

Microbiological Aspects of Peritonitis Associated with Continuous Ambulatory Peritoneal Dialysis

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INTRODUCTION: HISTORY AND BACKGROUND

For patients with end-stage renal disease, peritoneal dialysis has been shown to be a practical, safe, effective, and cost-effective alternative to chronic hemodialysis. Since 1985, peritoneal dialysis has been recognized as a major form of therapy for chronic renal failures. While the application of this process continues to expand, a limiting factor is the threat of infection, i.e., peritonitis, associated with this procedure.

As of 1988, the CAPD Registry of the National Institutes of Health had listings for more than 25,000 U.S. patients on continuous ambulatory peritoneal dialysis (CAPD) or one of its alternative forms. It is estimated that over 35,000 people were maintained on CAPD worldwide in 1988 (99) compared with 24,000 patients in 1985 (106).

The idea of using the peritoneal membrane as a natural filtration device for eliminating toxic components from the blood has a long history. Its experimental beginnings might be traced to work by Ganter in 1923 (41). In that early work, Ganter described the intermittent infusion into and removal of saline solution from the peritoneal cavity of guinea pigs who were rendered experimentally uremic by ureteral ligation. The modern era of dialysis can be traced to Popovich and coworkers (111). In 1976 they described the intraperitoneal infusion of 2 liters of dialysate fluid into a patient. The dialysate was equilibrated for 5 h while the patient was capable of conducting usual activities. The dialysate was then drained and fresh fluid was instilled again. In a subsequent article, additional experience with several other patients was reported by Popovich et al., who changed the method to CAPD (112). As noted in recent reviews (93, 129, 131), advances in CAPD were made possible by the Palmer catheter, designed in 1964; its replacement, the silicone rubber long-term indwelling Tenckhoff catheter (128); and

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the availability of commercial dialysate fluids that protect patients against large shifts of water and minerals and the potential for acidosis that occurs during the dialysis process.

Today, peritoneal dialysis encompasses a closed system of commercially prepared dialysate fluid packaged in plastic bags that are connected by silastic tubing to the Tenckhoff catheter. The effectiveness of CAPD is achieved by hyperosmolar ultrafiltration across the peritoneal membrane. Usually 1 to 2 liters of dialysate is infused for a dwell time of 4 to 8 h, and cycles are repeated every 6 h. When empty, bags are reused for recovery of effluent drainage by gravity at the end of a cycle.

Peritonitis is still the main complication of CAPD. This review will cover the microbiological aspects of CAPD peritonitis: pathogenesis, diagnostic features, epidemiology, etiology, cultivation of microorganisms, and prevention. Issues related to specific therapeutic management are omitted. The literature on individual agents emphasizes more recent publications.

PATHOGENESIS

Surgical and Spontaneous versus CAPD Peritonitis

Microbiologists and infectious disease specialists are most familiar with the microbial flora of surgical peritonitis, which is associated with perforation of the bowel accidentally or surgically. The pathogenesis of peritonitis associated with CAPD (CAPD peritonitis) is markedly different. In the former case, polymicrobial infections involving gram-negative aerobic and anaerobic bacteria predominate. In the case of CAPD peritonitis, infections associated with single organisms, usually gram-positive species (e.g., coagulase-negative staphylococci), are the rule. The density of the inoculum associated with surgical peritonitis is usually high compared with that in peritoneal dialysis patients. With surgical peritonitis, approximately 30% of patients go on to develop bacteremic disease; in CAPD patients, the evidence of positive blood cultures is rare (106). More closely allied to peritonitis infections in CAPD patients is a disease referred to as spontaneous bacterial peritonitis (26), which is observed in patients diagnosed as having cirrhosis of the liver with ascites. Like CAPD patients, these patients have large volumes of fluid in their abdominal cavities. However, the prime cause of spontaneous peritonitis is the absence of the reticuloendothelial function of the liver. For these reasons, CAPD peritonitis is recognized as a separate disease entity, and its diagnosis and management necessitate a different approach (25).

Portals of Entry and Microbial Pathogenicity Factors

There are several potential portals of entry for infection in CAPD patients. The three most frequent sites associated with CAPD infections are the exit site, i.e., the area where the catheter is connected to lines from the peritoneal dialysate; the tunnel associated with the implant of the Tenckhoff catheter in the abdominal wall; and the peritoneum itself.

Intraluminal infections occur when bacteria enter the space in the internal tubing pathway through cracks that develop in the tubing or through accidental contamination of the spike by manipulation of the connector. Infections around the silastic catheter, which is never completely sealed with the junction of the skin or the subcutaneous tissue, can also occur and are referred to as periluminal infections. Penetration of bacteria around this potentially

weak area can be a serious factor in the development of peritonitis. Infections in these areas are referred to as either exit site (at the site of cutaneous entry) or tunnel (in the subcutaneous tunnel) infections. Transmural infections, i.e., infections of intestinal origin, indicate a fecal leak. The isolation of multiple organisms of intestinal origin from the peritoneal fluid (including anaerobic microorganisms) is strongly associated with fecal contamination (100). Wu et al. have shown that the most likely source of an intestinal leak is through a preexisting diverticulosis in these patients (157). Some studies indicate that transmural migration of *Escherichia coli* from the gastrointestinal tract into the peritoneal cavity does occur (115, 143). Other contributing endogenous routes of infection have included vaginal leaks of peritoneal dialysis fluid (135).

Among the several factors that may contribute to or enhance microbial pathogenicity is the extracellular slime (biofilm) produced by certain organisms on surfaces (54). Biofilms associated with peritoneal catheters have been described before (92). It has been shown that staphylococci can grow as microcolonies on the polymeric silicone materials used in the production of the catheter materials and that this ability plays an important role in the pathogenesis of staphylococcal peritonitis (92). The extracellular slime substance, or biofilm, produced by these organisms may serve to protect them from host defenses as well as from antimicrobial action and could explain the relapses that occur in many patients with staphylococcal peritonitis (54). *Candida albicans*, the fungal species most frequently found in patients with peritonitis, has also been shown to grow on silastic surfaces, and biofilm production has been implicated in its pathogenesis (106).

