm/day
Posaconazole (300)	IV 400 mg every 12 hours
Voriconazole (301–303)	oral 200 mg every 12 hours

BD = twice a day; IV = intravenous; BW = body weight.

^a Ciprofloxacin 500 mg BD may be needed if residual glomerular filtration rate is above 5 mL/min.

^b Expressed as colistin base activity (CBA).

Intraperitoneal antibiotics can be given as continuous (i.e. in each exchange) or intermittent dosing (i.e. once daily) (306–310). In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption. Many antibiotics have significantly enhanced absorption during peritonitis, which permits reentry into the peritoneal cavity during subsequent PD cycles.

For vancomycin, about 50% of IP dosing is absorbed when there is no peritonitis, but nearly 90% in the presence of peritonitis (304,306). A randomized controlled trial in children found that intermittent dosing of vancomycin is as efficacious as continuous dosing (311). The role of monitoring serum vancomycin levels is controversial (284,312). In general, a dosing interval of every 4 to 5 days would keep serum trough levels above 15 µg/mL, but there is substantial inter-individual variability (284,304). Re-dosing is probably appropriate when serum vancomycin levels are below 15 µg/mL (304,313,314).

At the dosage currently recommended, the peak gentamicin concentration in dialysis solution is at least 8 times the minimal inhibitory concentration (MIC) of the likely pathogens (315). Two studies showed that once-daily gentamicin is as effective as continuous dosing for CAPD patients (256,316). However, systemic absorption of intermittent IP gentamicin is highly

variable and depends on the peritoneal transport characteristics (315), and the high systemic absorption of gentamicin in patients with peritonitis and prolonged plasma elimination half-life may lead to systemic accumulation and subsequent toxicity (315). At the currently recommended dosing regimen, serum gentamicin levels might be excessive in over 50% of patients (304), and higher serum levels were not associated with better cure rates (304). However, there is no firm evidence that monitoring aminoglycoside levels mitigates toxicity risk or enhances efficacy (314). The serum gentamicin level on day 2 is not associated with treatment efficacy or adverse effects during short-course therapy (317). Studies on the relationship between serum aminoglycoside levels following IP administration and the subsequent risk of ototoxicity are conflicting and often show a negative result (318–321). Taken together, serum aminoglycoside level monitoring for PD patients receiving IP treatment seems to play a small role. Once the causative bacteria are identified and sensitivity confirmed, early switch from empirical aminoglycoside to other agents (e.g. third-generation cephalosporin) could minimize the risk of ototoxicity (314).

For cephalosporins, there are few data on whether continuous dosing is more efficacious than intermittent dosing. In CAPD patients, IP cefazolin 500 mg/L once daily results in acceptable 24-hour levels in the PD fluid (308). Although continuous IP ceftazidime is traditionally given at the same dose as cefazolin (13), once-daily IP ceftazidime at a dose of 20 mg/kg once daily may not provide adequately therapeutic levels in dialysis solution throughout 24 hours (267). One pharmacokinetic study showed that a loading dose of 3 g is necessary to achieve an adequate dialysis solution drug concentration (322), which could be followed by maintenance IP dosing of 1 gm q24h or 2 gm q48h (322).

Oral administration of fluoroquinolones is commonly used alone or in combination with other antibiotics (237). Oral ciprofloxacin and moxifloxacin reach adequate levels within the peritoneum (293,323). However, adequate IP levels may require a day to be reached, and some oral phosphate binders can bind fluoroquinolones and reduce their bioavailability (324,325). Ciprofloxacin is effective against *Pseudomonas* species, while moxifloxacin has better coverage of gram-positive organisms. A systematic review of 2 low-quality studies concluded that IP fluoroquinolone may achieve better complete cure rate than oral treatment, although failure rates were high in both arms of these studies (203,276,279).

Antibiotic Delivery and Stability

The stability and compatibility of various antibiotics for IP administration was reviewed previously (326). In essence, vancomycin, aminoglycosides, and cephalosporins can be mixed in the same dialysis solution bag without loss of bioactivity. Aminoglycosides and cephalosporins can be added to the same bag, although aminoglycoside should not be added to the same bag with penicillins because of chemical incompatibility (326). For any antibiotics that are to be admixed, separate syringes

must be used for adding the antibiotics. Although vancomycin and ceftazidime are compatible when added to dialysis solutions (1 L total volume or greater), they are incompatible if combined in the same syringe or added to an empty dialysis solution bag for reinfusion into the patient.

Antibiotics are stable for variable times after being added to the PD solution (327). Vancomycin is stable for 28 days in dialysis solutions stored at room temperature, although higher ambient temperatures will reduce the duration of stability. Gentamicin is stable for 14 days both at room temperature and under refrigeration, but the duration of stability is reduced by admixture with heparin. Cefazolin is stable for 8 days at room temperature or for 14 days if refrigerated; addition of heparin has no adverse influence. Ceftazidime is stable for 4 days at room temperature or 7 days if refrigerated. Cefepime is stable for 14 days if the solution is refrigerated (328).

Data on the stability of various new antibiotics and PD solutions are limited and often fragmented (329–332). Clinicians should remain alert for new studies in this area. In general, icodextrin-based PD solutions are compatible with vancomycin, cefazolin, ceftazidime, and gentamicin (329,333,334). When premixed in icodextrin solution, these antibiotics are least stable at 37°C and most stable at 4°C, permitting storage for 14 days when refrigerated and pre-warming to body temperature prior to administration (334).

