

# ISPD GUIDELINES/RECOMMENDATIONS

## ADULT PERITONEAL DIALYSIS-RELATED PERITONITIS TREATMENT RECOMMENDATIONS: 2000 UPDATE

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Peritonitis is a common clinical problem that occurs in patients with end-stage renal disease treated by peritoneal dialysis (PD). Although the incidence of peritonitis varies from center to center, since the 1980s it has progressively declined, and during the past decade approximately 1 episode every 24 patient-treatment-months was routinely observed. In some centers, 1 episode every 60 patient-treatment-months has been achieved, in large part because of exceptional patient education, as well as new connector and catheter technologies. The more recent introduction of automated peritoneal dialysis (APD) has also contributed to the growth of PD, but this technique is also complicated by episodes of peritonitis.

The development of disconnect systems has had an important effect on overall reduction of the incidence of peritonitis episodes, particularly those due to skin organisms. A variety of micro-organisms may cause PD peritonitis. Gram-positive organisms, particularly *Staphylococcus aureus* and *S. epidermidis*, have been the most frequent pathogens. However, in patients utilizing the disconnect systems, with the reduction in the incidence of gram-positive staphylo-

coccus peritonitis, the relative incidence of gram-negative infection has increased.

Many different antimicrobial agents have been used to treat PD peritonitis. As in the past, the current Committee reviewed experiences reported in the literature and formulated recommendations based upon these assessments. Over the years, a variety of different regimens have been proposed based upon these experiences. Antibiotics have been administered intraperitoneally (IP), or intravenously (IV), or orally, and a number of different dosing regimens have been utilized. Unfortunately, no single regimen has been shown in appropriate clinical trials to be most efficacious.

A diagnostic and therapeutic approach to the patient with presumptive PD peritonitis was published in 1987 and revised in 1989, 1993, and 1996. These latter recommendations contained a number of new recommendations based upon intermittent dosing. In addition, the recent emergence of vancomycin resistance has created a therapeutic dilemma of international proportions (see *Recommendations for*

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*Preventing the Spread of Vancomycin Resistance*, in Suggested Reading). As a result, major modifications to our recommendations were proposed in 1996. As always, individual clinical situations and variability in patient populations may necessitate modification of these recommendations. Importantly, it is recognized that there are clinical situations in which vancomycin is the appropriate antibiotic to be used; however, the committee still recommends that routine and prophylactic use of this antimicrobial agent be avoided.

We do not suggest that the recommendations outlined in this report represent the only acceptable ways to manage PD patients with peritonitis. Nonetheless, the purpose of this document is to present a systematic approach reflecting a changing microbial environment and the emergence of new antibiotics.

In addition to these therapeutic recommendations, an important clinical management tool has been the development and utilization of techniques in each center for monitoring the incidence of peritonitis, exit-site infections (ESI), and tunnel infections in the PD population. This epidemiological approach should allow program directors to assess whether a change in the frequency and incidence of peritonitis has occurred in their patient population, and thus to provide an index of quality of care. Attention to changing microbial biograms within a center is also of major importance in the setting of increasing prevalence of vancomycin-resistant staphylococcus and enterococcus organisms. Finally, this year 2000 Update is focused on the adult population; separate pediatric recommendations will be published later this year.

#### CLINICAL PRESENTATION

*Diagnosis of Peritonitis in Continuous Ambulatory PD (CAPD) Patients:* In patients with cloudy fluid and/or abdominal pain and/or fever, a sample of the appropriate (i.e., > 4 hours' dwell time) dialysate effluent should be obtained for laboratory evaluation including a cell count with differential, Gram stain, and culture (Table 1). An elevated dialysate count of white blood cells (WBC) of more than  $100/\text{mm}^3$ , of which at least 50% are polymorphonuclear neutrophils (PMN), is supportive of the diagnosis of microbial-induced peritonitis, and calls for immediate initiation of antimicrobial therapy. In asymptomatic patients with only cloudy fluid, it is reasonable to delay initiation of therapy until the results of the cell count, differential, and Gram stain are available, as long as these studies can be performed expeditiously (i.e., within 2 - 3 hours). If there is no increase in the peritoneal WBC count, the differential does not show a predominance of PMN, and no bacteria are seen on

Gram stain, immediate therapy is not indicated. Similarly, if more than 10% of peritoneal leukocytes are eosinophils and the Gram stain is negative, immediate antimicrobial therapy is usually unnecessary.

Patients with cloudy fluid accompanied by abdominal pain and/or fever require prompt initiation of empiric therapy (Table 2). Neither the differential nor the magnitude of the WBC elevation has been shown to be helpful in predicting the causative organism. There is some evidence that peritonitis caused by *S. aureus* or gram-negative bacilli may be accompanied by more severe symptoms than an infection caused by coagulase-negative staphylococci. However, altering the empiric therapy based on the severity of symptoms or the dialysate cell count is not recommended. A Gram stain is positive in 9% - 40% of peritonitis episodes and, when positive, is predictive of eventual culture results in approximately 85% of cases. A Gram stain is particularly useful in the early recognition of fungal peritonitis. Culture of dialysate effluent should always be performed prior to initiation of antibiotic therapy, but treatment should not be delayed while waiting for culture results.

*Diagnosis of Peritonitis in APD Patients:* Patients on various forms of APD require a modified approach to diagnosis and treatment of peritonitis. These patients receive a period of consecutive, relatively short exchanges during the night (nocturnal exchanges), and may have only a partial exchange or a dry abdomen during the day (daytime exchanges).

Diagnostic criteria for peritonitis were established based on clinical experience with CAPD patients whose dwell times were 4 - 6 hours in duration. Concerns have been raised that the shorter dwell times of APD patients with suspected peritonitis could result in misleadingly low dialysate cell counts and falsely negative cultures. In pediatric patients, 70% of whom are treated with APD, this has not been the case. For more than a decade, CAPD peritonitis diagnostic and treatment criteria and methods have been successfully applied to the management of pediatric patients receiving APD, with only minor modifications (see Kuizon *et al.*, 1995). The following recommendations are based on this pediatric experience and may prove useful in the management of adults on APD.

TABLE 1

Initial Clinical Evaluation of Patient with Suspected Peritoneal Dialysis-Related Peritonitis

- 
- Symptoms: cloudy fluid and abdominal pain
  - Do cell count and differential
  - Gram stain and culture on initial drainage
  - Initiate empiric therapy
  - Choice of final therapy should always be guided by antibiotic sensitivities
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TABLE 2  
Empiric Initial Therapy, for Peritoneal Dialysis-Related Peritonitis, Stratified for Residual Urine Volume

Antibiotic	Residual urine output	
	< 100 mL/day	> 100 mL/day
Cefazolin or cephalothin	1 g/bag, q.d. or 15 mg/kg BW/bag, q.d.	20 mg/kg BW/bag, q.d.
Ceftazidime	1 g/bag, q.d.	20 mg/kg BW/bag, q.d.
Gentamicin, tobramycin, netilmycin	0.6 mg/kg BW/bag, q.d.	Not recommended
Amikacin	2 mg/kg BW/bag, q.d.	Not recommended

q.d. = once/day; BW = body weight.