Although slime may play a role in the recurrence of infection, evidence from the study of Horsman and coworkers challenges the role of slime (56). Using plasmid profiles of coagulase-negative staphylococci as an epidemiologic marker, the investigators identified cases in which isolates from surveillance skin cultures taken before an episode of peritonitis were identical to those isolated from the effluent. The staphylococcal strains from most patients had identical plasmid profiles when isolated during the initial episode and a second episode of peritonitis occurring 10 days to 4 weeks later. Slime production did not discriminate between pre- and postepisodic conditions (56).

The principal pathogens associated with CAPD peritonitis, i.e., *Staphylococcus epidermidis*, *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa*, have been studied in vitro to determine their growth capabilities and survival in peritoneal dialysis fluids (86, 126, 145). Verbrugh and colleagues found that staphylococci could not survive in commercially prepared dialysis solutions but grew well in the peritoneal dialysis effluents recovered from patients after the dwell time (postdialysis fluid). In contrast, *E. coli* grew readily in both pre- and postdialysis peritoneal fluids (145). These findings were supported by Sheth et al., who reported similar findings for the staphylococci and demonstrated a 1,000-fold increase in the growth of *P. aeruginosa* and *E. coli* in peritonitic fluids from patients with peritonitis compared with growth in fluids from uninfected patients (126). On the basis of their findings, Sheth et al. reasoned that culture-negative cases of peritonitis were probably due to gram-positive cocci, especially coagulase-negative staphylococci, since these organisms may not be readily culturable because of their poor survival in peritoneal fluid (126). The viability of *S. epidermidis* in commercial dialysis fluids fortified with 0.5 to 4.25% glucose was studied by MacDonald and coworkers (86). They found

that fresh dialysis fluid (of all osmolarities tested) neither supported the growth of *S. epidermidis* nor was bactericidal.

Defense Mechanisms

The cell population of the normal peritoneum is composed primarily of mononuclear cells, i.e., macrophages from the blood and mesothelial cells from the peritoneal lining. Organisms that invade the peritoneal cavity are challenged by peritoneal macrophages (PMs) and polymorphonuclear leukocytes (PMNs). Bacterial penetration into this space triggers an inflammatory response that stimulates the rapid migration of PMNs. This sudden change in the cellular population from predominantly mononuclear to polymorphonuclear can be used as a valuable laboratory index in the laboratory diagnosis of infection (see below). Conversely, diminished cellular response can be used as a positive indicator of therapeutic success.

According to recent observations, PMs react like "stimulated" or "activated" cells and represent the primary defense barrier against bacterial invasion (146). When PMs are overwhelmed, PMNs move into the peritoneal cavity. Phagocytosis by PMs and PMNs is facilitated by opsonins, and their absence (and low pH) interferes with this activity (53).

When used for CAPD, the peritoneal cavity does not provide a supportive environment for normal host defenses. A low pH (5.5 to 6.0), hyperosmolarity (275 to 479 mosmol/kg), and dilution effects of the dialysis fluid contribute to diminished host defenses. In studies from several laboratories, it has been shown that the activity of peritoneal leukocytes, when measured by chemiluminescence, phagocytosis, and bacterial killing, is diminished because of the low pH and the high osmolarity of the dialysis fluid (33, 53, 49, 140a).

Normal peritoneal fluid contains immunoglobulin G and complement (C3) at levels comparable to those in serum. However, the peritoneal fluid of CAPD patients contains only about 1% of the normal concentration of these components. Some evidence supports the role of immunoglobulin G deficiency as a risk factor in CAPD peritonitis caused by coagulase-negative staphylococci (62). Depletion of C3 levels could place CAPD patients at risk for infections caused by gram-negative organisms because phagocytosis of these organisms is complement mediated (49). However, as noted above, infections caused by gram-negative organisms are less prevalent than those caused by gram-positive organisms. Mackenzie and coworkers considered differential effects on the overall response of PMs to gram-positive and gram-negative bacteria (87). Their study clearly demonstrated that the response of PMs to bacteria is not specific to the individual isolate but may be determined by the species.

Against intracellular microorganisms such as fungi, the role of PMs and PMNs is less clear. Activated PMs can kill intracellular *C. albicans*, but this activity is significantly less than that of peripheral blood PMNs (105). Survival of yeasts and their multiplication in PMs may contribute to infection. A similar explanation has been proposed for CAPD patients experiencing relapses of staphylococcal peritonitis (13).

DIAGNOSTIC FEATURES

Definition of Peritonitis

A working definition of CAPD peritonitis is warranted in order to establish clinical and laboratory diagnoses and determine their applications in the epidemiology of the disease. The definition of CAPD peritonitis varies slightly

among investigators. At present, the most frequently used definition includes at least two of the following criteria: symptoms or signs (or both) of peritonitis, a cloudy dialysate (effluent), and a positive culture (and/or Gram stain) of the dialysate (106, 109, 143). A few authors (e.g., see references 40 and 97) rely only on a turbid effluent with a leukocyte (WBC) count of $>100/\text{mm}^3$; others have added symptoms of peritonitis (e.g., see reference 132). These individual components of the diagnosis will be discussed in the following section.

Symptoms

Most cases of CAPD peritonitis are clinically less severe than cases of surgical peritonitis. Some cases may even be asymptomatic and can be detected only by a cloudy effluent. The severity of symptoms depends largely on the infecting microorganisms, with coagulase-negative staphylococci generally eliciting mild illness and *S. aureus*, gram-negative rods, and mixed organisms eliciting severe illness. Diffuse abdominal pain (with bowel sounds present) is found in 70 to 80% of patients; rebound tenderness, in 50 to 80%; fever, in 35 to 60%; nausea, in 30 to 35%; vomiting, in 25 to 30%; chills, in 20 to 25%; and diarrhea, in $<10\%$ (106, 143). Drainage problems may occur in approximately 15% of patients (106), and peripheral leukocytosis is seen in 30 to 45% (66). Positive blood cultures are very rare. Exit site and tunnel infections rarely give rise to subjective complaints and are usually detected by local purulent discharge.

