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ISPD GUIDELINES/RECOMMENDATIONS

PERITONEAL DIALYSIS-RELATED INFECTIONS RECOMMENDATIONS: 2010 UPDATE

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Peritonitis remains a leading complication of peritoneal dialysis (PD). Around 18% of the infection-related mortality in PD patients is the result of peritonitis. Although less than 4% of peritonitis episodes result in death, peritonitis is a "contributing factor" to death in 16% of deaths on PD. In addition, severe and prolonged peritonitis can lead to peritoneal membrane failure and peritonitis is probably the most common cause of technique failure in PD. Peritonitis remains a major cause of patients discontinuing PD and switching to hemodialysis. Therefore, the PD community continues to focus attention on prevention and treatment of PD-related infections (1–9). Peritonitis treatment should aim for rapid resolution of inflammation and preservation of peritoneal membrane function.

Recommendations under the auspices of the International Society for Peritoneal Dialysis (ISPD) were first published in 1983 and revised in 1989, 1993, 1996, 2000, and 2005 (10–13). The previous recommendations included sections on treatment as well as prevention of peritonitis. In the present recommendations, the Committee focused on the treatment of peritonitis; prevention of PD-related infections will be covered in a separate ISPD position statement.

The present recommendations are organized into five sections:

1. Reporting of peritonitis rate
2. Exit-site and tunnel infections
3. Initial presentation and management of peritonitis
4. Subsequent management of peritonitis (organism specific)
5. Future research

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Although many of the general principles could be applied to pediatric patients, recommendations outlined here focus on PD-related infections in adult patients. Clinicians who take care of pediatric PD patients should refer to other sources for detailed treatment regimens and dosages.

These recommendations are evidence based where such evidence exists. The bibliography is not intended to be comprehensive as there have been nearly 10 000 references to peritonitis in PD patients published since 1966. The Committee has chosen to include articles that are more recently published (*i.e.*, after the most recent recommendation, published in 2005) and those considered key references. These recommendations are not based solely on randomized controlled trials because such studies in PD patients are limited. Where there is no definitive evidence but the group feels there is sufficient experience to suggest a certain approach, this is indicated as "opinion" based. The recommendations are not meant to be implemented in every situation but are recommendations only. Each center should examine its own pattern of infection, causative organisms, and sensitivities and adapt the protocols as necessary for local conditions.

REPORTING OF PERITONITIS RATE

- Every program should regularly monitor infection rates, at a minimum, on a yearly basis (*Opinion*) (14–16).

Programs should carefully monitor all PD-related infections, both exit-site infections and peritonitis, including the presumed cause and cultured organisms, as part of a continuous quality improvement program.

Causative organisms, their antibiotic sensitivity, and presumed etiology must be reviewed in a regular fashion by the PD team, including both the nurses and the physician(s) and, if appropriate, the physician assistant or nurse practitioner. In this way, interventions can be implemented if infection rates are rising or unacceptably high. Table 1 provides an easy method to calculate infection rates. Infection rates for individual organisms should also be calculated and compared to the literature. The center's peritonitis rate should be no more than 1 episode every 18 months (0.67/year at risk), although the rate achieved will depend to some extent on the patient population. However, overall rates as low as 1 episode every 41 – 52 months (0.29 – 0.23/year) have been reported, a goal that centers should strive to achieve (17,18).

TABLE 1
Methods for Reporting Peritoneal Dialysis-Related Infections (Peritonitis, Exit-Site Infections) (16)

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

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

EXIT-SITE AND TUNNEL INFECTIONS

DEFINITIONS

- Purulent drainage from the exit site indicates the presence of infection. Erythema may or may not represent infection (*Evidence*) (19–22).

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter–epidermal interface. Pericatheter erythema without purulent drainage is sometimes an early indication of infection but can also be a simple skin reaction, particularly in a recently placed catheter or after trauma to the catheter. Clinical judgment is required to decide whether to initiate therapy or to follow carefully. A positive culture in the absence of an abnormal appearance is indicative of colonization rather than infection. Intensification of exit-site cleaning with antiseptics is advised.

A tunnel infection may present as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult, as shown by sonographic studies (22). A tunnel infection usually occurs in the presence of an exit-site infection but rarely occurs alone. In the present article, exit-site and tunnel infections are collectively referred to as catheter infections. *Staphylococcus aureus* and *Pseudomonas aeruginosa* exit-site infections are very often associated with concomitant tunnel infections and are the organisms that most often result in catheter infection-related peritonitis; aggressive management is always indicated for these organisms.

THERAPY FOR EXIT-SITE AND TUNNEL INFECTIONS

- The most serious and common exit-site pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. As these organisms frequently lead to peritonitis (*Evidence*), such infections must be treated aggressively (7,8,19,23–41).
- Oral antibiotic therapy is generally recommended, with the exception of methicillin-resistant *S. aureus* (MRSA) (*Opinion*) (21).

Exit-site and tunnel infections may be caused by a variety of micro-organisms. Although *S. aureus* and *P. aeruginosa* are responsible for the majority of infections, other bacteria (diphtheroids, anaerobic organisms, nonfermenting bacteria, streptococci, nontuberculous mycobacteria, Legionella, yeasts, and fungi) can also be involved. Empiric antibiotic therapy may be initiated immediately. Alternatively, the healthcare team may decide to defer therapy until the results of the exit-site culture can direct the choice of antibiotic. Microbiological examination should preferably include a combination of microscopy with aerobic and anaerobic culture. The Gram stain of exit-site drainage and the microbiological culture findings can guide the initial therapy. Cultures should be taken to the laboratory using appropriate transport materials also allowing anaerobic bacteria to survive. Oral antibiotic therapy has been shown to be as effective as intraperitoneal (IP) antibiotic therapy.

Empiric therapy should always cover *S. aureus*. If the patient has a history of *P. aeruginosa* exit-site infections, empiric therapy should be with an antibiotic that will cover this organism. In some cases, intensified local care or a local antibiotic cream may be felt to be sufficient in the absence of purulence, tenderness, and edema.

Gram-positive organisms are treated with oral penicillinase-resistant (or broad spectrum) penicillin or a first-generation cephalosporin, such as cephalexin. Dosing recommendations for frequently used oral antibiotics are shown in Table 2 (41). To prevent unnecessary exposure to vancomycin and thus emergence of resistant organisms, vancomycin should be avoided in the routine treatment of gram-positive exit-site and tunnel infections but will be required for MRSA infections. Clindamycin, doxycycline, and minocycline are sometimes useful for the treatment of community-acquired MRSA and other organisms; these drugs do not require dose adjustment for end-stage renal disease. In slowly resolving or particularly severe *S. aureus* exit-site infections, rifampicin 600 mg daily may be added, although this drug should be held in reserve in areas where tuberculosis is endemic. Rifampicin should never be given as monotherapy. It should also be noted that rifampicin is a potent inducer of drug-metabolizing enzymes and would reduce the levels of medications such as warfarin, statins, and anticonvulsants.

TABLE 2
Oral Antibiotics Used in Exit-Site and Tunnel Infection

Amoxicillin	250–500 mg b.i.d.
Cephalexin	500 mg b.i.d. to t.i.d. (41)
Ciprofloxacin	250 mg b.i.d. (29)
Clarithromycin	500 mg loading dose, then 250 mg b.i.d. or q.d. (30)
Dicloxacillin	500 mg q.i.d.
Erythromycin	500 mg q.i.d.
Flucloxacillin (or cloxacillin)	500 mg q.i.d.
Fluconazole	200 mg q.d. for 2 days, then 100 mg q.d. (41)
Flucytosine	0.5–1 g/day titrated to response and serum trough levels (25–50 µg/mL) (41)
Isoniazid	200–300 mg q.d. (42)
Linezolid	400–600 mg b.i.d. (41)
Metronidazole	400 mg t.i.d.
Moxifloxacin	400 mg daily
Ofloxacin	400 mg first day, then 200 mg q.d.
Pyrazinamide	25–35 mg/kg 3 times per week (31)
Rifampicin	450 mg q.d. for <50 kg; 600 mg q.d. for >50 kg
Trimethoprim/sulfamethoxazole	80/400 mg q.d.

b.i.d. = 2 times per day; q.d. = every day; t.i.d. = 3 times per day; q.i.d. = 4 times daily.

Pseudomonas aeruginosa exit-site infections are particularly difficult to treat and often require prolonged therapy with two antibiotics. Oral fluoroquinolones are recommended as the first choice, preferably not as monotherapy since resistance develops rapidly. If quinolones are given concomitantly with sevelamer, multivalent cations, such as calcium, oral iron, zinc preparations, sucralfate, magnesium–aluminum antacids, or milk, chelation interactions may occur that reduce quinolone absorption. Administration of the quinolone should therefore be separated from these drugs by at least 2 hours (with the quinolone administered first). If resolution of the infection is slow or if there is recurrent Pseudomonas exit-site infection, a second antipseudomonal drug, such as, but not limited to, IP aminoglycoside, ceftazidime, cefepime, piperacillin, imipenem–cilastatin, or meropenem, should be added.

Many organisms can cause exit-site and tunnel infections, including micro-organisms belonging to the normal skin flora, such as corynebacteria (7,32). Therefore, culture with sensitivity testing is important in determining antibiotic therapy. Close follow-up is necessary to determine the response to therapy and relapse. Unfortunately, both *S. aureus* and *P. aeruginosa* catheter infections tend to recur; repeating PD effluent cultures 1 – 2 weeks after the discontinuation of antimicrobial treatment may be useful for risk assessment.

Ultrasonography of the exit site is a useful adjunctive tool in the management of exit-site and tunnel infections (33). A sonolucent zone around the external cuff over 1 mm thick following a course of antibiotic treatment and the involvement of the proximal cuff are associated with poor clinical outcome. In exit-site infections caused by *P. aeruginosa*, clinical outcome has been uniformly poor irrespective of the sonographic findings.

Antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time; treatment for 3 weeks is probably necessary for exit-site infections caused by *P. aeruginosa*. If prolonged therapy (*e.g.*, longer than 3 weeks) with appropriate antibiotics fails to resolve the infection, the catheter can be replaced as a single procedure under antibiotic coverage (34–37). If the cuffs are not involved, revision of the tunnel may be performed in conjunction with continued antibiotic therapy. This procedure, however, may result in peritonitis, in which case the catheter should be removed. Sonography of the tunnel has been shown useful in evaluating the extent of infection along the tunnel and the response to therapy and may be used to decide on tunnel revision, replacement of the catheter, or continued antibiotic therapy (38). In general, catheter removal should be considered earlier for exit-site infections caused by *P. aeruginosa* or if there is tunnel infection.

A patient with an exit-site infection that progresses to peritonitis, or who presents with an exit-site infection in conjunction with peritonitis with the same organism, will usually require catheter removal. Catheter removal should be done promptly rather than submitting the patient to prolonged peritonitis or relapsing peritonitis. The exception is peritonitis due to coagulase-negative staphylococcus (CoNS), which is generally readily treated. Simultaneous removal and reinsertion of the dialysis catheter (with a new exit site) is feasible in eradicating refractory exit-site infections due to *P. aeruginosa* (39). In selected cases, cuff shaving may be considered an alternative to catheter replacement for tunnel infection (40).

INITIAL PRESENTATION AND MANAGEMENT OF PERITONITIS

CLINICAL PRESENTATION OF PERITONITIS

- Peritoneal dialysis patients presenting with cloudy effluent should be presumed to have peritonitis. This is confirmed by obtaining effluent cell count, differential, and culture (*Evidence*) (43–52).
- It is important to initiate empiric antibiotic therapy for PD-associated peritonitis as soon as possible. There are potentially serious consequences of peritonitis (relapse, catheter removal, permanent transfer to hemodialysis, and death) that are more likely to occur if treatment is not initiated promptly (*Opinion*).

Patients with peritonitis usually present with cloudy fluid and abdominal pain; however, peritonitis should always be included in the differential diagnosis of the PD patient with abdominal pain, even if the effluent is clear, as a small percentage of patients present in this fashion. Other causes, such as constipation, renal or biliary colic, peptic ulcer disease, pancreatitis, and acute intestinal perforation, should also be investigated in the PD patient with abdominal pain and clear fluid. Conversely, while patients with peritonitis most often have severe pain, some episodes are associated with mild or even no pain. The degree of pain is somewhat organism specific (*e.g.*, generally less with CoNS and greater with Streptococcus, gram-negative rods, *S. aureus*) and can help guide the clinician in the decision to admit or treat as an outpatient. Patients with minimal pain can often be treated on an outpatient basis with IP therapy and oral pain medication. Those requiring intravenous (IV) narcotics always require admission for management.

Cloudy effluent will usually represent infectious peritonitis but there are other causes (48). The differential diagnosis is shown in Table 3. Case reports of sterile peritonitis associated with icodextrin-based dialysis solutions have been reported from Europe (49). Randomized

TABLE 3
Differential Diagnosis of Cloudy Effluent

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

trials comparing icodextrin- to glucose-based dialysis solutions show similar peritonitis risk with the two solutions (50–52).

