

Peritonitis in Children Who Receive Long-Term Peritoneal Dialysis: A Prospective Evaluation of Therapeutic Guidelines

Bradley A. Warady,* Reinhard Feneberg,[†] Enrico Verrina,[‡] Joseph T. Flynn,[§] Dirk E. Müller-Wiefel,^{||} Nesrin Besbas,[¶] Aleksandra Zurowska,** Nejat Aksu,^{††} Michel Fischbach,^{‡‡} Ernesto Sojo,^{§§} Osman Donmez,^{|||} Lale Sever,^{¶¶} Aydan Sirin,^{***} Steven R. Alexander,^{†††} and Franz Schaefer,[†] for the International Pediatric Peritonitis Registry (IPPR)

*Section of Pediatric Nephrology, Children's Mercy Hospital, Kansas City, Missouri; [†]Division of Pediatric Nephrology, University of Heidelberg, Heidelberg, Germany; [‡]Division of Pediatric Nephrology, Instituto Gaslini, Genoa, Italy; [§]Pediatric Nephrology, Montefiore Medical Center, Bronx, New York; ^{||}University Children's Hospital, Hamburg-Eppendorf, Germany; [¶]Department of Pediatric Nephrology, Hacettepe University, Ankara, Turkey; ^{**}Department of Pediatric Nephrology, Medical University of Gdansk, Gdansk, Poland; ^{††}Department of Pediatric Nephrology, Tepecik Training and Research Hospital, Izmir, Turkey; ^{‡‡}Children's Unit, University Louis Pasteur, Strasbourg, France; ^{§§}Pediatric Nephrology, R. Garrahan Children's Hospital, Buenos Aires, Argentina; ^{|||}Department of Pediatric Nephrology, Uludag University, Bursa, Turkey; ^{¶¶}Department of Pediatric Nephrology, Istanbul University, Cerrahpasa Medical Faculty, Cerrahpasa, Turkey; ^{***}Department of Pediatric Nephrology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey; ^{†††}Lucile Salter Packard Children's Hospital Stanford University, Palo Alto, California

ABSTRACT

In children who are on chronic peritoneal dialysis, peritonitis is the primary complication compromising technique survival, and the optimal therapy of peritonitis remains uncertain. An Internet-based International Pediatric Peritonitis Registry was established in 47 pediatric centers from 14 countries to evaluate the efficacy and safety of largely opinion-based peritonitis treatment guidelines in which empiric antibiotic therapy was stratified by disease severity. Among a total of 491 episodes of nonfungal peritonitis entered into the registry, Gram-positive organisms were cultured in 44%, Gram-negative organisms were cultured in 25%, and cultures remained negative in 31% of the episodes. *In vitro* evaluation revealed 69% sensitivity of Gram-positive organisms to a first-generation cephalosporin and 80% sensitivity of Gram-negative organisms to a third-generation cephalosporin. Neither the risk factors assumed by the guidelines nor the choice of empiric therapy was predictive of either the early treatment response or the final functional outcome of the peritonitis episodes. Overall, 89% of cases achieved full functional recovery, a portion after relapsing peritonitis (9%). These data serve as the basis for new evidence-based guidelines. Modification of empiric therapy to include aminoglycosides should be considered.

J Am Soc Nephrol 18: 2172–2179, 2007. doi: 10.1681/ASN.2006101158

Peritoneal dialysis (PD) remains the most common form of dialysis that initially is prescribed to children with ESRD worldwide.¹ Although it serves as an effective means of accomplishing solute and fluid removal, infectious complications frequently occur and often compromise the continued function of the procedure. Peritonitis and catheter exit-site infections are the most common infections, with the rate of these infections routinely demonstrated to be greater in children than in adults.²

In 1983, the International Society of Peritoneal Dialysis (ISPD) published its first set of peritonitis

Received October 26, 2006. Accepted April 20, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Bradley A. Warady, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO 64108. Fax: 816-234-3494; E-mail: bwarady@cmh.edu

Copyright © 2007 by the American Society of Nephrology

treatment guidelines, which were designed to optimize the efficacy of antibiotic therapy, minimize patient morbidity, and hopefully preserve the function of the peritoneal membrane. Updated versions were published in 1989, 1993, 1996, 2000, and 2005.^{3–6} Although the initial three sets of guidelines were intended to address the needs of both children and adult PD patients, the need for pediatric-specific guidelines that incorporated the specific risk factors and unique clinical aspects of children was recognized. An international committee was established, and pediatric-specific, largely opinion-based guidelines were published in 2000.⁷

Once published and implemented, the efficacy of the peritonitis treatment guidelines in children ideally required formal evaluation in a wide variety of pediatric centers to determine best whether subsequent modification of the recommendations was required. This information was also crucial to the development of evidence-based guidelines. It was for this reason that the International Pediatric Peritonitis Registry (IPPR) was organized.⁸ The primary results of the registry are presented in this article.

