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# ISPD GUIDELINES/RECOMMENDATIONS

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## CONSENSUS GUIDELINES FOR THE TREATMENT OF PERITONITIS IN PEDIATRIC PATIENTS RECEIVING PERITONEAL DIALYSIS

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Bradley A. Warady, Franz Schaefer,<sup>1</sup> Maggie Holloway,<sup>2</sup> Steven Alexander,<sup>3</sup> Marianne Kandert,<sup>1</sup> Beth Piraino,<sup>4</sup> Isidro Salusky,<sup>2</sup> Anders Tranæus,<sup>5</sup> Jose Divino,<sup>6</sup> Masataka Honda,<sup>7</sup> Salim Mujais,<sup>8</sup> and Enrico Verrina,<sup>9</sup> for the International Society for Peritoneal Dialysis (ISPD) Advisory Committee on Peritonitis Management in Pediatric Patients

*The Children's Mercy Hospital, Kansas City, Missouri, U.S.A.; University Children's Hospital, Heidelberg, Germany; U.C.L.A. Hospital,<sup>2</sup> Los Angeles, California; Stanford University Medical Center,<sup>3</sup> Stanford, California; University of Pittsburgh,<sup>4</sup> Pittsburgh, Pennsylvania, U.S.A.; Baxter Limited, Japan,<sup>5</sup> Tokyo, Japan; Baxter SA,<sup>6</sup> Brussels, Belgium; Tokyo Metropolitan Children's Hospital,<sup>7</sup> Tokyo, Japan; Renal Division,<sup>8</sup> Baxter Healthcare Corporation, Deerfield, Illinois, U.S.A.; G. Gaslini Children's Hospital,<sup>9</sup> Genoa, Italy*

### GUIDELINE 1: DIAGNOSIS OF PERITONITIS

An empiric diagnosis of peritonitis should be made if the peritoneal effluent is cloudy, the effluent white blood cell (WBC) count is greater than 100/mm<sup>3</sup>, and at least 50% of the WBCs are polymorphonuclear leukocytes. The diagnostic workup should be performed using a standardized procedure (Table 1).

#### RATIONALE

Although the diagnostic criteria for peritonitis have not been validated in clinical studies, they represent an international consensus among adult and pediatric nephrologists (4–11). Abdominal pain and fever are generally features that are too nonspecific in children to predict peritonitis in the absence of an elevated dialysate leukocyte count. If the effluent is cloudy, the initial sample is optimal for evaluation, irrespective of the length of the exchange dwell time.

In equivocal cases, or in patients on cyclical dialysis with short exchange dwell times and with systemic or abdominal symptoms, and in whom the effluent appears to be clear, a second exchange is performed with a dwell time of at least 1 hour and the appearance of the effluent is re-evaluated. It is noteworthy that 6% of adults with culture-positive peritonitis present with clear fluid and abdominal pain (10). (Only two thirds of these patients subsequently develop cloudy effluent.) Dialysate culture results are typically not available before 24 hours and, albeit confirming the diagnosis in retrospect, are not helpful in initial clinical decision making. A negative culture does not exclude bacterial peritonitis. In up to 20% of pediatric peritonitis episodes, culture results are negative (4,11–14).

Eosinophilic peritonitis (diagnosed when eosinophils represent more than 10% of the total dialysate polymorphonuclear leukocyte count) is commonly associated with the development of cloudy effluent in an asymptomatic patient new to dialysis. It is likely secondary to a local allergic reaction to components of the dialysis fluid or substances released from the dialysis equipment. It is typically self-limited (4,10).

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Correspondence to: B.A. Warady, Section of Pediatric Nephrology, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, Missouri 64108 U.S.A.

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**TABLE 1**  
Diagnostic Workup of Peritonitis [Refs. (1–3)]

Specimen	Procedure
<p><b>Collection and transport</b></p> <ol style="list-style-type: none"> <li>1. Sample should be obtained from first cloudy bag as it has the greatest probability of yielding a positive culture.</li> <li>2. 50–100 mL peritoneal effluent should be concentrated and cultured to maximize bacterial recovery rates.</li> <li>3. For immediate delivery, transport sample at room temperature.</li> <li>4. For delayed delivery (&gt;1 hour after collection), refrigerate but <i>do not</i> freeze sample.</li> </ol> <p><b>Processing</b></p> <ol style="list-style-type: none"> <li>1. Place effluent sample into two 50-mL tubes and centrifuge for 15 minutes at 3000g.</li> <li>2. Decant supernatant aseptically .</li> <li>3. Vortex to resuspend sediment.</li> <li>4. Perform Gram stain and microscopy from sediment.</li> </ol> <p><b>Materials</b></p> <ul style="list-style-type: none"> <li>Blood agar plate</li> <li>Chocolate agar plate</li> <li>EMB agar plate or MacConkey agar</li> <li>IMA agar plate</li> <li>BHI/Blood agar plate or Sabourod’s agar</li> <li>BacT/Alert fan blood bottle or BACTEC bottle</li> </ul>	<p><b>Microscopic examination</b></p> <p>Perform Gram stain on sediment.</p> <p><b>Culture</b></p> <p><b>Bacteria:</b> Using Pasteur pipette, draw up sediment and place 1 drop on bacteriological culture plates. Place 5 mL of sample into blood culture bottle. Incubate plates in carbon dioxide (5%) at 35°C for 48 hours, and hold the blood bottle for 5–7 days in the BacT/Alert or BACTEC Blood System.</p> <p><b>Fungus:</b> Inoculate BHI/blood agar or Sabourod’s agar and IMA plates with the sediment. Wrap plates and incubate in 30°C incubator for 4 weeks.</p> <p><b>Hematology</b></p> <p><b>Effluent polymorphonuclear leukocyte count</b></p> <p>Count unspun sample using a counting chamber or hemocytometer</p> <p><b>Cell differential</b></p> <p>Spin peritoneal effluent sample (200 µL) in a cyto-centrifuge (1:10–1:100 dilution in physiological saline for leukocyte count &gt;1000) at 8000g for 7 minutes. Stain sample according to Pappenheim for evaluation.</p>

IMA = inhibitory mold agar.

BacT/Alert, Organon Teknika, Durham, NC; BACTEC Blood System, BD Biosciences, Franklin Lakes, NJ, U.S.A.