The incubation period of CAPD peritonitis (as inferred from contamination accidents) is usually 24 to 48 h but is sometimes as short as 6 h (142). Symptoms generally disappear within 2 to 3 days after therapy has been started.

Cell Count and Turbidity

The lack of sensitivity and specificity of symptoms and signs of CAPD peritonitis extends, albeit to a lesser degree, to another component of the definition, i.e., a cloudy, turbid effluent. Cloudiness generally reflects a WBC count of $>100/\text{mm}^3$. Fluids with WBC counts of 50 to $100/\text{mm}^3$ may or may not be cloudy (68). In rare instances, cloudiness may also be caused by fibrin, chyle, blood (e.g., from menstruation), peritonitis from another source (156), or accumulation of PMs if dialysate dwell times are prolonged beyond 10 h (39). Rapid exchanges and protracted handling, on the other hand, may dilute or clot the effluent, leading to lower counts (39).

The specificity of cell counts of $<100/\text{mm}^3$ and between 100 and $500/\text{mm}^3$ is $<100\%$, since several observations have shown overlaps between WBC counts from patients with and without peritonitis (as defined by two of the three criteria listed above). In one series, 10% of peritonitis episodes yielded <100 WBC per mm^3 (139); in another series, 10 to 15% of patients without peritonitis showed counts above that number (89). In a further study, 28 uninfected patients, on 137 separate occasions, had WBC counts ranging from 0 to $191/\text{mm}^3$ (mean, 13 ± 2), while 43 infected patients had counts of between 10 and $10^4/\text{mm}^3$ (mean, $2,311 \pm 645$) (39). Cell counts are independent of the causative microbiological agent (116).

The percentage of PMNs seems to be a more sensitive indicator of peritonitis than the absolute cell count. In nonperitonitic fluids, most cells are mononuclear (143). In one study, uninfected patients showed PMN counts of 0 to 40% (mean, $12\% \pm 2\%$) whereas infected patients showed

PMN counts of 50 to 100% (mean, $85.5\% \pm 2.2\%$) (39). Occasionally, the number of eosinophils may increase, as in patients with etiologically unclear "eosinophilic peritonitis" (46) (which resolves spontaneously within days to weeks) or fungal peritonitis (3, 55, 60, 128, 133), or in those who have had intraperitoneal administration of antibiotics (116). In mycobacterial peritonitis, lymphocytosis is rarely observed (76, 101); most dialysates show a predominance of PMNs (67, 79). Cell counts return to normal within 3 to 5 days after initiation of treatment (116).

Microbiological Findings

Microbiological findings show even less sensitivity than signs and symptoms or counts. There is unanimity that the sensitivity of the Gram stain (even on centrifuged samples) and the acridine orange stain (139) is low. Because of the low concentration of microorganisms in the dialysate, tinctorial sensitivity compared with that of culture results has been reported to range only between 10 and 50% (36, 68, 90, 115, 116). Gram-positive organisms may have a higher chance of being detected on Gram stain than gram-negative ones (82). Positivity rates of Gram stains increase with the cellularity of the effluent (90) and decrease after the initiation of antimicrobial therapy (89).

Results of dialysate cultures show a better correlation with turbidity (total and differential counts) and with clinical signs and symptoms than with staining procedures. Specificity is less of a problem than sensitivity. In one study of 3,876 daily surveillance cultures of dialysates, 183 positive cultures were detected, but only 30 of them were associated with peritonitis (as defined by cloudy fluid plus abdominal pain); the other 153 did not indicate present or future infection (152). Other authors (29, 31, 89, 116) also found growth in up to 10% of effluents from nonperitonitis patients. In such cultures, coagulase-negative staphylococci, *Propionibacterium*, *Acinetobacter*, and *Bacillus* species (130, 152), and (rarely) agents known to cause more severe forms of CAPD peritonitis (116, 152) were found. None of these fluids, however, yielded positive Gram stains (94), indicating that the concentration of organisms must have been very low. Colony counts in one study were $<10/\text{dl}$ of dialysate (116). Growth was also slower than for the causative agents of peritonitis (130). These studies clearly point to the lack of utility of surveillance cultures that were recommended in the early 1980s (160).

Cultures of fluids from patients with CAPD peritonitis have been reported as negative in 4 to 48% of all episodes (31, 73, 89, 123, 124, 139, 148). Such results are significantly more frequent when WBC counts are below $500/\text{mm}^3$ (36, 90). There are several reasons for the lack of sensitivity of dialysate cultures (148). One includes the low concentrations of microorganisms (presumably) due to the dwell time of 1 to 2 liters of fluid for 4 to 8 h, phagocytosis and killing (136), the die-off of bacteria in undiluted effluent (57), and, possibly, a primary infection of the catheter. As a consequence, a large volume must be cultured, as will be discussed below. Another reason is the presence of antibiotics in the peritoneal cavities of patients under treatment, as exemplified by the low yield of cultures in such patients (57, 89, 148). A third reason is intracellular survival of and surface tension between bacteria, which account for the fact that positivity rates of cultures are higher when WBC lysis precedes culture (50, 82, 136). Fourth, patients with eosinophilic peritonitis (46) and peritonitis caused by endotoxin (one report; 61) are symptomatic and show increased numbers of WBCs but are

culture negative. Finally, inappropriate media or inappropriate temperature or duration of incubation may explain some negative cultures, notably those of fungi and, rarely, of mycobacteria, nocardiae, anaerobes (20, 67, 79, 101, 116, 143, 144), and psychrophilic (59, 82, 118, 154) or phagocytosed (81) organisms.

EPIDEMIOLOGY

In 1986, the CAPD Registry of the National Institutes of Health reported peritonitis rates of 1.07 to 1.47 episodes per patient year (97), which are lower than the rates of 2.0 to 2.4 observed before 1983 (140). There is no unanimity of opinion regarding increased risks of peritonitis at the extremes of age (106, 140, 149) and in diabetics (106, 140). Known risk factors, often intertwined, are lack of compliance with asepsis and treatment (106), low patient motivation (131), lack of social support (131), less formal education (115), lower economic status (115), and, in one study, use of lactate-buffered dialysis fluid (91). There is no correlation with sex, blood chemistry, or nutritional or immunological parameters (106, 109) except for human immunodeficiency virus disease (32).