RESULTS

Patients and Peritonitis Episodes

Between October 2001 and December 2004, data on 392 children and adolescents, aged 1 mo to 22 yr (median 9.8 yr), each of whom experienced one or more episodes of peritonitis while receiving long-term PD, were entered into the database. Data from both incident and prevalent patients were included. In these patients, a total of 548 episodes of peritonitis were recorded (mean 1.4 ± 0.8 [median 1] episodes per patient; range 1 to 6; 54% male). The 47 participating centers each contributed an average of 11.6 ± 10.4 (median 8) peritonitis episodes in 8.7 ± 7.1 (median 6) patients. The distribution of peritonitis episodes was 72% by European centers, 25% by American centers, and 3% by Asian centers; the mean number of peritonitis episodes by center per geographic region was 13.5 ± 12 in European, 12 ± 9.9 in American, and 6.5 ± 7.8 (NS) in Asian centers. The dialysis modality used was continuous ambulatory peritoneal dialysis in 24% of episodes, continuous cycling PD in 50% of episodes, and nocturnal intermittent PD in 26% of episodes. Patients who received nocturnal intermittent PD had no daytime dwell (dry day), whereas patients who received continuous cycling PD had a daytime dwell (wet day). Eighty-two percent of the episodes occurred with a two-cuff catheter, and the catheter exit-site was directed up in 20%, down in 45%, and lateral in 34% of all catheters. Mean dialysis duration at the time of initial registry entry was 1.7 ± 1.5 yr (median 3 d to 8.3 yr).

A total of 501 (91.4%) of the 548 peritonitis episodes met the criteria for an episode that was treated according to the ISPD guidelines and were included in the analyses. At diagnosis, the dialysate effluent was clear in 3.8% of episodes, the cell count was <100 cells/ μL in 2.8% of episodes, and the percent-

age of polymorphonuclear cells was $<50\%$ in 8.5% of cases. Ten (2%) of the 501 episodes were fungal peritonitis episodes and were excluded from all analyses presented here, if not stated explicitly otherwise. The remaining 491 episodes comprised 218 (44%) Gram-positive, 122 (25%) Gram-negative, and 151 (31%) culture-negative episodes. Staphylococcal organisms accounted for the greatest number of positive cultures, with *S. epidermidis*/other coagulase-negative staphylococcal organisms accounting for 24% and *S. aureus* for 22%. Among the 77% of staphylococcal episodes in which the *S. aureus* carrier status was known, 16% of peritonitis episodes were associated with *S. aureus* nasal carriage (NS for association). The relative risk for acquiring *S. aureus* peritonitis was increased 2.7-fold (95% confidence interval [CI] 1.5 to 4.7; $P = 0.0005$) in the presence of *S. aureus* nasal carriage when controlling for concomitant antibiotic prophylaxis. *Pseudomonas* species and *Klebsiella* species accounted for the greatest number of Gram-negative organisms. The distribution of causative organisms is shown in Figure 1.

Cause and Clinical Manifestation

No identifiable factors were associated with the development of peritonitis in 355 episodes. In the remainder, the most common reported causes were touch contamination (12% of all episodes), exit-site/tunnel infection (7% of episodes), and catheter perforation/leakage (2.1% of episodes). The presence of a nasogastric tube, gastrostomy button/tube, and a ureterostomy was associated with 9.5, 7, and 5.5% of the 491 episodes of peritonitis, respectively.