**GUIDELINE 2: EMPIRIC THERAPY OF PERITONITIS**

In patients with cloudy effluent, without fever and/or severe abdominal pain, and no risk factors for severe infection (listed below), the combined intraperitoneal

administration of a first-generation cephalosporin and ceftazidime is recommended (Figure 1). In patients with fever and/or severe abdominal pain, a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, a recent history or current evidence of an exit-site/tunnel infection or nasal/exit-site colonization

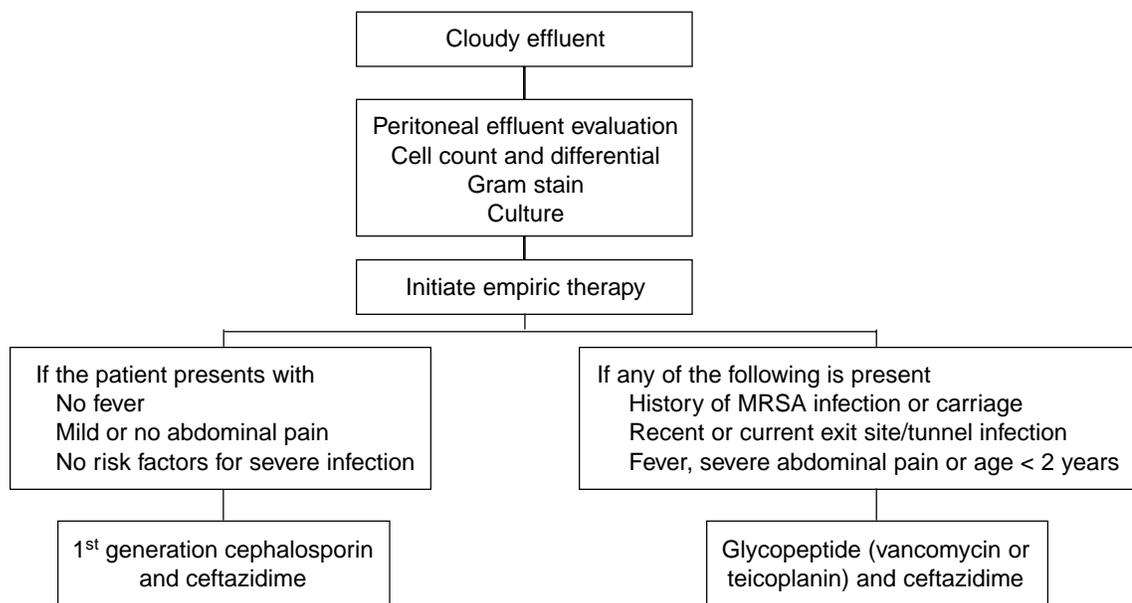


Figure 1 — Empiric therapy. MRSA = methicillin-resistant *Staphylococcus aureus*.

with *S. aureus*, and in patients younger than 2 years, a glycopeptide (vancomycin or teicoplanin) combined with ceftazidime should be administered intraperitoneally (Figure 1). Aminoglycosides should not be used as initial treatment in children.

#### RATIONALE

Children with end-stage renal failure may be dependent upon a functional peritoneum for a prolonged period of time (15,16). Moreover, children are at a high cumulative risk of experiencing severe adverse effects of various drugs, including ototoxicity and nephrotoxicity (17–19). The latter is particularly important in view of the considerable residual renal function that commonly is preserved in children with hypoplastic kidney disorders. Hence, antibiotic therapy of peritonitis in children should aim to provide the highest efficacy and lowest potential for side effects.

Antibiotic treatment should be initiated as soon as the diagnosis of peritonitis is made. While it is advisable to perform and review the results of a dialysate cell count and Gram stain prior to the initiation of treatment (and possibly obtain a blood culture during infancy), treatment should be started immediately upon recognition of effluent cloudiness if signs of severe infection, such as pain and fever, are present. In such cases, dialysate samples should be collected for subsequent cytological analysis, Gram stain, and culture *prior to initiating treatment*. The initial antibiotic regimen should be selected according to symptom severity, peritonitis history, and the patient's risk factor profile.

The combined administration of a glycopeptide (*e.g.*, vancomycin or teicoplanin) and a third-generation cephalosporin (*e.g.*, ceftazidime) has been found to be superior to other antibiotic combinations by meta-analysis in adults, and the excellent efficacy and safety profile of this regimen has been demonstrated in children (20–22). Intermittent peritoneal treatment with a glycopeptide (*e.g.*, 2 loading doses of vancomycin or teicoplanin 5 – 7 days apart) is equally effective as and more convenient and economical than continuous treatment (20). Intermittent therapy with ceftazidime (*e.g.*, antibiotic added to a single exchange daily) may also be as effective as continuous therapy in children, in a manner similar to other cephalosporins in adults (23–25). On the other hand, the possible spread of vancomycin-resistant enterococci and the potential emergence of glycopeptide-resistant staphylococci, in general, mandate the restricted use of glycopeptides in all end-stage renal failure patients (26–30). Therefore, the use of a glycopeptide/ceftazidime combination is recommended only for children at risk for a severe clinical course and/or an

infection with a methicillin-resistant causative organism, whereas a first-generation cephalosporin (*e.g.*, cefazolin or cephalothin) instead of a glycopeptide should be prescribed in asymptomatic patients with cloudy effluent and without such risk factors. Aminoglycosides should not be a part of empiric peritonitis therapy in children due to their oto- and nephrotoxic potential.

#### **GUIDELINE 3: MODIFICATION OF APD REGIMEN FOR TREATMENT OF PERITONITIS**

In patients who receive nocturnal automated peritoneal dialysis (APD) with short dwell times for routine therapy, the initial (24 – 48 hours) treatment of peritonitis should include a prolongation of the dialysate dwell time to 3 – 6 hours, until there is clearing of the peritoneal effluent. This does not apply to asymptomatic patients in whom the routine prescription can be continued, or to patients with ultrafiltration needs requiring more-frequent exchanges. Patients receiving continuous ambulatory peritoneal dialysis (CAPD) do not require any change in their exchange frequency.