More than half of all peritonitis episodes are observed in only 25% of all patients on CAPD (109, 134). Approximately 60% of patients on CAPD will have developed at least one episode of peritonitis during the first year of dialysis (97, 134). The mean and median intervals are not significantly different between episodes (115), and, with the possible exception of corynebacteria (1, 74, 94, 107), bacteria (but not fungi) do not show any preference for any episode (131, 136). Multiple episodes are observed in more than 50% of all patients who have gone through one episode (47, 115, 134); in one series, two-thirds of the episodes were relapses, i.e., infections with the same microorganisms (47). Exit site infections have occurred at a mean rate of 0.7 per patient per year (83); this value, of course, would increase with an increased incidence of peritonitis caused by *S. aureus* and *P. aeruginosa*, the main agents of exit site infections.

Mortality for CAPD peritonitis was 2 to 3% in patients with a mean age of 45 years (129) but 7% in patients over 55 years of age (140). In the latter group, signs of systemic sepsis (symptoms plus a mean WBC count of $5,300 \pm 1,170/\text{mm}^3$) presaged a worse prognosis (25% mortality); such deaths were invariably associated with fungal, pseudomonal, or polymicrobial infections (140). While peritonitis is the second most frequent cause of death in CAPD patients, it causes, at best, 25% of all their fatalities (109).

DISTRIBUTION OF AGENTS

As is the case in culture-negative CAPD peritonitis, laboratories have reported various percentages of microbial agents associated with positive cultures. Ranking, however, has been fairly uniform. Viruses and parasites have thus far not been incriminated in any case of CAPD peritonitis. Most series have found coagulase-negative staphylococci to be the most frequently encountered agents (40 to 60% of all positive cultures), followed by *S. aureus* and streptococci (10 to 20% each), members of the family *Enterobacteriaceae* (5 to 20%), nonfermentative gram-negative rods (3 to 15%), and gram-positive rods (2 to 4%). Values for mixed bacteria, fungi, mycobacteria, and anaerobes are generally $<5\%$ (45, 106, 109, 134, 144), but recovering these agents depends on special culture conditions not fulfilled in every study. In studies with appropriate media, however, fungi seem to be

encountered more often than mycobacteria or anaerobes (106, 109, 144). Polymicrobial infections seem to be particularly frequent in elderly patients (140). These distributions are independent of the number of episodes. Eosinophilic peritonitis was seen only by one group in 1 to 4% of cases (45).

Catheter (exit site and tunnel) infections show a different spectrum of microorganisms. Exit site infections are most often caused by coagulase-negative or -positive staphylococci (20 to 40%) and by *P. aeruginosa* (ca. 5 to 10%), while tunnel infections are caused by *S. aureus* (35 to 65%), *P. aeruginosa* (ca. 15%), and members of the *Enterobacteriaceae* (ca. 5%) (108, 109). Mixed infections were found with particular frequency (32%) in one series of exit site infections (108). The same study showed 17% of all catheter infections, but 20% of those with *S. aureus* and 33% of those with *P. aeruginosa*, to be associated with peritonitis (108).

SELECTED AGENTS

Staphylococcus spp.

Episodes of peritonitis caused by *S. aureus* or coagulase-negative staphylococci differ in frequency, severity of illness, and complications. The organisms causing both infections can infect by intraluminal or periluminal routes. Coagulase-negative staphylococci cause about two to three times more episodes than *S. aureus* and show a slightly higher recurrence rate (66, 108). In a series of cases of staphylococcus-caused CAPD peritonitis, WBC counts in the dialysis fluid were only marginally higher in patients with *S. aureus*, but these patients were twice as often "ill looking" as those with peritonitis caused by coagulase-negative staphylococci (66). Furthermore, complications such as hypotension, *Candida* esophagitis, and ultrafiltration failure were observed only in the *S. aureus* group, as were fatalities (66), toxic-shock-like symptoms (143), and abscess formation (131). Exit site and tunnel infections as well as catheter removal (for these and other reasons) were more than five times as frequent with *S. aureus* as with coagulase-negative staphylococcal infection (28, 66, 150). Recurrent *S. aureus*-caused peritonitis was always associated with exit-site infection (28). Length of hospital stay and duration of antibiotic treatment were significantly longer in the *S. aureus* group (66).

Several studies have shown that nasal carriers of *S. aureus* have significantly higher frequencies of exit site infections (28, 83) and peritonitis (83) due to *S. aureus* than noncarriers. Both groups, however, showed identical overall frequencies of peritonitis and of peritonitis due to organisms other than *S. aureus* (83). All *S. aureus*-caused peritonitis episodes occurred in carriers, and 85% of these episodes were caused by strains identical to nasal strains in bacteriophage types and antibiotic profiles (83).

Among the coagulase-negative staphylococci, the most frequently encountered species is *S. epidermidis* (up to 80% of cases), while *S. haemolyticus*, *S. hominis*, *S. warneri*, and *S. capitis* each occurred in $\leq 5\%$ of cases (6, 7, 34, 81, 150). Only one case of *S. lugdunensis* has been reported (80). One study (6) claimed an association between in vitro adherence and in vivo infection. Two later investigations (81, 150), however, could not confirm these data. Also, slime production was no more frequent in infecting than in skin-colonizing strains of the same individual (7, 56, 81, 150); in fact, peritonitis-causing strains lacking adherence and slime production were more frequently associated with complications than strains exhibiting such putative virulence factors (150).

By plasmid profiling, two studies found no identity (7, 34) and one found identity (56) between colonizing and infecting strains. In yet another study in which a highly discriminatory scheme was used, including phage typing, antibiograms, biotyping, and plasmid profiling, isolates indistinguishable from peritonitis-causing strains were found in 6 of 10 patients studied <12 weeks before a peritonitis episode (81). Possible explanations for the different results were inadequate skin sampling and selection of single instead of multiple strains from one site (81).