The abdomen should be drained and the effluent carefully inspected and sent for cell count with differential, Gram stain, and culture. An effluent cell count with white blood cells (WBC) more than 100/μL (after a dwell time of at least 2 hours), with at least 50% polymorphonuclear neutrophilic cells, indicates the presence of inflammation, with peritonitis being the most likely cause. To prevent delay in treatment, antibiotic therapy should be initiated as soon as cloudy effluent is seen, without waiting for confirmation of the cell count from the laboratory. Patients with cloudy effluent may benefit from the addition of heparin (500 units/L) to the dialysate to prevent occlusion of the catheter by fibrin. Heparin is also usually added in cases of hemoperitoneum. An experienced observer can differentiate hemoperitoneum from cloudy effluent due to peritonitis. If there is a question, a cell count with differential should be performed.

The number of cells in the effluent will depend, in part, on the length of the dwell. For patients on automated PD (APD) who present during their nighttime treatment, the dwell time is much shorter than with continuous ambulatory PD (CAPD); in this case, the clinician should use the percentage of polymorphonuclear cells rather than the absolute number of white cells to diagnose peritonitis. The normal peritoneum has very few polymorphonuclear cells; therefore, a proportion above 50% is strong evidence of peritonitis, even if the absolute white cell count does not reach 100/μL. Patients on APD with a day dwell who present during the day generally have cell counts similar to those of CAPD patients and are not difficult to interpret. However, APD patients without a daytime exchange who present with abdominal pain may have no fluid to withdraw. In this case, 1 L of dialysate should be infused and permitted to dwell a minimum of 1 – 2 hours, then drained and examined for turbidity, and sent for cell count with differential and culture. The differential (with a shortened dwell time) may be more useful than the absolute WBC count. In equivocal cases, or in patients with systemic or abdominal symptoms in whom the effluent appears clear, a second exchange is performed with a dwell time of at least 2 hours. Clinical judgment should guide initiation of therapy.

Even though the Gram stain is often negative in the presence of peritonitis, this test should be performed as the Gram stain may indicate the presence of yeast, thus allowing for prompt initiation of antifungal therapy and permitting timely arrangement of catheter removal. With this exception, empiric therapy should not be based on the Gram stain but should cover the usual pathogens, as discussed below.

The patient should always be questioned in a nonthreatening manner about a break in technique and in particular whether contamination or disconnection occurred recently. Information about recent exit-site infections and the last (if any) episode of peritonitis should be obtained. The patient should also be questioned about any recent endoscopic or gynecological procedures, as well as the presence of either constipation or diarrhea.

In peritonitis, abdominal tenderness is typically generalized and is often associated with rebound. Localized pain or tenderness should raise the suspicion of an underlying surgical pathology such as acute appendicitis. The physical examination of the patient presenting with peritonitis should always include a careful inspection of the catheter exit site and tunnel. Any drainage from the exit site should be cultured along with the effluent. If the exit site grows the same organism as the effluent (with the exception of CoNS), then it is very likely that the origin of the peritonitis is the catheter.

Although an abdominal x-ray image is generally not necessary, if there is any suspicion of a bowel source, an abdominal film should be obtained. The presence of free air under the diaphragm is suggestive of perforation, although it should be noted that a small amount of IP air is common among PD patients due to inadvertent infusion of air by the patient. Routine peripheral blood cultures are unnecessary since they are usually negative but they should be obtained if the patient appears septic.

Some PD patients reside in locations that are remote from medical facilities and thus cannot be seen expeditiously after the onset of symptoms. These patients also may not have immediately available microbial and laboratory diagnostic services. 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 in the home. A delay in treatment could be dangerous. Whenever possible, prior to starting antibiotic, cultures should be obtained either at a local facility or by having the patient keep blood-culture bottles at home for use. Alternatively, the patient may place the cloudy effluent bag in the refrigerator to slow bacterial multiplication and white cell killing until they are able to bring in the sample. The benefit of self-initiated treatment, however, should be carefully balanced against the potential problems of overdiagnosis and habitual misuse of antibiotics.

SPECIMEN PROCESSING

- Culture-negative peritonitis should not be greater than 20% of episodes. Standard culture technique is the use of blood-culture bottles but a large-volume culture (*e.g.*, culturing the sediment after centrifuging 50 mL of effluent) could further improve the recovery of micro-organisms (*Evidence*) (53–57).

In the ideal situation (*e.g.*, in specialized academic centers), one could achieve a less than 10% rate of culture-negative peritonitis. Correct microbiological culturing of peritoneal effluent is of utmost importance to establish the micro-organism responsible. Identification of the organism and subsequent antibiotic sensitivities will not only help guide antibiotic selection but, in addition, the type of organism can indicate the possible source of infection. An optimal culture technique is the combination of sediment culturing of 50 mL effluent and bedside inoculation of 5 – 10 mL effluent in two blood-culture bottles. The specimens should arrive within 6 hours at the laboratory. If immediate delivery to the laboratory is not possible, the inoculated culture bottles should ideally be incubated at 37°C. When the causative micro-organism has been established, subsequent cultures for monitoring may be performed by only inoculating the effluent in blood-culture bottles. Centrifugation of 50 mL peritoneal effluent at 3000*g* for 15 minutes, followed by re suspension of the sediment in 3 – 5 mL of sterile saline, and inoculation of this material both on solid culture media and into a standard blood-culture medium, is a sensitive method to identify the causative organisms. With this method, less than 5% will be culture negative. The solid media should be incubated in aerobic, microaerophilic, and anaerobic environments. Blood-culture bottles can be directly injected with 5 – 10 mL of effluent if equipment for centrifuging large amounts of fluid is not available; this method generally results in a culture-negative rate of 20%. If the patient is already on antibiotics, removal of antibiotics present in the specimen may increase the isolation rate.

The speed with which bacteriological diagnosis can be established is very important. Concentration methods not only facilitate correct microbial identification but also reduce the time necessary for bacteriological cultures. Rapid blood-culture techniques (*e.g.*, BACTEC, Septi-Chek, BacT/Alert; Becton Dickinson) may further speed up isolation and identification and are probably the best approach. Two recent prospective studies also support the routine use of the broth culture technique (56,57), while the lysis–centrifugation technique needs further evaluation. The majority of cultures will become positive after the first 24 hours and, in over 75% of cases, diagnosis can be established in less than 3 days. When cultures remain negative after 3 – 5 days of incubation and clinical suspicion is high, subculture of blood-culture bottles on media with aerobic, anaerobic, and microaerophilic incubation conditions for a further 3 – 4 days may help to identify slow-growing bacteria and yeasts that are undetectable in an automated culture system.

OTHER NOVEL DIAGNOSTIC TECHNIQUES

- There is not enough evidence for recommending the use of novel techniques [such as leukocyte esterase, broad-spectrum polymerase chain reaction (PCR), quantitative bacterial DNA PCR] for the diagnosis of peritonitis (58–64).

A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis. Park *et al.* (58) and Akman *et al.* (59) reported that leukocyte esterase reagent strip has excellent accuracy for the diagnosis of peritonitis. Various commercially available strips have been tested to diagnose non-PD peritonitis but the results vary enormously; more studies are required before this can be applied in a routine setting (60).

Broad-spectrum PCR with RNA sequencing (61) and quantitative bacterial DNA PCR assays (62) may also complement culture methods in the diagnosis of CAPD peritonitis, especially in patients with previous or current antibiotic use. The latter technique may also help to identify those patients likely to relapse despite apparent clinical improvement with standard antibiotic therapy (62). Another study suggests that the matrix metalloproteinase-9 test kit may be a reliable method for early diagnosis of PD peritonitis (63). The role of rapid detection of the causative pathogen of peritonitis using *in situ* hybridization has also been explored (64).

EMPIRIC ANTIBIOTIC SELECTION

- Empiric antibiotics must cover both gram-positive and gram-negative organisms. The Committee recommends center-specific selection of empiric therapy, dependent on the local history of sensitivities of organisms causing peritonitis (*Opinion*). Gram-positive organisms may be covered by vancomycin or a cephalosporin, and gram-negative organisms by a third-generation cephalosporin or aminoglycoside (*Evidence*) (Figure 1) (65–105).

Intraperitoneal administration of antibiotics is superior to IV dosing for treating peritonitis; intermittent and

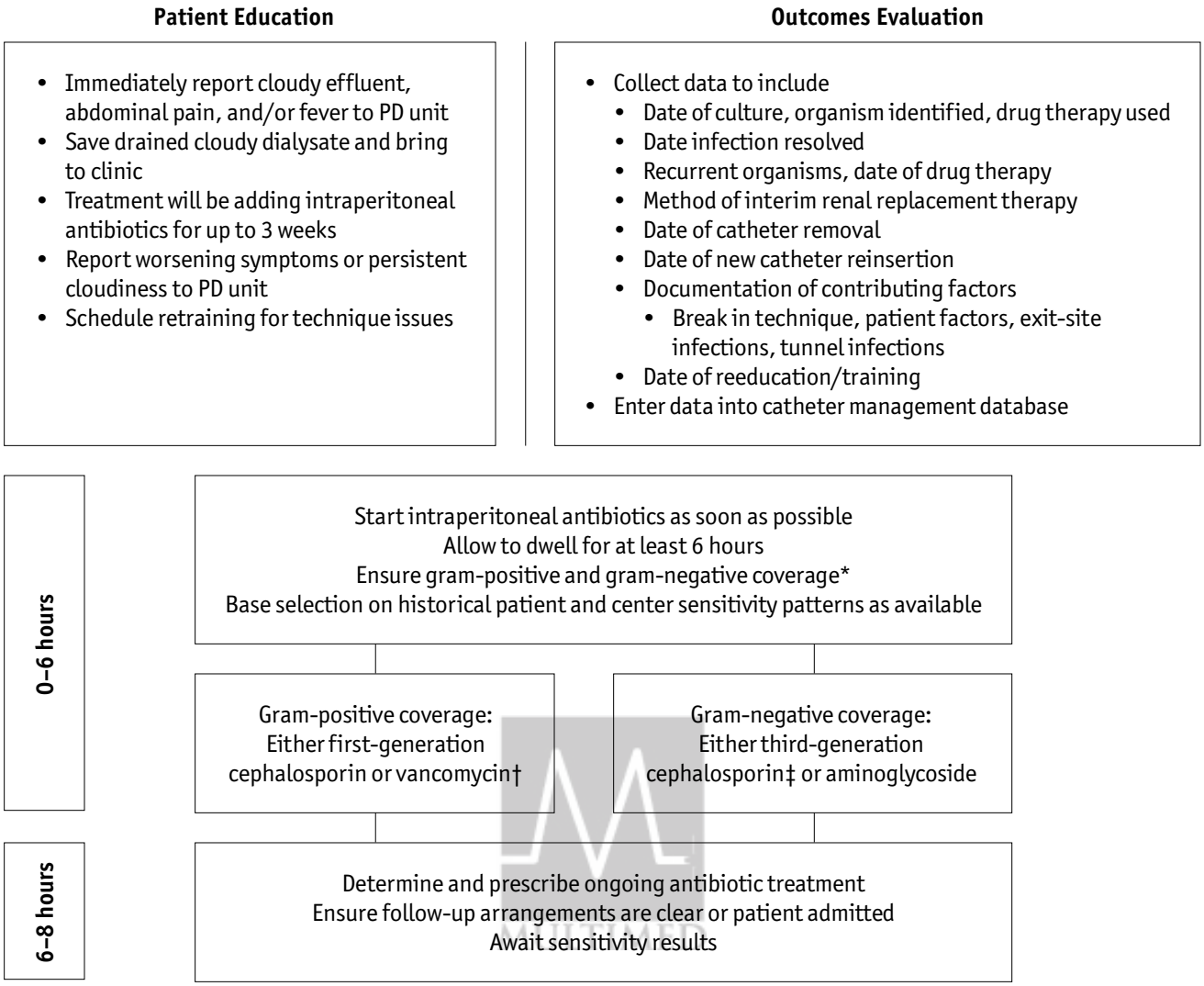

Figure 1 — Initial management of peritonitis: *Continued assessment and modification of therapy based on culture and sensitivity results; refer to subsequent sections for specific organisms cultured. Dwell time of the exchange for intermittent therapy must be a minimum of 6 hours. †Vancomycin may be considered if patient has a history of methicillin-resistant *Staphylococcus aureus* colonization/infection, is seriously unwell, or has a history of severe allergy to penicillins and cephalosporins. If the center has an increased rate of methicillin resistance, vancomycin may also be considered. ‡If the patient is cephalosporin allergic, aztreonam is an alternative to ceftazidime or cefepime. Vancomycin and ceftazidime are compatible when mixed in a dialysis solution volume greater than 1 L; however, they are incompatible when mixed in the same syringe or empty dialysis solution bag for reinfusion. Aminoglycosides should not be added to the same exchange with penicillins as this results in incompatibility.

continuous dosing of antibiotics are equally efficacious (88).

Therapy is initiated prior to knowledge of the causative organism and should be initiated as soon as possible after appropriate microbiological specimens have been obtained. The selection of empiric antibiotics must be made in light of both the patient's and the program's history of micro-organisms and sensitivities. It is important that the protocol cover all serious pathogens that are likely to be present. For many programs, a first-generation cephalosporin, such as cefazolin or cephalothin, with a second drug for broader gram-negative coverage (including coverage for Pseudomonas) will prove suitable. This protocol has been shown to have results equivalent to vancomycin plus a second drug for gram-negative coverage (77,87). Many programs, however, have a high rate of methicillin-resistant organisms and thus should use vancomycin for gram-positive coverage with a second drug for gram-negative coverage (88).