#### RATIONALE

Many children who receive APD characteristically receive dialysis exchanges with short ( $\leq 2$  hours) dwell times in order to enhance solute and fluid removal. However, the cellular components of local host defense mechanisms are depleted by frequent exchanges, and the cytotoxicity of fresh conventional dialysis solutions compromises the function of peritoneal macrophages (31,32). Accordingly, prolongation of the dwell time allows for at least partial normalization of the peritoneal "milieu," which hopefully enhances bacterial killing. (This may, however, be preceded by several rapid flushes of dialysis solution at diagnosis to help reduce abdominal pain.) The patient can be disconnected from theycler during the prolonged dialysate dwell times, if symptoms permit. When the effluent demonstrates clearing, which typically occurs within the initial 48 hours of treatment, the patient may return to a more standard APD regimen. However, the daytime dwell that contains antibiotics should be a full exchange (approximately 1100 mL/m<sup>2</sup> body surface area) as long as antibiotic treatment is continued. If, on the other hand, the peritoneal volume is slightly (*e.g.*, < 25%) decreased during the initial 24 – 48 hours of therapy because of abdominal pain (Guideline 11), the concentration of antibiotics must be increased to ensure the infusion of the same mass of antibiotics that would be provided in a full dwell volume (Table 2).

TABLE 2  
Antibiotic Dosing Recommendations  
Administration should be via *intrapertoneal* route unless specified otherwise.

	Continuous therapy		Intermittent therapy <sup>b</sup>
	Loading dose <sup>a</sup>	Maintenance dose	
<b>Glycopeptides<sup>b</sup></b>			
Vancomycin	1000 mg/L	30 mg/L	30 mg/kg q 5–7 days
Teicoplanin <sup>c</sup>	400 mg/L	20 mg/L	15 mg/kg q 5–7 days
<b>Cephalosporins</b>			
Cefazolin/Cephalothin	500 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefuroxime	200 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg q 24 hrs
Ceftazidime	250 mg/L	125 mg/L	15 mg/kg q 24 hrs
Ceftizoxime	250 mg/L	125 mg/L	—
<b>Antifungals</b>			
Amphotericin B	1 mg/kg IV	1 mg/kg/day IV	—
Fluconazole	—	—	3–6 mg/kg IP, IV, or PO q 24–48 hrs (max dose 200 mg)
Flucytosine	50 mg/kg IV or PO (max dose 2.0 g)	25–37.5 mg/kg PO q 24 hrs (max dose 1.0 g)	—
<b>Aminoglycosides<sup>d</sup></b>			
Amikacin	25 mg/L	12 mg/L	—
Gentamicin	8 mg/L	4 mg/L	—
Netilmycin	8 mg/L	4 mg/L	—
Tobramycin	8 mg/L	4 mg/L	—
<b>Penicillins<sup>d</sup></b>			
Azlocillin	500 mg/L	250 mg/L	—
Piperacillin	—	250 mg/L	150 mg/kg IV q 12 hrs
Ampicillin	—	125 mg/L	—
Oxacillin	—	125 mg/L	—
Nafcillin	—	125 mg/L	—
Amoxicillin	250–500 mg/L	50 mg/L	—
<b>Quinolones</b>			
Ciprofloxacin	50 mg/L	25 mg/L	—
<b>Combinations</b>			
Ampicillin/Sulbactam	1000 mg/L	100 mg/L	—
Imipenem/Cilastatin	500 mg/L	200 mg/L	—
Trimethoprim/ Sulfamethoxazole	320/1600 mg/L	80/400 mg/L	—
<b>Others</b>			
Clindamycin	300 mg/L	150 mg/L	—
Metronidazole	—	—	35–50 mg/kg/day PO in 3 doses
Rifampin	—	—	20 mg/kg/day PO (max dose 600 mg/day)
Aztreonam	1000 mg/L	250 mg/L	—

q = every; IV = intravenously; IP = intraperitoneally; PO = orally.

<sup>a</sup> Loading dose should be administered during a standardized 3- to 6-hour dwell period. Concentration-related loading doses assume usual patient-specific fill volume (*i.e.*, approximately 1100 mL/m<sup>2</sup> body surface area). If a smaller volume is instilled, the concentration must be increased to ensure infusion of an equal mass of antibiotic. Intermittent antibiotic dosing should be administered over ≥ 6 hours in one bag per day for CAPD patients, or during a full fill volume daytime dwell for APD patients, unless otherwise specified.

<sup>b</sup> Accelerated glycopeptide elimination may occur in patients with residual renal function. If intermittent therapy is used in this setting, the second dose of antibiotic should be time-based on a blood level obtained 3 – 5 days after the initial dose. Redosing should occur when the blood level is < 12 mg/L for vancomycin, or 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum drug levels can be monitored in a timely manner.

<sup>c</sup> Teicoplanin is not currently available in the United States.

<sup>d</sup> Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation.

The therapeutic recommendations provided above are those of the ISPD Advisory Committee on Peritonitis Management in Pediatric Patients and are, in large part, based upon adult experiences.

**GUIDELINE 4: MODIFICATION OF THERAPY FOR GRAM-POSITIVE PERITONITIS**

If a gram-positive organism is cultured, the empiric use of ceftazidime should be discontinued. A first-generation cephalosporin should be continued for non methicillin-resistant staphylococci; vancomycin, clindamycin, or teicoplanin for methicillin-resistant staphylococci; and ampicillin for enterococci and streptococci (Figure 2). Treatment duration should be 2 weeks for all organisms except *S. aureus*, which should be treated for 3 weeks.

**RATIONALE**

Gram-positive organisms are the cause of peritonitis in more than 50% of pediatric cases (7,9,11–14, 33,34). Peritonitis secondary to coagulase-negative staphylococci is typically the result of touch contamination, while infections secondary to *S. aureus* are commonly associated with a catheter tunnel/exit-site infection with/without *S. aureus* nasal carriage.

In patients whose peritoneal culture is positive for methicillin-sensitive *S. aureus* or coagulase-negative staphylococci, who are clinically improved, and whose empiric therapy included the use of a first-generation cephalosporin, the cephalosporin should be continued to complete therapy. In patients who received a glycopeptide as part of empiric therapy, substitution of this antibiotic with a first-generation cephalosporin should be considered. In some cases, the coagulase-negative staphylococci susceptibility profile will suggest “resistance” to the first-generation cephalosporin when the organism is actually susceptible *in vivo* because of the high intraperitoneal drug levels that are obtained. Rifampin may also be added to the cephalosporin if the clinical response is less than optimal.

