Intermittent versus Continuous Intraperitoneal Glycopeptide/Ceftazidime Treatment in Children with Peritoneal Dialysis-Associated Peritonitis

FRANZ SCHAEFER,* GÜNTER KLAUS,† DIRK E. MÜLLER-WIEFEL,‡ OTTO MEHLS,* and THE MID-EUROPEAN PEDIATRIC PERITONEAL DIALYSIS STUDY GROUP (MEPPS)*

*Division of Pediatric Nephrology, University Children’s Hospital, Heidelberg, Germany; †Division of Pediatric Nephrology, University Children’s Hospital, Marburg, Germany; and ‡Department of Pediatric Nephrology, University Children’s Hospital, Hamburg, Germany.

Abstract. Intermittent intraperitoneal antibiotic administration appears as a practical and economical therapeutic concept in continuous peritoneal dialysis (CPD)-related peritonitis, but the equivalence of this principle with standard continuous treatment awaits confirmation by prospective, randomized clinical trials. This study evaluates the efficacy, safety, and clinical acceptance of an initial combination treatment including a glycopeptide (vancomycin or teicoplanin) and ceftazidime, each applied either intermittently or continuously, in a cohort of pediatric patients with CPD-related peritonitis. Patients randomized for continuous treatment received an intraperitoneal loading dose of glycopeptide and ceftazidime followed by maintenance doses added to each dialysate bag. In the intermittent treatment groups, the glycopeptide was administered in two loading doses 7 d apart, and ceftazidime during one dialysis cycle per day. Initial treatment response was evaluated after 60 h by the change in a Disease Severity Score and by the clinical decision to continue initial treatment. Of 152 patients observed for a total of 234 patient years, 90 patients developed 195 episodes of peritonitis (including 27 relapses within 4 wk after end of treatment). Dialysate cultures were positive in 83% of the episodes. In Gram-positive peritonitis (79% of culture-positive cases), the primary success (overall 95%) and relapse rates (21%) were not different between continuous and intermittent, or between vancomycin and teicoplanin treatment. Oversensitivity reactions occurred in three and ototoxicity in one vancomycin-treated patient, whereas no such side effects were observed with teicoplanin. Residual renal function declined during peritonitis episodes regardless of treatment modality. In Gram-negative peritonitis (18% of cases), intermittent ceftazidime treatment was less successful than continuous treatment according to clinical judgment (3 of 11 versus 10 of 14, P < 0.05), but not when rated by Disease Severity Score (8 of 11 versus 12 of 14). In conclusion, intermittent and continuous intraperitoneal treatment of CPD-related peritonitis with glycopeptides and ceftazidime is equally efficacious and safe when measured by objective clinical criteria. This contrasts with a strong tendency of clinicians to move from intermittent to continuous treatment in severe peritonitis.

Bacterial infections remain the most severe complication and most common cause of technical failure of continuous peritoneal dialysis (CPD) in patients with end-stage renal failure (1,2). Because the peritoneal adhesions and fibrosis caused by severe or recurrent peritonitis may irreversibly prevent any further use of the peritoneal membrane, the control of infectious complications is particularly relevant to pediatric patients (3). Children may be dependent on dialysis for several decades during their long expected life span. Moreover, for infants with end-stage renal failure, CPD may be the only acceptable long-term dialysis treatment modality.

Poor success rates have been reported for the treatment of CPD-associated peritonitis both in adults and children, with primary response rates ranging between 60 and 85% (4,5). Reasons for the insufficient treatment success include primary insensitivity of the causing organisms to the first-line antibiotics applied, persistence of organisms in the catheter biofilm, and also the lack of standardized and validated diagnostic and therapeutic concepts. In 1993, an international committee developed recommendations for the management of CPD-related peritonitis based on a meta-analysis of the available literature (6). It proposed the use of a combination of vancomycin with either ceftazidime or an aminoglycoside administered intraperitoneally until identification of the causing organism. Because of the markedly prolonged half-life of vancomycin in chronic renal insufficiency, it was proposed that vancomycin be administered intermittently by two bolus doses 7 d apart, using the patient’s body as a reservoir for the drug. Teicopla-
nin, another glycopeptide antibiotic with an even longer half-life in uremic patients due to higher protein binding (7,8) and a reportedly milder adverse effect profile (9), might be an attractive alternative to vancomycin for intermittent administration, but the experience with its use in CPD-related peritonitis is limited (10,11). As the elimination of ceftazidime is also diminished in uremia, intermittent dosing should also be possible (12,13). Intermittent drug administration offers an economic treatment modality that may considerably facilitate outpatient management of peritonitis. However, this approach has not been readily accepted by clinicians because of concerns with the possibility of fatal consequences of single dosing errors, unpredictable decreases of glycopeptide tissue levels in patients with residual renal function, and potentially increased toxicity of intermittent high-dose boluses. Moreover, it may frequently not be acceptable to clinicians to withhold effective local antibiotic administration while waiting for improvement of a potentially life-threatening infection. At present, the controversial discussion about intermittent peritonitis treatment suffers from an almost complete lack of controlled clinical trials. Therefore, we performed a prospective multicenter study designed to evaluate the efficacy, safety, and clinical acceptability of intermittent versus continuous glycopeptide and cephalosporine, and of teicoplanin versus vancomycin treatment of CPD-related peritonitis in children.