Streptococci

Comparatively little is known about the pathogenesis of streptococcal CAPD peritonitis. The most frequent agents, viridans streptococci (*Streptococcus mitis*, *Streptococcus sanguis*, and *Streptococcus salivarius*) (90, 131), mostly of oral origin, could contaminate the connecting site (2) or spread via a hematogenous route, e.g., after dental work (65). Enterococcal peritonitis corresponds in pathogenesis and severity to peritonitis caused by members of the *Enterobacteriaceae* (143). Other streptococci are listed in Table 1.

Gram-Positive Rods

Corynebacterium spp. are not rare as agents of CAPD peritonitis. They tend to adhere to the catheter and to cause postprimary infections or relapses or both, be they *Corynebacterium jeikeium* (1, 107), "*Corynebacterium aquaticum*" (16, 94), or strains not identified to species level (74). Rare gram-positive rod species are listed in Table 1.

Nonfermentative Gram-Negative Rods

Among the gram-negative rods, *P. aeruginosa* is the species most frequently causing CAPD peritonitis (71, 109). The infection is severe and frequently associated with exit site or tunnel infection (10), loss of peritoneal space, and abscess formation (59). Coexisting catheter infection is difficult to treat and is the main reason for the excess catheter removal rate in *P. aeruginosa*-caused peritonitis compared with rates in peritonitis of other etiology (10). In most cases, the source of *P. aeruginosa* could not be determined, but in one miniepidemic a water bath used to preheat the dialysis fluid was incriminated (69). In another epidemic, infections were significantly associated with the use of providone-iodine solution which was used to cleanse the catheter site (44). Cultures of the antiseptic, however, were negative; local irritation and alteration of the skin flora were cited as possible explanations. In human immunodeficiency virus-positive patients, a 24-fold increase in *P. aeruginosa* CAPD infections over that of a CAPD population at low risk for human immunodeficiency virus infection has been observed (32).

Acinetobacter spp. are the only other agents observed with some frequency among the nonfermenters (5, 82, 109, 117, 134, 155). Low-grade (5) and severe (117) infections have been reported. The origin may be the skin or a contaminated water bath used to heat the dialysis bag (5). The latter mechanism also operated in the pathogenesis of CAPD peritonitis due to other rare nonfermenters (43, 118). These are listed in Table 1.

Enterobacteriaceae

The presence of members of the *Enterobacteriaceae* in dialysis fluid most often indicates fecal contamination due to

TABLE 1. Unusual bacteria in CAPD peritonitis (except anaerobes and mycobacteria)

Bacterium	Associated factors/remarks	Reference(s)
Gram-positive cocci		
Group A streptococci	Severe illness	18, 102
Group B streptococci	Severe illness	131
Group C streptococci	Severe illness	122
<i>Streptococcus pneumoniae</i>	IUD carriage	70
<i>Micrococcus</i> sp.		131
<i>Stomatococcus mucilaginosus</i>		72
Gram-positive rods		
<i>Bacillus cereus</i>		2, 11
<i>Lactobacillus acidophilus</i>		124
<i>Listeria monocytogenes</i>	Positive blood cultures	96
<i>Nocardia asteroides</i>	Soil origin, require prolonged incubation	20, 115
<i>Actinomadura madurae</i>	Soil origin, require prolonged incubation	158
<i>Oerskovia xanthineolytica</i>		113
<i>Tsukamurella aurantiaca</i>		17
<i>Rothia dentocariosa</i>		147
Gram-negative cocci		
<i>Neisseria gonorrhoeae</i>	Pathway through fallopian tube ^a	153
<i>N. sicca</i> , <i>N. subflava</i>		27, 125, 127
<i>Branhamella catarrhalis</i>	Penicillinase production	85
Gram-negative rods, fastidious		
<i>Campylobacter fetus</i>	Some patients bacteremic	48
<i>C. jejuni</i> , <i>C. coli</i>	Some patients showed diarrhea	48
<i>Gardnerella vaginalis</i>		30
<i>Haemophilus influenzae</i>	— ^a	45, 90
<i>H. parainfluenzae</i>	— ^a	37, 135
<i>Pasteurella</i> sp.		121
Gram-negative rods, nonfermenters		
<i>Alcaligenes faecalis</i>	One associated with CDC group IV-c	53, 58
<i>A. denitrificans</i> subsp. <i>xylosoxidans</i>		95
<i>Agrobacterium</i> sp.		131
<i>Bordetella bronchiseptica</i>	Canine origin	14
<i>Chryseomonas luteola</i>		24
<i>Flavimonas oryzihabitans</i>		8
<i>Flavobacterium</i> spp.		9, 59
<i>Moraxella</i> spp.		82, 123
<i>Pseudomonas cepacia</i>		132
<i>P. fluorescens</i>	— ^b	59, 82
<i>P. mesophilica</i> (<i>Methylobacterium mesophilicum</i>)	— ^b	118
<i>P. paucimobilis</i>		43, 155
<i>P. putida</i>	— ^b	82, 132
<i>P. stutzeri</i>		71, 82
<i>Xanthomonas maltophilia</i>		59, 151
Gram-negative rods, <i>Vibrionaceae</i>		
<i>Aeromonas caviae</i>	Houseplant spray	2
<i>Vibrio alginolyticus</i>	Scuba diving	137

^a Requires culture on chocolate agar.

^b Requires incubation at 35 to 30°C.

bowel perforation (e.g., in diverticulitis) or possible migration through the bowel wall (115, 143, 157). In an occasional hospitalized patient, organisms may migrate into the lumen from the skin or the patient's feces (2). The most common species seen are *E. coli*, *Klebsiella*, and *Enterobacter* sp. (90, 109, 125, 131). They can cause severe illness and are associated with higher morbidity and mortality rates than gram-positive organisms (129, 139). Few individual reports are extant, but there is one of a recurrent *Serratia marcescens* peritonitis with adherence of the organism to the catheter (23).