In the setting of methicillin-resistant *S. aureus* or coagulase-negative staphylococci, the use of clinda-

mycin, vancomycin, or teicoplanin with/without the addition of rifampin is recommended. The choice of antibiotics should take into consideration the clinical symptoms of the patient and the concerns in relation to emerging resistance to glycopeptides.

If the culture is positive for enterococcus, the first-generation cephalosporin or glycopeptide and ceftazidime should be discontinued and replaced with ampicillin. On occasion, a second antibiotic, such as an aminoglycoside, may be added based on sensitivity results and patient response. Vancomycin or clindamycin should be used in the setting of ampicillin resistance.

**GUIDELINE 5: MODIFICATION OF THERAPY FOR GRAM-NEGATIVE PERITONITIS**

If a single ceftazidime-sensitive gram-negative organism (*e.g.*, *Escherichia coli*, *Klebsiella*, or *Proteus* species) is cultured, the empiric use of ceftazidime should be continued and the first-generation cephalosporin or glycopeptide should be discontinued. If the single organism is a pseudomonad (*e.g.*, *Pseudomonas aeruginosa*), ceftazidime should be continued and a second antibiotic with activity against the isolated organism should be added. If anaerobic bacteria or multiple gram-negative organisms are isolated, intra-abdominal pathology should be considered and treatment should include the use of metronidazole (Figure 3). Treatment duration should be 2 weeks for a single gram-negative organism other than *Pseudomonas/Stenotrophomonas* species. Treatment duration should be 3 weeks for *Pseudomonas/Stenotrophomonas* species, multiple organisms, and/or anaerobes.

**RATIONALE**

Gram-negative peritonitis is particularly troublesome because it is frequently unresponsive to antibi-

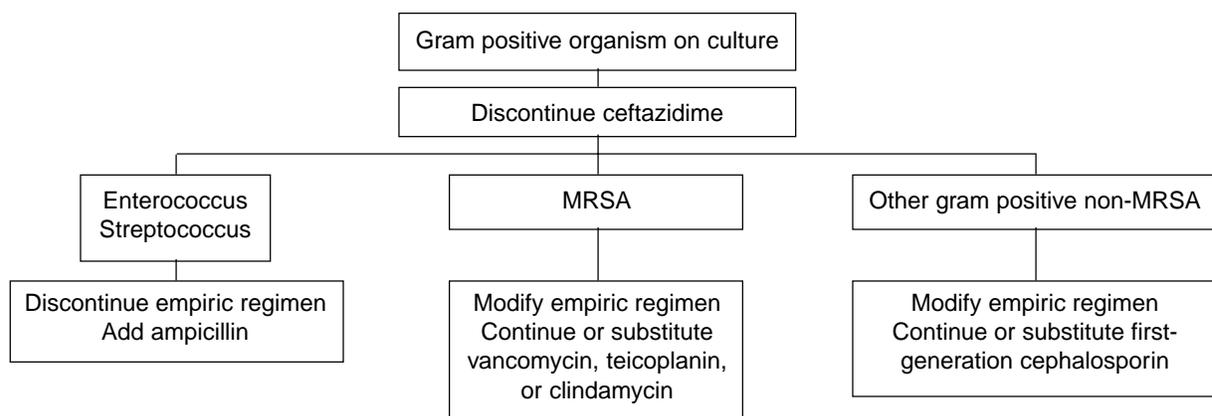


Figure 2 — Gram-positive organism on culture.

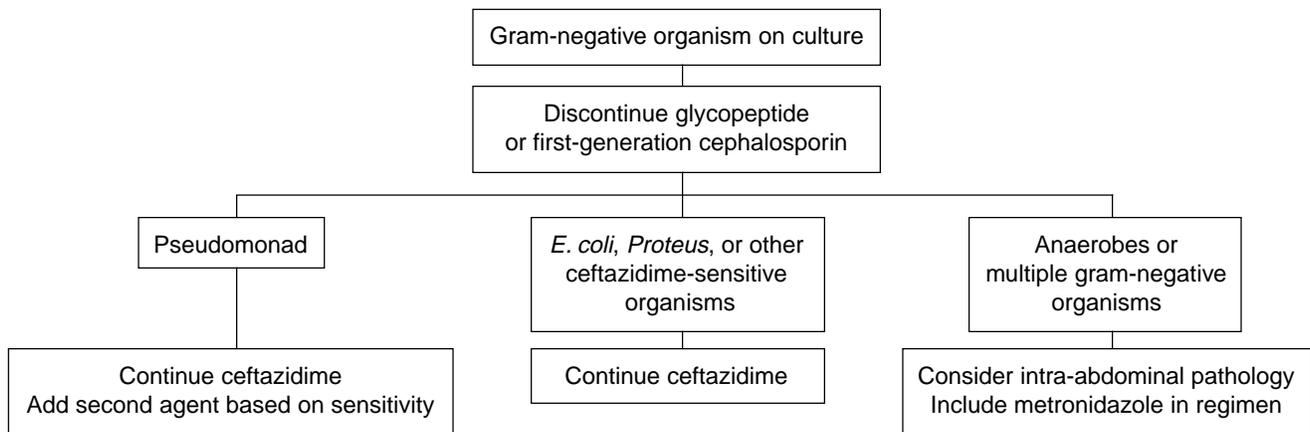


Figure 3 — Gram-negative organism on culture.

otic therapy alone, and because it can have long-term adverse consequences on peritoneal membrane function and lead to inability to conduct peritoneal dialysis (PD). Studies in children have demonstrated chronic alterations of peritoneal membrane transport capacity following the development of peritonitis (35–37). There is evidence that the changes are most dramatic in children with a history of gram-negative peritonitis, a complication that may lead to peritoneal membrane failure. In many situations, the unsuccessful treatment of gram-negative peritonitis results in the need for catheter removal (Guideline 12).

A third-generation cephalosporin such as ceftazidime is generally recommended for treatment of peritonitis secondary to a gram-negative organism (other than *Pseudomonas/Stenotrophomonas* species or anaerobes) in contrast to an aminoglycoside because of the risks of ototoxicity and the loss of residual renal function associated with the latter antibiotic (18,19). On occasion, however, the use of a first-generation cephalosporin, which is less expensive than ceftazidime, may suffice for treatment of *E. coli* peritonitis based on antibiotic susceptibility testing. Whereas most clinical experience with ceftazidime treatment has been with continuous therapy (e.g., presence of antibiotic in each bag of dialysate), a single pediatric study evaluated the use of intermittent ceftazidime therapy (e.g., antibiotic administered during 1 cycle/day) (20). The intermittent therapy was less successful than continuous treatment according to clinical judgment, but not when rated by a standardized disease severity score.