Materials and Methods

Patients

Between June 1993 and January 1997, the families of 152 children and adolescents on chronic CPD, aged 0.7 to 21.8 (median 11.4) yr, agreed to be enrolled in the trial, and were monitored for the appearance of signs and symptoms of peritonitis in 13 Mid-European pediatric dialysis centers. New CPD patients and patients already on CPD treatment were enrolled. Patients with prevalent CPD were included only after a period of ≥4 wk without peritonitis, exit-site infections, or other infections treated with antibiotics. Patients receiving continuous local or systemic antibiotic prophylaxis were excluded from the study.

In 98 patients, the follow-up was terminated during the study period due to transplantation (n = 70), transfer to hemodialysis (n = 15), change of treating center (n = 5), partial recovery of renal function (n = 1), or patient death (n = 7). The median duration of follow-up was 19 (range 1 to 44) mo.

Study Protocol

At the time of manifestation of peritonitis symptoms, the patients were randomized for one out of four intraperitoneal antibiotic treatment schedules (Figure 1) comprising a combination of ceftazidime with either vancomycin (Ia, Ib) or teicoplanin (IIa, IIb), administered either continuously (Ia, IIa) or intermittently (Ib, IIb). Peritonitis was assumed in the presence of a cloudy dialysate with or without fever and abdominal pain, and later confirmed by the presence of ≥100 cells/µl dialysate with ≥50% neutrophil granulocytes. If peritonitis was not confirmed by cytologic analysis, the randomization was recalled. Randomization was performed locally with a blocking factor of four.

In the continuously treated groups, the intraperitoneal loading doses were 15 mg/kg body wt for vancomycin, 7.5 mg/kg for teicoplanin, and 250 mg/L dialysate for ceftazidime. The intermittently treated patients received 30 mg/kg vancomycin or 15 mg/kg teicoplanin, and 500 mg/L ceftazidime. In patients on automated PD (APD) in whom peritonitis symptoms were noted during cycler treatment, the cycler was either reprogrammed to a dwell period of 4 h and the antibiotics were injected during dialysis fluid inflow via a puncture site at the inflow line, or the patients were disconnected and received a manual instillation using a 2-L CAPD twin bag system.

The families were usually instructed to administer the loading doses immediately after drainage of the cloudy dialysate at home, and asked to come to the hospital during the loading dwell period. The bag containing the cloudy dialysate was brought in for microbiological processing. After 4 h, the patient’s clinical status was assessed according to a standardized Disease Severity Score (DSS, see below). Differential blood and (standardized 4-h) dialysate cell counts were performed, and C-reactive protein and glycopeptide antibiotic blood concentrations were measured. Two 10-ml aliquots of the last dialysate were processed for microbiological analysis, and the remaining cloudy dialysate was kept for subsequent microbiological analysis.
confirmed by the local ethics committees at each treatment center. Approval was con-
clusive. The catheter exit site was assessed according to a standardized score (ESS, see below), and a bacterial swab of the skin surrounding the exit site was taken.

If neutrophil leukocytosis was confirmed as the cause of the dialysate cloudiness, antibiotic treatment was continued. In the continuous treatment groups, 30 mg/L vancomycin (Ia) or 20 mg/L teicoplanin (IIa), combined with 125 mg/L ceftazidime, was administered with each dialysis fluid. In APD patients, the drugs were injected into each bag of dialysis fluid, and the cycle regimen was performed according to the individual clinical requirements. In the intermittently treated patients, a second loading dose of vancomycin (Ib, 30 mg/kg) or teicoplanin (IIb, 15 mg/kg) was administered after 7 d, while ceftazidi-
me (250 mg/L) was administered once per day during a 9- to 12-h dwell (nighttime dwell in CAPD, daytime dwell in APD patients). All patients received 200 IU/L heparin intraperitoneally to inhibit fibrin clot formation until the dialysate had completely cleared.

After the initial visit, the patients usually continued ambulatory treatment unless the severity of the peritonitic symptoms necessitated hospitalization. The treatment response was assessed in subsequent (usually outpatient) examinations after 60 h and 7 d of treatment. At these time points, the clinical assessment, blood and dialysate cytology, blood chemistry including glycopeptide concentrations, and dialysate and exit-site cultures were repeated. The treatment response was evaluated according to a standardized Disease Severity Score (DSS, see below). Independent of the treatment response expressed by the DSS, the local physician in charge was free to change treatment at any time starting from the 60-h evaluation according to his or her general clinical impression and further laboratory results. If the initial (60-h) treatment response was considered satisfactory, ceftazidime was discontinued in case of a Gram-positive infection and the glyco-
peptide in case of a Gram-negative infection. If the dialysate cultures revealed no organism or a mixed Gram-positive/Gram-negative infec-
tion, both antibiotics were continued. The antibiotics were adminis-
tered for a total of 10 d (continuous glycopeptide, ceftazidime) or in two bolus doses 7 d apart (intermittent glycopeptide). The second loading dose in the intermittent glycopeptide study arms was ad-
vanced to the fifth day if the 60-h blood level was below the arbitrarily defined “safe” limit of 12 mg/L for vancomycin or 8 mg/L for teicoplanin, respectively. In case of insufficient clinical improvement after 60 h of treatment or in vitro resistance of the cultured organism, the antibiotic or the mode of administration was individually modi-
fied.

A follow-up examination was performed 2 to 3 wk after termina-
tion of antibiotic treatment. If possible, dialysate and residual renal clearances were measured.