Gram-negative coverage can be provided with an aminoglycoside, ceftazidime, cefepime, or carbapenem. Quinolones should be used for empiric coverage of gram-negative organisms only if local sensitivities support such use. For the cephalosporin-allergic patient, aztreonam

is an alternative to ceftazidime or cefepime for gram-negative coverage if aminoglycosides are not used. Antibiotic resistance may develop with empiric use of extended-spectrum cephalosporins and quinolones. Resistance should be monitored, especially for enterococci, staphylococci, yeasts, and gram-negative organisms such as *Pseudomonas* species, *Escherichia coli*, *Proteus* species, *Providencia* species, *Serratia* species, *Klebsiella* species, and *Enterobacter* species, but catheter removal should not be delayed until the result of antibiotic resistance testing is available.

While an extended course of aminoglycoside therapy may increase the risk for both vestibular and ototoxicity, short-term use appears to be safe and inexpensive and provides good gram-negative coverage. Gentamicin given in once-daily dosing (40 mg IP in 2 L) is as effective as dosing in each exchange (10 mg/2 L, IP, in 4 exchanges/day) for CAPD peritonitis (89,90). There does not appear to be convincing evidence that short courses of aminoglycosides harm residual renal function (65,91). Repeated or prolonged courses (*e.g.*, longer than 2 weeks) of aminoglycoside therapy are probably not advisable if an alternative approach is possible. If an aminoglycoside is used for the initial gram-negative coverage, intermittent dosing is strongly encouraged and prolonged courses of longer than 3 weeks should be avoided.

Either ceftazidime or cefepime is an appropriate alternative for gram-negative coverage. Cefepime is not broken down by many of the beta-lactamases that are currently produced by gram-negative bacilli worldwide so, theoretically, it has better coverage than ceftazidime.

In addition to the above combinations, a variety of regimens have been tested in prospective trials, with acceptable results (92). In a randomized control study of 102 patients, IP cefazolin plus netilmicin and cefazolin plus ceftazidime had similar efficacy as empirical treatment for CAPD peritonitis (93). In CAPD patients with residual renal function, significant but reversible reduction in residual renal function and 24-hour urine volume could occur after an episode of peritonitis, despite successful treatment by antibiotics. However, the effect of both regimens on residual renal function is similar (93).

Other combination therapy may also be effective. A recent study showed that systemic vancomycin and ciprofloxacin administration might also be an effective first-line antibiotic therapy (94). Lima *et al.* (95) reported satisfactory response rates with ciprofloxacin plus cefazolin as the empirical regimen for peritonitis. Meropenem plus tobramycin followed by meropenem plus vancomycin is another regimen recently reported to have reasonable success (96), but this combination is too broad for routine application and should be considered only for highly resistant cases. The increased isolation rate of gram-negative rods (Enterobacteriaceae, *Acinetobacter* species, and *Pseudomonas* species) resistant to carbapenems is of increasing concern (97).

Monotherapy is also possible. In a randomized trial, imipenem/cilastatin (500 mg IP with a dwell of 6 hours, followed by IP 100 mg per 2 L dialysis solution) was as effective in curing peritonitis as was cefazolin plus ceftazidime in CAPD patients (98). Cefepime (2 g IP load with a dwell time of >6 hours, followed by 1 g/day IP for 9 consecutive days) was as effective as vancomycin plus netilmicin in another randomized trial of CAPD-related peritonitis (69).

Quinolones (oral levofloxacin 250 mg daily, or oral pefloxacin 400 mg daily) appear to be an acceptable alternative to aminoglycosides for gram-negative coverage (94,99,100) and do reach adequate levels within the peritoneum, even with cycler PD (101). In another study, oral ofloxacin alone (400 mg, followed by 300 mg daily) was equivalent to cephalothin 250 mg/L for all CAPD exchanges, in combination with tobramycin 8 mg/L (102). However, resolution of *S. aureus* may prove to be slow with the use of ciprofloxacin alone and it is not the ideal drug (103).

In the early days of PD, mild cases of peritonitis such as those caused by *S. epidermidis* were treated effectively with oral cephalosporin therapy (104). If the organism is sensitive to methicillin and first-generation cephalosporin, then this approach is still possible if, for some reason, IP or IV antibiotic therapy is not feasible. Oral therapy is not suitable for more severe cases of peritonitis. No role has been shown for routine peritoneal lavage or use of urokinase (88), although one or two rapid exchanges often help to relieve pain, and continuous peritoneal lavage (for 24 – 48 hours) is often used for patients with septic shock and grossly turbid PD effluent. In a recent randomized control trial of 88 patients, IP urokinase had no significant benefit as an adjunct therapy in the treatment of bacterial peritonitis resistant to initial antibiotic therapy (105).

DRUG DELIVERY AND STABILITY

Vancomycin, aminoglycosides, and cephalosporins can be mixed in the same dialysis solution bag without loss of bioactivity. However, aminoglycosides should not be added to the same exchange with penicillins because of chemical incompatibility (although aminoglycoside and cephalosporin can be added to the same bag). For any antibiotics that are to be admixed, separate syringes must be used for adding the antibiotics. Even though

vancomycin and ceftazidime are compatible when added to dialysis solutions (1 L or higher), they are incompatible if combined in the same syringe or added to an empty dialysate bag for reinfusion into the patient. This approach is not recommended.

Antibiotics should be added using sterile technique: placing povidone iodine, rubbing with alcohol 70% stripe, or chlorhexidine on the medication port for 5 minutes prior to insertion of the needle through the port. Dwell time of the exchange must be a minimum of 6 hours.

Data suggest that some antibiotics are stable for variable times when added to dextrose-containing dialysis solution. Vancomycin (25 mg/L) is stable for 28 days in dialysis solution stored at room temperature, although high ambient temperatures will reduce the duration of stability. Gentamicin (8 mg/L) is stable for 14 days but the duration of stability is reduced by admixture of heparin. Cefazolin (500 mg/L) is stable for at least 8 days at room temperature or for 14 days if refrigerated; addition of heparin has no adverse influence. Ceftazidime is less stable: concentrations of 125 mg/L are stable for 4 days at room temperature or 7 days refrigerated, and concentrations of 200 mg/L are stable for 10 days if refrigerated. Cefepime is stable in dialysis solution for 14 days if the solution is refrigerated (106).

These data are derived from duration of stability studies. It is possible that the agents are stable for longer periods; more research is needed to identify the optimal stability conditions for antibiotics added to dialysis solutions. Icodextrin-containing dialysis solutions are compatible with vancomycin, cefazolin, ampicillin, cloxacillin, ceftazidime, gentamicin, and amphotericin (107). Nonetheless, data on the stability of individual antibiotics in various new PD solutions are limited. Clinicians should remain alert to new studies in this area.

In a recent retrospective study of 613 patients, Blunden *et al.* (108) confirmed that dosing recommendation for vancomycin in CAPD and APD patients produces adequate serum concentrations of the antibiotics in the vast majority (over 85%) of patients. In contrast, the currently recommended dosing regimen of gentamicin resulted in high levels for more than 50% patients, but switching gentamicin to ceftazidime at day 5 appeared safe and limited aminoglycoside exposure. In this study, increasing vancomycin and gentamicin concentrations did not appear to improve cure rates (108). Since standard microbiological tests [*e.g.*, minimum inhibitory concentration (MIC) test] do not account for the unique factors of PD peritonitis, and IP antibiotics act primarily locally, checking of antibiotic levels in peripheral blood should be used for the detection of toxicity rather than a proof of efficacy.

INTERMITTENT OR CONTINUOUS DOSING OF ANTIBIOTICS: SPECIAL CONSIDERATIONS FOR APD PATIENTS

Little is known about intermittent dosing requirements in patients treated with APD. The optimal ratio of antibiotic concentration and MIC value of a bacterium depends on various variables, such as bacterial species, presence of postantibiotic effect, and duration of antibiotic concentration above MIC value. The Committee agrees that IP dosing of antibiotics for peritonitis is preferable to IV dosing in CAPD, since IP dosing results in very high local levels of antibiotics. For example, 20 mg/L IP gentamicin is well above the MIC of sensitive organisms. The equivalent dose of gentamicin given IV would result in much lower IP levels. The IP route has the added advantage that it can be done by the patient at home after appropriate training and it avoids venipuncture. Monitoring of drug levels for aminoglycosides and vancomycin is recommended if toxicity is suspected.

Intraperitoneal antibiotics can be given in each exchange (*i.e.*, continuous dosing) or once daily (*i.e.*, intermittent dosing) (109–114). In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption of the antibiotic into the systemic circulation. Most antibiotics have significantly enhanced absorption during peritonitis (*e.g.*, IP vancomycin is about 50% absorbed in the absence of peritonitis but closer to 90% in the presence of peritonitis), which permits subsequent reentry into the peritoneal cavity during ensuing exchanges of fresh dialysis solution. Table 4 provides doses for both continuous and intermittent administration for CAPD, where there is information available.

There are insufficient data on whether continuous dosing is more efficacious than intermittent for first-generation cephalosporins. A once-daily IP cefazolin dose of 500 mg/L results in acceptable 24-hour levels in the dialysis fluid in CAPD patients (111). An extensive body of evidence exists for the efficacy of intermittent dosing of aminoglycosides and vancomycin in CAPD but less for APD. Table 5 provides dosing recommendations for APD where such data exist or sufficient experience can allow a recommendation to be made. A randomized trial in children that included both CAPD and APD patients found that intermittent dosing of vancomycin/teicoplanin is as efficacious as continuous dosing (65). Intraperitoneal vancomycin is well absorbed when given in a long dwell and subsequently crosses again from the blood into the dialysate with fresh exchanges.

Rapid exchanges in APD, however, may lead to inadequate time to achieve IP levels. There are fewer data concerning efficacy of first-generation cephalosporins

TABLE 4
Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients[a]

	Intermittent (per exchange, once daily)	Continuous (mg/L; all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin, netilmicin, or tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin, cephalothin, or cephradine	15 mg/kg	LD 500, MD 125
Cefepime	1000 mg	LD 500, MD 125
Ceftazidime	1000–1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Amoxicillin	ND	LD 250–500, MD 50
Ampicillin, oxacillin, or nafcillin	ND	MD 125
Azlocillin	ND	LD 500, MD 250
Penicillin G	ND	LD 50000 units, MD 25000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Aztreonam	ND	LD 1000, MD 250
Daptomycin (115)	ND	LD 100, MD 20
Linezolid (41)	Oral 200–300 mg q.d.	
Teicoplanin	15 mg/kg	LD 400, MD 20
Vancomycin	15–30 mg/kg every 5–7 days	LD 1000, MD 25
Antifungals		
Amphotericin	NA	1.5
Fluconazole	200 mg IP every 24–48 hours	
Combinations		
Ampicillin/sulbactam	2 g every 12 hours	LD 1000, MD 100
Imipenem/cilastin	1 g b.i.d.	LD 250, MD 50
Quinupristin/dalfopristin	25 mg/L in alternate bags[b]	
Trimethoprim/sulfamethoxazole	Oral 960 mg b.i.d.	

ND = no data; q.d. = every day; NA = not applicable; IP = intraperitoneal; b.i.d. = 2 times per day; LD = loading dose in mg/L; MD = maintenance dose in mg/L.

[a] For dosing of drugs with renal clearance in patients with residual renal function (defined as >100 mL/day urine output), dose should be empirically increased by 25%.

[b] Given in conjunction with 500 mg intravenous twice daily.

TABLE 5
Intermittent Dosing of Antibiotics in Automated Peritoneal Dialysis

Drug	IP dose
Cefazolin	20 mg/kg IP every day, in long day dwell (112)
Cefepime	1 g IP in 1 exchange per day
Fluconazole	200 mg IP in 1 exchange per day every 24–48 hours
Tobramycin	LD 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP each day in long dwell (112)
Vancomycin	LD 30 mg/kg IP in long dwell; repeat dosing 15 mg/kg IP in long dwell every 3–5 days (aim to keep serum trough levels above 15 µg/mL)

IP = intraperitoneal; LD = loading dose.

given intermittently for peritonitis, particularly for the patient on a cycler. For patients given a daytime exchange of a cephalosporin only, the nighttime IP levels are below the MIC of most organisms. This raises a concern that biofilm-associated organisms may survive and result in subsequent relapsing peritonitis. Until a randomized trial with large numbers is done, adding first-generation cephalosporin to each exchange would appear to be the safest approach.

The Committee agrees that vancomycin can be given intermittently for patients on APD, even though there are few studies. However, a randomized European trial in children showed that intermittent dosing of vancomycin or teicoplanin (and many of the children were on APD) was as effective as continuous dosing. Generally, a dosing interval of 4 – 5 days will keep serum trough levels above 15 μg/mL but, in view of the variability of losses due to residual renal function and peritoneal permeability, it is best to obtain levels. Intraperitoneal levels of vancomycin after the initial dose will always be lower than serum levels of vancomycin; therefore, the serum levels need to be kept higher than would be otherwise indicated (75). Re-dosing is appropriate once serum vancomycin levels go below 15 μg/mL.

Whether or not patients on a cycler need to convert temporarily to CAPD or lengthen the dwell time on the cycler is unclear at present. It is not always practical to switch patients from APD to CAPD, especially if the patient is treated as an outpatient, since the patient may not have supplies for CAPD and may not be familiar with the technique. Resetting the cycler in such cases to permit a longer exchange time is an alternative approach; however, it has not been well studied. Further research is needed in this area.