Peritonitis diagnosis and treatment data in adults on APD are gradually emerging.

Cloudy fluid and abdominal pain remain the hallmark of peritonitis in APD-treated patients. Occasionally, the initial drain of the "residual" fluid that has been present in the abdomen all day in patients with only partial or dry diurnal exchanges will appear cloudy in the absence of peritonitis. The WBC may exceed 100/mm<sup>3</sup>, but mononuclear cells predominate and abdominal pain is not present. More important, in the absence of infection the initially cloudy dialysate rapidly clears with initiation of APD.

If cloudy fluid, and/or abdominal pain, and/or fever is/are observed at any point in the daily APD treatment cycle, the patient should notify the dialysis center immediately for further specific instructions, including clinical evaluation. A sample of dialysate effluent should be obtained for cell count, differential, Gram stain, and culture, as with CAPD patients. If the fluid is very turbid, the initial sample is sufficient for study, regardless of the length of the dwell time that produced it. In equivocal cases, or in patients with systemic or abdominal symptoms in whom dialysate appears to be clear, a second exchange is performed with a dwell time of at least 2 hours. Obviously, clinical judgment should guide initiation of therapy. Using this technique, the incidence of culture-negative peritonitis has remained approximately 20%, similar to that reported in CAPD patients.

*Clinical Utility of the Gram Stain:* If, on initial evaluation, the Gram stain reveals a gram-positive organism, therapy with a single antibiotic with activity against gram-positive organisms should be initiated. However, identification of a single species by Gram stain does not preclude the presence of other species present in lesser concentrations. Thus, the Gram stain results must be considered preliminary. In rare cases, the Gram stain may indicate gram-negative organisms, and the selection of an antimicrobial agent with activity against gram-negative bacteria is appropriate. The Gram stain may also be useful in revealing the presence of yeast, and thus allow for

prompt initiation of antifungal therapy. The finding of gram-positive cocci and gram-negative rods together suggests the possibility of a perforated abdominal viscous, and prompt surgical evaluation is warranted.

Unfortunately, on many occasions the Gram stain is unavailable, delayed, or negative for any specific organisms. Empiric therapy is indicated in these conditions (Tables 1 and 2). There are some clinical clues that may be helpful. There is a slight statistical likelihood that the causative pathogen will be the same as the most recent infection. If the exit site is infected with pseudomonas or *S. aureus* when peritonitis presents, there is a high probability that the peritonitis is caused by the same organism. If the patient is having frequent peritonitis episodes, then relapse or recurrence with the same organism is likely.

It is recognized that many patients treated with PD reside in locations that are remote from medical facilities, and thus may not be seen expeditiously following the onset of symptoms. In addition, these PD patients may not have immediately available microbial and laboratory diagnostic services. Since most experts agree that prompt initiation of therapy for peritonitis is critical, it is necessary that the patient report symptomatology to the center immediately. Prompt initiation of therapy by these patients remote from the center is of obvious importance and requires the availability of antimicrobials in the patient's home. This approach has been broadly accepted by medical care providers worldwide and has demonstrated efficacy. Instructions for the reporting of symptomatology and the utilization of home antimicrobial therapy should be considered part of PD patient training.

#### INITIATION OF THERAPY

In the past few years, the increasing prevalence of vancomycin-resistant micro-organisms has been noted. Initially, vancomycin resistance was confined to enterococci isolated from patients who were critically ill in intensive care units. It has subsequently

been documented that similar organisms could be isolated from patients who had chronic illnesses treated with multiple antibiotics and that frequently had prolonged hospital stays. Internationally, the prevalence of vancomycin-resistant organisms has dramatically increased and this increase has been particularly evident in larger university hospitals where up to 14% of enterococci may be resistant. Vancomycin resistance has been associated with resistance to other penicillins and aminoglycosides, thus presenting a treatment dilemma, since many of the second-line antimicrobial agents that could be used have not been proven in therapeutic trials. This change in vancomycin sensitivity has prompted a number of worldwide agencies to discourage routine use of vancomycin for prophylaxis, for empiric therapy, or for oral use for *Clostridium difficile* enterocolitis. The major concern is that the vancomycin-resistance gene is transmitted to staphylococcal strains, creating an issue of major epidemiological importance. While a great deal of concern has been raised about vancomycin, it is still an important antimicrobial option. Indeed, it is recommended for use in methicillin-resistant *S. aureus* (MRSA) infections and in treatment of infections due to beta-lactam-resistant organisms, as well as in treatment for infections in patients that have serious gram-positive infections and that are allergic to other agents, and in the treatment of *C. difficile* enterocolitis that does not respond to metronidazole.

#### INITIAL EMPIRIC ANTIBIOTIC SELECTION

If the effluent sediment Gram stain suggests gram-positive bacteria, a gram-negative organism, or is unavailable, delayed, or negative for any specific organisms, empiric therapy is indicated (Table 2). To prevent routine use of vancomycin and thus prevent emergence of resistant organisms, it is recommended that a first-generation cephalosporin, for example, cefazolin or cephalothin (1 g daily in the long dwell), in combination with ceftazidime be initiated. These antibiotics can be mixed in the same dialysate bag as either loading or maintenance doses, without significant loss of bioactivity. The dose for ceftazidime is 1.0 g (Table 3).

A single antibiotic for initial treatment needs to satisfy several criteria, including good antibacterial efficacy for coagulase-negative staphylococcus, *S. aureus*, gram-negative *Enterobacteriaceae*, and reasonable efficacy for pseudomonas. In addition, it needs to have a reasonable half-life for once-per-day therapy and clinically proven efficacy. The 1996 Recommendations involved the use of a combination of a first-generation cephalosporin and an aminoglycoside. The need to avoid routine use of aminoglycoside arises from the concern to preserve residual renal function,

which is an independent predictor of patient survival. There is good evidence showing a more rapid loss of residual renal function in patients receiving aminoglycosides, even for short periods. First-generation cephalosporins do not adequately cover MRSA.

Alternatives to ceftazidime (in patients with a residual urine volume of < 100 mL/day) may be cefazolin or cephalothin in combination with an aminoglycoside, or clindamycin, or vancomycin in that order of preference (Table 3).

This strategy is consistent with the desire to preserve vancomycin for true methicillin-resistant organisms. Ceftazidime was selected as empiric therapy because of its activity against both gram-positive and gram-negative organisms.

New insights into the pharmacodynamic principles governing the activity of ceftazidime have led to a single daily-dose regimen, which has the advantage of ease of use by patient and staff, both in hospital and at home.

If gentamicin, tobramycin, or netilmicin are used, they are dosed at 0.6 mg/kg body weight in only 1 exchange per day. Amikacin is dosed at 2.0 mg/kg body weight, also in only 1 exchange per day (Table 2).

*Gram Stain Reveals Yeast:* If yeast is seen on Gram stain, prompt initiation of antifungal therapy should be initiated. Although the mainstay of therapy in the past has been amphotericin B, its toxicity has frequently precluded its effective use. Experience with the newer imidazoles/triazoles and flucytosine suggest that these agents are well tolerated and efficacious.