Special Considerations for APD

There is a substantial knowledge gap regarding the antibiotic dosing requirements for the treatment of peritonitis in APD patients. In general, the intermittent IP dosing listed in Table 4 could be given in the day dwell of APD patients. However, extrapolation of data from CAPD to APD may result in significant under-dosing in APD patients because rapid exchanges in APD may lead to inadequate time to achieve therapeutic levels when antibiotics are given IP intermittently, and APD results in a higher peritoneal clearance of antibiotics than CAPD. This problem is particularly obvious amongst high peritoneal transporters. Alternatively, APD patients who develop peritonitis may switch temporarily to CAPD. However, it is not always practical to switch because patients may not be familiar with the exchange technique, and the supplies for CAPD may not be immediately available. A recent report also found that this practice is associated with an increased risk of technique failure and fluid overload (335). Resetting the cyclor to permit a longer exchange time in such cases is a logical alternative, but the efficacy of this approach has not been well studied.

For patients who remain on rapid-cycle APD, there are few data concerning efficacy of first-generation cephalosporins given intermittently. For APD patients treated with cephalosporins added to the daytime exchange only, the nighttime IP levels are below the MIC of most organisms. Adding first-generation cephalosporin to each exchange would appear to be the safest approach. Although the IP vancomycin level may be low in APD patients due to slow diffusion from blood to dialysis solution, a randomized controlled trial in children

showed that intermittent dosing of vancomycin was as effective as continuous dosing in children receiving APD (311). Vancomycin can probably be given intermittently for APD patients. Oral ciprofloxacin can also achieve adequate levels within the peritoneum in APD patients (323). In a retrospective, single-center observational cohort study of 508 episodes of PD-associated peritonitis in 208 patients, no differences in relapse rates, mortality, or the combined end-point of mortality and catheter removal were observed between APD and CAPD patients continuing their own PD modality during continuous IP antibiotic treatment in each PD exchange, although elevated dialysis effluent leukocyte counts and antibiotic treatment durations were longer in the former (90).

Adjunctive Treatments

Some patients with PD-related peritonitis could be managed on an outpatient basis. The decision to hospitalize a patient depends on many factors, including hemodynamic status of the patient, severity of signs and symptoms, and, for APD patients, the type of treatment schedule chosen, as well as the ability to provide IP antibiotics as an outpatient and the reliability of the patient. The rationale for anti-fungal prophylaxis has been discussed in a previous section (see Secondary Prevention, above).

Patients with cloudy effluent may benefit from the addition of heparin 500 units/L IP to prevent occlusion of the catheter by fibrin. Depending on the severity of symptoms, some patients would require analgesics for pain control. At the initial presentation and before IP antibiotics are initiated, 1 or 2 rapid PD exchanges are often performed for pain relief, although there are no data supporting this approach. A randomized controlled trial showed that more extensive rapid-cycle peritoneal lavage during the first 24 hours of peritonitis did not affect the rate of complete cure or relapse as compared to the usual practice of 2 rapid exchange cycles (336).

Intraperitoneal urokinase has been advocated for the treatment of biofilm, which may be the cause of refractory or relapsing peritonitis. A retrospective study found that IP urokinase and oral rifampicin, in addition to conventional antibiotics, resulted in catheter salvage in 64% of cases with persisting asymptomatic infection following coagulase-negative staphylococcus peritonitis (337). Randomized controlled trials, however, failed to show any benefit of IP urokinase for the treatment of refractory peritonitis (338–340). The rates of complete cure, catheter removal, or relapsing episode, as well as overall mortality were not affected by adjunctive treatment with IP urokinase. In contrast, 1 randomized controlled study showed that simultaneous catheter removal and replacement was superior to IP urokinase in reducing relapsing peritonitis episodes (341).

Peritoneal permeability to water, glucose, and proteins typically increases during peritonitis. Reduction in ultrafiltration is commonly observed, and fluid overload is a frequent complication. Temporary use of hypertonic exchanges and short dwell times may be needed to maintain adequate fluid

removal. Temporary use of icodextrin solution may prevent fluid overload in PD patients with acute peritonitis (342). Because of rapid glucose absorption, glycemic control may worsen in diabetic patients. Blood glucose monitoring with appropriate adjustments of insulin dosage may be needed. Protein loss during peritonitis is also increased. Screening for malnutrition should be undertaken in patients with prolonged peritoneal inflammation.

SUBSEQUENT MANAGEMENT OF PERITONITIS

- We recommend that antibiotic therapy be adjusted to narrow-spectrum agents, as appropriate, once culture results and sensitivities are known. **(1C)**.

The management algorithms for gram-positive cocci and gram-negative bacilli identified in dialysis effluent are summarized in Figures 2 and 3, respectively. Within 48 hours of initiating therapy, most patients with PD-related peritonitis will show considerable clinical improvement. The effluent should be visually inspected regularly to determine whether clearing is occurring. If there is no improvement after 48 hours, cell counts and repeat cultures should be performed. In

addition, monitoring of WBC count in PD effluent may predict treatment response. A retrospective study showed that dialysis effluent WBC count $\geq 1,090/\text{mm}^3$ on day 3 was an independent prognostic marker for treatment failure (343).