A peritonitis relapse was defined as the recurrence of peritonitis with the same organism (defined by biochemical differentiation and resistogram) within 4 wk after termination of antibiotic treatment. If a peritonitis relapse occurred after successful primary therapy, the initially randomized antibiotic regimen was repeated. After clearing of the dialysate fluid, a catheter decontamination procedure was per-
formed comprising the exchange of the connector piece, disinfection of the catheter end, and intracatheter instillation of high-dose antibi-
otic (teicoplanin or vancomycin, 100 mg/ml) and, optionally, of urokinase (5000 IU/ml) on 3 consecutive days.

The study protocol was approved by the ethics committee of the medical faculty of the University of Heidelberg. Approval was con-
firmed by the local ethics committees at each treatment center.

Assessments

The patient’s clinical status was evaluated by a Disease Severity Score (DSS, 0 to 5) defined by the sum of points for pain (0, no pain; 1, moderate pain or nausea not requiring specific therapy; 2, severe pain, usually requiring analgesic therapy, or vomiting; 3, peritonitic pain with tense abdomen and/or paralytic bowel) and fever (0, <37.5°C; 1, 37.5 to 38.9°C; 2, >38.9°C). The body temperature at start of treatment, and the maximum body temperature recorded at 48 to 60 h and 156 to 168 h after start of treatment were used to calculate DSS on day 0, 3, and 7 of treatment, respectively.

The catheter exit site was judged by an Exit-Site Score (ESS, 0 to 10) considering the presence of an erythema (0, none; 1, <0.5 cm; 2, >0.5 cm), a crust (0, none; 1, <0.5 cm; 2, >0.5 cm), tenderness (0, none; 1, moderate; 2, severe), swelling (0, none; 1, moderate; 2, severe), and discharge (0, none; 1, clear; 2, purulent).

End Point Definitions

The treatment response as evaluated 60 h after start of treatment was the primary end point of the study. A positive treatment response was recorded in case of a decrease in the DSS by ≥2 or, if less than 2 initially, when the dialysate cell count had decreased by more than 50%. Any deterioration of the clinical status after 60 h (increase in DSS) was rated as primary treatment failure. Independent of the DSS assessment, the clinician in charge was permitted to change treatment after 60 h based on his general clinical impression and further laboratory results. Both the DSS assessment and the clinical decision were evaluated independently as primary outcome measures. Secondary study end points were the clinical outcome as assessed 7 d after start of treatment, and the occurrence of relapsing peritonitis.

Statistical Analyses

To allow for the therapeutic selectivity of the antibiotic agents applied in combination, treatment response rates were analyzed after stratification for the type of organism cultured (Gram-positive, Gram-
negative, and culture-sterile peritonitis).

Effects of the mode of application (continuous versus intermittent) on the end point parameters (primary response rate, relapse rate) were checked for significance by the Fisher exact test. In case of Gram-positive and culture-sterile or mixed infections, potential independent effects of the application mode and the type of glycopeptide (vancomycin versus teicoplanin) on the outcome parameters were evaluated by calculating the relative risk of treatment failure with each of the two factors using a Mantel–Haenszel estimate, each time controlling for the other variable as a possible confounder.

Between-group comparisons of normally distributed continuous or ordinal-scaled variables were made by ANOVA followed by Duncan’s test for multiple comparisons. If the assumption of a Gaussian distribution was rejected by the Shapiro–Wilk test, the Kruskal–Wallis statistic was used to assess between-group differences. Means ± SD and medians and interquartile ranges were used to describe data with normal and skewed distributions, respectively. The duration of peritonitis-free survival was calculated by Kaplan–Meier life table analysis, and differences between subgroups were assessed for significance by log-rank test.

Results

Epidemiology

The cohort of 152 patients who entered the study between June 1993 and January 1997 was followed for a total of 233.6 patient years. During this period, 168 new cases of peritonitis
(166 bacterial or sterile, 2 fungal) and 27 relapses (22 first, 3 second, 2 third relapses) occurred. No peritonitis was observed in 72 patients, one episode in 41, two in 17, three in 8, four in 8, and more than four in 6 patients. The overall incidence of peritonitis was one episode per 16.9 mo, and the median peritonitis-free survival as from study entrance was 12.7 mo. The first peritonitis occurred significantly earlier in children younger than 6 yr (median 4.1; 95% confidence interval [CI], 1.5 to 7.3 mo) than in older children and adolescents (median 17; 95% CI, 10.6 to 27.6 mo) (P = 0.0006) (Figure 2).

Microbiology

Of the 166 new peritonitis episodes observed, 109 were caused by Gram-positive, 25 by Gram-negative organisms, and in four cases both Gram-positive and Gram-negative germs were cultured. Cultures remained sterile in 28 cases. The spectrum of cultured organisms is given in Table 1. All Gram-positive organisms were in vitro sensitive to vancomycin and teicoplanin. Four of the 33 Gram-negative organisms cultured (12%) were resistant to ceftazidime in vitro (3 Acinetobacter, 1 Enterobacter). Seventeen percent of the Staphylococcus aureus strains and 28% of the coagulase-negative staphylococci were methicillin-resistant. Aminoglycoside resistance was not observed in any of the Gram-negative organisms or Staphylococcus aureus, but in all enterococci, in two of the seven other streptococci, and in 30% of the coagulase-negative staphylococci.