Other Gram-Negative Rods

Infections caused by other gram-negative bacilli are rare (see Table 1).

Fungi

A large number of fungal species have been found in patients with CAPD peritonitis. Predominating is *C. albicans* (21, 35, 64, 103), followed by *C. tropicalis* and other *Candida* spp. (21, 32, 35, 98, 103). Unusual species are listed in Table

TABLE 2. Unusual fungi in CAPD peritonitis

Species/genus	Reference(s)
<i>Alternaria</i> sp.	55
<i>Aspergillus</i> sp.	35, 133
<i>Cephalosporium</i> sp.	35
<i>Coccidioides immitis</i>	3, 40
<i>Cryptococcus laurentii</i>	128
<i>Cryptococcus neoformans</i>	60
<i>Drechslera spicifera</i>	103
<i>Exophiala jeanselmei</i>	35
<i>Fusarium</i> sp.	22, 64
<i>Histoplasma capsulatum</i>	75
<i>Mucor</i> sp.	64
<i>Rhizopus</i> sp.	12
<i>Rhodorula glutinis</i> ^a	154
<i>Rhodorula rubra</i>	35
<i>Torulopsis glabrata</i>	35
<i>Trichoderma</i> sp.	35
<i>Trichosporon</i> sp.	21, 64, 159

^a Requires incubation at 35 to 30°C.

2. Except for the dimorphic fungi, peritonitis originates from the environment or from the patient's skin or mucous membranes. Certain predisposing factors exist: bacterial peritonitis episodes within the preceding month, previous antimicrobial treatment, hospitalization (some cases are nosocomially acquired) (35), and human immunodeficiency virus antibody positivity (32). The contributions of other kinds of immunosuppression, bowel perforation, peritoneal-vaginal fistulas, and extraperitoneal fungal infections remain unresolved. Diabetes was not more frequent in patients with fungal peritonitis than it was in patients with bacterial CAPD peritonitis. While symptoms are not more severe than in bacterial infections, treatment is more difficult, hospitalization is longer, and catheter removal is necessary in >50% of cases. Complications such as adhesions, abscess formation, and sclerosing peritonitis as well as fatalities (at least 15% even under treatment) are also more frequent (35, 129). Occasionally, eosinophilia is observed in the dialysate (3, 55, 60, 128, 133). Prolonged incubation of media is crucial for detection.

Algae

Two cases of *Prototheca wickerhamii* peritonitis have been reported; they also required catheter removal (42). The organism is susceptible to amphotericin B (42).

CULTIVATION OF MICROORGANISMS

General Principles

The yield of culture methods depends on (i) the definition of peritonitis, (ii) the number of culturable microorganisms present in the inoculum, and (iii) the sensitivities of the culture methods.

The most commonly used definition of CAPD peritonitis does not depend on a positive culture as long as symptoms and signs of peritonitis and a cloudy dialysate (or a WBC count of >100/mm³ with >50% PMNs) are present. Cases for which both criteria are fulfilled would be called CAPD peritonitis even if the culture were negative. If, however, the definition also mandates a positive culture, the percentage of culture-negative peritonitis episodes would be zero. Intermediate definitions would require corresponding results.

A few quantitative studies on dialysates have been done. Investigators have found numbers of microorganisms in peritonitis that ranged from 1 CFU/ml to "too numerous to count" (36, 40, 82, 116, 136). Gram-positive organisms had higher mean counts than gram-negative rods (36, 82, 116). In patients without symptoms of peritonitis and counts of <100 WBC/mm³, microbial concentrations ranged from 1 to 10 CFU/dl (116), indicating an overlap in this range of counts with true pathogens. Counts increased when WBC-lysing agents that free bacteria trapped intracellularly were used (136). Storage at 4°C for 12 h did not change cell counts appreciably (68), although culture yields have been found either unchanged (141) or negatively associated with ≥12-h storage times (57). Microbe counts under antibiotic treatment are not extant.

Indirect methods of testing for microbial presence, such as gas-liquid chromatography (36) or the *Limulus* lysate test (15), have such low sensitivities that they are useless.

The sensitivity of a culture method depends on the pretreatment of the dialysate effluent (e.g., centrifugation or lysis); the media used; and the length, atmosphere, and temperature of incubation. Studies on the relationship between relative centrifugal force and culture yields from centrifuged pellets are not extant; many authors have used a relative centrifugal force of approximately 1,800 to 2,350 × g. Unfortunately, most of the 30-odd studies in the literature have compared methods that vary in several factors (e.g., volume cultured and pretreatment of the specimen). Results from approximately 20 studies available by 1987 were reviewed by one of us in 1988 (148). In most of them, <5-ml amounts of dialysate were used for direct culturing, a volume now considered too insensitive, and if a conclusion could be reached, it was that at least 10 ml should be used with an enrichment method (148). Explanations for contradictory results emerging from some of these studies are the presence of antibiotics (either effectively or ineffectively diluted in the enrichment medium but not present in centrifuged, washed pellets) and various degrees of phagocytosis. Even more recent studies have not been able to determine optimal techniques. These studies will be reviewed briefly.

Results of Recent Studies

Traditional systems. When the volume of dialysate was the same (10 to 20 ml), enrichment in broth of comparative nutritional value yielded more (89) or as many (144) positive cultures as a plated centrifugate. When volumes used for enrichment were larger than those used for direct plating or for centrifuging (and subsequent plating or enrichment), the yield of the larger volume was generally better (50, 144). In one study, however, in which 5 to 50 ml of dialysate was placed in enrichment broth, 0.5 ml of uncentrifuged dialysate was plated directly, and a centrifugate from 100 ml of dialysate was plated, no significant differences were found between enriched and directly plated samples (82). The number of positive cultures from the pellets (sediments) was even significantly smaller than that from the uncentrifuged plated samples; however, the percentage of cultures with ≤5 CFU/50 ml of dialysate was higher (41 versus 19%) in the uncentrifuged sample (82). Another study found enrichment of 2 to 3 ml of dialysate to be superior to culture of the pellets from 10 ml of dialysate and of 0.5 ml of uncentrifuged samples (68). Washing of the centrifuged sediment did (144) or did not (50) increase the yield over that of direct plating. Broth enrichment, of course, excludes determining colony counts.