#### MODIFICATION OF TREATMENT REGIMEN ONCE CULTURE AND SENSITIVITY RESULTS ARE KNOWN

*Gram-Positive Micro-Organisms Cultured:* Within 24 - 48 hours after the appropriate culture of dialysate fluid, 70% - 90% of these samples yield a specific micro-organism (Table 4). If the organism is an enterococcus, the first-generation cephalosporin (cephalothin or cefazolin) and ceftazidime are replaced with ampicillin, 125 mg/L in each exchange; another antibiotic such as an aminoglycoside may be added, if necessary, based on sensitivity. A factor to consider in deciding whether or not to continue the aminoglycoside is the recognition that a high ampicillin level will be achieved at the site of infection using this regimen.

As previously discussed, we urge restraint in immediately utilizing vancomycin for enterococci without considering all the implications. Since enterococci are frequently derived from the gastrointestinal tract, intra-abdominal pathology must be considered. Moreover, care should be exercised in evaluating the dialysate culture since other more fastidious and

TABLE 3  
Antibiotic Dosing Recommendations for CAPD (Only) Patients With and Without Residual Renal Function<sup>a</sup>

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
<b>Aminoglycosides</b>				
Amikacin	2 mg/kg	Increase all	MD 24 mg	Increase all
Gentamicin	0.6 mg/kg	doses by 25%	MD 8 mg	MD by 25%
Netilmicin	0.6 mg/kg		MD 8 mg	
Tobramycin	0.6 mg/kg		MD 8 mg	
<b>Cephalosporins</b>				
				All LD same as anuric
Cefazolin	15 mg/kg	20 mg/kg	LD 500 mg, MD 125 mg	MD increase by 25%
Cephalothin	15 mg/kg	N D	LD 500 mg, MD 125 mg	MD, ND
Cephradine	15 mg/kg	N D	LD 500 mg, MD 125 mg	MD, ND
Cephalexin	500 mg p.o., q.i.d.	N D	As intermittent	MD, ND
Cefuroxime	400 mg p.o./IV, q.d.	N D	LD 200 mg, MD 100-200 mg	MD, ND
Ceftazidime	1000-1500 mg	N D	LD 250 mg, MD 125 mg	MD, ND
Ceftizoxime	1000 mg	N D	LD 250 mg, MD 125 mg	MD, ND
<b>Penicillins</b>				
				All LD same as anuric
Piperacillin	4000 mg IV, b.i.d.	N D	LD 4 g IV, MD 250 mg	MD, ND
Ampicillin	250-500 mg p.o., b.i.d.	N D	MD 125 or 250-500 mg p.o., b.i.d.	MD, ND
Dicloxacillin	250-500 mg p.o., q.i.d.	N D	250-500 mg p.o., q.i.d.	MD, ND
Oxacillin	N D	N D	MD 125 mg	MD, ND
Nafcillin	N D	No change	MD 125 mg	MD, no change
Amoxicillin	N D	N D	LD 250-500 mg, MD 50 mg	MD, ND
Penicillin G	N D	N D	LD 50 000 U, MD 25 000 U	MD, ND
<b>Quinolones</b>				
Ciprofloxacin	500 mg p.o., b.i.d.	N D	LD 50 mg, MD 25 mg	N D
Ofloxacin	400 mg p.o., then 200 mg p.o., q.d.	N D	As intermittent	N D
<b>Others</b>				
Vancomycin	15-30 mg/kg q.5-7 d	Increase doses by 25%	MD 30-50 mg/L	Increase MD by 25%
Teicoplanin	400 mg IP, b.i.d.	N D	LD 400 mg, MD 40 mg <sup>b</sup>	N D
Aztreonam	N D	N D	LD 1000 mg, MD 250 mg	N D
Clindamycin	N D	N D	LD 300 mg, MD 150 mg	N D
Metronidazole	250 mg p.o., b.i.d.	N D	As intermittent	N D
Rifampin	300 mg p.o., b.i.d.	N D	As intermittent	N D
<b>Antifungals</b>				
				All LD same as anuric
Amphotericin	N A	N A	MD 1.5 mg	N A
Flucytosine	2 g LD, then 1 g q.d., p.o.	N D	As intermittent	N D
Fluconazole	200 mg q.d.	N D	As intermittent	N D
Itraconazole	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr
<b>Antituberculars</b>				
	Isoniazid 300 mg p.o., q.d. + rifampin 600 mg p.o., q.d. + pyrazinamide 1.5 g p.o., q.d. + pyridoxine 100 mg/d	N D	As intermittent	N D
<b>Combinations</b>				
				All LD same as anuric
Ampicillin/sulbactam	2 g q.12 hr	N D	LD 1000 mg, MD 100 mg	N D
Trimeth/sulfamethox	320/1600 mg p.o., q.1-2 days	N D	LD 320/1600 mg p.o., MD 80/400 mg p.o.	N D

MD = maintenance dose; LD = loading dose; ND = no data; p.o. = oral; q.i.d. = four times per day; IV = intravenous; q.d. = once per day; b.i.d. = twice per day; IP = intraperitoneally; NA = not applicable.

CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens. For penicillins: "No change" is for those predominantly hepatically metabolized, or hepatically metabolized and renally excreted; "ND" means no data, but these are predominantly renally excreted, therefore probably an increase in dose by 25% is warranted; "NA" = not applicable, that is, drug is extensively metabolized and therefore there should be no difference in dosing between anuric and nonanuric patients. Anuric = <100 mL urine/24 hours; nonanuric = >100 mL/24 hours. These data for CAPD only.

<sup>a</sup> The route of administration is IP unless otherwise specified. The pharmacokinetic data and proposed dosage regimens presented here are based on published literature reviewed through January 2000, or established clinical practice. There is no evidence that mixing different antibiotics in dialysis fluid (except for aminoglycosides and penicillins) is deleterious to the drugs or patients. Do not use the same syringe to mix antibiotics.

<sup>b</sup> This is in each bag × 7 days, then in 2 bags/day × 7 days, and then in 1 bag/day × 7 days.

TABLE 4  
Treatment Strategies After Identification of Gram-Positive Organism on Culture

Enterococcus	<i>Staphylococcus aureus</i>	Other gram-positive organism (Coagulase-negative staphylococcus)
At 24 to 48 hours		
Stop cephalosporins	Stop ceftazidime or aminoglycoside	Stop ceftazidime or aminoglycoside
Start ampicillin 125 mg/L/bag	Continue cephalosporin	Continue cephalosporin
Consider adding aminoglycoside	Add rifampin 600 mg/day, oral	
If ampicillin-resistant, start vancomycin or clindamycin	If MRSA, start vancomycin or clindamycin	If MRSE and clinically not responding, start vancomycin or clindamycin
If VRE, consider quinupristin/dalfopristin		
Duration of therapy		
14 days	21 days	14 days
At 96 hours		
If no improvement, reculture and evaluate for exit-site or tunnel infection, catheter colonization, etc.		
Choice of final therapy should always be guided by antibiotic sensitivities.		

VRE = vancomycin-resistant enterococcus; MRSA = methicillin-resistant *S. aureus*; MRSE = methicillin-resistant enterococcus.

slow-growing organisms from the bowel may be present in conjunction with the enterococci.