Analysis of the exit-site swabs revealed that in 53% of the cases of Staphylococcus aureus peritonitis, the same organism (according to resistogram) was also isolated from the exit site, compared with only 5.3% Staphylococcus aureus colonization in Staphylococcus aureus-negative peritonitis (P < 0.001). The relative risk for Staphylococcus aureus peritonitis in patients with Staphylococcus aureus exit-site colonization was 9.9 (95% CI, 4.5 to 21.8). The only other organism which, if present at the exit site, conveyed an increased risk for peritonitis with the same organism was Pseudomonas aeruginosa, which colonized the exit site in three of eight Pseudomonas-positive (RR 58.9; 95% CI, 6.9 to 504), but only in one of 158 Pseudomonas-negative peritonitis episodes (P < 0.001). Other organisms isolated at the exit site, such as Staphylococcus epidermidis, were not detected, with increased prevalence in patients who acquired a peritonitis with the same organism. Staphylococcus aureus and Pseudomonas colonization were usually associated with significant exit-site infection (ESS: 4.1 ± 2.4 and 3.0 ± 1.8, respectively), whereas local colonization with other organisms did not affect the exit-site appearance (ESS: 1.1 ± 1.4, diff. versus Staphylococcus aureus and Pseudomonas: P < 0.01). Relapsing peritonitis after successful primary treatment occurred exclusively with Staphylococcus aureus (45%), Staphylococcus epidermidis (36%), and aerobe spore formers (e.g., bacillus sp. (18%).

Clinical Presentation

At initial presentation, 78% of the patients had signs of abdominal pain, and 62% had elevated body temperature. In 17%, cloudy dialysate was the only sign of peritonitis. The mean DSS at onset of peritonitis was 1.95 ± 1.32. It was significantly higher when Staphylococcus aureus was cultured (2.70 ± 1.16) compared with other Gram-positive (1.89 ± 1.26, P = 0.002) or Gram-negative organisms (2.08 ± 1.38, P = 0.06). The median initial dialysate cell count was 1750 (interquartile range, 800 to 5000/mm³) without a difference between causative organisms.

After 60 h of antibiotic treatment, 74% of all cases were free of any clinical symptoms with a dialysate cell count <250/mm³. Symptoms resolved more rapidly in patients with non-Staphylococcus aureus-related Gram-positive peritonitis (DSS at 60 h: 0.14 ± 0.39) than in cases caused by Staphylococcus aureus (0.88 ± 1.13, P = 0.001) or by Gram-negative organisms (0.81 ± 1.23, P = 0.01). Dialysate cell count was >1000/mm³ after 60 h in 24% of the patients positive for Staphylococcus aureus and in 23% of the Gram-negative peritonitis episodes, whereas only one case with coagulase-negative staphylococci showed persistent dialysate cloudiness.

After 7 treatment days, 95% of the patients in whom the initial treatment was continued beyond day 3 showed complete resolution of clinical symptoms and dialysate cell counts <250 cells/mm³. The seven patients with persistent mild (DSS = 1, n = 6) or moderate clinical symptoms (DSS = 3, n = 1) were all infected with Staphylococcus aureus. Three of the seven patients had concomitant exit-site infection (ESS ≥ 4) with Staphylococcus aureus, compared with five of 22 cases of Staphylococcus aureus peritonitis with early resolution of symptoms (NS). None of the peritonitis episodes that had resolved clinically by day 3 showed recurrence of symptoms before the end of antibiotic therapy.

Treatment Efficacy

The initial treatment response rates are given in Table 2. When controlling for the type of glycopeptide in cases of Gram-positive infection, the relative risk for primary treatment

![Graph](image-url)
failure according to DSS did not differ between the continuously treated (RR 1.17; 95% CI, 0.51 to 2.67) and the intermittently treated patients (RR 0.83; 95% CI, 0.30 to 2.27). When controlling for the application mode, the relative risk of treatment failure was also similar with vancomycin (RR 1.41; 95% CI, 0.58 to 3.45) and teicoplanin (RR 0.70; 95% CI, 0.28 to 1.76). When treatment efficacy was evaluated according to the clinical decision, the treatment response also did not differ with respect to the application mode when controlling for glycopeptide type and vice versa. The seven cases of *Staphylococcus aureus* peritonitis with persistent mild or moderate clinical symptoms on day 7 after continued initial treatment were evenly distributed over the treatment groups (four continuous, three intermittent treatment). The five cases that were unresponsive to initial treatment were also caused by *Staphylococcus aureus*. The four intermittently treated episodes rated as initial treatment failures according to clinical decision eventually resolved after switching to the continuous treatment schedule; the peritonitis with insufficient clinical response under continuous treatment improved after addition of floxacinil to the therapeutic regimen.

In case of *Staphylococcus aureus* peritonitis, the presence of a concomitant *Staphylococcus aureus* exit-site infection (ESS ≥4) did not significantly increase the risk for primary treatment failure or prolonged clinical symptoms (6 of 18 versus 6 of 16).

In those patients with Gram-positive peritonitis in whom the initial treatment was continued, dialysate white blood cell counts were similar in the continuously (day 3: median 66, interquartile range 28 to 200 cells/mm³; day 8: median 5, interquartile range 6 to 20) and intermittently treated groups (day 3: median 38, interquartile range 27 to 400; day 8: median 6, interquartile range 4 to 31). However, patients treated with teicoplanin showed significantly lower dialysate cell counts on day 3 (median 35, interquartile range 10 to 168) and on day 8 (median 5, interquartile range 0 to 14) than patients treated with vancomycin (day 3: median 80, interquartile range 32 to 271 [P = 0.06]; day 8: median 13, interquartile range 5 to 78 [P = 0.004]).