Infections secondary to *Pseudomonas/Stenotrophomonas* species are difficult to treat because of the organisms' capacity to generate a biofilm that decreases the likelihood of successful treatment without catheter removal. While combination therapy

with ceftazidime and an additional agent (e.g., piperacillin, ciprofloxacin, aminoglycoside, aztreonam) to which the organism is susceptible is indicated, the use of ciprofloxacin should be restricted to patients older than 12 years, unless the antibiotic susceptibility pattern, severity of illness, or mitigating circumstances suggest otherwise. The use of intermittent intraperitoneal dosing of aminoglycosides and cephalosporins with CAPD, and intermittent intravenous dosing of tobramycin and ceftazidime with APD, has been demonstrated to be efficacious in adults, but not yet in children (23–25,38).

Finally, the intraperitoneal combination of an aminoglycoside and piperacillin may be incompatible and mandates the provision of piperacillin by the intravenous route when prescribed in this setting.

#### GUIDELINE 6: MODIFICATION OF THERAPY FOR CULTURE-NEGATIVE PERITONITIS

If the initial cultures remain sterile at 72 hours and signs and symptoms of peritonitis are improved, the combined empiric antibiotic therapy prescribed to cover the gram-positive and gram-negative spectra should be continued for 2 weeks.

#### RATIONALE

In the absence of outcome data concerning the early termination of antibiotic therapy with sterile peritonitis, it appears safe to apply full antibiotic coverage for a complete treatment course to decrease the risk of recurrent infection. In centers where culture-negative peritonitis represents more than 20% of peritonitis episodes, applied sampling and culture techniques (Table 1) should be reviewed with the dialysis staff and the respective laboratory.

## GUIDELINE 7: MODIFICATION OF THERAPY FOR FUNGAL PERITONITIS

If fungi are identified by Gram stain or culture, treatment should be initiated with either intravenous amphotericin B or a combination of an imidazole/triazole (*e.g.*, intraperitoneal or oral fluconazole) and flucytosine. In each case, it is recommended that treatment should be associated with early catheter removal. In patients in whom the catheter is not removed initially, immediate catheter removal should take place if improvement does not occur within 3 days of treatment initiation. Treatment duration following catheter removal for all patients should be 2 weeks or longer following complete resolution of the clinical symptoms of infection. Treatment duration without catheter removal should be 4 – 6 weeks.

### RATIONALE

Fungal peritonitis is an infrequent but potentially serious complication of PD. In pediatrics, this infection represents less than 2% of all peritonitis episodes (4, 12–14, 39, 40). Historically, the development of fungal peritonitis has resulted in the frequent conversion of patients to hemodialysis. A recent study of 51 pediatric patients suggests that successful therapy can frequently result in preservation of the peritoneal membrane and continued PD (40).

Several factors appear to predispose patients to the development of fungal peritonitis, the most common of which is the prior use of antibiotics to treat bacterial peritonitis or a catheter-related infection. However, Warady *et al.* found that, in nearly 50% of children who developed fungal peritonitis, there was no history of a prior peritoneal infection. Despite a previous suggestion to the contrary, it is also likely that the presence of a gastrostomy does not predispose to the development of fungal peritonitis (40–42). The role of antifungal prophylaxis (*e.g.*, nystatin, fluconazole) in the setting of antibiotic therapy remains controversial, but is generally advocated (Guideline 11) (43–45).

Whereas amphotericin B has generally been recommended as treatment for fungal peritonitis in patients receiving PD, data collected in children and adults provide evidence that the peritoneal penetration of amphotericin B with systemic administration is poor. In addition, the intraperitoneal administration of amphotericin B is characteristically irritating to the peritoneum and may result in severe abdominal pain. On the other hand, fluconazole is characterized by excellent bioavailability and peritoneal penetration, and is currently the drug of choice for most *Candida* species other than *C. krusei* and some

isolates of *C. glabrata* (46–53). Since oral absorption is essentially complete, the recommended dose of fluconazole is the same for oral, intraperitoneal, and intravenous administration. Ideally, fungal susceptibilities should be obtained to help direct therapy. The reliability of susceptibility results has recently improved following the development of standardized techniques for yeast, but not molds (54,55).

The recommendation that the duration of antifungal treatment following catheter removal be 2 weeks or longer following complete resolution of the clinical symptoms of infection (or 4 – 6 weeks without catheter removal) takes into consideration the inability to create an evidence-based recommendation because of the lack of pediatric or adult data in the literature, and the treatment goal of long-term peritoneal membrane function in children (5).

The inclusion of the recommendation for catheter removal following the diagnosis of fungal peritonitis is due to the propensity of fungi to colonize the PD catheter and prevent eradication of the infection despite drug therapy (Guideline 12). The optimal timing of catheter removal, in terms of number of days post treatment initiation, has not been determined.

## GUIDELINE 8: EVALUATION OF PRIMARY TREATMENT RESPONSE

The response to the initial antibiotic treatment should be evaluated daily after treatment initiation. Treatment can be considered successful if an improvement in clinical status (*e.g.*, cessation of abdominal pain and fever, reduction of effluent cloudiness) has been achieved by 72 hours of therapy. A reduction of the dialysate WBC count by more than 50% is additional evidence of successful therapy.

### RATIONALE

The early assessment of treatment efficacy characteristically consists of an evaluation of the patient's symptoms and the appearance of the peritoneal effluent. Improvement in patient symptoms (*e.g.*, decrease of pain and fever) and clearing of effluent cloudiness at 72 hours is, in most cases, evidence of successful therapy.

In some cases, the use of objective, standardized response criteria can be helpful to avoid unnecessary premature changes of treatment and delayed recognition of an insufficient treatment response. This approach was applied in a pediatric prospective trial, with excellent agreement between an initial response rating and the final outcome (20). A decrease in the effluent WBC count 3 days after initiation of treatment was a helpful diagnostic indicator of treatment response. A relative shift from polymorphonuclear to

mononuclear cells should also start at this time, but occurs with much greater temporal variability than the absolute decrease in the number of WBCs.