Enrichment of large dialysate volumes has yielded high sensitivities compared with other methods but is impractical for routine use (because of handling and preparation of special concentrated broths for mixing) and may yield false-positives. Dialysate volumes of 1,000 (29, 31) and 500 (125) ml have been cultured. Sensitivity (compared with clinical signs and symptoms) was limited by the presence of antibiotics and has ranged from 100% (29) to 88% (125) to 61% (31). We found that 1,000 ml of sample gave the same results as 50 ml (sensitivity, 70%) (52). One study found equal results for 50 and 5 ml (82), and another found a lower yield for 1 ml than for 10 ml (141). An optimal dilution factor has not been determined.

Pour plates (1 ml per plate) seem to represent some form of enrichment (156) since their yield in positive specimens is higher than or equal to that of cultures of centrifuged pellets from a larger volume (132, 141).

Filtration. Addi-Chek (Millipore Corp., Bedford, Mass.) filtration has been recommended (144), but in our and other authors' (90) experience, the filters tend to clog. In one series, 20 to 400 ml of filtered dialysate gave results similar to 10 ml of plated and enriched pellets (90). Likewise, 100 ml of dialysate filtered through a 0.45- μ m-pore-size filter gave results identical to those obtained with 10 ml of enriched specimen (115) but was superior to results with plated pellets from 5 to 10 ml of centrifuged dialysate (31). Millipore filtration of 300 ml of dialysate was equal in qualitative yield to direct plating of 0.5 ml (82), although the number of colonies was higher.

Breakup of phagocytic cells. The use of Triton X, saponin, Tween, sodium deoxycholate, sonication, and freeze-thaw cycles increases the yield of positive cultures (141). Two drops of Triton X added for 30 min to the dialysate or 2% Tween 80 incorporated in the agar medium contributed significantly to the number of positive cultures and colony counts (50). Saponin (10%) mixed for 5 min with the pellet of a centrifuged dialysate increased the specimen positivity rate by 9% and also gave higher colony numbers (73). The latter effect was probably due to separation of bacteria through reduction of surface tension. Tween 20 plus a proteolytic enzyme added to the dialysate for 1 h lysed WBCs as well. Subsequent filtration of 300 ml of dialysate did not affect the yield, but centrifugation of 100 ml resulted in more positive cultures and higher colony counts than for nonlysed dialysates (82). Sonication, freeze-thawing, and deoxycholate treatment of dialysates (136, 141) all added substantially to the culture positivity rate. In a recent comparison of distilled water-lysis centrifugation, filtration, mechanical lysis, and bile salt lysis, sensitivities were 81, 74, 74, and 67%, respectively (77). The last two techniques were not recommended because of destruction of bacterial cells, contamination, and inhibition of gram-positive organisms.

Use of newer semiautomated blood culture systems. Semi-automated blood culture systems have been used only recently. Besides their technical advantages, they may provide enrichment, antiphagocytic and antibiotic-neutralizing capacity (through the addition of sodium polyanethol sulfonate), and WBC lysis. A 20-ml culture of dialysate in the Septi-Chek (Hoffmann-La Roche, Nutley, N.J.) blood culture system (which contains sodium polyanethol sulfonate) was as efficient as the Millipore filtration of 250 ml of dialysate and plating plus enrichment of the pellet from 20 ml of dialysate (120). The yield was even higher in the same system with spike and filter adaptor (38).

The BACTEC system (Becton Dickinson Diagnostic Instrument Systems, Sparks, Mo.) with 5 ml in each of two

bottles was superior to a plated pellet from 50 ml of dialysate (125) but equal to a pellet from 10 ml that was plated and enriched in broth (90). It performed as well as the Isolator system (DuPont Co., Wilmington, Del.) with 10 ml of dialysate (40, 155), although detection with the latter was 24 to 72 h earlier in 20% of the isolates (40). In another study identification (but not isolation) was 24 to 48 h earlier with the Isolator than the BACTEC, and the Isolator performed equally as well as culture of 50 ml of plated and enriched centrifuged sample in nearly all respects (155). The BACTEC system with antimicrobial removal resins (centrifuged pellet from 50 ml of dialysate in each of two bottles) was superior in yield to culture of the pellet from an equal amount of dialysate injected into BACTEC bottles without resins (144). The Signal system (Oxoid Ltd., Basingstoke, United Kingdom) performed in one study as well as BACTEC bottles without resins (123).

Media and incubation. Most studies have used blood and chocolate agars as solid media and brain heart infusion and thioglycolate as fluid media. A few have included solid media for anaerobes (blood agar) and mycobacteria (Lowenstein-Jensen medium). An incubation time of at least 7 days is important, because in cultures without WBC lysis deteriorating phagocytes tend to release bacteria slowly (82). A lower incubation temperature was favored for fungal cultures (156) and for psychrophiles such as *P. fluorescens* (82), *P. mesophilica* (118), and *Rhodotorula glutinis* (154).

Recommendations. (i) Only cloudy fluids should be sent to the microbiology laboratory. Total WBC and PMN counts before culture are desirable.

(ii) The requisition slip should mention time of drainage and antibiotic coverage.

(iii) If the sample cannot be worked up right away, it should be briefly (<6 h) stored at 4°C.

(iv) The amount of dialysate required should be such that maximum sensitivity and specificity can be expected; on the other hand, handling should be practical, and service and information should be prompt. Since there is evidence that 1,000- and 50-ml amounts (52) as well as 50- and 10-ml amounts (90, 110, 125) of dialysate yield identical culture results, a minimum of 10 ml should be cultured, using enrichment broth with antiphagocytic and lytic properties. When sodium polyanethol sulfonate is used, rare organisms such as *Gardnerella vaginalis*, *Neisseria* spp., *Peptostreptococcus anaerobius*, and *Streptobacillus moniliformis* may be inhibited. Subcultures of the enrichment should be done at least on aerobic chocolate agar and anaerobic blood agar plates. Colony counts are unnecessary unless contamination is suspected (low counts, however, may occur in infection as well). The need for a Gram stain arises only if empiric therapy does not suffice.