In Gram-negative peritonitis, the response to treatment was considered insufficient significantly more frequently according to the clinical decision (12 of 25) than when rated according to the DSS (5 of 25, P = 0.04). Because this discrepancy was more marked for the intermittent treatment arm, the primary success rate according to clinical decision was by borderline significance (P = 0.05) lower with intermittent ceftazidime treatment than with continuous treatment. This difference completely vanished when treatment success was evaluated by DSS (P = 0.62). In four of the five patients who did not respond by DSS, the cultured organisms were in vitro resistant to ceftazidime (3 *Acinetobacter*, 1 *Enterobacter*). Eight of the 12 cases recorded as treatment failures by clinical decision resolved after switching to or adding continuous intraperitoneal aminoglycoside treatment. In three cases, the catheter was exchanged, and one patient was transferred to hemodialysis.

In the 32 cases in which treatment success could not be attributed to one single antibiotic due to sterile or mixed Gram-positive/Gram-negative culture, high primary success rates were observed in each study arm, without any differences with respect to the mode of application or the type of glycopeptide used.

Peritonitis relapses after successful primary treatment were observed exclusively with Gram-positive organisms. The relapse rate differed neither between continuously and intermittently treated patients (24% versus 18%) nor between patients receiving vancomycin and teicoplanin (22% versus 21%). Moreover, no relationship between the occurrence of relapses and the plasma glycopeptide concentrations or the presence of an exit-site infection on days 1, 3, or 8 was noted. A second relapse followed in three and a third relapse in two cases. Surgical removal of the Tenckhoff catheter became necessary in 2 first, 1 second, and 1 third relapse episode.

Eradication of the causative organism from the dialysate was observed significantly more frequently in the continuous than in the intermittent treatment groups both after 60 h (94 versus 67%, P < 0.001) and after 7 d (99 versus 90%, P = 0.03). Persistent bacterial growth in the dialysate was associated with a higher rate of treatment failure by day 3 according to the clinical decision (29% versus 10%, P = 0.004) but not according to the DSS. All seven patients with persistently positive cultures by day 7 were free of clinical symptoms (DSS = 0), whereas the seven patients with persistent clinical symptoms were culture-negative. The eradication rate on day 3 or day 8 did not affect the risk of relapse after successful primary treatment of Gram-positive peritonitis.

**Safety Aspects**

The pharmacokinetic profiles of the glycopeptide antibiotics are shown in Figure 3. Inappropriately high glycopeptide blood levels were observed in four continuously treated patients (2

---

**Table 1. Distribution of organisms**

<table>
<thead>
<tr>
<th>Organism</th>
<th>New Infections*</th>
<th>Relapse Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>35 (21%)</td>
<td>10 (45%)</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>49 (30%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Other coagulase-negative staphylococci</td>
<td>8 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Gram-positive rods (areobe spore formers)</td>
<td>16 (9.7%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td><em>Enterococcus</em> sp.</td>
<td>9 (5.5%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em> sp.</td>
<td>7 (4.2%)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter</em> sp.</td>
<td>8 (4.8%)</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp.</td>
<td>8 (4.8%)</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em> sp.</td>
<td>6 (3.6%)</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> sp.</td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella</em> sp.</td>
<td>4 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative, not specified</td>
<td>2 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Sterile</td>
<td>29 (18%)</td>
<td></td>
</tr>
</tbody>
</table>

* Sum of percentages >100 due to occurrence of mixed infections.
vancomycin: 72, 67 mg/L; 2 teicoplanin: 112, 63 mg/L), three of which were noted on day 3 and one on day 8. During intermittent glycopeptide treatment, overdosing (due to erroneous continued administration of the loading dose) occurred in two teicoplanin-treated patients until day 3 (143, 74 mg/L). Underdosing (due to dosing errors or noncompliance) was noted in three patients on continuous vancomycin (1 on day 1, 2 on day 8; blood levels: 0 to 3 mg/L), and in two intermittently treated patients with inadequate blood levels immediately after loading (1 vancomycin: 1.1 mg/L, 1 teicoplanin: 5 mg/L). In summary, problems with either underdosing/noncompliance or overdosing occurred in seven of 85 (8.2%) continuously treated compared with four of 82 (4.9%) intermittently treated patients (NS).

In the intermittently treated patients, plasma levels decreased by a median of 47 (interquartile range 18) % (vancomycin) and 57 (interquartile range 14) % (teicoplanin) from the first to the third treatment day, and again by 53 (interquartile range 50) % (vancomycin) and 38 (interquartile range 37) % (teicoplanin) between day 3 and day 8. Early reloading (usually on day 5) due to 60-h blood levels below the assumed safe limit was performed in six of 42 vancomycin-treated patients (blood levels 6.5 to 11.2 mg/L), and in 1 of 40 teicoplanin-treated patients (7.8 mg/L). None of the patients with glycopeptide blood levels below the safe limit on day 3 showed an insufficient clinical treatment response or an increased incidence of peritonitis relapse. In the patients receiving intermittent vancomycin, the blood level 60 h after administration was inversely correlated with residual GFR \( (r = -0.53, P < 0.001) \). In contrast, no relationship between blood levels and GFR was observed in the patients treated with intermittent teicoplanin \( (r = -0.17, \text{NS}) \).