If the organism is *S. aureus*, the first decision is based on its sensitivity to methicillin. If it is sensitive to methicillin, the first-generation cephalosporin is continued and the ceftazidime should be discontinued.

Since 24 - 48 hours will have elapsed since initiation of therapy, the clinician can judge whether the empiric regimen is working. If the clinical response is less than desired, rifampin 600 mg/day orally (in single or split dose) can be added to the IP-administered first-generation cephalosporin. If there is MRSA, rifampin should be added as above, and the first-generation cephalosporin should be changed to clindamycin or vancomycin. Vancomycin may be administered 2 g (30 mg/kg body weight) IP every 7 days. This dose should be modified for smaller individuals and reflect a dose based on body weight. Moreover, in the presence of residual renal function (> 500 mL/day urine output) a dosing interval of every 5 days is appropriate. Teicoplanin, where available, can be used in a dose of 15 mg/kg body weight every 5 - 7 days.

If the organism is identified as a gram-positive organism other than enterococcus or *S. aureus*, ceftazidime should be discontinued. *Staphylococcus epidermidis* is the most frequently identified organism in this situation. Peritonitis caused by coagulase-negative staphylococci that are "resistant" to first-generation cephalosporin may not resolve. However, if there is a clear response to empiric therapy (cefazolin or cephalothin), continued therapy with either antibiotic alone is appropriate. In this setting of methicillin-resistant *S. epidermidis* not respond-

ing to therapy, consideration should be given to use of clindamycin or vancomycin. Also, if clear improvement is not observed within 48 hours, or if the current peritonitis episode is a recurrence or a relapse, switching to an alternative agent such as clindamycin or vancomycin is warranted.

**Cultures Negative:** Occasionally (less than 20%), cultures may be negative for a variety of technical or clinical reasons. Experience would indicate that, if the patient is clinically improving, the first-generation cephalosporin should be continued and the ceftazidime discontinued (Table 5). Duration of therapy should be 2 weeks. If, on the other hand, no clinical improvement occurs within 96 hours, repeat evaluation is mandatory with consideration of mycobacteria or fungi, and catheter replacement or removal should be contemplated.

**Gram-Negative Micro-Organisms Cultured:** If a single ceftazidime-sensitive gram-negative organism, such as *Escherichia coli*, klebsiella, or proteus is isolated, this antibiotic is continued and first-generation cephalosporin stopped (Table 6). Utilization of ceftazidime must be guided by *in vitro* sensitivity testing. If the culture report reveals multiple gram-negative organisms, it is imperative to consider the possibility of intra-abdominal pathology, necessitating surgical exploration (Table 5).

In addition, if anaerobic bacteria are isolated, either alone or in combination with other gram-negative organisms, serious consideration should be given to surgical intervention because of the likelihood of bowel perforation. In this setting, metronidazole, in combination with ceftazidime or an aminoglycoside in the recommended doses, is the therapy of choice.

TABLE 5

Treatment Strategies if Peritoneal Dialysis Fluid Cultures Are Negative at 24 to 48 Hours or Not Performed

		Duration of therapy
Continue initial therapy		
If clinical improvement	Discontinue ceftazidime or aminoglycoside	
	Continue cephalosporin	14 days
If no clinical improvement at 96 hours	Repeat cell count, Gram stain, and culture	
If culture positive, adjust therapy accordingly		14 days
If culture negative, continue antibiotics, consider infrequent pathogens and/or catheter removal		14 days

TABLE 6

Treatment Recommendations if a Gram-Negative Organism Is Identified on Culture at 24 to 48 hours

		Duration of therapy
Single gram-negative organism	Adjust antibiotics to sensitivity < 100 mL urine, aminoglycoside > 100 mL urine, ceftazidime	14 days
<i>Pseudomonas/stenotrophomonas</i>	Continue ceftazidime and add < 100 mL urine, aminoglycoside (see Empiric Therapy, Table 2) > 100 mL urine, ciprofloxacin 500 mg, p.o. b.i.d. or piperacillin 4 g IV q.12 hours or sulfamethoxazole/trimethoprim 1-2 DS/day or aztreonam load 1 g/L; maintenance dose 250 mg/L IP/bag	21 days
Multiple gram-negatives and/or anaerobes	Continue cefazolin and ceftazidime and add metronidazole, 500 mg q.8 hours, p.o., IV, or rectally If no change in clinical status, consider surgical intervention	21 days

IV = intravenously; DS = double strength; IP = intraperitoneally.

Metronidazole is administered IV, orally, or rectally, in a dose of 500 mg every 8 hours.

Should the isolate be a pseudomonad (e.g., *Pseudomonas aeruginosa*), ceftazidime is continued. Also, an agent with activity against the isolated organism determined by *in vitro* sensitivity testing should be added. Piperacillin, ciprofloxacin (see Treatment of Exit-Site Infections, below), aztreonam, an aminoglycoside, or sulfamethoxazole/trimethoprim are possible candidates to combine with the ceftazidime (Table 6). At least two antibiotics with activity against pseudomonads will be necessary for cure. Should piperacillin be preferred, its dose is 4 g every 12 hours IV in adults. This dose is also appropriate for APD patients. Pseudomonal peritonitis is extremely difficult to cure, particularly when it develops as the consequence of a catheter-related infection. These organisms are known to protect themselves with a biofilm that makes effective antimicrobial penetration difficult. Thus, in the setting of catheter-related infection with these organisms, antibiotic treatment without catheter removal has a low likelihood of therapeutic success.

The isolation of a *Stenotrophomonas* species, while infrequent, requires special attention since they display sensitivity only to a few antimicrobial agents

(Table 6). Infection with this organism type is generally not as severe as with pseudomonas, and is usually not associated with an ESI. Therapy for pseudomonas/stenotrophomonas peritonitis is recommended for 3 - 4 weeks if the patient is clinically improving. The consequences of persistent gram-negative peritonitis, particularly pseudomonas, on peritoneal membrane integrity over the long term are poorly understood. However, it is thought that it could lead to loss of peritoneal transport function. Therefore, consideration of early catheter removal is important to preserve peritoneal function and to avoid repeated long-term treatment with potentially toxic antibiotics.

**Antibiotic Toxicities:** The intermittent dosing recommendation for aminoglycosides (amikacin, tobramycin, gentamicin, and netilmycin) may reduce the risk of ototoxicity and cochlear toxicity. However, some risk for such toxicity will remain, especially if treatment courses are extended beyond 2 - 3 weeks, or when repeated courses, for example, for relapsing peritonitis, are given. Thus, prolonged treatment with these agents should be limited to the rare occasion when no alternative, less toxic agents are likely to be effective.

In intermittent dosing, dialysate and serum concentrations depend on residual renal function. In pa-

tients with residual renal function who are treated with intermittent vancomycin, once-weekly monitoring of serum concentrations may be useful to prevent underdosing. Monitoring of aminoglycoside serum concentrations in CAPD peritonitis may be performed routinely for similar reasons.