Incomplete eradication of micro-organisms from the peritoneal cavity after 3 days of antibiotic therapy should not be considered treatment failure. In a prospective evaluation, Schaefer *et al.* found persistent bacterial growth in 20% of peritonitis episodes 60 hours after treatment initiation (20). After 7 days of continued therapy, the eradication rate was 95%; eradication by treatment days 3 or 7 did not predict the risk for peritonitis relapse.

### **GUIDELINE 9: APPROACH TO PATIENTS WHO FAIL TO DEMONSTRATE CLINICAL IMPROVEMENT**

If no clinical improvement occurs within 72 hours of treatment initiation, potential sources of persistent infection should be evaluated. Treatment modifications may include an alteration of antibiotic therapy and/or catheter removal.

#### **RATIONALE**

Most pediatric patients demonstrate prompt clinical improvement soon after the initiation of successful treatment for peritonitis. In one pediatric study, Schaefer *et al.* found that 74% of all peritonitis episodes were free of any associated clinical symptoms after 60 hours of antibiotic treatment (20). Accordingly, it is reasonable to pursue further investigation if a patient has not demonstrated any improvement after 3 days of therapy. In all cases, the re-evaluation should include a repeat assessment of the peritoneal effluent cell count, Gram stain, and effluent culture. In some cases (*e.g.*, tuberculosis, capnocytophagia), special culture techniques may be necessary.

In the setting of coagulase-negative staphylococci and *S. epidermidis* treatment-resistant infections, a brief (48- to 72-hour) trial with the addition of oral rifampin therapy should be considered. If the patients are receiving a first-generation cephalosporin and the organism is methicillin-resistant, the cephalosporin should be discontinued and therapy with a glycopeptide (*e.g.*, vancomycin or teicoplanin) or clindamycin should be instituted. Continued treatment failure, especially with *S. aureus*, may be the result of a concomitant catheter tunnel infection and should result in catheter removal (Guideline 12) (56). Detection of a tunnel infection can be made by a combination of clinical evaluation and ultrasound assessment in the majority of cases (57). Infections secondary to *Pseudomonas sp* that are resistant to combination therapy should also result in catheter removal and subsequent intravenous antibiotic therapy. In patients

with treatment-resistant peritonitis secondary to anaerobic bacteria or multiple gram-negative organisms, the possibility of intraperitoneal pathology (*e.g.*, ruptured appendix) should be considered, the catheter removed, and intravenous therapy prescribed (58). In the rare case of tuberculous peritonitis in children, exploratory laparotomy or laparoscopy with biopsy of the peritoneum in addition to cultures may be necessary for diagnosis (4,5,10,59). Therapy consists of a combination of isoniazid, rifampin, and pyrazinamide.

Finally, although not recommended, some pediatric patients may be prescribed antifungal therapy without catheter removal for treatment of fungal peritonitis. In these patients, failure to demonstrate clinical improvement within 72 hours should result in catheter removal and intravenous/oral antifungal therapy for a minimum of 2 or more weeks following the resolution of clinical symptoms.

### **GUIDELINE 10: APPROACH TO THE PATIENT WITH RELAPSING PERITONITIS**

Relapsing peritonitis is defined as a recurrence of peritonitis with the same organism as in the immediately preceding episode, according to antibiotic susceptibilities, within 4 weeks of completion of antibiotic treatment. Since the causative organism is not known at the time of onset of symptoms, empiric treatment should be reinitiated according to Guideline 2. After bacteriologic confirmation of a relapse, treatment should be organism specific (see treatment recommendations below) and (except for *Pseudomonas/Stenotrophomonas* species) treatment duration should be 3 weeks (Table 3).

#### **RATIONALE**

Relapsing peritonitis is most frequently seen when *S. aureus* or coagulase-negative staphylococci are the causative organisms (60). Because of its important therapeutic implications, the diagnosis of a relapse should not rely solely on the genus/species, but also on the antibiotic susceptibilities of the cultured organism. In sophisticated laboratory settings, strain identity can be confirmed by DNA genotype analysis (21).

Slime-forming coagulase-negative staphylococci are believed to survive antibiotic therapy in fibrinous adhesions and biofilm matrix on the catheter surface. Catheter decontamination by local installation of fibrinolytic agents and high-dose antibiotics has been shown to improve final cure rates in adults and children (60–62).

In relapsing peritonitis caused by *S. aureus*, an occult (*e.g.*, subclinical) tunnel infection or intra-

TABLE 3  
Treatment Recommendations in Relapsing Peritonitis

Organism	Treatment	Duration (weeks)
Methicillin-sensitive staphylococci	First-generation cephalosporin and rifampin	3
Methicillin-resistant staphylococci	Glycopeptide or clindamycin with or without rifampin	3
Enterococci	Ampicillin and aminoglycoside	3
Gram-negative organism (other than <i>Pseudomonas/Stenotrophomonas</i> )	Ceftazidime	3
<i>Pseudomonas/Stenotrophomonas</i>	Remove catheter, plus ceftazidime and 2 <sup>nd</sup> antibiotic	≥2–3

abdominal abscess should be sought. Also, screening for nasal *S. aureus* carriage should be performed in the child and his/her caregivers.

Patients with relapsing gram-negative peritonitis should be evaluated for an intra-abdominal abscess, and may require surgical exploration and catheter removal. In the case of pseudomonas or stenotrophomonas infections, the catheter should be removed and intravenous antibiotics prescribed for a minimum of 2 – 3 weeks prior to consideration of catheter replacement.

Finally, if a second relapse occurs secondary to any organism and no other pathology is identified, the catheter should be removed.

#### GUIDELINE 11: ADJUNCTIVE THERAPY FOR PERITONITIS

In patients who are being treated for peritonitis, adjunctive therapy should be considered on an individual basis and may include the following:

- Decreased peritoneal fill volume in patients with significant abdominal discomfort;
- Oral antifungal prophylaxis during the course of antibiotics;
- Low-dose intraperitoneal heparin as long as peritoneal effluent is cloudy; and
- Intravenous immune globulin (IVIG) in patients with hypogammaglobulinemia.