### Adverse Effects

Three of the patients receiving vancomycin but no patient on teicoplanin developed a hypersensitivity reaction (“red man” syndrome) during instillation of the loading dose. Audiograms were obtained in patients with apparent glycopeptide overdosing. Although normal results were obtained in the two patients with teicoplanin overdosing, one patient with vancomycin intoxication exhibited a 20- to 30-dB increase in hearing threshold. A normal audiogram obtained a few months before the peritonitis strongly suggested a causal relationship with the vancomycin intoxication. No adverse effects were noted that could be directly attributed to the administration of cefazidime.

Residual renal GFR declined significantly during peritonitis episodes \( (P = 0.005) \). Nineteen percent of the patients with residual diuresis turned irreversibly anuric in the course of peritonitis. The patients who became anuric during episodes of peritonitis had a marginal preperitonitic residual GFR \( (0.71 \pm 0.32 \text{ ml/min per } 1.73 \text{ m}^2) \). In those patients who retained residual renal function, residual GFR decreased from \( 3.4 \pm 3.5 \) to \( 3.0 \pm 3.5 \text{ ml/min per } 1.73 \text{ m}^2 \) (mean relative change \( 11 \pm 30\% \), \( P = 0.06 \)). The magnitude of loss in residual renal function, including the rate of developing anuria, did not differ with respect to the type of glycopeptide (vancomycin versus teicoplanin) or the mode of application (continuous versus intermittent). The use of aminoglycosides, which were administered in a total of 12 patients throughout

<table>
<thead>
<tr>
<th>Group</th>
<th>Ia</th>
<th>IIa</th>
<th>Continuous Total</th>
<th>Ib</th>
<th>IIb</th>
<th>Intermittent Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary success by Disease Severity Score</td>
<td>22 of 25</td>
<td>31 of 31</td>
<td>53 of 56 (95%)</td>
<td>22 of 22</td>
<td>29 of 31</td>
<td>51 of 53 (96%)</td>
</tr>
<tr>
<td>primary success by clinical decision</td>
<td>24 of 25</td>
<td>31 of 31</td>
<td>55 of 56 (98%)</td>
<td>22 of 22</td>
<td>27 of 31</td>
<td>49 of 53 (92%)</td>
</tr>
<tr>
<td>relapse after therapy</td>
<td>6 of 24</td>
<td>7 of 31</td>
<td>13 of 55 (24%)</td>
<td>4 of 22</td>
<td>5 of 27</td>
<td>9 of 49 (18%)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary success by Disease Severity Score</td>
<td>7 of 7</td>
<td>5 of 7</td>
<td>12 of 14 (86%)</td>
<td>8 of 10</td>
<td>0 of 1</td>
<td>8 of 11 (73%)</td>
</tr>
<tr>
<td>primary success by clinical decision</td>
<td>4 of 7</td>
<td>6 of 7</td>
<td>10 of 14 (71%)(^a)</td>
<td>2 of 10</td>
<td>1 of 1</td>
<td>3 of 11 (27%)</td>
</tr>
<tr>
<td>relapse after therapy</td>
<td>0 of 4</td>
<td>0 of 6</td>
<td>0 of 10 (0%)</td>
<td>0 of 2</td>
<td>0 of 1</td>
<td>0 of 3 (0%)</td>
</tr>
<tr>
<td>Sterile or mixed culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary success by Disease Severity Score</td>
<td>6 of 8</td>
<td>7 of 7</td>
<td>13 of 15 (87%)</td>
<td>8 of 8</td>
<td>8 of 9</td>
<td>16 of 17 (94%)</td>
</tr>
<tr>
<td>primary success by clinical decision</td>
<td>7 of 8</td>
<td>7 of 7</td>
<td>14 of 15 (93%)</td>
<td>8 of 8</td>
<td>9 of 9</td>
<td>17 of 17 (100%)</td>
</tr>
</tbody>
</table>

\(^a\) \( P < 0.05. \)
the course of the study, did not affect the evolution of residual GFR.

**Discussion**

This study represents the largest controlled prospective trial of intraperitoneal antibiotic treatment of CPD-related peritonitis performed to date. It provides important epidemiologic and microbiologic information about this complication of CPD in children, demonstrates the excellent efficacy and safety of the combination of a glycopeptide with ceftazidime as first-line peritonitis treatment, and proves the equivalence of continuous and intermittent as well as of vancomycin and teicoplanin treatment.

Although the improvements of peritoneal dialysis technology during the last two decades have resulted in a continuous decline in the incidence of CPD-related peritonitis, peritonitis rates appear to be persistently higher in pediatric compared with adult populations. Our monitoring of peritonitis in nearly
all specialized pediatric dialysis units in Mid-Europe between 1993 and 1997 showed an overall incidence of one peritonitis episode every 16.9 patient months (14.6 including relapsing infections), a figure comparable with recent pediatric surveys performed in North America (one every 13.3 mo (14)) and Italy (one every 16.1 mo (2)), but still considerably higher than typically reported in adults (15,16). Concordant with previous results (14,17), the higher pediatric incidence appears to be entirely attributable to infants under 6 yr of age. The much higher incidence of peritonitis in young children may be related to anatomical and handling problems, but immunologic factors may also play a role (18).

The spectrum of causative organisms was similar to that usually observed in adults and children with CPD-related peritonitis, with staphylococci accounting for approximately 60%, and Gram-negative organisms for 20% of the infections (19). The definition of a Disease Severity Score permitted us to compare quantitatively the initial clinical manifestation as well as the course of the disease between groups of causative organisms. The most severe infections were unequivocally caused by *Staphylococcus aureus*, followed by Gram-negative organisms. Confirming and extending findings reported in adults to children (20), concomitant colonization and/or manifest infection of the exit site with *Staphylococcus aureus* was associated with a 10-fold increased risk for occurrence of a peritonitis with the same organism. A similar association, albeit less frequent in absolute numbers, was noted for pseudomonal infections.