*Fungal Organisms Cultured:* Many clinicians still feel that catheter removal is indicated immediately after fungi are identified by Gram stain or culture. As indicated above (in the section, Gram Stain Reveals Yeast), recent experience with the newer imidazoles/triazoles and flucytosine (orally or, if available, IP) suggest that these agents may also be efficaciously administered (Table 7). Although prospective clinical trials of PD-related fungal peritonitis comparing amphotericin B to the imidazole/triazoles-flucytosine combinations have not been performed, a retrospective analysis of published data suggests this latter combination is as efficacious as amphotericin B, particularly for nonfilamentous fungi. However, emergence of resistance to the imidazoles has occurred, thus raising some concerns. Where available, fungal sensitivities should be obtained. It is reasonable that successful therapy should be continued for 4 - 6 weeks (Table 7); however, if clinical improvement does not occur after 4 - 7 days of therapy, the catheter should be removed. Therapy with these agents should be continued, after catheter removal, orally with flucytosine and fluconazole daily for an additional 10 days (Table 7). Oral flucytosine has been withdrawn from some markets (e.g., in Canada) and this will influence local protocols.

#### TREATMENT OF PERITONITIS IN APD PATIENTS

As in CAPD peritonitis, the majority of APD peritonitis episodes are caused by gram-positive bacteria. There have been some reports indicating a higher incidence of culture-negative or gram-negative peritonitis in APD, but these differences were small and were not confirmed in other studies. Consequently, the choice of first-line antibiotics in CAPD applies also to APD.

In many centers, during peritonitis, APD patients are changed to a CAPD schedule because it is then easier to evaluate the clinical course using standardized procedures for obtaining dialysate for cell count and culture and sensitivity. Furthermore, the recommendations for antibiotic treatment are based mainly on data obtained using CAPD and limited experience in APD (Manley *et al.*, 2000, *J Am Soc Nephrol* ).

If patients stay on APD, antibiotics can be given continuously or intermittently (See Table 8). Because the bactericidal action of aminoglycosides is dose-dependent, once-daily administration of aminoglycosides is recommended. Vancomycin and other glycopeptides can be given intermittently because of their unique pharmacokinetic properties. With all other antibiotics, the dose in APD can only be extrapolated from pharmacokinetic studies in CAPD, as no such studies are available in APD patients. Only one study on the clinical outcome of peritonitis in APD patients has been published. In this study, the results of once-daily IP cefazolin and oral ciprofloxacin as empiric therapy were considered suboptimal (Troidle *et al.*, 1999). Attention should be given to an adequate dwell time of at least 4 hours to allow absorption of antibiotic agents.

An interesting option for treatment of peritonitis in APD patients is oral administration of antibiotics. However, here also pharmacokinetic studies are lacking and this route of administration can therefore only be recommended in uncomplicated episodes due to coagulase-negative staphylococci.

As with CAPD, adjustments for APD prescription may be needed in patients who experience altered ultrafiltration during episodes of peritonitis.

#### ASSESSMENT OF PATIENTS WHO FAIL TO DEMONSTRATE CLINICAL IMPROVEMENT

Within 48 hours of initiating therapy, most patients with PD-related peritonitis will show considerable clinical improvement. Occasionally, symptoms may persist beyond 48 - 96 hours. At 96 hours, if patients have not shown definitive clinical improvement, a re-

TABLE 7  
Treatment Recommendations if Yeast or Other Fungus Identified on Gram Stain or Culture

At 24 to 48 hours	
Flucytosine and Fluconazole	Loading dose 2 g p.o.; maintenance dose 1 g p.o.  200 mg, p.o., or intraperitoneally, daily
If organism is resistant, consider itraconazole	
At 4 to 7 days	
If clinical improvement, duration of therapy 4-6 weeks	
If no clinical improvement, remove catheter and continue therapy for 7 days after catheter removal	

TABLE 8  
Dosing of Antibiotics, by IP Intermittent Route, in Automated PD (These data for APD only)

Drug	
Piperacillin <sup>a</sup>	4000 mg IV, b.i.d.
Vancomycin <sup>a</sup>	Loading dose 35 mg/kg Maintenance dose 15 mg/kg IP q.d.
Cefazolin <sup>b</sup>	20 mg/kg q.d., in first or second ambulatory dwell
Tobramycin <sup>b</sup>	Loading dose 1.5 mg/kg day 1 Maintenance dose 0.5 mg/kg q.d., in first or second ambulatory dwell.
Fluconazole	200 mg IP, q.24-48 hr

IP = intraperitoneal; PD = peritoneal dialysis; IV = intravenous; b.i.d. = two times daily; q.d. = every day.

Unless otherwise specified, IP doses to be added to the 1st ambulatory dwell after the automated exchanges.

<sup>a</sup> Unpublished data.

<sup>b</sup> *J Am Soc Nephrol* 2000; 11:1310-16.

evaluation is essential. Specifically, cell counts, Gram stain, and cultures should be repeated. Antibiotic removal techniques may be used in an attempt to maximize culture yield.

Among the paramount clinical concerns in patients with persistent symptomatology is the presence of intra-abdominal or gynecological pathology requiring surgical intervention, or the presence of unusual organisms, such as mycobacteria, fungi, or fastidious organisms. Identification of these latter organisms will often require special culture techniques and must be coordinated with the microbiology laboratory.

In patients with *S. aureus* infections that have not shown significant improvement, the possibility of an underlying tunnel infection or an intra-abdominal abscess must be considered. Ultrasonography, or possibly computed tomography, may be performed to assess the presence of an occult abscess. In addition, in the re-evaluation of the patient's medical status, the antimicrobial regimen should be reassessed. Patients with *S. aureus* peritonitis treated with a first-generation cephalosporin to which rifampin has already been added, and that demonstrate failure to clinically improve, should be re-evaluated. Specifically, evaluation for an occult tunnel infection should be considered. If a coagulase-negative staphylococcus (*S. epidermidis*) has been cultured from the dialysate effluent, and the patient has failed to respond to the initial therapy, rifampin may also be added in the doses recommended. Alternatively, in the setting of methacillin-resistant staphylococcus, vancomycin should be used.

If anaerobic bacteria have been identified by culture, and the patient has not improved clinically by 96 hours, the catheter should be removed, surgical exploration considered, the antibiotic regimen re-evaluated, and therapy should be continued IV for 5 -7 additional days after catheter removal. Similarly, if more than one gram-negative organism, other than pseudomonas, has been identified, catheter removal

is warranted and IV antibiotics should be continued for 5 -7 days. In those patients with anaerobic bacteria or gram-negative organisms, exclusive of pseudomonas, the possibility of an intra-abdominal process necessitating surgical exploration should be considered. Finally, if pseudomonas has been identified and, the patient has failed to demonstrate any significant clinical improvement within 48 - 72 hours after initiating therapy, the catheter should be removed. As described above, two antibiotics with antipseudomonal activity should be continued IV for at least 5 - 7 days. The suggested duration of antibiotic therapy after removal of the catheter may be modified, depending upon the clinical course. There are no studies establishing the appropriate duration of antimicrobial therapy following catheter removal.

If therapy for fungal peritonitis was initially instituted but no clinical improvement has been seen, the catheter should be removed. Finally, for those patients in whom the original cultures were negative, and who are still demonstrating persistence of symptomatology at 96 hours, the catheter should be removed and cultured, and IV antifungal agents should be continued for 5 -7 days.