Refractory Peritonitis

- We recommend that the PD catheter be removed promptly in refractory peritonitis episodes, defined as failure of the PD effluent to clear up after 5 days of appropriate antibiotics **(1C)**.

After initiation of antibiotic treatment, there is usually clinical improvement in 72 hours. Refractory peritonitis is defined as failure of the PD effluent to clear up after 5 days of appropriate antibiotics (Table 7). Catheter removal is indicated in case of refractory peritonitis, or earlier if the patient's clinical condition is deteriorating, in order to preserve the peritoneum for future PD as well as preventing morbidity and mortality. Prolonged attempts to treat refractory peritonitis by antibiotics without catheter removal are associated with extended hospital stay, peritoneal membrane damage, increased risk of fungal peritonitis, and excessive mortality (344).

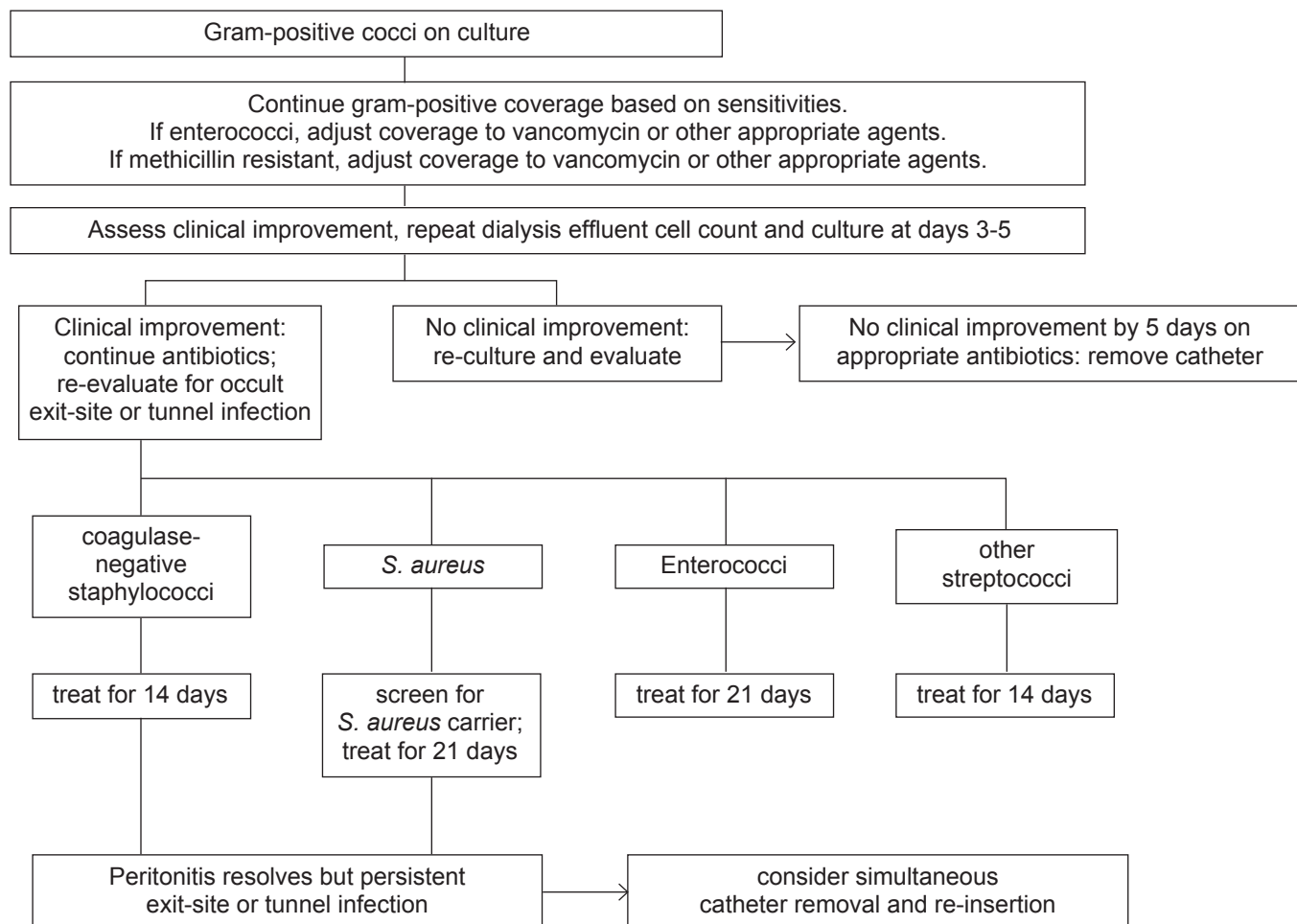


Figure 2 — Management algorithm for gram-positive cocci identified in dialysis effluent.