#### RATIONALE

Significant abdominal pain is frequently noted in children who develop peritonitis. Early in the course of treatment, the pain may be worsened by the presence of the routine exchange volume. Accordingly, the peritoneal volume can be slightly (*e.g.*, < 25%) decreased during the initial 24 – 48 hours of therapy until clinical symptoms improve. If this occurs, the concentration of antibiotics must be increased during this period of time to ensure the infusion of an appropriate mass of antibiotics (Table 2). The ex-

change volume should subsequently be increased to the normal prescription to prevent a prolonged period of underdialysis.

The association between antibiotic therapy and fungal peritonitis has prompted several trials of antifungal prophylaxis during antibiotic treatment in patients receiving PD (40,43–45). Studies in adults have been inconclusive with respect to the benefits of oral nystatin. In a pediatric study, oral nystatin (10 000 U/kg/day) or oral ketoconazole was associated with a significant decrease in the risk of fungal peritonitis in patients receiving antibiotics (43). When used, the antifungal agent should likely be continued for several days following completion of the antibiotic therapy to allow for repopulation of the gastrointestinal tract with the normal bacterial flora. Empirically, the provision of *Lactobacillus* might also be considered for this purpose.

Although the efficacy of intraperitoneal heparin has not been formally proven, its inhibitory effect on fibrin clot formation is believed to contribute to catheter patency in cases of severe peritonitis with massive protein exudation (63). Heparin also has bacteriostatic and anti-inflammatory properties. The recommended dose of heparin is 500 – 1000 U/L dialysate until the effluent clears.

Finally, the presence of low serum levels of IgG has repeatedly been demonstrated in patients receiving PD during infancy (64,65). While there are no data to support the routine use of prophylactic immunoglobulin in this population, the provision of IVIG should be considered in the infant with documented hypogammaglobulinemia and peritonitis/sepsis.

#### GUIDELINE 12: INDICATIONS FOR CATHETER REMOVAL AND REPLACEMENT

Peritoneal dialysis catheter removal should occur as part of the recommended treatment course in situations in which failure to do so is unlikely to result in successful peritonitis therapy. The timing of catheter replacement should be 2 – 3 weeks following catheter removal in most cases.

## RATIONALE

Catheter removal should be considered an important component of peritonitis therapy. This approach to therapy is often necessary in patients with treatment-resistant peritonitis because of concerns for long-term damage to the peritoneal membrane (16,35). In most cases, patients treated in this manner receive hemodialysis for a variable period of time and are then able to return to PD. In pediatric patients, catheter removal and subsequent replacement should be strongly considered in certain situations as shown in Table 4.

There are no data in the pediatric or adult literature that permit an evidence-based recommendation with respect to the length of antibiotic treatment following catheter removal. The recommendation of 2 – 3 weeks takes into consideration the absence of data and the treatment goal of long-term peritoneal membrane function in children. In all cases, recommendations concerning the duration of antibiotic therapy and the timing of catheter replacement may require modification based upon the patient's clinical response.

**GUIDELINE 13: PROPHYLACTIC ANTIBIOTIC THERAPY**

Prophylactic antibiotic therapy for *S. aureus* nasal carriage is recommended to decrease the risk of *S. aureus* catheter exit-site/tunnel infections. Prophylactic antibiotic therapy should be given at the time of catheter placement in the form of a single dose of a

first-generation cephalosporin. Antibiotic prophylaxis should also be considered following accidental intraluminal contamination, prior to dental procedures, and prior to procedures involving the gastrointestinal or urinary tract. Prophylactic systemic long-term antibiotic treatment is not indicated.

## RATIONALE

*Staphylococcus aureus* nasal carriage is associated with a high incidence of PD catheter-related infections with this organism. Intrafamilial transmission of the organism is common. Intermittent (*i.e.*, 3 – 4 days/month) intranasal treatment of nasal carriers with mupirocin eliminated carriage and markedly reduced infections with *S. aureus* in adult CAPD patients (66). Similar results were obtained with cyclic local mupirocin ointment applied to the exit site of *S. aureus* nasal carriers. More recently, Piraino *et al.* recommended that a small amount of mupirocin ointment be applied daily to the exit site, using a cotton swab, for all PD patients, eliminating the need for nasal cultures (67). Pediatric data on the impact of treating *S. aureus* nasal carriers (patients and care providers) is currently limited, making it reasonable to extrapolate the adult experience to children (68–70). Whereas the daily use of mupirocin in all patients has the potential for generating antibiotic resistance, this has not been a significant problem as of this time.

The recommendation concerning perioperative and post contamination prophylaxis takes into account the current state of knowledge of intra-abdomi-

**TABLE 4**  
Situations in Which Catheter Removal and Subsequent Replacement Should Be Strongly Considered in Pediatric Peritoneal Dialysis Patients

Clinical setting	Antibiotics	Interval between catheter removal and replacement (weeks)
Relapse of treated <i>Staphylococcus aureus</i> peritonitis with a <i>S. aureus</i> catheter-related infection	2 weeks (intravenous); simultaneous catheter removal and replacement with 3 weeks of antibiotics is possible in patient with low (<100/ $\mu$ L) effluent white blood cell count	2–3
Relapse of treated <i>Pseudomonas/ Stenotrophomonas</i> peritonitis	2 weeks (intravenous)	2–3
Fungal peritonitis	$\geq 2$ weeks (intravenous/oral)	$\geq 2$ –3
Refractory (at 72–96 hours) peritonitis (any pathogen or culture negative)	2 weeks (intravenous)	2–3
Refractory (at 72–96 hours) anaerobic peritonitis	2 weeks (intravenous)	2–3
Refractory (1 month) catheter exit-site/tunnel infection	2 weeks (intravenous); simultaneous catheter removal and replacement is possible unless infection is severe with purulent discharge	2–3

nal surgery, where antibiotic administration immediately prior to and within the first 6 hours after conducting abdominal surgery appears to be effective in preventing infection. A single pediatric experience on the topic revealed that patients who received preoperative antibiotic therapy prior to PD catheter placement had a significantly decreased incidence of postoperative peritonitis when compared to untreated patients (71). The most appropriate prophylactic agent is a first-generation cephalosporin (*e.g.*, cefazolin or cephalothin), unless the patient is known to be colonized with a methicillin-resistant organism. A glycopeptide should not be the initial agent routinely chosen because of the emerging bacterial resistance to glycopeptides.