#### DURATION OF ANTIBIOTIC THERAPY

There have been no carefully conducted trials to define the length of treatment. In clinical practice, the length of treatment is determined mainly by clinical response. After the initiation of antibiotic treatment, clinical improvement should be present in the first 72 hours. In patients in whom a change in the antibiotic regimen has been made, an additional 72 hours will be needed to assess clinical response.

*Patients Demonstrating Clinical Improvement:* In patients with gram-positive peritonitis and in patients with culture-negative peritonitis, antibiotic treatment should be continued for at least 1 week after a clear

dialysate ( $< 100$  leukocytes/ $\text{mm}^3$ ) and negative cultures have been obtained. This means that 10 - 14 days are usually adequate for treatment of peritonitis in uncomplicated episodes due to coagulase-negative staphylococci. In patients with *S. aureus* peritonitis, the infection is usually more severe than in other gram-positive episodes. Therefore, a 3-week treatment is recommended for these episodes.

In patients with an uncomplicated peritonitis episode due to a single gram-negative micro-organism, treatment with an effective antibiotic agent for about 21 days is usually adequate. Therapy for pseudomonas/stenotrophomonas should be at least 21 days in duration.

In patients with multiple gram-negative micro-organisms, a high relapse-rate is common even with adequate antibiotic therapy. Therefore, even in episodes with initial clinical improvement, removal of the catheter should be considered. If the catheter is not removed, antibiotic treatment should be continued for at least 21 days. Computed tomography should be considered in order to detect possible abscess formation.

Fungal peritonitis can be treated with appropriate antibiotics. This applies especially to *Candida* species. If successful, treatment should be continued for at least 4 weeks.

*Patients Failing to Demonstrate Clinical Improvement:* In patients who fail to demonstrate clinical improvement, daily clinical judgment is of vital importance. In those patients with persistent symptomatology during appropriate antibiotic treatment, one should remove the catheter. Antibiotic treatment should be continued for at least 1 week after catheter removal. In patients with peritonitis due to multiple organisms and/or anaerobes, not only catheter removal but also an exploratory surgical intervention should be considered. If, after removal of the catheter, clinical improvement does not occur, an intra-abdominal abscess should be considered.

#### TUBERCULOUS PERITONITIS

Tuberculous (TB) peritonitis is a rare complication of PD (see Vas, 1994), although in some studies, the prevalence of this infection has been as high as 3%, particularly in populations with a high prevalence of TB. Clinically, it should be considered in patients with peritonitis that is not responding to appropriate antibiotic treatment, whether it is a culture-negative peritonitis, so-called sterile peritonitis, or proven bacterial peritonitis. In general, TB peritonitis is due to reactivation of a latent focus rather than a primary infection through the catheter. However, in cases of prior pulmonary TB, re-infection can be confirmed by deoxyribonucleic acid

(DNA) fingerprinting with restriction-fragment-length polymorphism and analysis. Re-infection from a pulmonary source should be considered in high-risk populations. Most TB patients present with fever and abdominal pain. Peritoneal fluid differential leukocyte count, and radionucleotide imaging methods are not usually helpful in the differential diagnosis of this entity. Smears of the peritoneal effluent often fail to reveal acid-fast bacilli, thus diagnosis must rely on TB cultures. Since peritoneal fluid culture for acid-fast organisms usually takes 6 weeks, the diagnosis is frequently delayed in the majority of patients. In order to make an earlier diagnosis in patients not responding to therapy, invasive procedures such as exploratory laparotomy or laparoscopy with biopsy of the peritoneum or omentum should be considered. Detection of mycobacterial DNA amplified by polymerase chain reaction techniques from peritoneal effluent hold the greatest promise for rapid detection of TB. Recently, non-TB mycobacteria have been associated with clinical peritonitis; *M. fortuitum*, *M. kansasii*, and *M. goodnae* have been isolated from infected patients. In some episodes of sterile peritonitis, the use of molecular techniques is necessary to identify mycobacterium as the causative organism.

Few data exist for the optimal choice and duration of chemotherapy of TB peritonitis. Based on the usual conservative approach to extrapulmonary TB, most reported cases have been treated with three drugs (isoniazid 300 mg orally, four times daily; rifampicin 600 mg orally, four times daily; and pyrazinamide 1.5 g orally, four times daily), usually for 12 months (Table 3). Pyridoxine (100 mg/day orally) should be routinely ordered. Since streptomycin, even in reduced doses, may cause ototoxicity after prolonged use, it should not be administered to the end-stage renal disease patient. Similarly, ethambutol is not recommended because of the high risk of optic neuritis. Catheter removal appears to be necessary in all cases.

#### PROPHYLACTIC ANTIBIOTIC USE

*Extended Use of Prophylactic Antibiotics:* Long-term prophylactic use of penicillins or cephalosporins has not been shown to decrease the risk of peritonitis. In patients with chronic ESI, there are no data to show whether long-term antibiotic therapy for chronic ESI is preferable to replacing the catheter. However, the regular use of intranasal or exit-site mupirocin decreases the risk of *S. aureus* ESI (see section below). Data on the effectiveness of oral prophylaxis with nystatin ( $3 \times 500$  IU) during antibiotic therapy to decrease the risk of fungal peritonitis are conflicting.

*Short-Term Antibiotic Prophylaxis:* Invasive procedures associated with transient bacteremia may infrequently cause peritonitis in PD patients. Therefore, a single dose of amoxicillin (2 g) before extensive dental procedures is reasonable. Patients undergoing colonoscopy with polypectomy are at risk for enteric peritonitis, presumably from movement of bacteria across the bowel wall and into the peritoneal cavity. Ampicillin plus an aminoglycoside, with or without metronidazole, given just prior to the procedure may decrease the risk of peritonitis. The abdomen should be emptied of fluid prior to all procedures involving the abdomen or pelvis (such as colonoscopy, renal transplantation, or endometrial biopsy).

*Prophylactic Antibiotics and Catheter Placement:* Prophylactic antibiotics given before catheter placement decrease the risk of subsequent infection. A first-generation cephalosporin has been most frequently used in this context. Routine use of vancomycin should be avoided in this setting.

*Use of Prophylactic Antibiotics After a Technique Break:* Although there are no data on the use of prophylactic antibiotics after a known break in technique, most nephrologists give a 1- to 2-day course of antibiotics. A first-generation cephalosporin is probably adequate. Vancomycin use as prophylaxis in this setting should be avoided, unless the patient is a known carrier of MRSA or has had some recent antecedent event making MRSA more of a concern.