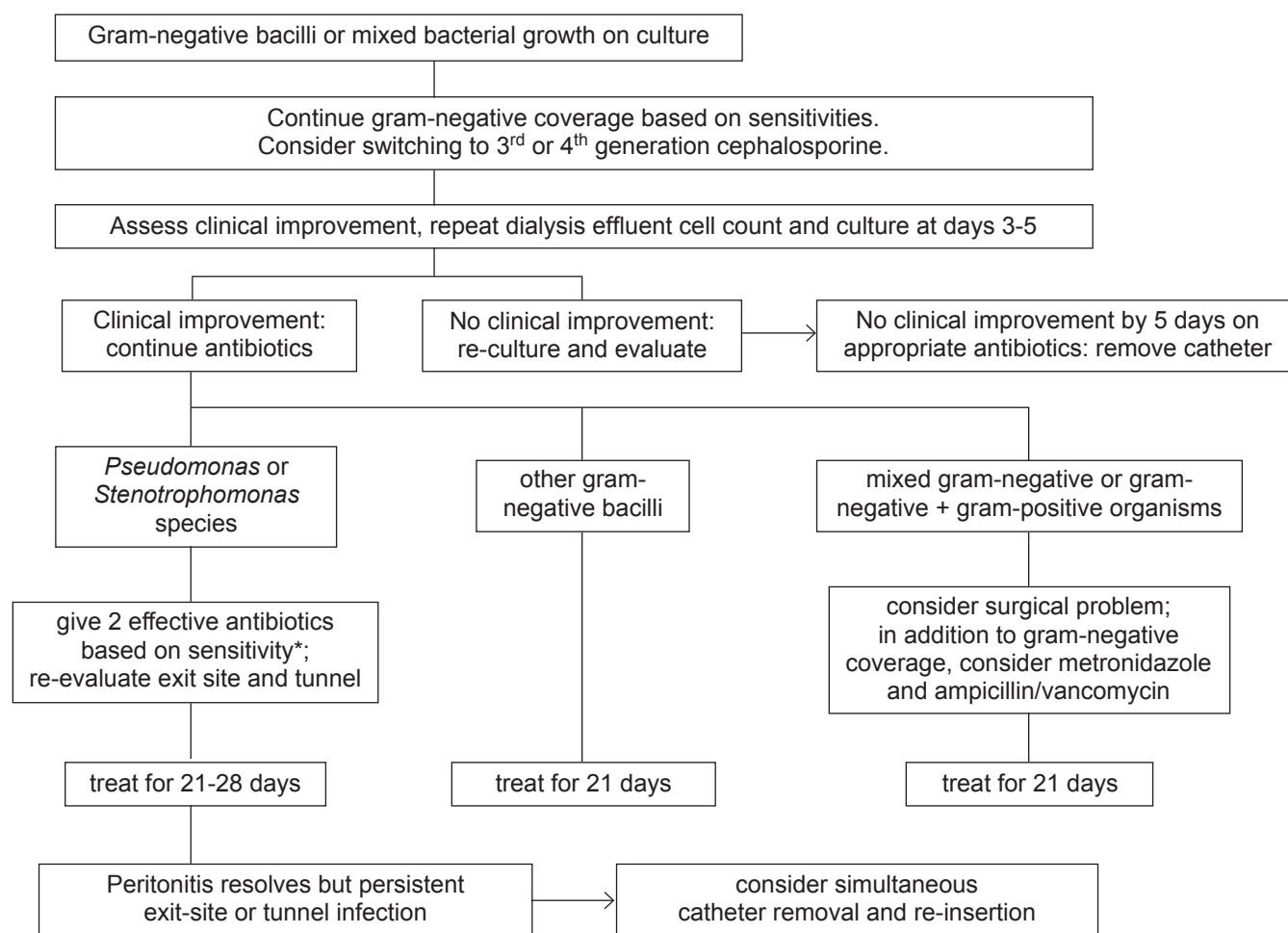


Figure 3 — Management algorithm for gram-negative bacilli or mixed bacterial growth identified in dialysis effluent.

* Trimethoprim/sulfamethoxazole is preferred for *Stenotrophomonas* species.

Relapsing, Recurrent, and Repeat Peritonitis

- We recommend that timely catheter removal be considered for relapsing, recurrent, or repeat peritonitis episodes **(1C)**.

The definitions of relapsing, recurrent, and repeat peritonitis are summarized in Table 7. Retrospective studies showed that relapsing, recurrent, and repeat peritonitis episodes are caused by different species of bacteria and probably represent distinct clinical entities (166,345–347). When compared to non-relapsing episodes, relapsing ones are associated with a lower rate of cure, more ultrafiltration problems, and higher rate of technique failure (166,348). Recurrent peritonitis episodes had a worse prognosis than relapsing ones (166,345). A recent study suggested that bacterial DNA fragment levels in PD effluent are significantly higher 5 days before and on the date of completion of antibiotics amongst patients who subsequently develop relapsing or recurrent peritonitis (349). Another study suggests that effluent white cell count and leukocyte strip test at the time of stopping antibiotics may also predict relapse (350). However, further studies are needed to validate these results and confirm their clinical utility.

Coagulase-Negative Staphylococcus

- We suggest that coagulase-negative staphylococci generally be treated with IP cephalosporins or vancomycin, according to antimicrobial susceptibility, for a period of 2 weeks. **(2C)**.

Coagulase-negative *Staphylococcus* peritonitis episodes, especially those caused by *S. epidermidis*, are mostly due to touch contamination. Many patients with *S. epidermidis* peritonitis have mild clinical symptoms and respond well to treatment as outpatients (351–353). In some centers, the prevalence of methicillin resistance is now very high (354,355), and vancomycin may have to be considered as empirical therapy. Even for methicillin-sensitive strains, it is important to avoid inadequate IP antibiotic levels, which may lead to relapsing peritonitis. For this reason, continuous dosing of IP first-generation cephalosporins is preferable to intermittent dosing. Effective antibiotic treatment for 2 weeks is generally sufficient (351–354). The patient's exchange technique should be reviewed to prevent another episode.