ADJUNCTIVE TREATMENTS

The majority of fungal peritonitis episodes are preceded by courses of antibiotics (116–118). Fungal prophylaxis during antibiotic therapy may prevent some cases of Candida peritonitis in programs that have high rates of fungal peritonitis (119–124). A number of studies have examined the use of prophylaxis, either oral nystatin or a drug such a fluconazole, given during antibiotic therapy to prevent fungal peritonitis, with mixed results. Programs with high baseline rates of fungal peritonitis found such an approach to be beneficial, while 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/patient-year) but the difference did not reach statistical significance (125). There was, however, a significant decrease in the incidence and proportion of antibiotic-related fungal peritonitis in the nystatin group (125). The Work Group recognizes that nystatin is not available in some countries and that there are few data on the efficacy and potential problem of fluconazole prophylaxis. Each PD program must examine its history of fungal peritonitis and decide whether such a protocol might be beneficial.

Studies of IP urokinase failed to show any benefit of urokinase over placebo with respect to complete cure in persistent peritonitis, or primary response to treatment in the setting of resistant peritonitis (105,126,127). Similarly, catheter removal and relapse rates were not affected by treatment with urokinase, either in the setting of persistent peritonitis or on initiation of fibrinolytic therapy at the time peritonitis was diagnosed. In contrast, one randomized control study showed that simultaneous catheter removal and replacement was superior to urokinase in reducing recurrent episodes of peritonitis (128).

One, small, randomized control trial reported that the use of IP immunoglobulin provides significant improvement in laboratory parameters (especially dialysate leukocyte count), but that there was no effect on the rate of treatment failure or relapse (129).

SUBSEQUENT MANAGEMENT OF PERITONITIS

- Once culture results and sensitivities are known, antibiotic therapy should be adjusted to narrow-spectrum agents as appropriate. For patients with substantial residual renal function (*e.g.*, residual glomerular filtration rate ≥ 5 mL/minute/1.73 m^2), the dose of antibiotics that have renal excretion may need to be adjusted accordingly (*Opinion*).

Few data exist that provide dosing recommendations for patients treated with APD. Extrapolation of data from CAPD to APD may result in significant underdosing of APD patients for two reasons: First, intermittent administration to any exchange other than a prolonged daytime exchange would prevent an adequate proportion of the dose from being absorbed into the systemic circulation, but this problem can be avoided by ensuring a minimum of 6 hours' dwell during the daytime. Second, data exist that suggest APD may result in higher peritoneal clearances of antibiotics than is the case with CAPD (85). This would result in reduced dialysate concentrations, reduced serum concentrations, and the possibility of prolonged intervals during a 24-hour period when dialysate concentrations are less than the MIC for susceptible

organisms. Table 5 lists the most commonly used antibiotics that have been studied in APD and provides dosing recommendations. Patients who are high transporters and those with high dialysate clearances may have a more rapid removal of some antibiotics. Adjustments in dosing for such patients are not yet known but the clinician should choose the side of higher dosing.

Within 48 hours of initiating therapy, most patients with PD-related peritonitis will show considerable clinical improvement. The effluent should be visually inspected daily to determine if clearing is occurring. If there is no improvement after 48 hours, cell counts and repeat cultures should be done. Antibiotic removal techniques may be used by the laboratory on the effluent in an attempt to maximize culture yield.

REFRACTORY PERITONITIS

- Refractory peritonitis, defined as failure of the effluent to clear after 5 days of appropriate antibiotics, should be managed by removal of the catheter to protect the peritoneal membrane for future use (*Evidence*) (3,130–132).

Refractory peritonitis is the term used for peritonitis treated with appropriate antibiotics without resolution after 5 days (see Table 6 for terminology).

A recent retrospective study that had a validation group of patients from another center showed that peritoneal dialysate white cell count ≥1090/mm^3 on day 3 was an independent prognostic marker for treatment failure after adjustment for conventional risk factors (hazard ratio 9.03) (132). Catheter removal is indicated to prevent morbidity and mortality due to refractory peritonitis and to preserve the peritoneum for future PD (Table 7). If the organism is the same as that of the preceding episode, strong consideration should be given to replacing the catheter after PD effluent becomes clear. The primary goal in managing peritonitis should always be the optimal treatment of the patient and protection of the peritoneum, not saving the catheter. Ideally, attempts should be made at the laboratory to identify the causative micro-organism to the exact species level (*e.g.*, *S. epidermidis*, *S. hominis*, or a species other than CoNS). Prolonged attempts to treat refractory peritonitis are associated with extended hospital stay, peritoneal membrane damage, increased risk of fungal peritonitis, and, in some cases, death. Death related to peritonitis — defined as death of a patient with active peritonitis, or admitted with peritonitis, or within 2 weeks of a peritonitis episode — should be a very infrequent event. The risk of death is highest with peritonitis due to gram-negative bacilli and fungus.

TABLE 7
Indications for Catheter Removal for Peritoneal Dialysis-Related Infections

- Refractory peritonitis
- Relapsing peritonitis
- Refractory exit-site and tunnel infection
- Fungal peritonitis
- Catheter removal may also be considered for
  - Repeat peritonitis
  - Mycobacterial peritonitis
  - Multiple enteric organisms

RELAPSING, RECURRENT, AND REPEAT PERITONITIS

- Treatments of relapsing, recurrent, or repeat peritonitis represent distinct clinical entities that portend a worse outcome (particularly for recurrent peritonitis). Stronger consideration should be given to timely catheter removal (*Opinion*) (133).

TABLE 6
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 1 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 1 site sterile

Relapsing episodes should *not* be counted as another peritonitis when calculating peritonitis rates; recurrent and repeat episodes should be counted.

A recent retrospective study showed that relapsing and recurrent peritonitis episodes are caused by different species of bacteria and probably represent two distinct clinical entities (133). Recurrent peritonitis episodes have a worse prognosis than relapsing episodes.

COAGULASE-NEGATIVE STAPHYLOCOCCUS

- Coagulase-negative staphylococcus peritonitis, including *S. epidermidis*, is due primarily to touch contamination, is generally a mild form of peritonitis, and responds readily to antibiotic therapy but can sometimes lead to relapsing peritonitis due to biofilm involvement. In such circumstances, catheter replacement is advised (*Evidence*) (Figure 2) (37,134–136).

Coagulase-negative staphylococcus, especially *S. epidermidis*, is still a very common organism in many programs, usually denotes touch contamination, generally responds well to antibiotic therapy, and is seldom related to a catheter infection. Most patients with *S. epidermidis* peritonitis have mild pain and often can be managed as outpatients. In some programs, and depending on the precise species involved, there is a very high rate of methicillin resistance (>50%); therefore, these programs may wish to use vancomycin as empiric therapy. The PD program should inquire of the laboratory the definition of "resistance" based on MIC levels and, ideally, molecular data (*e.g.*, the presence of the *mecA* gene). Methicillin resistance of staphylococci is defined as the presence of the *mecA* gene and indicates that the organism is considered resistant to all beta-lactam-related antibiotics, including penicillins, cephalosporins, and carbapenems. Every effort should be made to avoid inadequate levels that may lead to relapsing peritonitis. The Committee feels the existing data are inadequate to recommend intermittent dosing of first-generation cephalosporins and, until more data are available, continuous dosing may be preferable. Ideally, repeated cell counts and cultures of the effluent should guide the therapy but 2 weeks of therapy is generally sufficient. The patient's technique should be reviewed to prevent recurrence.

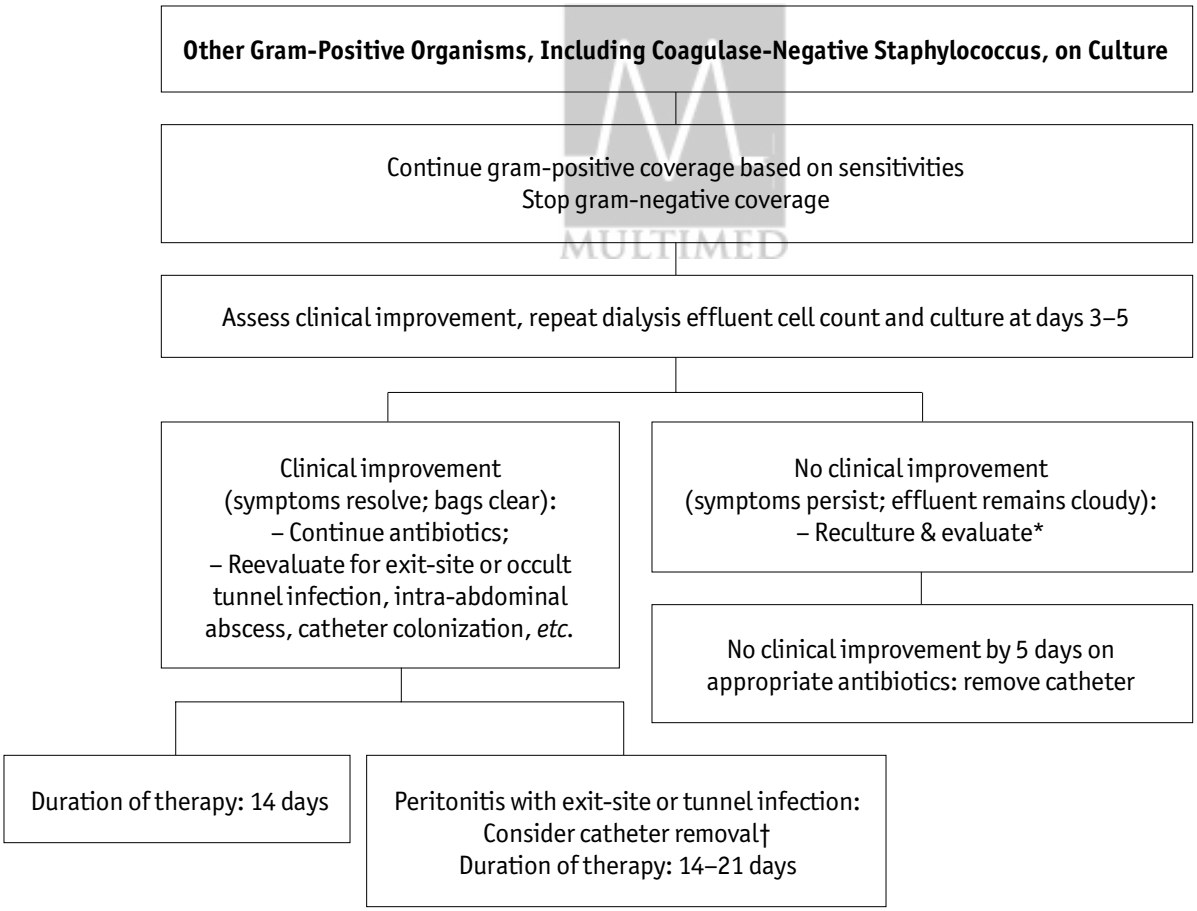

Figure 2 — Coagulase-negative staphylococcus (CoNS; *Staphylococcus epidermidis*): *CoNS can sometimes lead to relapsing peritonitis, presumably due to biofilm involvement. †The duration of antibiotic therapy following catheter removal and timing of resumption of peritoneal dialysis may be modified depending on clinical course.

Coagulase-negative staphylococci consist of at least 20 clinically relevant species that are sometimes difficult to identify by automated systems and therefore require a molecular approach by 16S DNA sequencing. If facilities are available, identification to the exact species level may be useful as some CoNS can cause serious infections (*e.g.*, *S. schleiferi*, *S. lugdunensis*, *S. warneri*) and it may help to differentiate contaminated cultures from true infections. The introduction of matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF) techniques for routine bacterial identification in several European countries enables microbiologists to recognize correctly the spectra of various species of CoNS (137,138). A recently performed comparative study between MALDI-TOF and two rapid identification automates for identification of 234 CoNS isolates, representing 20 different species, revealed significantly better performance of MALDI-TOF (139).

Relapsing *S. epidermidis* peritonitis suggests colonization of the intra-abdominal portion of the catheter with biofilm and is best treated by replacing the catheter (128). This can be done under antibiotic coverage as a single procedure once the effluent clears with antibiotic therapy. Often, hemodialysis can be avoided by using either supine PD or low volumes for a short period of time.

STREPTOCOCCUS AND ENTEROCOCCUS

- In general, streptococcal peritonitis is readily curable by antibiotics but enterococcal peritonitis tends to be severe and is best treated with IP ampicillin when the organism is susceptible (*Opinion*) (Figure 3) (140,141).
- If vancomycin-resistant enterococcus (VRE) is ampicillin susceptible, ampicillin remains the drug of choice; otherwise, linezolid or quinupristin/dalfopristin should be used to treat VRE peritonitis (*Opinion*).

Streptococcal and enterococcal peritonitis generally cause severe pain. Ampicillin 125 mg/L in each exchange is the preferred antibiotic. An aminoglycoside (given once daily IP as 20 mg/L) may be added for synergy for enterococcal peritonitis. Addition of gentamicin is potentially useful only if there is no laboratory evidence of high-level resistance to the antibiotic. Since enterococci are frequently derived from the gastrointestinal tract, intra-abdominal pathology must be considered but touch contamination as a source is also possible. The microbiology laboratory should optimize techniques to recognize the presence of other bacterial species (*e.g.*, anaerobic species) that can lead to more suspicion of an intra-abdominal focus. The patient's technique should be reviewed as well.