*Exit-Site Infections and Prophylactic Antibiotics:* *Staphylococcus aureus* nasal carriage is associated with an increased risk of *S. aureus* ESI, tunnel infections, peritonitis, and catheter loss. Diabetic patients and those on immunosuppressive therapy are also at increased risk for *S. aureus* catheter infections. Prophylaxis with intranasal mupirocin, exit-site mupirocin, or oral rifampin is effective in reducing *S. aureus* ESI (see Zimmerman *et al.*, 1991; Bernardini *et al.*, 1996). A small amount of mupirocin ointment applied daily to the exit site, using a cotton swab, after routine exit-site care is as effective as oral rifampin in reducing ESI rates. Mupirocin is preferred to rifampin for prophylaxis because toxicity from mupirocin is negligible. The use of mupirocin ointment at the exit site, however, should be avoided in patients with polyurethane catheters (Cruz catheter) as structural damage to the catheter has been reported. Data on the use of cream at the exit site of polyurethane catheters are not available. All patients at an increased risk for *S. aureus* infections, including *S. aureus* carriers, diabetics, and immunocompromised patients, should be provided with prophylaxis. A practical approach is to prescribe exit-site mupirocin for all such PD patients, thus eliminating the need for nasal cultures.

## TREATMENT OF EXIT-SITE INFECTIONS

An ESI is defined by the presence of purulent drainage with or without erythema of the skin at the catheter-epidermal interface. A culture of the purulent drainage should be obtained (Figure 1). Empiric antibiotic therapy may be initiated immediately if the clinical appearance warrants early intervention, or delayed until the results of the culture are available. Gram-positive organisms are treated with an oral penicillinase-resistant penicillin, cephalexin, or sulfamethoxazole trimethoprim (see Flanigan *et al.*, 1994). To prevent unnecessary exposure to vancomycin, and thus emergence of resistant organisms, vancomycin should be avoided in the routine treatment of gram-positive ESI and tunnel infections. In slowly-resolving or particularly severe-appearing *S. aureus* ESI, add rifampin 300 mg two times daily. Gram-negative organisms may be treated with oral quinolones such as ciprofloxacin 500 mg two times daily. Chelation interactions may occur between fluoroquinolones and concomitantly administered multivalent cations. Calcium salts, oral iron supplements, zinc preparations, sucralfate, magnesium-aluminum antacids, and milk may reduce oral ciprofloxacin absorption by 75% - 91%, with a possible significant reduction in antimicrobial activity. It is suggested that administration of the preparations be staggered as much as possible. A minimum spacing of 2 hours between preparations is recommended, with the ciprofloxacin administered first (see Lomaestro and Bailie, 1995). If the organism is *P. aeruginosa* and resolution is slow or there is recurrence, IP ceftazidime may be added. Therapy should be continued until the exit site appears completely normal. Prolonged antibiotics may be necessary. If 3 - 4 weeks of antibiotics fails to resolve the infection, the catheter may be replaced. Alternatively, 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 promptly removed.

Pericatheter erythema without purulent drainage is sometimes an early indication of infection. If the clinician suspects infection, then therapy should be initiated, which may be either intensified local care, a local antibiotic ointment, or an oral antibiotic that covers gram-positive organisms. An alternative approach is careful observation for additional signs of infection.

## RELAPSING PERITONITIS

Relapsing peritonitis is defined arbitrarily as another episode of peritonitis caused by the same genus/species that caused the immediately preceding episode and occurs within 4 weeks of completion of the antibiotic course. Clinically, these patients will have

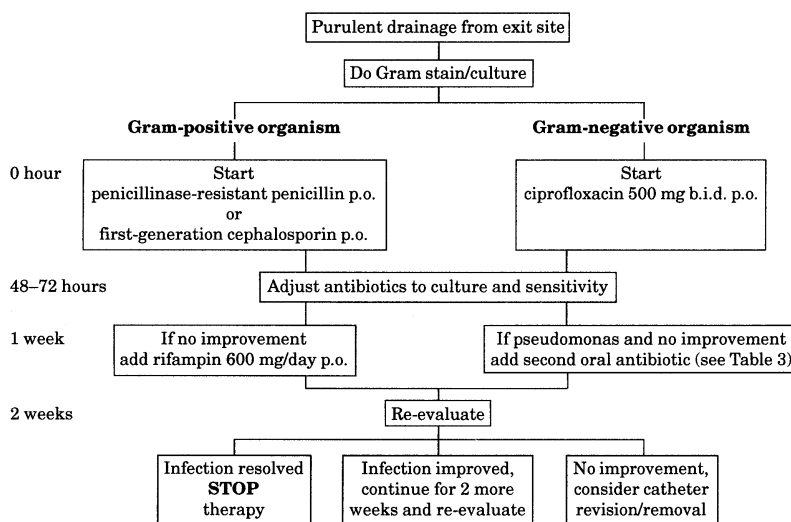


Figure 1 – Flow chart for diagnosis and management of exit-site infections is shown.

signs and symptoms similar to those described in patients with sporadic peritonitis. Relapsing infections with coagulase-positive or -negative staphylococci should be treated with cephalosporins and rifampin for approximately 4 weeks. However, in the setting of relapsing peritonitis with methicillin-resistant *S. aureus* or *S. epidermidis*, clindamycin or vancomycin should be considered for therapy. In the presence of coagulase-positive staphylococcus infection, a search for an occult tunnel infection should also be made. If enterococci are recultured, ampicillin and an aminoglycoside should be used in the recommended doses. Consideration should also be given to the possibility of an intra-abdominal abscess. If no clinical response is noted after 96 hours of therapy for relapsing peritonitis, catheter removal is indicated. If the patient responds clinically, but subsequently relapses an additional time, catheter removal and replacement are recommended.

In relapsing peritonitis caused by gram-negative organisms, one should evaluate clinically for an intra-abdominal abscess. Catheter removal and surgical exploration should be strongly considered in these patients. Treatment with ceftazidime or an aminoglycoside alone can be used once culture results are known. If pseudomonas or stenotrophomonas organisms are identified again on culture, the catheter should be removed. Finally, in those patients with relapsing peritonitis, short-term interruption of PD may be of value; however, the availability of supportive hemodialysis will dictate whether this option can be considered.

#### CATHETER INSERTION AFTER REMOVAL FOR CAPD PERITONITIS

The optimal period of time between catheter removal for infection and reinsertion of a new cath-

eter is not known. Empirically, a minimum of 3 weeks between catheter removal and reinsertion of a new catheter is recommended. However, removal of the old catheter and insertion of a new one during the same operation has been done successfully in the setting of refractory tunnel infections as well as relapsing peritonitis (see Swartz *et al.*, 1991). This simultaneous procedure may be recommended when the relapsing peritonitis is due to either biofilm formation on the intra-abdominal section of the catheter (predominately relapsing peritonitis due to coagulase-negative staphylococcus), or to tunnel involvement (primarily relapsing peritonitis due to *S. aureus*). This approach should be limited to those episodes in which the effluent WBC count has fallen to less than 100/ $\mu$ L with antibiotic therapy. Simultaneous catheter replacement should not be used for peritonitis episodes due to pseudomonas, fungus, or mycobacterium, nor should it be used if the patient has an intra-abdominal abscess or a suspected intra-abdominal source for the peritonitis (Swartz and Messana, 1999). Since a PD-free interval (with or without a catheter in place) may also be helpful in resolving peritonitis, the timing of catheter reinsertion should be individualized.