TABLE 7
Terminology for Peritonitis

- Recurrent: An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
- Relapsing: An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode
- Repeat: An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
- Refractory: Failure of the effluent to clear after 5 days of appropriate antibiotics
- Catheter-related peritonitis: Peritonitis in conjunction with an exit-site or tunnel infection with the same organism or one site sterile

N.B. Relapsing episodes should not be counted as another episode during the calculation of peritonitis rates; recurrent and repeat episodes should be counted.

Relapsing coagulase-negative *Staphylococcus* peritonitis suggests colonization of the PD catheter with biofilm, and catheter removal should be considered. When the PD effluent becomes clear with antibiotic therapy, many of these patients could have simultaneous re-insertion of a new catheter as a single procedure under antibiotic coverage, and temporary hemodialysis could be avoided (204). In addition to conventional antibiotics, a retrospective study found that IP urokinase and oral rifampicin resulted in catheter salvage in 64% of cases with persisting asymptomatic infection following coagulase-negative *Staphylococcus* peritonitis (337), but the benefit of this approach needs to be confirmed by further studies.

Enterococcus Species

- We suggest that enterococcal peritonitis be treated for 3 weeks with IP vancomycin (2C).
- We suggest adding IP aminoglycoside for severe enterococcal peritonitis (2D).
- For peritonitis due to vancomycin-resistant *Enterococcus* (VRE), we suggest treatment for 3 weeks with IP ampicillin if the organism is susceptible or with alternative antibiotics (linezolid, quinupristin/dalfopristin, daptomycin or teicoplanin, based on antimicrobial susceptibilities) if the organism is ampicillin-resistant (2D).

Enterococci are normal flora of the gastrointestinal tract (356,357). Intra-abdominal source must be considered. Other pathogenic organisms are isolated in about half of the cases of enterococcal peritonitis, and the coexistence of other organisms was associated with high rates of catheter removal, permanent hemodialysis transfer, and death (356,357).

Enterococcal species are always resistant to cephalosporins. Identification of the exact species is important because resistance to penicillins and carbapenems is far more frequently observed in *E. faecium* than in *E. faecalis* (358). Although there may be clinical response to empirical therapy with first-generation cephalosporins (359), peritonitis episodes should

be treated with IP vancomycin if the organism is susceptible. For patients with severe signs or symptoms, an aminoglycoside may be added for synergy. However, aminoglycosides should not be added to the same bag with penicillins because of chemical incompatibility (see Antibiotic Delivery and Stability). Although ampicillin has little *in vitro* activity when added to common PD solutions (331), clinical experience suggests clinical efficiency (356). For vancomycin-resistant enterococcus (VRE) causing peritonitis, if the bacterial isolate is ampicillin-susceptible, ampicillin remains the drug of choice. Otherwise, linezolid, quinupristin/dalfopristin, or daptomycin are valid options (278,281,292,360–363). Given the clinical efficacy and profile of adverse effects, daptomycin is probably the first-line antibiotic of choice for peritonitis episodes caused by VRE (278,363–365). Bone marrow suppression usually occurs after 10 to 14 days of linezolid therapy, and prolonged therapy may also result in neurotoxicity. One previous study showed that removal of the PD catheter within 1 week of the onset of refractory enterococcal peritonitis was associated with a significant reduction in the risk of permanent hemodialysis transfer (356).

Streptococcal Species

- We suggest that streptococcal peritonitis be treated with appropriate antibiotics, such as IP ampicillin, for 2 weeks (2C).

Streptococci frequently originate from the mouth (175), although *S. bovis* typically comes from the colon (366). Peritonitis episodes caused by streptococci usually respond well to antibiotic treatment (175,367), but viridans streptococcal peritonitis are more likely to be refractory (368). Cefazolin and vancomycin are often effective.

Staphylococcus Aureus

- We suggest that *Staphylococcus aureus* peritonitis be treated with effective antibiotics for 3 weeks (2C).

Peritonitis episodes caused by *Staphylococcus aureus* are often secondary to exit-site or tunnel infection, although touch contamination is also common. If the bacterial isolate is methicillin-sensitive, a first-generation cephalosporin is the drug of choice. Two retrospective studies found that the initial empiric antibiotic choice between vancomycin and cefazolin had similar clinical outcomes (369,370). If the isolate is methicillin-resistant, IP vancomycin is the drug of choice, but teicoplanin and daptomycin can be used as alternatives (371). One study showed that the use of adjuvant rifampicin for 5 to 7 days may reduce the risk for relapsing or repeat *S. aureus* peritonitis (369). However, rifampicin is a potent liver enzyme inducer and interaction with other concomitant medications may be problematic.

Observational data suggest that treatment with effective antibiotics for 3 weeks is needed (369,370,372). Prolonged vancomycin therapy may predispose to the emergence of vancomycin-resistant *S. aureus* and should be avoided

whenever possible. For patients with concomitant *S. aureus* exit-site or catheter tunnel infection, catheter removal should be considered.

Corynebacterium Peritonitis

- We suggest that corynebacterial peritonitis be treated with effective antibiotics for 3 weeks **(2C)**.