The main end point of this trial was to compare the efficacy of intermittent and continuous initial treatment with a glycopeptide/ceftazidime combination therapy. Three response criteria were considered: the improvement of clinical symptoms according to a clinical scoring system, the clinician’s decision to continue treatment without changing the class or mode of application of antibiotics, and the recurrence of peritonitis within 4 wk after the end of treatment. All isolated Gram-positive organisms were sensitive to glycopeptides in vitro. In vivo, the initial success rate was more than 96%, without a difference between intermittent and continuous or vancomycin and teicoplanin treatment. Although apparent peritonitis relapses were observed in 20% of the initially responsive patients after the end of treatment, all but four of these cases were eventually cured conservatively by repeated application of the original antibiotic regimen with an additional catheter decontamination procedure using high-dose intraluminal antibiotics with or without urokinase according to a previously established protocol (21), resulting in a final cure rate of 92.7% of all new peritonitis episodes. The few cases of ultimate treatment failure were unanimously related to persistent tunnel infections caused by *Staphylococcus aureus*. The excellent results obtained here with intermittent glycopeptide treatment in a large cohort of patients confirm the conclusions of a meta-analysis of the vancomycin treatment experience published in 1990, summarizing six clinical studies with similar success rates in a total of 54 continuously and 53 intermittently treated patients (4). The validity of the concept of intermittent glycopeptide administration in patients with end-stage renal failure was documented by our pharmacokinetic monitoring. All patients retained safe glycopeptide blood levels during the first 60 h of treatment, and no patient showed secondary treatment failure due to insufficient tissue levels with intermittent dosing. In a subset of patients with residual renal function, however, early reloading was required.

One common prejudice against intermittent dosing is that single dosing errors might have fatal consequences because they cannot be compensated for during further treatment. The outlier analysis of the pharmacokinetic profiles revealed that despite two cases of erroneous continued administration of the loading dose in the intermittent treatment arm, the cumulative account of dosing problems was, if anything, lower in the intermittently treated patients, since neither noncompliance nor maintenance dosing errors are a point of concern.

Our results provide evidence that teicoplanin, which had thus far been evaluated only in a small number of patients (10,11), is as effective as vancomycin in the treatment of CPD-related peritonitis. The well known oversensitivity reaction to vancomycin, reported here for the first time with intra-peritoneal administration, apparently does not occur with teicoplanin. Although one case of apparent vancomycin ototoxicity was noted, overdosing of teicoplanin up to plasma levels of 143 mg/L did not result in a measurable hearing loss. The nephrotoxic action of glycopeptides is a concern even in patients on dialysis, because residual renal function may contribute considerably to total solute and water clearance and is a major determinant of dialysis morbidity (22). Although residual renal function deteriorated in the course of peritonitis, we were unable to detect a difference with respect to the type of glycopeptide used. Because the natural history of residual renal function in children on CPD without peritonitis or with peritonitis treated by non-nephrotoxic agents was not surveyed, it is not possible to attribute the loss in renal function to the nephrotoxic action of glycopeptides. With respect to the mode of application, it is noteworthy that blood levels of teicoplanin, in contrast to those of vancomycin, on the third treatment day were not affected by residual renal function. Because of its higher degree of plasma protein binding, teicoplanin blood levels may be more stable for several days after administration of the loading dose, rendering teicoplanin even more suitable for intermittent administration than vancomycin in dialysis patients with residual renal function.

Of note, lower dialysate cell counts on days 3 and 8 of treatment were observed with teicoplanin than with vancomycin. Intraperitoneal vancomycin administration can cause peritoneal irritation even in the absence of bacterial inflammation (23). Since no differences in bacterial eradication rates or signs of infection were observed between the drug treatment groups, low-grade vancomycin-induced dialysate leukocytosis may have been present in individual patients.

Although the clinical efficacy of glycopeptide treatment in Gram-positive peritonitis is remarkable, an apparent spread of vancomycin-resistant enterococci (VRE) and the isolated occurrence of fulminant infections with VRE in intensive care units but also in dialysis populations raise concern about the use of this class of antibiotics. The increased prevalence of
VRE has been attributed to the widespread use of glycopeptides in hospitals but also in veterinary medicine (24,25). Because high-level vancomycin resistance has been shown to be transferable to staphylococci in vitro (26), the emergence of multiresistant staphylococci appears to be possible. Therefore, the Ad Hoc Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis, revising its previous treatment recommendations, has recently discouraged the routine use of glycopeptides in the treatment of CPD-related infections (27). Although the committee’s decision was unanimous with respect to indications such as perioperative or postcontamination prophylaxis or treatment of exit-site infections, the committee was split with respect to the initial treatment of CPD-related peritonitis (28). The proposed return to an initial combination treatment with first-generation cephalosporins and aminoglycosides must take into account the poor clinical success achieved previously with this combination in Gram-positive peritonitis (70%; reference 4), the increase in the rates of methicillin and aminoglycoside resistance among coagulase-negative staphylococci, and the toxicity of aminoglycosides in dialyzed patients. In our population, 28% of the coagulase-negative staphylococci and 17% of the Staphylococcus aureus strains were methicillin-resistant, and aminoglycoside resistance was found in 30% of the coagulase-negative staphylococci. Thus, epidemiologic risks and clinical patient benefits must be carefully weighed against each other in the decision about the preferred initial treatment of peritonitis in a CPD population. In view of their decreasing peritonitis incidence combined with relatively short dialysis times but potential long-term dependence on a functional peritoneum, children represent a population in which antibiotic treatment of peritonitis is required infrequently and in a minority of patients but clinical success is most relevant. Therefore, the primary use of glycopeptides may be justified in the treatment of peritonitis, but it should be dismissed for all other, less vital indications.