Associations of the bacterial cause of peritonitis (Gram positive, Gram negative, or culture negative) with a variety of baseline patient characteristics were evaluated. Patients with Gram-negative peritonitis were younger (7.9 ± 5.9 yr) than patients with Gram-positive (10.6 ± 5.6 yr) or culture-negative peritonitis (10.2 ± 6 yr; $P < 0.001$). In patients with culture-negative peritonitis, a higher portion were on continuous ambulatory PD (36%) than in patients with a Gram-negative infection (20%; $P < 0.005$). The use of spike connection systems was more prevalent in patients with a Gram-negative infection (17%) than in culture-negative peritonitis (5%; $P < 0.0005$). Gastrostomy buttons were more frequently present in

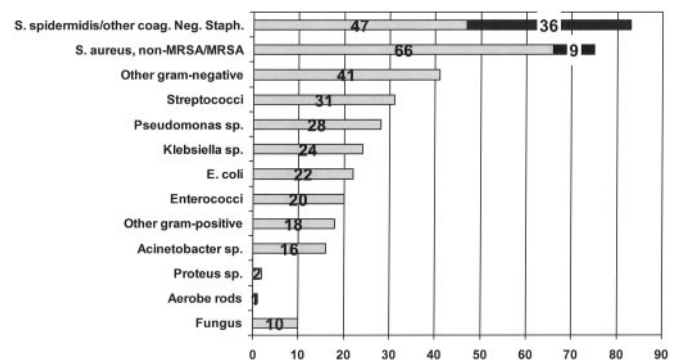


Figure 1. Distribution of causative organisms.

cases of Gram-negative (13%) than Gram-positive (6%) or culture-negative peritonitis (2%; $P < 0.005$). Multiple logistic regression revealed that the likelihood of acquiring Gram-negative peritonitis was independently associated with patient age (odds ratio [OR] 0.94; 95% CI 0.90 to 0.98; $P < 0.005$) and the use of a spike connection system (OR 2.74; 95% CI 1.37 to 5.46; $P < 0.005$). There was also a trend for an association with the presence of a gastrostomy tube/button that did not reach statistical significance (OR 2.21; 95% CI 0.94 to 5.18; $P = 0.06$).

Clinical features at presentation that differed by peritonitis cause included severity of abdominal pain, cloudiness of peritoneal effluent, temperature $>38^{\circ}\text{C}$, peritoneal cell count, and disease severity score (DSS; Table 1). Culture-negative peritonitis was associated with a significantly lower DSS (1.56 ± 1.1) than episodes caused by fungi (2.56 ± 1.33), streptococci (2.41 ± 1.09), Gram-negative organisms (2.38 ± 1.12) and *S. aureus* (2.34 ± 1.06 ; $P < 0.05$).

According to multivariate analysis, the likelihood of a Gram-negative causative organism independently increased with the DSS at presentation (OR 1.36; 95% CI 1.11 to 1.67; $P < 0.005$) and the percentage of polymorphonuclear lymphocytes (OR 1.03; 95% CI 1.01 to 1.05; $P < 0.001$) and decreased with age (OR 0.92; 95% CI 0.89 to 0.96; $P < 0.0005$). Gram-positive infections were independently positively associated with patient age ($P < 0.01$), marked cloudiness ($P < 0.05$), DSS ($P < 0.05$), and a history of *S. aureus* infection ($P < 0.05$) and were inversely associated with the percentage of polymorpho-

nuclear lymphocytes ($P < 0.0005$). Culture-negative infections were more likely in the presence of a low DSS (OR 0.59; 95% CI 0.48 to 0.73; $P < 0.0001$) and with the absence of or mild effluent cloudiness (OR 2.1; 95% CI 1.32 to 3.34; $P < 0.005$).

Antibiotic Sensitivities

The antibiotic chosen for empiric therapy in addition to ceftazidime and the frequency of its use in terms of percentage of peritonitis episodes were as follows: Vancomycin 34%, cefazolin 45%, teicoplanin 17% and cephalothin 4%. *In vitro* evaluation revealed that only 69% of Gram-positive organisms ($n = 154$) were sensitive to either cefazolin or cephalothin, and 80% of the Gram-negative organisms ($n = 101$) were sensitive to ceftazidime (Table 2). In contrast, 97% of the Gram-positive organisms ($n = 192$) tested were sensitive to a glycopeptide, and 88% of Gram-negative organisms ($n = 120$) tested against an aminoglycoside agent were found to be sensitive. Ninety-four percent of Gram-positive organisms ($n = 163$) and 93% of Gram-negative organisms ($n = 113$) were sensitive to the combination of either a first-generation cephalosporin or an aminoglycoside, on the basis of their individual susceptibility data. Finally, 90% of the Gram-positive organisms tested ($n = 101$) and 96% of the Gram-negative organisms tested ($n = 81$) were sensitive to ciprofloxacin, whereas 50% of the coagulase-negative staphylococci and 14% of the *S. aureus* strains were resistant to methicillin.