Corynebacterium species belong to the natural flora of the skin. Infections due to *Corynebacterium* have been increasingly recognized over the past decades, largely due to improved recognition and microbiological techniques. In a retrospective study, *Corynebacterium* peritonitis often resulted in relapse or repeat episodes, catheter removal, permanent hemodialysis transfer, and death (373). Another retrospective study found that relapsing *Corynebacterium* peritonitis was common after a 2-week course of antibiotic treatment, but relapsing episodes can usually be cured with a 3-week course of IP vancomycin (374). For refractory *Corynebacterium* peritonitis, observational data suggest that catheter removal within 1 week after the onset of peritonitis significantly reduces the risk of permanent hemodialysis transfer (373). For patients with concomitant exit-site or catheter tunnel infection caused by *Corynebacterium*, early catheter removal should be considered.

Pseudomonas Peritonitis

- We suggest that *Pseudomonas* peritonitis be treated with 2 antibiotics with different mechanisms of action and to which the organism is sensitive (e.g. IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks **(2C)**.
- We suggest that *Pseudomonas* peritonitis with concomitant exit-site and tunnel infection be treated with catheter removal **(2D)**.

Pseudomonas peritonitis is generally severe and often associated with infection of the catheter. *Pseudomonas aeruginosa* is the most common species. Retrospective studies have shown that *Pseudomonas* peritonitis is associated with greater frequencies of hospitalization, high rates of catheter removal and permanent hemodialysis transfer (375–377). The use of 2 anti-pseudomonal antibiotics is associated with better outcomes (377). Carbapenems, such as imipenem, meropenem, and doripenem are valid alternatives, especially if the bacterial isolate is resistant to cephalosporin and anti-pseudomonal penicillins. If fluoroquinolone is used as part of the regimen, ciprofloxacin should be used, while moxifloxacin has very little anti-pseudomonal activity. If concomitant catheter infection is present, catheter removal is often needed.

Other Gram-Negative Bacteria

- We suggest that non-*Pseudomonas* gram-negative peritonitis be treated with effective antibiotics for at least 3 weeks **(2C)**.

If single gram-negative organisms are isolated, the antibiotic should be chosen according to sensitivity, safety, and convenience. It is important to note that bacteria in biofilm are considerably less sensitive than that indicated by laboratory testing (378), which may account for the high percentage of treatment failures, even though the organism appears to be sensitive to the antibiotic *in vitro* (379,380). Retrospective studies have shown that gram-negative peritonitis had higher risks of catheter loss and death than gram-positive episodes (379–384). In one study, recent antibiotic therapy was the major risk factor of antibiotic resistance, while ESI, and possibly recent antibiotic therapy, were associated with poor therapeutic response (382). The SPICE organisms (*Serratia*, *Pseudomonas*, indole-positive organisms such as *Proteus* and *Providentia*, *Citrobacter*, and *Enterobacter*) have amp-C beta-lactamases, which inactivate cephalosporins, and have a high risk of relapse. Although single antibiotic therapy is often effective, 1 retrospective study suggested that treatment with 2 antibiotics may reduce the risk of relapse and recurrence (382).

In recent years, there has been widespread emergence of 2 antibiotic resistance mechanisms: extended-spectrum beta-lactamases (ESBLs) (385,386) and carbapenem-resistant Enterobacteriaceae (CRE) (385,387); the latter are also called *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria when the carbapenem resistance is mediated by beta-lactamases. Extended-spectrum beta-lactamases are resistant to all cephalosporins but usually susceptible to carbapenems. Carbapenem-resistant Enterobacteriaceae/KPC-producing bacteria are usually resistant to all classes of beta-lactams, usually resistant to fluoroquinolones, variably susceptible to aminoglycosides, but usually susceptible to polymyxin and colistin.

The isolation of a *Stenotrophomonas* species, while infrequent, requires special attention, as it is sensitive to only a few antimicrobial agents (388,389). Recent treatment with carbapenems, fluoroquinolones, or third- or fourth-generation cephalosporins usually precedes *Stenotrophomonas* infections. Based on limited observational data, therapy with 2 antibiotics for 3 to 4 weeks is recommended (388,389). If the isolate is sensitive to trimethoprim/sulfamethoxazole, this agent should be included in the regimen. Tigecycline, polymyxin B, and colistin are other possible alternatives.

Polymicrobial Peritonitis

- If multiple enteric organisms (multiple gram-negative or mixed gram-negative/gram-positive organisms) are grown from PD effluent, we suggest that surgical evaluation be obtained immediately when there is no prompt clinical response **(1C)** and that the patient be treated with metronidazole in conjunction with IP vancomycin and either IP aminoglycoside or IP ceftazidime for a minimum period of 3 weeks **(2C)**.
- If multiple gram-positive organisms are grown from PD effluent, we suggest that patients be treated with effective antibiotics for 3 weeks **(2C)**.

When multiple enteric organisms are grown from the PD effluent, there is a possibility of intra-abdominal pathology. Presentation with hypotension, sepsis, lactic acidosis, or elevated dialysis effluent amylase level should also raise the possibility of abdominal catastrophe (390,391). When a surgical cause of peritonitis is suspected, the antibiotics of choice are metronidazole plus vancomycin, in combination with ceftazidime or an aminoglycoside. Monotherapy with a carbapenem or piperacillin/tazobactam may also be considered. Assessment by a surgeon is needed. Computed tomographic (CT) scan may help to identify the pathology, but a normal CT scan does not eliminate that possibility. If laparotomy is needed, the PD catheter is usually removed and antibiotics are continued via IV route.