There are no data demonstrating the benefits of antibiotic prophylaxis following a break in dialysis technique. However, the use of a first-generation

cephalosporin for 1 – 3 days in this setting is typically recommended by adult and pediatric nephrologists. A glycopeptide should be used only in the setting of a patient previously known to be colonized with a methicillin-resistant organism.

Prophylactic antibiotic therapy is also recommended in the setting of dental procedures because of the risk of bacteremia and subsequent peritonitis (72,73). Amoxicillin is the preferred agent in a dose comparable to what is recommended by the American Heart Association for subacute bacterial endocarditis prophylaxis (Table 5) (74). Consideration should also be given to the provision of prophylactic therapy for children on PD having gastrointestinal (*e.g.*, gastrostomy tube placement) or genitourinary surgery because of the likely increased risk of peritonitis. Ampicillin plus ceftazidime are recommended.

TABLE 5  
Prophylactic Antibiotic Guidelines

Prophylactic regimens for dental procedures		
Situation	Agent	Regimen
Standard general prophylaxis Unable to take oral medications	Amoxicillin	50 mg/kg (max 2.0 g) orally 1 hr before procedure
	Ampicillin	50 mg/kg (max 2.0 g) IM or IV within 30 min before procedure
Allergy to penicillin	Clindamycin	20 mg/kg (max 600 mg) orally 1 hr before procedure
	<b>or</b> Cephalexin or cefadroxil	50 mg/kg (max 2.0 g) orally 1 hr before procedure
	<b>or</b> Azithromycin <b>or</b> clarithromycin	15 mg/kg (max 500 mg) orally 1 hr before procedure
Allergy to penicillin and unable to take oral medications	Clindamycin	20 mg/kg (max 600 mg) IV within 30 min before procedure;
	<b>or</b> Cefazolin	25 mg/kg (max 1.0 g) IM or IV within 30 min before procedure
Prophylactic regimens for genitourinary/gastrointestinal procedures		
Situation	Agents	Regimen
Standard general prophylaxis	Ampicillin plus ceftazidime	Ampicillin 50 mg/kg (max 2.0 g) IM or IV plus ceftazidime 50 mg/kg (max 1.0 g) within 30 min of starting procedure; 6 hr later, ampicillin 25 mg/kg (max 1.0 g) IM/IV, or amoxicillin 25 mg/kg (max 1.0 g) orally
Allergy to penicillin	Clindamycin plus ceftazidime	Clindamycin 20 mg/kg (max 600 mg) IV plus ceftazidime 50 mg/kg (max 1.0g) IM or IV; complete injection/infusion within 30 min of starting procedure

IM = intramuscular; IV = intravenous.

TABLE 6  
Exit-Site Scoring System<sup>a</sup> [Ref. (20)]

	0 Points	1 Point	2 Points
Swelling	No	Exit only (<0.5 cm)	Including part of or entire tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

<sup>a</sup> Infection should be assumed with a cumulative exit-site score of 4 or greater.

#### GUIDELINE 14: DIAGNOSIS OF CATHETER EXIT-SITE INFECTION

The diagnosis of a catheter exit-site infection should be made in the presence of a purulent discharge from the sinus tract, or marked pericatheter swelling, redness, and/or tenderness, with or without a pathogenic organism cultured from the exit site. Infectious symptoms should be rated according to an objective scoring system (Table 6).

##### RATIONALE

As the subjective judgment of an exit-site status may differ widely, it is imperative that objective criteria be used to diagnosis an exit-site infection. Work by Twardowski has also led to a better classification of exit-site morphology and a more uniform approach to the diagnosis of infection (75). *Staphylococcus aureus* accounts for the majority of infections, followed by enterococci, *Pseudomonas*, *E. coli*, *Klebsiella*, and other gram-negative species. *Staphylococcus epidermidis* is frequently cultured, but is usually not causative of an exit-site infection. Whereas a positive culture is not required for the diagnosis of an exit-site infection, positive cultures in exit sites that are not inflamed indicate colonization, not infection.

#### GUIDELINE 15: TREATMENT OF CATHETER EXIT-SITE INFECTION

Antibiotic treatment of a catheter exit-site infection should be started after culture results have been obtained, unless signs of severe infection are present. The antibiotic should be chosen according to the susceptibilities of the cultured organism. Treatment duration should be 2 – 4 weeks.

##### RATIONALE

In view of the risks of increasing antibiotic resistance in children with end-stage renal disease, strict criteria should be applied to antibiotic prescribing

recommendations. Glycopeptides (*e.g.*, vancomycin or teicoplanin) should be avoided for the routine treatment of exit-site infections secondary to *Staphylococcus* species because of concerns of emerging bacterial resistance. Instead, a first-generation cephalosporin or a penicillinase-resistant penicillin with/without the addition of rifampin is preferred. Gram-negative infections should be treated with oral ciprofloxacin in children older than 12 years, or with intraperitoneal ceftazidime. In patients in whom the exit-site culture is negative, the choice of antibiotics should be governed by Gram-stain results, if available. In the absence of a positive culture or Gram stain, or prior to obtaining the results in a patient with a severe infection, empiric therapy with either a first-generation cephalosporin or oral ciprofloxacin should be initiated. Close monitoring of this patient group is essential, with modification of the antibiotic regimen contingent upon early response to therapy. Screening for *S. aureus* nasal carriage may be helpful in this situation to detect a possible etiologic organism.

Adjunctive therapy should include the use of daily or twice daily dressing changes as long as significant discharge from the sinus tract is present (75). Nonalcoholic disinfectants (*e.g.*, octenidine) should be used if available. Povidone iodine solutions and hydrogen peroxide irritate the skin and may impair local host defenses, and therefore should not be routinely applied. Large crusts should be removed with nonionic nontoxic surfactants such as 20% poloxamer 188 (76–78). The exit site should be kept dry between the dressing changes; this can be achieved with a nonocclusive sterile dressing. Exuberant granulomatous tissue (“proud flesh”) should be cautiously removed by cauterization with silver nitrate. The catheter should be immobilized and protected from trauma.

Treatment should continue for 2 – 4 weeks and for at least 7 days following complete clinical resolution of the infection. Failure to achieve resolution of the infection in this period of time, or the development of a catheter tunnel infection and peritonitis secondary to the same organism, is an indication for

catheter removal (Guideline 12). Shaving of the external cuff as an alternative to catheter removal for treatment of a persistent exit-site infection has occasionally been recommended, but with little pediatric experience (79).

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