Peritonitis with enterococci or streptococci may also derive from infection of the exit site and tunnel, which should be carefully inspected. Some streptococcal species originate from the mouth; assessment of dental hygiene could be considered in these cases. Isolated infections with viridans streptococci have been reported to be associated with slower response, poor outcome, and higher rates of recurrence (142). In contrast, a recent report from the Australian Registry showed that isolated streptococcal peritonitis tends to respond well to antibiotic therapy (141). A report of 116 episodes of enterococcal peritonitis from the ANZDATA Registry observed that this condition was generally more severe and had worse outcomes than other forms of gram-positive peritonitis (143). Moreover, it was reported that other pathogenic organisms were isolated in addition to *Enterococcus* species in approximately half of all cases of enterococcal peritonitis, and that the recovery of other organisms was associated with very high rates of catheter removal (52%), permanent transfer to hemodialysis (52%), and death (6%). Timely 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 transfer to hemodialysis (74% vs 100%).

Increased infection rates are reported for amoxicillin- or ampicillin-resistant *Enterococcus faecium* (ARE) but data on the incidence in PD infections are lacking (144). VRE has been reported and is seen most often in conjunction with recent hospitalization and prior antibiotic therapy. Vancomycin-resistant *E. faecium* has been reported but remains uncommon in PD patients. Limited data are available regarding the appropriate management of VRE peritonitis (145–148). If VRE is ampicillin susceptible, ampicillin remains the drug of choice. Linezolid or quinupristin/dalfopristin should be used to treat VRE peritonitis. Another recent report on two cases of VRE peritonitis suggests that IP daptomycin may also be effective (115) but the dosing and pharmacokinetics need further studies. Quinupristin/dalfopristin, however, may not be active against *E. faecalis* isolates. Bone marrow suppression usually occurs after 10 – 14 days of linezolid therapy and more prolonged therapy can also result in neurotoxicity. It is unclear if the catheter must be removed for VRE peritonitis but, if the peritonitis does not resolve readily, this certainly should be done.

STAPHYLOCOCCUS AUREUS

- *Staphylococcus aureus* causes severe peritonitis. Although it may be due to touch contamination, it is

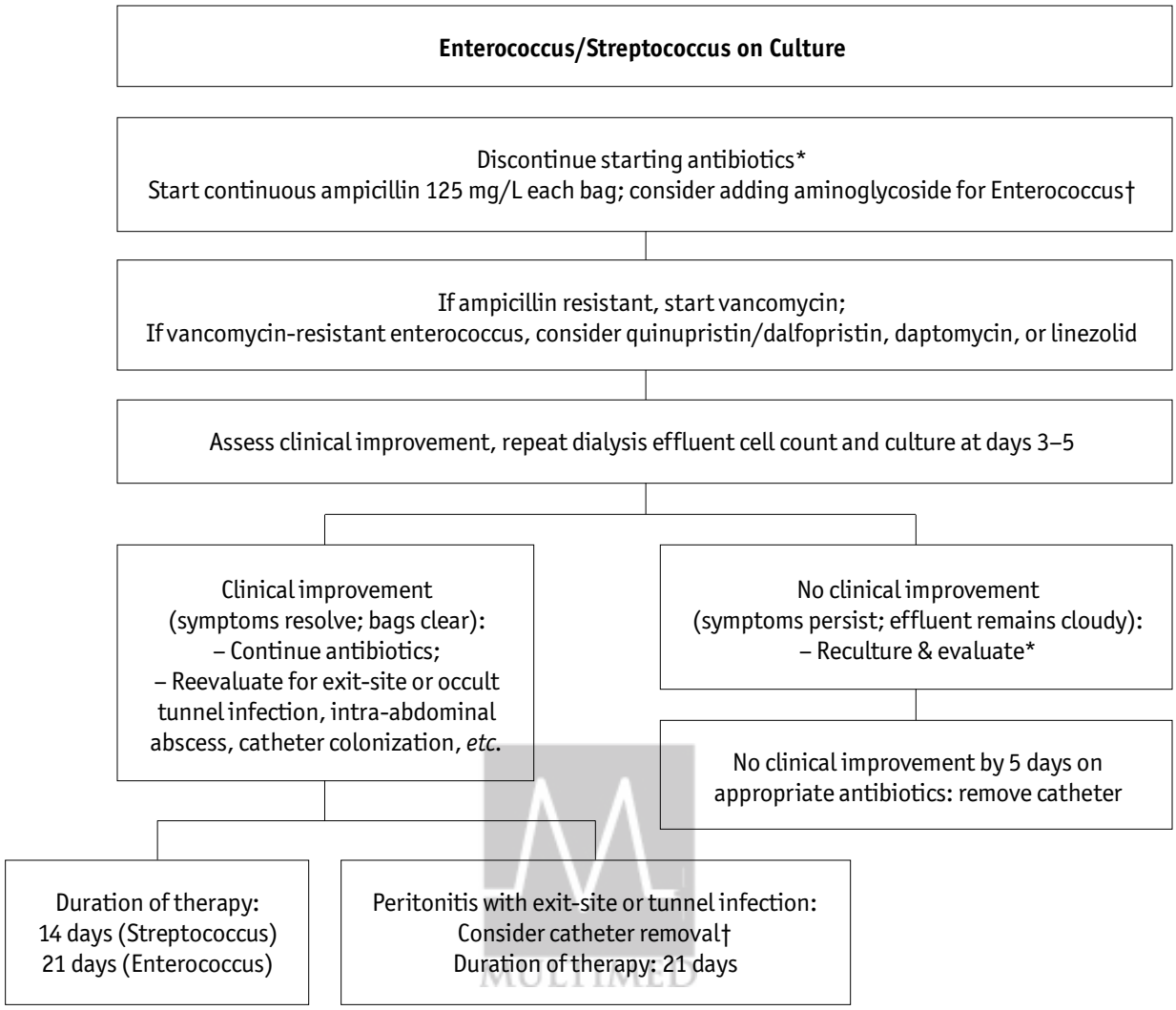

Figure 3 — Enterococcus or Streptococcus peritonitis: *Choice of therapy should always be guided by sensitivity patterns. If linezolid is used for vancomycin-resistant enterococcus, bone marrow suppression has been noted after 10 – 14 days. †The manufacturer's precaution label states that these antibiotics should not be mixed together in the same solution container. Physicians' own judgment is necessary. ‡The duration of antibiotic therapy following catheter removal and timing of resumption of peritoneal dialysis may be modified, depending on clinical course.

often due to catheter infection. Staphylococcal peritonitis with concurrent exit-site or tunnel infection is unlikely to respond to antibiotic therapy without catheter removal (*Evidence*) (Figure 4) (5,23,149).

- Rifampicin could be considered as an adjunct for the prevention of relapse or repeat *S. aureus* peritonitis but the enzyme-inducer effect of rifampicin should be considered in patients taking other medications (*Opinion*) (150).

If the organism is *S. aureus*, very careful attention must be paid to the exit site and tunnel of the catheter, as the mode of entrance of this organism is often via the catheter, although touch contamination is another source. If the episode occurs in conjunction with an exit-site infection with the same organism, then often the infection will prove to be refractory and the catheter must be removed. After a rest period off PD (generally a minimum of 2 weeks), PD can be tried again.

If the strain of *S. aureus* cultured is methicillin resistant then the patient must be treated with vancomycin. Such infections are more difficult to resolve. Compared with methicillin-sensitive *S. aureus* peritonitis, MRSA peritonitis has been reported to be independently predictive of an increased risk of permanent transfer to hemodialysis (odds ratio 2.11) (151). Rifampicin 600 mg/day orally (in single or split dose) can be added to the IP antibiotics but therapy with this adjunctive antibiotic should be limited to 1 week, as resistance often develops with longer courses. If the patient is considered at

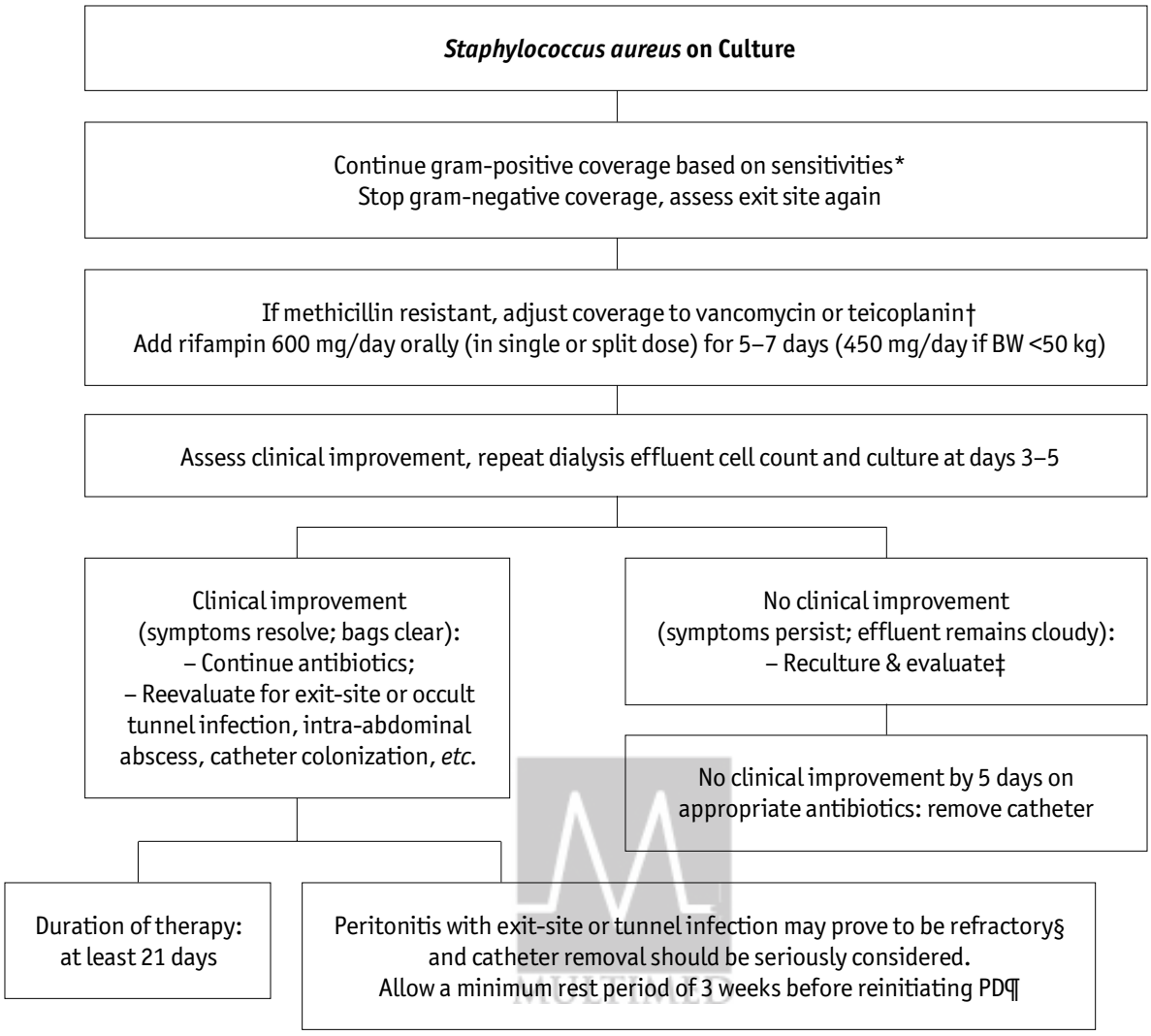

Figure 4 — *Staphylococcus aureus* peritonitis: *If vancomycin-resistant *S. aureus*, linezolid, daptomycin, or quinupristin/dalfopristin should be used. †Teicoplanin can be used in a dose of 15 mg/kg every 5 – 7 days. ‡In areas where tuberculosis is endemic, rifampicin use for treatment of *S. aureus* should be restricted. §"Refractory" is defined as failure to respond to appropriate antibiotics within 5 days. ¶The duration of antibiotic therapy following catheter removal and timing of resumption of peritoneal dialysis may be modified depending on clinical course. BW = body weight; PD = peritoneal dialysis.

high risk to have asymptomatic tuberculosis, rifampicin should be used with caution in order to preserve this drug for treatment of tuberculosis.

Vancomycin may be administered as 15 – 30 mg/kg body weight IP, with a maximum dose of 2 g. A typical protocol for a patient 50 – 60 kg is vancomycin 1 g IP every 5 days. Ideally, the timing of repetitive dosing should be based on trough levels and is likely to be every 3 – 5 days. The dosing interval is dependent on residual renal function and patients should receive another dose once trough serum levels reach 15 mg/mL. Teicoplanin, where available, can be used in a dose of 15 mg/kg body weight every 5 –7 days. Data for children suggest that this approach is successful for both CAPD and APD. Treatment should be for 3 weeks (115,148).