(v) Media should be incubated for up to 7 days, with plates sealed. One medium should be incubated at 30°C to detect psychrophilic bacteria.

(vi) If peritonitis is suspected but the culture remains negative, mycobacterial and fungal stains and cultures should be initiated, and the methods used should be reviewed.

PREVENTION OF INFECTION IN CAPD PATIENTS

Prevention of infection in CAPD patients seems to depend on three factors: the selection of patients and their education, the technical equipment available and its handling, and,

probably the least important, the use of prophylactic antimicrobial agents during the application of CAPD.

Intelligent, compliant patients who have their own good as a reasonable objective and have the appropriate family support do well on CAPD and have a low peritonitis rate (142). However, objective analyses of patient populations have defined some risk groups for prediction of peritonitis (32, 106, 115, 131). No evidence is available that clearly demonstrates increased risk of patients who are immunologically compromised and that indicates or contraindicates the use of CAPD for them, except for those with human immunodeficiency virus disease (32).

Significant advances in the use of catheter materials and connections have been made, and new materials are continually being devised and implemented to reduce the incidence of peritonitis. Tubing has been disinfected and filled with a rinse of sodium hypochlorite prior to connection, and this procedure has reduced the occurrence of peritonitis (93). Physical barriers, such as the use of bacterium-retaining filters, seem to be useful, and a device is available and has been used (4). There are mechanical devices designed to maintain sterility, such as a titanium adaptor (132), a clamp on the catheter to prevent air from entering the transfer set (104), an in-line membrane filter (131), UV and sterile weld devices (143), and connector types that employ disinfectants (such as the Oreopoulos-Zellermann connector or the Y set) (131). These devices add to the cost of CAPD, and only some have been properly evaluated. For typical sets of materials, disinfection of the connector with a povidone-iodine spray has been recommended (104). A defined alcohol rinse and alcohol spray of the connector and adjacent tubing, however, were superior to povidone-iodine washing and spray in preventing infections with coagulase-negative staphylococci (51). Chlorhexidine sprays have led to sclerosing peritonitis in a significant number of patients (131). The peritonitis rate with *Pseudomonas* spp. and other waterborne gram-negative rods can be reduced by minimizing contact with household water, e.g., by avoiding showering and avoiding warming dialysate bags in tap water (78). For the prevention of exit-site infections, stringent aseptic care is important (78). It can be augmented by using a protective nonocclusive dressing and povidone-iodine cleansing; compared with water and soap, such a system reduced the rate of exit-site infections but not the rate of peritonitis (84). The catheter could also be implanted under peritoneoscopic guidance.

Some dialysis centers have used prophylactic antimicrobial agents, especially for patients on intermittent peritoneal dialysis, but the conclusions from these studies are not definitive. When oral cephalexin or trimethoprim-sulfamethoxazole was used in a prophylactic regimen, the antimicrobial agents did not diminish the incidence of infection (117). However, antibiotic prophylaxis at the time of catheter implantation should be considered in accordance with each institution's surgical protocol. When perioperative antibiotic prophylaxis is used, the wound infection rate associated with this procedure is extremely low (143).

TREATMENT OF PERITONITIS

This review will not address specific therapeutic modalities or the kinetics and dosage regimens that are often suggested for the treatment of peritonitis. Reviews of antibiotic kinetics and doses exist (58, 63, 88, 114, 121), and Vas has proposed several tables indicating the antibiotic regi-

mens recommended for treating the complications of peritoneal dialysis (142).

The process of peritoneal dialysis permits a readily available route of drug administration that can be used both in the treatment of peritonitis and in the delivery of drugs to dialysis patients who are ill. Intraperitoneal administration of antimicrobial agents permits high local concentrations of drug. This is especially beneficial when drugs that are highly protein bound and that penetrate the peritoneal cavity slowly are used (119). Also, intraperitoneal administration of an antimicrobial agent in the treatment of CAPD peritonitis is the preferred route, since the method facilitates medication by the patient and allows for sufficient drug to be absorbed through the peritoneum so that adequate bactericidal levels in serum are achieved (121).

A wide array of antimicrobial agents have been used in the treatment of peritonitis and include the cephalosporins (narrow, expanded, and broad spectrum), aztreonam, quinolones, penicillins, aminoglycosides, erythromycin, clindamycin, metronidazole, tetracycline, and chloramphenicol. Because a majority of cases of peritonitis are associated with gram-positive bacteria and because these infections can be due to methicillin-resistant staphylococci, vancomycin has proved efficacious as coverage. Teicoplanin, a new glycopeptide compound, has also been used (114).

As noted in a previous section, fungal agents cause significant morbidity and mortality in patients with CAPD peritonitis. Fungal infections are usually more difficult to treat, and catheter removal and systemic therapy are frequently the recommended courses of action. For these infections, amphotericin B (31) has been used. Other antifungal medicaments include miconazole, its oral analog ketoconazole, and flucytosine (19) used alone or in combination with amphotericin B (or miconazole).

CAPD enjoys practical and widespread acceptance as a safe, effective, and relatively inexpensive alternative to chronic hemodialysis. Yet, the technique is limited by the prevalence of infection. As clinical microbiologists become cognizant of the expanding application of CAPD and the ongoing studies concerning its use, they will learn to meet the challenge of diagnosing infections. The diversity and distribution of microbial etiologic agents of peritonitis seem to expand. Although exotic species not previously encountered in human infections are seemingly routinely detected and identified, it is clear that gram-positive organisms represent the most frequent organisms isolated. A major difficulty for the laboratory is that routine cultural methods have not been fully validated, and the most suitable, "best" volume of dialysate fluid that would prove to be most sensitive for cultural detection has not been documented by laboratory studies. Future trends no doubt will incorporate the use of nucleic acid probes and signal amplification methods to increase the sensitivity and speed of microbial detection.

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