In contrast, polymicrobial peritonitis due to multiple gram-positive organisms often has a favorable prognosis (392,393). Their clinical behavior is similar to peritonitis episodes caused by single gram-positive organisms and the etiology may well be touch contamination. Antibiotic therapy is often effective without catheter removal (392).

Culture-Negative Peritonitis

- We suggest that negative effluent cultures on day 3 warrant a repeat dialysis effluent WBC count with differential **(2D)**.
- If the culture-negative peritonitis is resolving at day 3, we suggest discontinuing aminoglycoside therapy and continuing treatment with gram-positive coverage (e.g. first-generation cephalosporin or vancomycin) for 2 weeks **(2C)**.
- If the culture-negative peritonitis is not resolving at day 3, we suggest special culture techniques be considered for isolation of unusual organisms **(2C)**.

Recent antibiotic usage and technical problems of culturing the specimen are the major reasons for negative effluent cultures (394–396). If PD effluent yields no growth after 3 days, a repeat WBC count with differential should be obtained. If the repeat cell count indicates that the infection has not resolved, special culture techniques may be considered for the isolation of unusual organisms (e.g. mycobacteria, nocardia, legionella, filamentous fungus, and other fastidious bacteria). This would require close liaison with the microbiology laboratory.

Many culture-negative peritonitis episodes are probably caused by gram-positive organisms. If the patient improves clinically, initial therapy should be continued (394–396). Duration of therapy should be 2 weeks if the effluent clears promptly. In contrast, if there is suboptimal response after 5 days of empirical antibiotics, catheter removal should be strongly considered.

Fungal Peritonitis

- We recommend immediate catheter removal when fungi are identified in PD effluent **(1C)**.
- We suggest that treatment with an appropriate anti-fungal

agent be continued for at least 2 weeks after catheter removal **(2C)**.

Fungal peritonitis is a serious complication with high rates of hospitalization, catheter removal, transfer to hemodialysis, and death (397–400). Initial therapy is traditionally a combination of amphotericin B and flucytosine. However, IP amphotericin causes chemical peritonitis and pain, while IV administration has poor peritoneal bioavailability. In addition, flucytosine is not widely available. If flucytosine is used, regular monitoring of serum concentration is necessary to avoid bone marrow toxicity. Peak serum flucytosine levels, measured 1–2 hours after an oral dose, should be 25–50 mcg/mL (401,402).

Other agents of choice include fluconazole, an echinocandin (e.g. caspofungin, micafungin, or anidulafungin), posaconazole, and voriconazole. Although fluconazole is commonly used, the prevalence of azole resistance is increasing (403). Fluconazole only has activity against *Candida* species and *Cryptococcus*. Echinocandins have been advocated for the treatment of fungal peritonitis caused by *Aspergillus* species and non-albicans *Candida* species, or in patients intolerant to other antifungal therapies (297,298,398). Caspofungin has been used successfully as monotherapy or in combination with amphotericin (297,298). Posaconazole and voriconazole have been successfully used for the treatment of peritonitis caused by filamentous fungi (287,300,301).

Irrespective of the choice of anti-fungal agent, observational studies suggest that prompt catheter removal probably improves outcome and reduces mortality (300,301,397,398,400,404). Anti-fungal agents should be continued after catheter removal for at least 2 weeks. A recent study suggested that around one-third of patients could return to PD (399).

Tuberculous Peritonitis

Although classical symptoms of fever, abdominal pain, and cloudy effluent may occur with tuberculous peritonitis, the diagnosis should be considered in any patient with refractory or relapsing peritonitis with negative bacterial cultures. Similar to bacterial peritonitis, most cases of tuberculous peritonitis have PMN in the dialysis effluent at initial presentation, but lymphocytosis in the dialysis effluent usually becomes obvious later. Ziehl-Neelsen stain examination of the PD effluent is often unrevealing, and conventional culture technique (e.g. Löwenstein-Jensen agar) is slow and not sufficiently sensitive. The time to develop a positive culture is considerably decreased in fluid medium (e.g. Septi-Chek, BACTEC; Becton Dickinson, NJ, USA). Overall diagnostic yield could be improved by centrifuging a large volume of effluent (50 to 100 mL), followed by culturing the sediment in both solid and fluid media. Alternatively, mycobacterial DNA PCR can be performed on dialysis effluent, although false-positives are not uncommon (405). Laparoscopy with biopsy of the peritoneum or omentum has also been advocated for rapid diagnosis if the index of suspicion is high (406).

The treatment protocol should be based on general protocols for treatment of tuberculosis but is often started with 4 drugs: rifampicin, isoniazid, pyrazinamide, and ofloxacin. A previous study showed that rifampicin levels in PD effluent are often low (407). Intraperitoneal rifampicin treatment has been advocated but is not available in many countries. In general, pyrazinamide and ofloxacin could be stopped after 2 months, while rifampicin and isoniazid should be continued for a total of 12 to 18 months (407–413). Pyridoxine (50 to 100 mg/day) should be given to avoid isoniazid-induced neurotoxicity. On the other hand, long-term use of pyridoxine at a higher dose (e.g. 200 mg daily) is in itself associated with neuropathy and should be avoided. Streptomycin, even in reduced doses, may cause ototoxicity after prolonged use and should be avoided. Ethambutol is associated with a high risk of optic neuritis in dialysis patients and must be used with appropriate dosage reduction. Previous reports suggest a dose of 15 mg/kg every 48 hours or thrice weekly for up to 2 months (414). The optimal treatment for drug-resistant tuberculous peritonitis remains unknown.