In a recent review of 245 cases of *S. aureus* peritonitis, episodes that were treated initially with vancomycin had a better primary response rate than those that were treated with cefazolin (98.0% vs 85.2%, $p = 0.001$) but the complete cure rate was similar (150). Adjuvant rifampicin treatment for a period of 5 – 7 days was associated with a significantly lower risk for relapse or repeat *S. aureus* peritonitis than was treatment without rifampicin (21.4% vs 42.8%). In this study, recent hospitalization was a major risk factor for methicillin resistance. However, it should be noted that rifampicin is a potent inducer of drug-metabolizing enzymes and would reduce the levels of many medications. Similarly, an evaluation of 503 cases of staphylococcal peritonitis in Australia found that the initial empiric antibiotic choice

between vancomycin and cephazolin was not associated with any significant differences in subsequent clinical outcomes (151).

Unfortunately, prolonged therapy with vancomycin may predispose dialysis patients to infections with vancomycin-resistant *S. aureus* and should be avoided whenever possible. If vancomycin-resistant *S. aureus* peritonitis develops, linezolid, daptomycin, or quinupristin/dalfopristin could be considered.

CORYNEBACTERIUM PERITONITIS

- Corynebacterium is an uncommon but significant cause of peritonitis and exit-site infection. Complete cure with antibiotics alone is possible in many patients (*Opinion*) (152,153).

Like CoNS, *Corynebacterium* species belong to the natural flora of the skin and are therefore difficult to recognize as pathogens. Previously, Corynebacterium was thought to have little pathogenic potential in man. However, reporting of infections due to Corynebacterium has increased over the past few decades, in large part due to improved recognition of the clinical relevance of *Corynebacterium* species. In a retrospective study, recurrent Corynebacterium peritonitis was common after a 2-week course of antibiotics, but recurrent episodes can usually be cured with a 3-week course of IP vancomycin (152). Another large, retrospective, observational cohort study of 82 episodes of Corynebacterium peritonitis by the ANZDATA Registry (153) demonstrated that Corynebacterium peritonitis not infrequently resulted in relapse (18%), repeat peritonitis (15%), hospitalization (70%), catheter removal (21%), permanent transfer to hemodialysis (15%), and death (2%). The overall cure rate with antibiotics alone for a median period of 2 weeks was 67%. In individuals requiring catheter removal for refractory peritonitis, those who had their catheters removed more than 1 week after the onset of Corynebacterium peritonitis had a significantly higher risk of permanent transfer to hemodialysis than those who had their catheters removed within 1 week (90% vs 43%). Ideally, coryneform bacteria should be identified to the species level. As for CoNS, further attempts should be made to analyze the exact role of the gingival species because the group Corynebacterium actually encompasses at least 46 different species.

CULTURE-NEGATIVE PERITONITIS

- If a program has a rate of culture-negative peritonitis greater than 20%, then the culture methods should be reviewed and improved (*Opinion*) (Figure 5) (154,155).

Cultures may be negative for a variety of technical or clinical reasons. The patient should always be queried on presentation about use of antibiotics for any reason, as this is a known cause of culture-negative peritonitis (155). If there is no growth by 3 days, repeat cell count with differential should be obtained. If the repeat cell count indicates that the infection has not resolved, special culture techniques should be used for the isolation of potential unusual causes of peritonitis, including lipid-dependent yeast, mycobacteria, Legionella, slow growing bacteria, Campylobacter, fungi, Ureaplasma, Mycoplasma, and enteroviruses. This will require coordination with the microbiology laboratory.

In clinical practice, a large proportion of culture-negative peritonitis episodes are caused by gram-positive organisms (*e.g.*, due to touch contamination), while the causative organism is not identified for technical reasons. If the patient is improving clinically, the initial therapy can be continued. Duration of therapy should be 2 weeks if the effluent clears rapidly. If, on the other hand, improvement is inadequate by 5 days, catheter removal should be strongly considered. A recent review of 435 episodes of culture-negative peritonitis found that this condition was significantly more likely to be cured by antibiotics alone (77% vs 66%) and less likely to be complicated by hospitalization (60% vs 71%), catheter removal (12% vs 23%), permanent transfer to hemodialysis (10% vs 19%), or death (1% vs 2.5%) compared with culture-positive peritonitis (155).

PSEUDOMONAS AERUGINOSA PERITONITIS

- *Pseudomonas aeruginosa* peritonitis, similar to *S. aureus* peritonitis, is often related to a catheter infection and in such cases catheter removal will be required. Two antibiotics should always be used to treat *P. aeruginosa* peritonitis (*Evidence*) (Figure 6) (25,156,157).

Pseudomonas aeruginosa peritonitis is generally severe and often associated with infection of the catheter. If catheter infection is present or has preceded peritonitis, catheter removal is necessary. Antibiotics must be continued for 2 weeks while the patient is on hemodialysis. A large retrospective study of 191 episodes of Pseudomonas peritonitis recently confirmed that Pseudomonas peritonitis is associated with greater frequencies of hospitalization, high rates of catheter removal, and permanent transfer to hemodialysis but not with increased death rates. Prompt catheter removal and

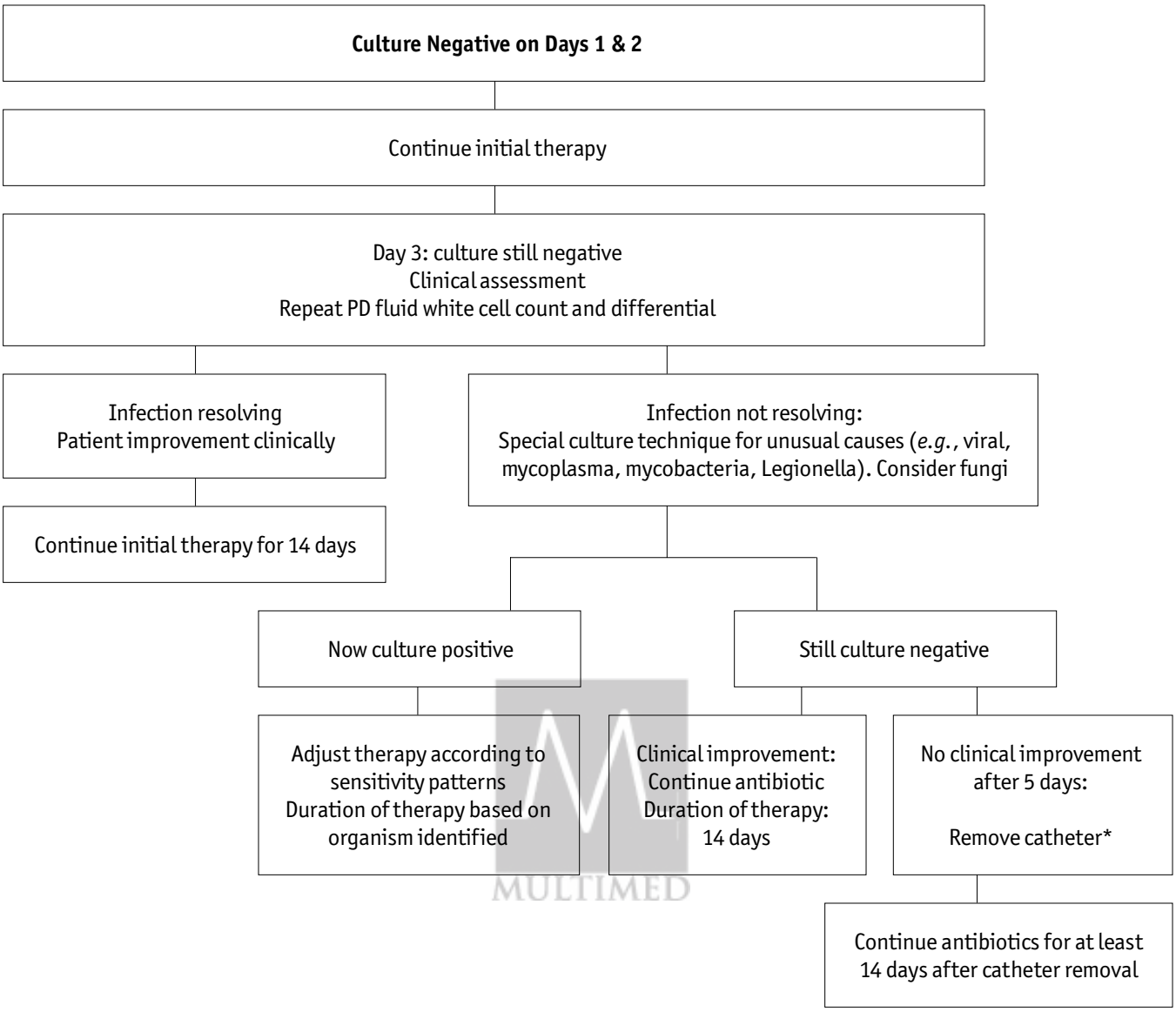

Figure 5 — Culture-negative peritonitis: *The duration of antibiotic therapy following catheter removal and timing or resumption of peritoneal dialysis (PD) may be modified depending on clinical course.

use of two antipseudomonal antibiotics are associated with better outcomes (157).

Occasionally, *P. aeruginosa* peritonitis occurs in the absence of a catheter infection. An oral quinolone can be given as one of the antibiotics for *P. aeruginosa* peritonitis. Alternative drugs include ceftazidime, cefepime, tobramycin, or piperacillin. Should piperacillin be preferred, its dose is 4 g IV every 12 hours in adults. Piperacillin cannot be added to the dialysis solution in conjunction with aminoglycosides.

Every effort to avoid *P. aeruginosa* peritonitis should be made by replacing the catheter for recurrent, relapsing, or refractory exit-site infections with *P. aeruginosa* prior to the development of peritonitis. In such cases, the catheter can be replaced as a single procedure; whereas, if peritonitis develops, the catheter must be removed and the patient taken off PD for a period of time. In many such cases, permanent peritoneal membrane damage may have occurred.

OTHER SINGLE GRAM-NEGATIVE MICRO-ORGANISMS CULTURED

- Single-organism gram-negative peritonitis may be due to touch contamination, exit-site infection, or transmural migration from constipation, diverticulitis, or colitis (*Evidence*) (Figure 7) (6,158–165).

If a single gram-negative organism, such as *E. coli*, Klebsiella, or Proteus, is isolated, the antibiotic to be

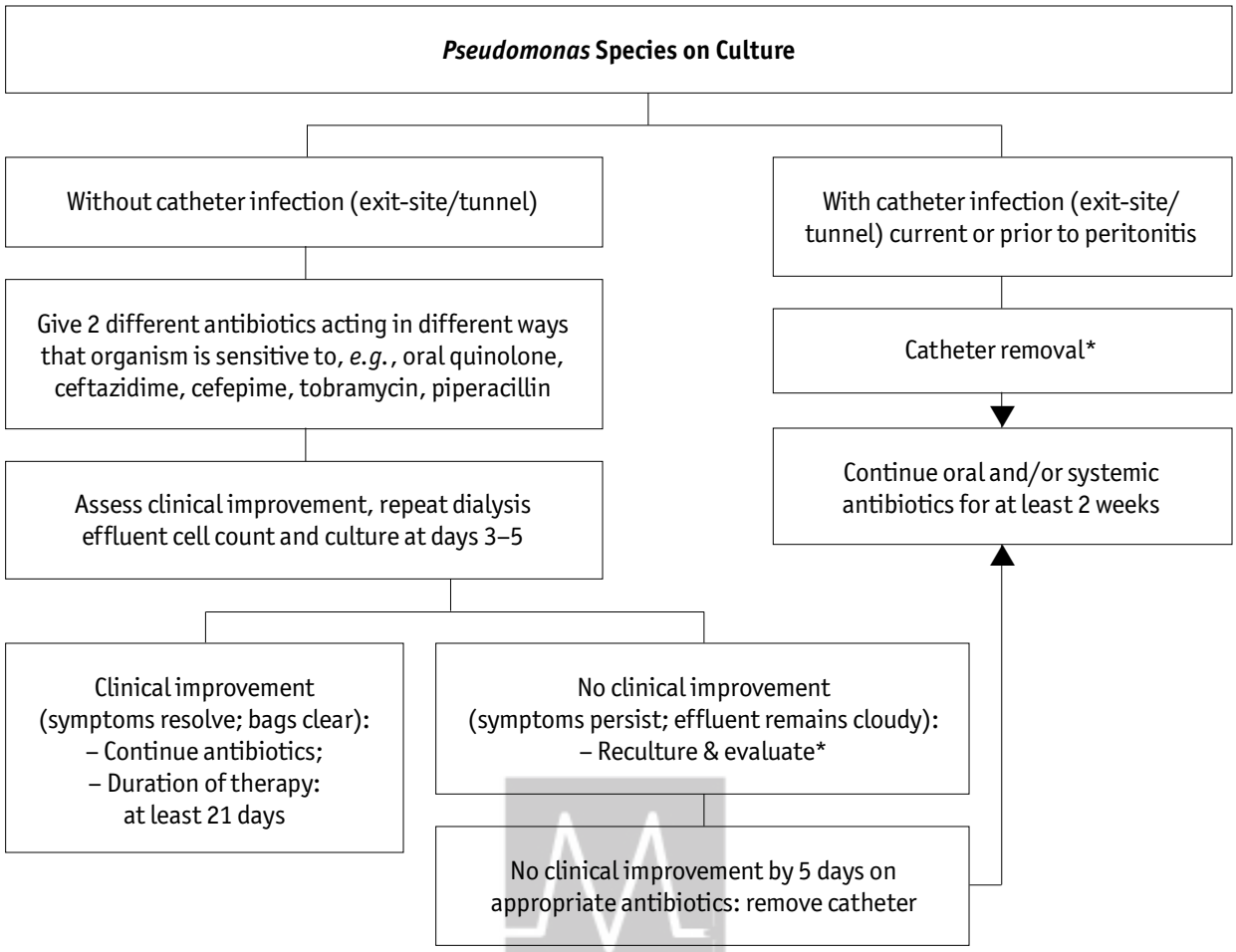

Figure 6 — Pseudomonas peritonitis. *The duration of antibiotic therapy following catheter removal and timing or resumption of peritoneal dialysis may be modified depending on clinical course.

used can be chosen based on sensitivities, safety, and convenience. A fluoroquinolone or cephalosporin may be indicated based on *in vitro* sensitivity testing. Unfortunately, organisms in the biofilm state may be considerably less sensitive than the laboratory indicates (160), which may account for the high proportion of treatment failures even when the organism appears to be sensitive to the antibiotic used (161). A recent retrospective study of 210 cases suggested that recent antibiotic therapy is the major risk factor for antibiotic resistance; exit-site infection, and probably recent antibiotic therapy, is associated with poor therapeutic response (163). The SPICE organisms (Serratia, Pseudomonas, and indol-positive organisms such as Providencia, Citrobacter, and Enterobacter) seem to have a particularly high risk of relapse. One retrospective study suggests that two antibiotics may reduce the risk of relapse and recurrence compared to single-agent therapy (163). Outcomes of these infections are worse than gram-positive outcomes and are more often associated with catheter loss and death. Single-organism gram-negative peritonitis may be due to touch contamination, exit-site infection, or possibly a bowel source, such as constipation, colitis, or transmural migration. Often the etiology is unclear. Response of gram-negative peritonitis in pediatric PD patients treated with empiric IP ceftazidime is often suboptimal (164).