Table 1. Relationship between bacterial cause and clinical features at presentation^a

Parameter	All Episodes	Gram Positive	Gram Negative	Culture Negative	P
Severe abdominal pain (n [%])	204 (42)	97 (45)	64 (53)	43 (28)	<0.0001
Temperature $>38^{\circ}\text{C}$ (n [%])	224 (46)	108 (51)	69 (58)	47 (31)	<0.0001
Marked effluent cloudiness (n [%])	343 (70)	161 (74)	95 (78)	87 (58)	<0.0005
DSS (mean \pm SD)	2.02 \pm 1.15	2.2 \pm 1.1	2.38 \pm 1.12	1.56 \pm 1.1	<0.0001
Effluent cell count (mean \pm SD)	1990 \pm 2196	2023 \pm 2055	2693 \pm 2700	1390 \pm 1787	<0.0001
% polymorphonuclear cells (mean \pm SD)	81 \pm 16.2	78 \pm 18	85 \pm 14	80 \pm 14	<0.05
Exit-site granuloma (n [%])	38 (8)	24 (11)	7 (6)	7 (5)	<0.05
Exit-site <i>S. aureus</i> (n [%])	39 (9)	26 (13)	5 (5)	8 (6)	0.01

^aStatistical significance indicative of difference between peritonitis cause groups. DSS, disease severity score.

Table 2. Sensitivities of organisms to different classes of antibiotics and their combinations^a

Parameter	All Organisms	Gram Positive	Gram Negative
First-generation cephalosporin	55 (192)	69 (129)	25 (63)
Second generation cephalosporin	61 (166)	62 (88)	60 (78)
Ceftazidime	69 (164)	51 (63)	80 (101)
Glycopeptide	58 (325)	97 (192)	0 (133)
Aminoglycoside	81 (273)	76 (153)	88 (120)
Imipenem/Cilastatin	89 (109)	85 (39)	91 (70)
Ciprofloxacin	93 (182)	90 (101)	96 (81)
First-generation cephalosporin or ceftazidime	86 (211)	82 (119)	91 (92)
Glycopeptide or ceftazidime	93 (299)	99 (198)	80 (101)
First-generation cephalosporin or aminoglycoside	93 (276)	94 (163)	93 (113)
Glycopeptide or aminoglycoside	94 (326)	99 (206)	88 (120)

^aData are % sensitive organisms (total number of organisms tested).

Response to Empiric Treatment

A total of 301 (61.3%) peritonitis episodes were treated according to the risk stratification scheme included in the treatment guidelines; 253 episodes were treated with a glycopeptide, and 258 episodes were treated with a cephalosporin. Although no overall relationship was noted between the 3-d clinical response and the empiric antibiotic regimen chosen, the clinical response was significantly poorer for Gram-negative than for Gram-positive or culture-negative infections ($P = 0.01$; Table 3). The response of Gram-negative organisms to empiric therapy with the glycopeptides/ceftazidime combination also tended to be less favorable than in those who received the combination of a first- and third-generation cephalosporin ($P = 0.06$).

Other factors that were associated with an increased likelihood of empiric treatment response failure 3 d after treatment initiation included a dry day *versus* a wet day for automated PD patients, intermittent ceftazidime therapy in Gram-negative peritonitis, and an exit site score >2 in association with Gram-positive infections (Table 4). The use of a single-cuff catheter nearly achieved statistical significance (OR 2.3; 95% CI 0.98 to 5.4; $P = 0.055$).

In the multivariate analysis, the risk for empiric treatment failure was independently increased by the presence of a Gram-negative infection (OR 3.9; 95% CI 1.8 to 8.3; $P = 0.0004$) and a high effluent cell count ($>500/\mu\text{l}$; OR 2.7; 95% CI 1.2 to 5.9; $P = 0.0123$) with no additional modifying effect of the choice of empiric treatment or the presence or absence of risk factors according to the guidelines. *In vitro* resistance to the selected antibiotic significantly increased the likelihood of empiric treatment failure (first-generation cephalosporin or glycopeptide in Gram-positive infections: OR 16.3 [95% CI 1.5 to 180; $P < 0.05$]; ceftazidime in Gram-negative infections: OR 9.3 [95% CI 1.6 to 52; $P < 0.05$]).