Many patients respond to anti-tuberculous therapy without catheter removal (407–413,415). However, it is important to differentiate patients with miliary tuberculosis, whose peritonitis is part of the disseminated disease, from those with isolated tuberculous peritonitis without extraperitoneal infection, because the duration of anti-tuberculous therapy is different.

Non-Tuberculous Mycobacterial Peritonitis

Data on peritonitis caused by non-tuberculous mycobacteria are limited but may be increasing (21,416–422). It is not uncommon for non-tuberculous mycobacteria to be misidentified as gram-positive diphtheroids. Over half of the isolates are rapidly growing species, such as *M. fortuitum* and *M. chelonae* (420), and often become positive on routine bacteriologic cultures in 3 to 5 days. It has been postulated that extensive use of topical gentamicin ointment for exit-site infection may predispose patients to non-tuberculous mycobacterial infection of the exit site (144). The treatment regimen for non-tuberculous mycobacterial peritonitis is not well established and requires individualized protocols based on susceptibility testing. Catheter removal is usually necessary, and experience with non-removal is limited (420–422). The type and duration of antibiotic therapy are variable, and the optimal treatment regimen is poorly defined and depends on species and drug susceptibilities (416–422).

Catheter Removal and Re-Insertion

- We recommend that PD catheters be removed for refractory, relapsing, or fungal peritonitis unless there are clinical contraindications (1C).
- We suggest that it is appropriate to consider return to PD for many patients who have had their catheter removed for refractory, relapsing, or fungal peritonitis (2C).

- We suggest that if re-insertion of a new catheter is attempted after a PD catheter is removed for refractory, relapsing, or fungal peritonitis, it be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms (2D).

Indications for catheter removal are summarized in Table 8. For refractory peritonitis and fungal peritonitis, simultaneous re-insertion of a new PD catheter is not recommended, and patients should be put on temporary hemodialysis. Observational studies suggest that effective antibiotics should be continued for at least 2 weeks after catheter removal for refractory peritonitis (423,424).

After severe episodes of peritonitis, around 50% of patients could potentially return to PD (423–425). An ANZDATA Registry study demonstrated that return to PD after catheter removal and temporary hemodialysis for peritonitis was not associated with inferior patient-level clinical outcomes when compared with other patients who either never required hemodialysis transfer for peritonitis or who had permanent hemodialysis transfer for peritonitis (426). Furthermore, subsequent peritonitis-free, technique and patient survival following return to PD were not associated with organism type or duration of time from hemodialysis transfer to PD restart (426). There are few data on the optimal duration between catheter removal for peritonitis and re-insertion of a new catheter. Observational studies suggest a minimum period of 2 to 3 weeks (423–425), although some would recommend later re-insertion in cases of fungal peritonitis (397,398). Re-insertion of a new catheter should be done by laparoscopic or mini-laparotomy approach so that adhesion can be directly visualized. Ultrafiltration problems are common after return to PD (423,424). A small proportion of patients with PD-related peritonitis develop recurrent intra-abdominal collection that requires percutaneous drainage after catheter removal (427). The chance of a successful return to PD is very low in this group of patients, and direct conversion to long-term hemodialysis should be considered (427).

FUTURE RESEARCH

There are some new antibiotics that, to the best of our knowledge, have not been tried for the treatment of PD-related peritonitis. For example, ceftaroline has good coverage of

TABLE 8
Indications for Catheter Removal

- | |
|--|
| <ul style="list-style-type: none"> • Refractory peritonitis • Relapsing peritonitis • Refractory exit-site and tunnel infection • Fungal peritonitis • Catheter removal may also be considered for <ul style="list-style-type: none"> – repeat peritonitis – mycobacterial peritonitis – multiple enteric organisms |
|--|

gram-negative bacteria and is also active against MRSA and methicillin-resistant coagulase-negative staphylococci. The pharmacokinetic data of many new antibiotics, administered either systemically or IP, are much needed and some are in the pipeline (428). Many data on antibiotic stability in PD solutions are old and need to be repeated in new PD solutions. Pharmacodynamic investigations specific to PD-related peritonitis are scarce. The impact of antibiotic resistance also requires further study.

MALDI-TOF mass spectrometry has recently been used in academic facilities to identify microorganisms in biologic fluids. This technique may shorten the time to species identification and also help to identify rare or unknown pathogens. The application of MALDI-TOF mass spectrometry and other novel techniques to the diagnosis of PD peritonitis deserves further study.

Clinical trials are also required in order to assess the efficacy and safety of various treatment regimens, especially for the treatment of peritonitis in APD. Outcomes to be examined should include not only resolution without catheter removal, but also the duration of peritoneal inflammation, relapsing and repeat episodes, as well as the change in peritoneal solute transport status after resolution of peritonitis. Further studies are also needed on primary and secondary prevention of peritonitis. The efficacy of treating many "modifiable" risk factors has not been formally tested. Research on the biology and management of catheter biofilm is also needed. Finally, whilst PD training is widely acknowledged as crucial to achieving good clinical outcomes in PD, high-level evidence guiding how, where, when, and by whom PD training should be performed is lacking. Research in this area should explicitly detail the training curriculum and approach (rather than vaguely alluding to adult-learning principles) to permit generalizability of study findings.

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