#### USE OF ADJUNCTIVE THERAPY IN TREATMENT OF APD PERITONITIS

The performance of two to three rapid exchanges of PD solution immediately after diagnosis of peritonitis is reported to be of symptomatic benefit, but does not appear to offer any other specific therapeutic benefits. A few rapid exchanges every 20 minutes is advocated only for severe symptomatic peritonitis at the start of therapy. Usual practice is the performance of one rapid cleansing exchange prior to the longer dwell

exchange with IP antibiotics. Heparin (500 - 1000 U/L) may be added to the regular regimen until dialysate effluent clears. This usually occurs within 48 - 72 hours.

Thrombolytic therapy should be reserved for those infections in which no other cause or complication is evident, and should probably be limited to coagulase-negative staphylococcal or culture-negative infections. Temporary discontinuation of PD with continuation of antibiotic therapy may be a reasonable adjunctive therapy for recurring, resistant, or relapsing infections. Although the duration of this approach has not been clearly established, durations of 7 - 28 days have been advocated (see Pagniez *et al.*, 1988; Locatelli *et al.*, 1995). Variations of this approach have also been proposed and include hyperconcentrated antibiotics (antibiotic lock technique) or fibrinolytics added within the catheter lumen at the time of peritoneal resting. Several small studies have reported some benefit using peritoneal rest with or without intracatheter agents, but only in cases of mildly symptomatic peritonitis. Overall, the role of thrombolytic therapy, as well as temporary discontinuation of PD, is limited. Furthermore, pain, fever, and peritonitis-like syndromes may be common with IP injection of streptokinase.

In a recent report (including patients with associated tunnel infections) evaluating the treatment of refractory and recurring peritonitis, simultaneous removal and replacement of the catheter was shown to be beneficial to patients with refractory peritonitis (see Innes *et al.*, 1994). It should be noted that the organisms involved in the failure of this approach included mycobacteria, fungi, and/or pseudomonas. Simultaneous catheter removal and replacement as an adjunctive therapy for peritonitis is described elsewhere in these recommendations.

#### TECHNIQUES FOR SAMPLING AND CULTURING PD EFFLUENT

*Specimen Processing:* In order to establish accurate microbiological diagnosis of peritonitis in APD patients, the following points are important:

1. Cultures should be taken as early as possible from suspected cases of peritonitis; the first cloudy fluid sample is the best specimen. A delay of several hours from the time of collection to the time of culture does not seem to decrease the efficiency of microbial recovery.
2. Large volumes should be cultured or concentrated to maximize bacterial recovery rates.
3. Washing the specimen sediment with sterile saline or using antibiotic-removing or -neutralizing resin has been shown to improve the sensitivity

of recovery in APD patients and should be considered routine procedure whenever possible.

4. Identification and sensitivity testing should be done as soon as possible to achieve rational antibiotic therapy.

*Culture Procedure:* The correct microbiological culture of PD samples is of utmost importance to establish the etiological agent and the appropriate antibiotic therapy. In addition, the type of organism can indicate the possible source of infection. In the early days of CAPD, PD effluent was handled by laboratories as any other clinical specimen, that is, small amounts of fluid were cultured. Culture of large amounts of fluid improves the accuracy of diagnosis (See Sewell *et al.*, 1990). Most methods presently employed incorporate either a concentration method, using filtration or centrifugation, or blood culture techniques. The removal of antibiotics present in the specimen may further improve the isolation rate. Some authors recommend lysis of peritoneal leukocytes to improve culture results.

Centrifugation of 50 mL of peritoneal effluent at 3000g for 15 minutes, followed by resuspension of the sediment in 3 - 5 mL of sterile saline, and inoculation of this material into a standard blood culture medium is usually adequate for primary isolation of the causative organisms, although the inclusion of antibiotic neutralizing medium may be advantageous (see Alfa *et al.*, 1997). The use of anaerobic blood culture media for inoculation is optional; some laboratories find its inclusion helpful.

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) may further speed up isolation and identification. 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.

The routine collection of peripheral blood cultures is unnecessary in all but the youngest patients since they are usually negative. If the patient appears to be septic or if an acute abdominal source is suspected (appendicitis, cholecystitis, etc.), blood cultures may be helpful in identifying the source of infection. Occasionally, blood cultures yield gram-positive organisms ( $\alpha$ - or  $\beta$ -hemolytic streptococci), suggesting upper respiratory tract infections or previous dental work.

*Frequency of Cultures:* It is important to obtain the first cloudy effluent for culture. The probability of positive diagnostic culture is greatest from this specimen. Patients should be instructed, therefore, to bring the first cloudy fluid to the laboratory immediately.

After the initial culture, repeat effluent cultures are not recommended if the cell count is decreasing appropriately and the patient is responding symptomatically. If cell counts are either rising or not decreasing appropriately by 3 days, repeat cultures should be taken and management guidelines should be consulted.

**"Sterile" or Culture-Negative Peritonitis:** The incidence of sterile peritonitis varies among units from 2% - 20%, depending on the methods used in the laboratory. In this context, sterile peritonitis is manifested by other clinical features of microbial peritonitis (e.g., evidence of inflammation and infection), and not just turbid effluent dialysate. Occasionally, "sterile" peritoneal fluid is reported by the laboratory when the causative organism is difficult to culture or inappropriate culture methods are used. This is typically the case when mycobacterial peritonitis or peritonitis due to a rare fungus is present. Leading diagnostic symptoms are persistently cloudy fluid, usually with relatively low cell counts, and lymphocytes or mononuclear cells predominant in the differential count. Possible causes of culture-negative peritonitis are listed below in order of decreasing importance:

1. Culture methods of low sensitivity are used. Many centers use laboratory facilities not experienced in the specialized culture techniques recommended for PD effluent.
2. Culture volumes are too small.
3. Causative organism (e.g., mycobacteria) requires specialized culture media.
4. Cultures are taken from patients on antibiotic treatment unknown to the PD center. A study performed to analyze surreptitious antibiotic use found that a surprisingly high percentage of PD fluids resulting in negative cultures contained antibiotic activity (see Sewell *et al.*, 1990).
5. The symptoms and signs are not due to infectious agents.

#### FUTURE DIRECTIONS

There have been a considerable number of therapeutic developments during the past decade. We continue to be faced with an increasing incidence of vancomycin-resistant gram-positive organisms, a situation that has created substantial concern worldwide. The Society's Web site (<http://ispd.org>) has provided a useful forum for dissemination of these recommendations, as well as an extensive reference list.

Although the establishment of a multicentered infection project was considered one way to develop new and needed data for the treatment of PD peritonitis, this concept proved difficult to implement effectively.

Nonetheless, there is a continued need for scientifically valid clinical trials in PD patients assessing alternative treatment strategies using newer and less toxic antibiotics. Inherent in this is the need to develop pharmacokinetic data in all PD modalities to guide our use of these antibiotics. In this respect, the impact of residual renal function on dosing, as well as the effect of antibiotics on residual renal function, is an important and fruitful area of research.

An area of continued investigation must be related to the improvement of catheter technology and the early detection and therapy of catheter-related infections. Additional insights into catheter management should be developed, particularly as they pertain to exit and tunnel infections. The optimal interval before catheter insertion can be performed safely must be defined, and improvement in catheter design and materials should be supported. The role of catheter biofilm in PD infections also remains a potential area for fruitful investigation.

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