With the initial antibiotic regimen used in this study, treatment success in the Gram-negative spectrum was dependent on the efficacy of ceftazidime. This third-generation cephalosporine was preferred because it covers a broad spectrum of Gram-negative organisms, including Pseudomonas, but lacks the toxicity of aminoglycosides. Although once-daily dosing was originally proposed for aminoglycosides in view of their so-called postantibiotic effect (29), this action has not been shown for cephalosporins. Nevertheless, due to the excellent bidirectional transperitoneal diffusion and prolonged half-life of ceftazidime in end-stage renal failure, once-daily intraperitoneal administration should be a suitable mode of application for this drug. We therefore studied the response of peritonitis to Gram-negative organisms to ceftazidime administered during one prolonged dwell period compared with continuous treatment. In line with recent epidemiologic surveys in Europe and the United States (30–32), primary in vitro resistance against ceftazidime was found in 14% of the Gram-negative organisms. The only class of antibiotics showing greater in vitro efficacy against the Gram-negative spectrum encountered in this study were the aminoglycosides. The treatment response was judged discrepantly according to the clinical decision and the DSS: Although 12 of 21 in vitro-sensitive organisms failed to respond according to the clinician’s impression by day 3, the DSS improved sufficiently in all but one ceftazidime-sensitive organism. The discrepancy between the clinicians’ behavior and the objective improvement in fever, pain, and dialysate cell count mainly concerned the intermittent treatment arm, and may be an expression of the clinicians’ mental reservations regarding this treatment modality in case of Gram-negative peritonitis. Hence, the question whether intermittent intraperitoneal ceftazidime treatment of Gram-negative infection is as effective as continuous administration must remain open. Recurrence after successful primary eradication of Gram-negative organisms is rare and restricted to pseudomonal peritonitis with associated catheter tunnel infection (20), and was not observed in any case in this study.

One factor influencing the clinicians’ inclination to be more skeptical about treatment success in intermittently treated patients despite clinical improvement was the higher incidence of persistent bacterial growth in the dialysate cultured on the third treatment day. In this context, it should be emphasized that in the patients on continuous treatment, no antibiotic-free dialysis fluid was instilled before taking the dialysate sample for culture. Thus, any viable organisms present in the dialysate were much less likely to be cultured in the continuously treated patients due to their excess dialysate antibiotic concentrations. On the other hand, a less efficient or delayed eradication of organisms due to lower intraperitoneal drug concentrations cannot be ruled out. Although this potential drawback of the intermittent treatment concept will require further attention, it is reassuring that delayed bacterial elimination in the intermittently treated patients did not affect final treatment outcome or the risk of relapse in this study.

In summary, this trial provided evidence that the initial combined treatment with a glycopeptide and ceftazidime is associated with an excellent primary cure rate of CPD-related peritonitis in children. Intermittent intraperitoneal administration of glycopeptides is as efficient and safe as continuous treatment. Teicoplanin appears to have some advantages over vancomycin with respect to adverse effects and reliability of blood levels after intermittent administration in patients with residual renal function.

Appendix

Members of MEPPS (centers participating in peritonitis study are marked by an asterisk): M. Zimmering (Berlin, Germany*); U. Querfeld (Cologne, Germany*); H. Ruder (Erlangen, Germany*); K. E. Bonzel, C. Laux (Essen, Germany*); D. E. Müller-Wiefel (coordinator, Hamburg, Germany); G. Offner (Hannover, Germany*); O. Mehrs, F. Schaefer (coordinators, Heidelberg, Germany*); J. Misselwitz (Jena, Germany*); C. Greiner (Leipzig, Germany*); G. Klaus (coordinator), M. Soergel (Marburg, Germany*); B. Klare (Munich, Germany*); J. Feber, E. Simkova (Prague, Czech Republic*); H.-J. Stolpe (Rostock, Germany*); M. Fischbach (Strasbourg, France*); E. Balzar (Vienna, Austria).
Acknowledgments

The study protocol was designed exclusively by the MEPPS participants. The study was supported by grants from Fresenius Medical Care Deutschland (Oberursel, Germany), Lederle (Wolfhagen, Germany), Hoechst Marion Merrell Dow (Frankfurt, Germany), and Cansan (Wiesbaden, Germany). The authors appreciate the invaluable help of Susanne Schaefer in collecting and administering data in the central study office. The dedicated laboratory work of Barbara Bollmann and Sylvia Gensler is gratefully acknowledged. We are also indebted to the nurses of the participating pediatric nephrology units for continued care of the patients and active support of the study.

References

23. Freiman JP, Graham DJ, Reed TG, McGoodin EB: Chemical peritonitis following the intraperitoneal administration of vancomycin. Perit Dial Int 12: 57–60, 1992

This article can be accessed in its entirety on the Internet at [http://wwwwwilkins.com/JASN along with related UpToDate topics.](http://wwwwwilkins.com/JASN)