The isolation of a Stenotrophomonas organism, while infrequent, requires special attention since it displays sensitivity to only a few antimicrobial agents (158,165). Prior therapy with carbapenems, fluoroquinolones, and third- or fourth-generation cephalosporins usually precedes Stenotrophomonas infections. Infection with this organism is generally not as severe as with Pseudomonas and is usually not associated with an exit-site infection. Therapy for Stenotrophomonas peritonitis is recommended for 3 – 4 weeks if the patient is clinically improving. Treatment with two drugs (chosen based on the sensitivities) is recommended: the most effective agents are usually oral trimethoprim/sulfamethoxazole, IP ticarcillin/clavulanate, and oral minocycline.

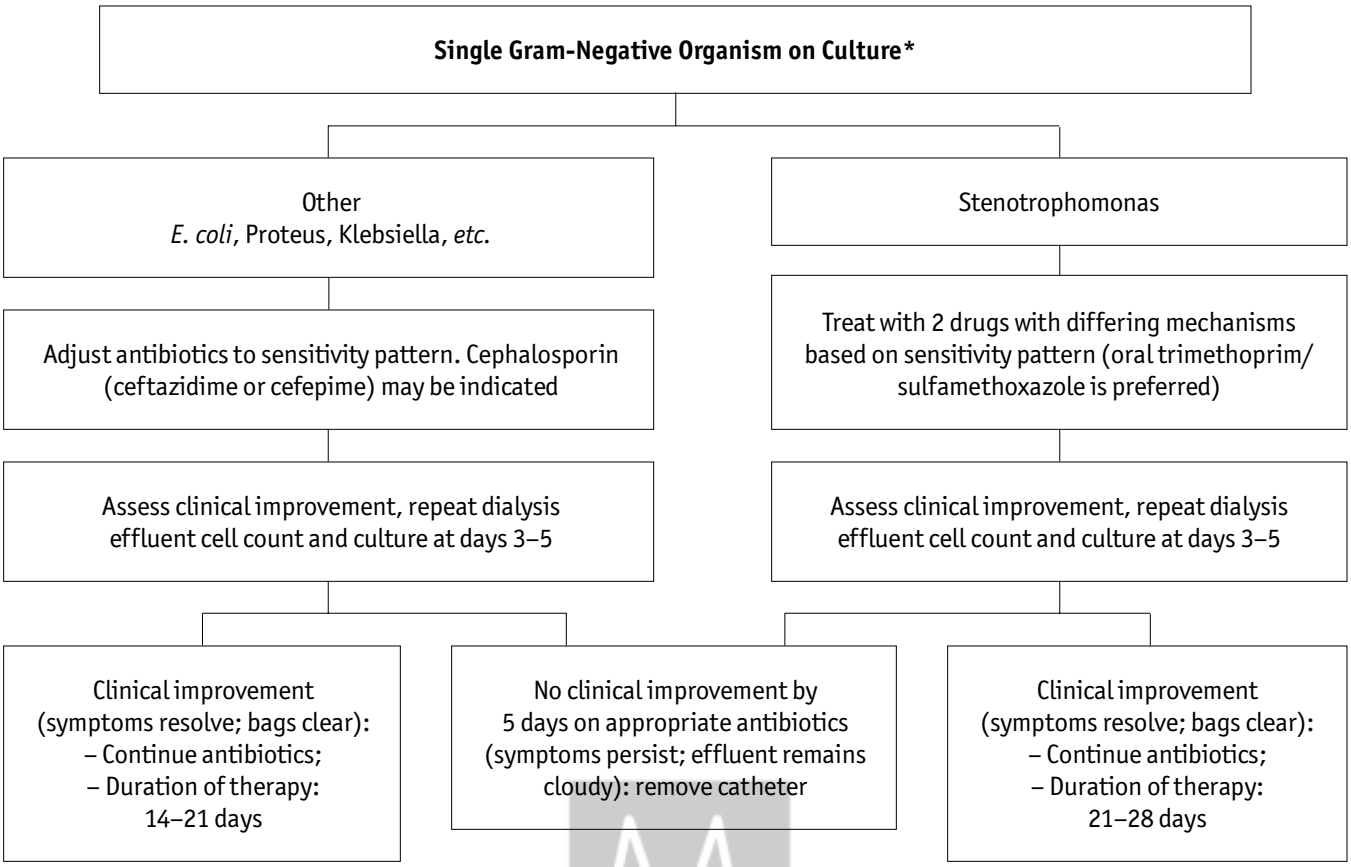

Figure 7 — Other single gram-negative organism peritonitis: *Choice of therapy should always be guided by sensitivity patterns.

POLYMICROBIAL PERITONITIS

- If multiple enteric organisms are grown, particularly in association with anaerobic bacteria, the risk of death is increased and a surgical evaluation should be obtained (*Evidence*) (Figure 8) (166–169).
- Peritonitis due to multiple gram-positive organisms will generally respond to antibiotic therapy (*Evidence*) (4,170–173).

In cases of multiple enteric organisms, there is a possibility of intra-abdominal pathology such as diverticulitis, cholecystitis, ischemic bowel, appendicitis, *etc*. Presentation with hypotension, sepsis, lactic acidosis, and/or elevation of peritoneal fluid amylase level should raise immediate concern for "surgical" peritonitis (174). A rapid Gram staining of the effluent may lead to the recognition of a mixed bacterial population suggestive for an intestinal origin. In this setting where the intestines are felt to be the source, the therapy of choice is metronidazole in combination with ampicillin and ceftazidime or an aminoglycoside in the recommended doses. The catheter may need to be removed, particularly if laparotomy indicates intra-abdominal pathology and, in that case, antibiotics should be continued via the IV route. Antibiotics can be tried, however, and in some cases the catheter may not need to be removed. Computed tomographic (CT) scan may help identify intra-abdominal pathology but a normal CT scan does not eliminate the possibility of intra-abdominal pathology as a source.

Polymicrobial peritonitis due to multiple gram-positive organisms — more common than that due to enteric organisms — has a much better prognosis (175). The source is most likely contamination or catheter infection; the patient's technique should be reviewed and the exit site carefully examined. Polymicrobial peritonitis due to contamination generally resolves with antibiotics without catheter removal, unless the catheter is the source of the infection.

FUNGAL PERITONITIS

- Fungal peritonitis is a serious complication and should be strongly suspected after recent antibiotic treatment for bacterial peritonitis. Catheter removal is indicated immediately after fungi are identified by microscopy or culture (*Evidence*) (116–118,176).

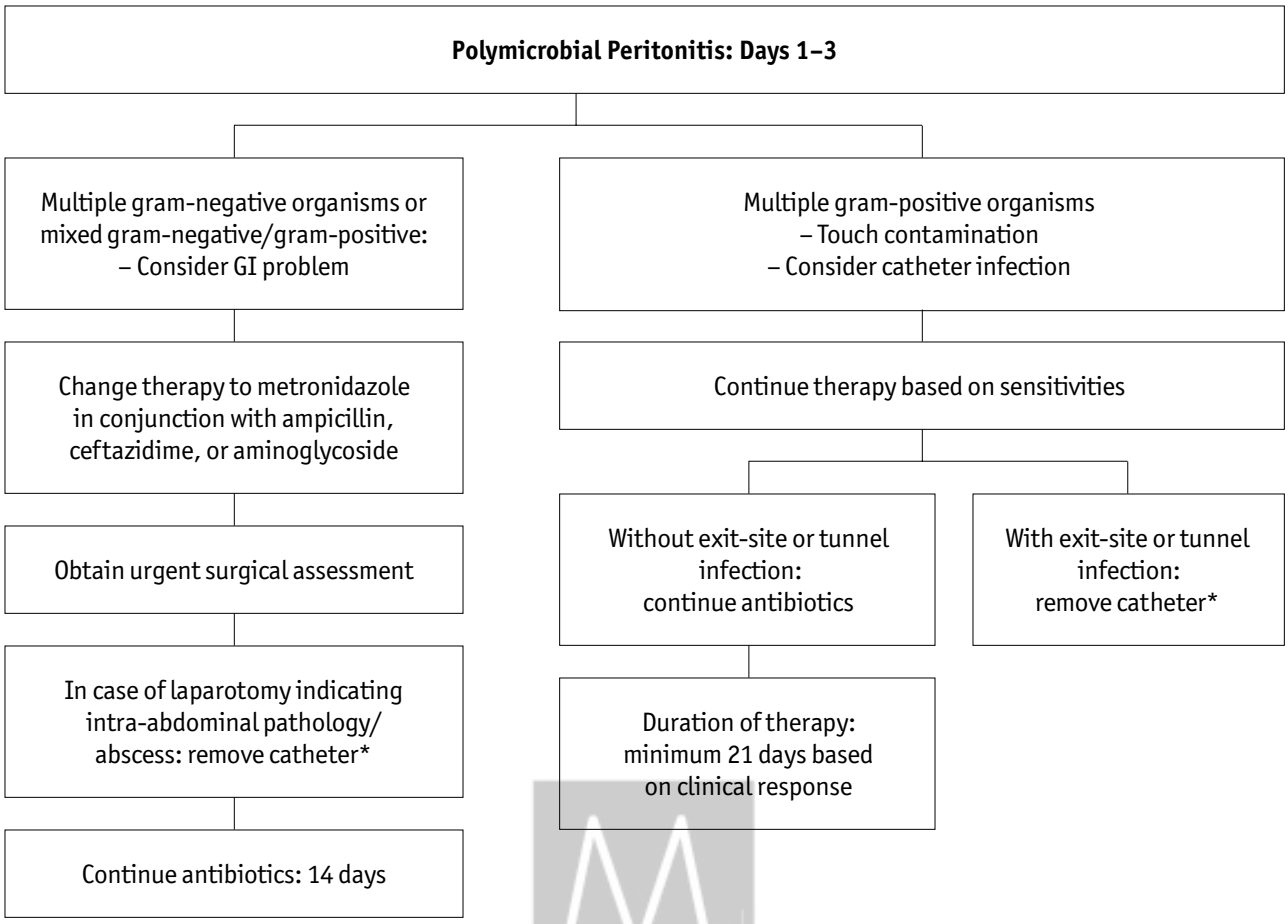

Figure 8 — Polymicrobial peritonitis: *The duration of antibiotic therapy following catheter removal and timing or resumption of peritoneal dialysis may be modified depending on clinical course. GI = gastrointestinal.

Prolonged treatment with antifungal agents to determine response and to attempt clearance is not encouraged. Fungal peritonitis is serious, leading to death of the patient in approximately 25% or more of episodes (116,117). Some evidence suggests that prompt catheter removal poses a lesser risk of death. A recent Australian report analyzed 162 episodes of fungal peritonitis retrospectively (176): *Candida albicans* and other *Candida* species were the most frequently isolated fungi. Compared with other micro-organisms, fungal peritonitis was associated with higher rates of hospitalization, catheter removal, transfer to hemodialysis, and death (176). Initial therapy may be a combination of amphotericin B and flucytosine, until the culture results are available with susceptibilities. An echinocandin (*e.g.*, caspofungin or anidulafungin), fluconazole, posaconazole, or voriconazole may replace amphotericin B based on species identification and MIC values. Intraperitoneal use of amphotericin causes chemical peritonitis and pain; IV use leads to poor peritoneal bioavailability. Voriconazole or posaconazole are alternatives for amphotericin B when filamentous fungi have been cultured. Neither of them can be used alone for Candida peritonitis (with catheter removal). Voriconazole at a dose of 200 mg IV twice daily for 5 weeks after catheter removal has been used successfully (177). Posaconazole at 400 mg twice daily for 6 months has been used successfully for the treatment of liposomal amphotericin B-resistant PD-related Mucor peritonitis (178). Echinocandins (*e.g.*, caspofungin, micafungin, and anidulafungin) have been advocated for the treatment of fungal peritonitis attributable to Aspergillus and non-responding non-*albicans Candida*, and in patients intolerant to other antifungal therapies (179). Caspofungin has been used successfully as monotherapy (70 mg IV loading dose, then 50 mg daily) (180) or in combination with amphotericin (181).

If flucytosine is used, regular monitoring of serum concentrations is necessary to avoid bone marrow toxicity. Generally, trough serum flucytosine concentrations should be 25 – 50 µg/mL and transiently not greater than 100 µg/mL (41). Emergence of resistance to the azoles has occurred, thus indicating the importance of sensitivities where available. Therapy with these agents should be continued orally with flucytosine 1000 mg and

fluconazole 100 – 200 mg daily for an additional 10 days after catheter removal. The withdrawal of oral flucytosine from many countries and the price of many new antifungal agents will affect local protocols.

PERITONITIS DUE TO MYCOBACTERIA

- Mycobacteria are an infrequent cause of peritonitis and can be difficult to diagnose. When under clinical consideration, special attention must be paid to culture techniques. Treatment requires multiple drugs (*Evidence*) (23,182–192).

Mycobacterial peritonitis can be caused by *Mycobacterium tuberculosis* or non-tuberculosis mycobacteria, such as *M. fortuitum*, *M. avium*, *M. abscessus*, and *M. chelonae*. The incidence of tuberculous peritonitis is higher in Asia than elsewhere. 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. While the classic symptoms of fever, abdominal pain, and cloudy effluent may occur with mycobacterial peritonitis, the diagnosis should be considered in any patient with prolonged failure to thrive, prolonged symptoms despite antibiotic therapy, and relapsing peritonitis with negative bacterial cultures.

The cell count cannot be used to differentiate mycobacterial peritonitis from other forms although chronic tuberculous peritonitis is frequently associated with lymphocytosis. Most cases of acute mycobacterial peritonitis have a predominance of polymorphonuclear WBC, similar to bacterial peritonitis. Smears of the peritoneal effluent should be examined with Ziehl–Neelsen stain but "smear negative" disease is common. The sensitivity of the smear examination by the Ziehl–Neelsen technique can be enhanced by centrifuging 100 – 150 mL of the dialysate sample, digestion with a mixture of 2% N-acetyl-L-cysteine (NALC)–2% NaOH, and smear preparation from the pellet. Alternatively, mycobacterial DNA PCR can be performed on peritoneal dialysate for improved sensitivity, although false positives are not uncommon (191). A specific diagnosis can be made by culturing the sediment, after centrifugation of a large volume of effluent (50 – 100 mL), using a combination of solid medium (such as Löwenstein–Jensen agar) with fluid media (Septi-Chek, BACTEC, *etc.*). The time of detection for growth of mycobacteria is decreased considerably in fluid medium. The recovery rate of nontuberculous mycobacteria may increase when lower incubation temperatures are applied and growth-promoting supplements are used for specific mycobacteria (*e.g.*, *M. haemophilum*). Repeat microscopic smear examination and culture of dialysis effluent is mandatory for better yield in suspected cases of mycobacterial peritonitis. Exploratory laparotomy or laparoscopy with biopsy of the peritoneum or omentum should be considered in patients in whom the diagnosis is being considered. When a Ziehl–Neelsen technique reveals the presence of acid-fast rods, and if facilities are available, a molecular test (*e.g.*, PCR) should be applied directly on the pellet to diagnose *M. tuberculosis* infection.

The treatment protocol for *M. tuberculosis* peritonitis should be based on general protocols for treatment of tuberculosis. The patient should be investigated for pulmonary disease and other extrapulmonary locations. Since streptomycin, even in reduced doses, may cause ototoxicity after prolonged use, it should generally be avoided. Similarly, ethambutol is not recommended because of the high risk of optic neuritis in end-stage renal disease. Treatment is started with four drugs: rifampicin, isoniazid, pyrazinamide, and ofloxacin. However, a recent study showed that rifampicin dialysis fluid levels are low due to its high molecular weight, high protein-binding capacity, and lipid solubility. Therefore, for treatment of tuberculous peritonitis, rifampicin may need to be given via the IP route. Treatment with pyrazinamide and ofloxacin is stopped after 3 months; rifampicin and isoniazid are continued for a total of 12 – 18 months. Pyridoxine (50 – 100 mg/day) should be given to avoid isoniazid-induced neurotoxicity. The optimal duration of treatment for multidrug-resistant tuberculous peritonitis remains unknown. The treatment protocol for nontuberculous mycobacterial peritonitis is not well established and requires individualized protocols based on susceptibility testing.

Removal of the catheter is still a contentious issue. While many people would remove the PD catheter in a patient with tuberculous peritonitis and consider reinsertion after 6 weeks of antituberculous treatment, there are some case series of successful treatment without catheter removal. Long-term continuation of CAPD is possible, especially if the diagnosis is made early and appropriate therapy promptly initiated.

Data on peritonitis caused by nontuberculous mycobacteria remain limited. Most nontuberculous mycobacteria have growth characteristics similar to normal "skin" bacteria and are only recognized by acid-fast staining. Although the case remains controversial, it has been postulated that extensive use of topical gentamicin ointment for exit-site infection might predispose patients to atypical mycobacterial infection of the exit site (192).

LENGTH OF THERAPY FOR PERITONITIS

- The Committee feels that the minimum therapy for peritonitis is 2 weeks; although 3 weeks is recommended for more severe infections (*Opinion*).

In clinical practice, the length of treatment is determined mainly by the clinical response. After initiation of antibiotic treatment, clinical improvement should be present during the first 72 hours. Patients having cloudy effluent on appropriate antibiotics after 5 days have refractory peritonitis and should have their catheter removed.

In patients with CoNS peritonitis and in patients with culture-negative peritonitis, antibiotic treatment should be continued for at least 7 days after the effluent clears, and for no less than 14 days total. This means that 14 days is usually adequate for treatment of peritonitis in uncomplicated episodes due to CoNS. In patients who respond slowly to the initial antibiotic therapy (especially episodes caused by *S. aureus*, gram-negative peritonitis, or enterococcal peritonitis), a 3-week treatment is recommended (whether the catheter is removed or not).

CATHETER REMOVAL AND REINSERTION FOR PERITONEAL INFECTION

- The Committee recommends removing the catheter for relapsing peritonitis, refractory peritonitis, fungal peritonitis, and refractory catheter infections. The focus should always be on preservation of the peritoneum rather than on saving the peritoneal catheter (*Opinion*) (3,34–37,134,193–195).

It is the impression of the Committee that catheter removal is not done often enough in managing peritoneal infections. Indications for catheter removal for infections are shown in Table 7. Timely replacement of the catheter for refractory exit-site infections can prevent peritonitis, a far better approach than waiting until the patient has the more serious infection. This approach has the added advantage of permitting simultaneous replacement, thus avoiding prolonged periods on hemodialysis. Some patients, especially those using a cycler, can avoid hemodialysis altogether by dialyzing only in the supine position for several days to avoid leaks and hernias, with subsequent addition of the daytime exchange.

Catheter replacement as a single procedure can also be done for relapsing peritonitis if the effluent can first be cleared. This procedure should be done under antibiotic coverage.

For refractory peritonitis and fungal peritonitis, simultaneous catheter replacement is not possible. The optimal time period between catheter removal for infection and reinsertion of a new catheter is not known. Empirically, a minimum period of 2 – 3 weeks between catheter removal and reinsertion of a new catheter is recommended, although some would recommend later reinsertion in cases of fungal peritonitis.

After severe episodes of peritonitis, some patients are able to return to PD. In other patients, adhesions may prevent reinsertion of the catheter, or continuation on PD is not possible due to permanent membrane failure. In a recent review of 189 peritonitis episodes, Troidle *et al.* (195) found that only 47% of the patients underwent a successful catheter reinsertion and, of those, only 34% remained on PD 1 year later. Unfortunately, it is difficult to predict who will have many adhesions and who will not. Reinsertion of a new catheter should preferably be done by laparoscopic approach or minilaparotomy so that any adhesion can be directly visualized by the surgeon.

PREVENTION OF FURTHER PERITONITIS

The frequency of relapsing peritonitis also must be examined. 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, single gram-positive infections have been associated predominantly with touch contamination or catheter infections; *S. aureus* infections have been associated with touch contamination or catheter infections; single-organism gram-negative infections have been associated with touch contamination, exit-site infections, or transmural migration (constipation or colitis). Prior antibiotic use by the patient may also be associated with culture-negative peritonitis. Identification of etiology may involve a review of the patient's technique. If necessary, retraining should be performed and this should be done only by an experienced PD nurse.

FUTURE RESEARCH

Pharmacokinetic data of many new antibiotics, administered either systemically or IP, are urgently needed. Further clinical trials in PD patients are required, particularly double-blinded randomized trials assessing different treatment strategies and powered to detect meaningful differences using appropriate numbers of patients, and with sufficient follow-up. Such studies require large enough patient numbers to evaluate

significant differences in outcomes and such studies may need to be multicenter in design. Outcomes to be examined should include not only resolution without catheter removal but also duration of peritoneal inflammation, relapse, and repeat peritonitis, as well as change in peritoneal solute transport. Investigations into the role of biofilm in repeat episodes are also needed.

Many of the antibiotic stability data are old and need to be repeated in new PD solutions (*e.g.*, glucose polymer and amino acid solutions). Pharmacodynamic research has advanced the management of infectious disease by characterizing complex antibiotic–pathogen–host interactions. Such investigations specific to dialysis-related peritonitis, however, are scarce. Therapeutic decisions in the management of peritonitis are guided largely by the standard MIC, even though it does not account for unique factors such as high IP antibiotic concentration, commonly used antibiotic combinations, and altered antibiotic activity in the peritoneal environment.

More information is needed on modifiable risk factors for peritonitis. The benefit of screening for *S. aureus* carriage, either after an episode of staphylococcal peritonitis or routinely in a PD unit, needs to be clarified. Conventional dialysis solutions inhibit peritoneal immune function, decreasing the ability of the patient to fight infection. More studies are needed on the newer dialysis solutions, which are more biocompatible and may possibly impact on peritonitis risk.

The development of antibiotic resistance in PD patients requires further study. The impact on the development of resistant organisms through of the use of vancomycin, fourth-generation cephalosporins, and carbapenems as opposed to cephalosporins and fluoroquinolones to treat PD-related infections should be examined in a large multicenter trial.

It is probably a matter of time before PD infections due to extended-spectrum beta-lactamase- and carbapenemase-producing gram-negative rods and multiresistant gram-positive bacteria will be diagnosed (97). Treatment protocols should always include simple and small-spectrum antibiotics but research is warranted on the dosage and pharmacokinetics of new antibiotics and antifungal agents so that we are better prepared when multiresistance is observed.

As described in the previous recommendations, all manuscripts relating to PD infections should be standardized to include sufficient data for interpretation and reproducibility. Information that reviewers and editors should look for is included in Table 8. Methods must include data on training methods and connection used to perform PD. Results should be presented not only as an overall rate but also as individual rates rather than percentages of infections due to specific organisms. Terminology for relapsing and refractory peritonitis as well as "primary cure" should be kept constant. Multicenter studies will probably be needed to enable recruitment of the number of patients required to answer most of these questions.

TABLE 8
Recommendations for Research in Peritoneal Dialysis (PD)-Related Infections

Manuscripts should include the following information

- Description of population
- Connection methodology (spike, Luer lock, *etc.*)
- Type of PD (CAPD with number of exchanges, CCPD, APD with dry day)
- Exit-site infection, tunnel infection, and peritonitis definitions
- Use of standard definitions for repeat, recurrent, relapsed, refractory, and cured peritonitis
- Use of a standard definition for peritonitis-associated death
- Exit-site care protocol
- *Staphylococcus aureus* prevention protocol, if there is one
- Training protocol
- Proportion of patients requiring a helper
- Proportion of patients who are carriers for all studies of *Staphylococcus aureus*
- Peritonitis rates: overall and for individual organisms
- Power calculations for determining the number of patients required for evaluation of an outcome
- Detailed antimicrobial regimen description to include agents, doses, frequency of administration, duration, route, concomitant serum and dialysate levels (specify peak, trough, mean, other)

CAPD = continuous ambulatory PD; CCPD = continuous cycling PD; APD = automated PD.

DISCLOSURES

Philip Kam-Tao Li has participated in clinical trials with Baxter. Cheuk-Chun Szeto declares no conflict of interest. Judith Bernardini is a consultant with Baxter Healthcare. Ana Figueiredo has received speakers' honoraria from Baxter and travel sponsorship from Baxter and Fresenius. David Johnson has received speakers' honoraria from Baxter and Fresenius and has participated in clinical trials with Baxter, Fresenius, and Gambro. He has been a consultant to Baxter and Gambro and has received travel sponsorships from Baxter and Fresenius. He is also the recipient of a Baxter Extramural Research Grant. Dirk Struijk has received lecturing honoraria from Baxter and has participated in clinical trials with Baxter.

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