When sensitivity to the administered antibiotic was in-

cluded in the multivariate logistic model that predicted 3-d outcome, *in vitro* resistance was the only variable that predicted response failure (OR 12.9; 95% CI 4.2 to 40; $P < 0.0001$). When Gram-positive infections were considered separately, *in vitro* resistance to the administered antibiotic (OR 19.7; 95% CI 3 to 131; $P < 0.005$) and the exit-site score (OR 1.65; 95% CI 1.01 to 2.71; $P < 0.05$) significantly increased the risk for failure. *In vitro* resistance to the administered antibiotic (OR 29.2; 95% CI 3.1 to 279; $P < 0.005$) and the absence of residual urine output (OR 10.5; 95% CI 1.2 to 93; $P < 0.05$) were associated with an increased likelihood of empiric treatment failure in the patients with Gram-negative infections.

Final Outcome

Of the 491 cases reviewed, nine were unavailable for final outcome evaluation because the patients received a kidney allograft within 4 wk of the onset of the peritonitis episode. The clinical outcome of the 482 available peritonitis episodes is summarized in Table 5, and the relationship between outcome and causative organism is described in Figure 2. Eighty-nine percent of episodes were associated with full functional recovery. Neither the risk factors assumed by the guidelines nor the choice of empiric antibiotic therapy was predictive of the final functional outcome. In 8.1% of cases, PD was permanently discontinued (technique failure) because of persistent ultrafiltration problems, abdominal adhesions, persistent infection, secondary development of fungal peritonitis, or general therapy failure. The last group included a single case of bowel perforation and five lethal outcomes; three patients died from uncontrolled hypervolemia and one from venous access complications when switched to hemodialysis, and in one case, the cause of death remained unclear. The PD catheter was removed as a consequence of peritonitis in 54 cases; in eight of these cases, PD was immediately resumed after catheter replacement, whereas in 12 patients, PD was resumed by insertion of a new catheter after a mean interval of 29 ± 19 d (range 3 to 70 d).

Relapsing peritonitis was observed in 24 (11%) of 219 Gram-positive and in 11 (9.2%) of 120 of Gram-negative episodes. In addition, relapsing culture-negative peritonitis occurred in 17 (11.3%) of 151 cases. Relapsing peritonitis led to temporary discontinuation of PD in four and permanent technique failure in nine of the 52 cases. In total, PD was continued without interruption in 91% of the nonrelapsing infections but in only 75% of the relapsing peritonitis episodes ($P < 0.05$).

DISCUSSION

Peritonitis is a frequent complication of long-term PD in children that can result

Table 3. Unsatisfactory clinical response rate after 3 d of empiric antibiotic treatment in children with PD-associated peritonitis^a

Parameter	Cefazolin/ Ceftazidime	Glycopeptide/ Ceftazidime	Any Treatment
Gram positive	5/90 (5.6%)	4/129 (3.1%)	9/219 (4.1%)
Gram negative	4/56 (7.1%)	12/65 (18.5%)	16/121 (13.2%) ^b
Culture negative	4/92 (4.4%)	2/59 (3.4%)	6/151 (4.0%)
Any culture result	13/238 (5.5%)	18/253 (7.1%)	31/491 (6.3%)

^aClinical response considered satisfactory when DSS <2 and effluent cloudiness improved. PD, peritoneal dialysis.

^bResponse rate significantly lower than Gram positive and culture negative ($P < 0.05$).

Table 4. Factors affecting the likelihood of empiric treatment response failure 3 d after treatment initiation^a

Factor	OR (95% CI), P
Gram-negative causative organism	3.61 (1.73 to 7.54), <0.001
APD modality: "dry day" <i>versus</i> "wet day"	2.53 (1.18 to 5.42), <0.01
Intermittent ceftazidime administration (only Gram negative)	6.65 (2.07 to 21.4), <0.005
Exit-site score >2 (only Gram positive)	5.46 (1.02 to 29.7), <0.05

^aOnly significant results are given. APD, automated PD; CI, confidence interval; OR, odds ratio.

Table 5. Final outcome of peritonitis in 482 children with PD-associated peritonitis^a

Outcome	PD Continued	PD Discontinued		Total (n [%])
		Temporary	Permanent	
Full functional recovery	420	9	0	429 (89)
Ultrafiltration problems	8	1	7	16 (3.3)
Adhesions	3	1	11	15 (3.1)
Uncontrolled infection	0	1	11	12 (2.5)
Secondary fungal peritonitis	0	0	4	4 (0.8)
General therapy failure	0	0	6	6 (1.3)
Total (n [%])	431 (89)	12 (2.5)	39 (8.1)	482 (100)

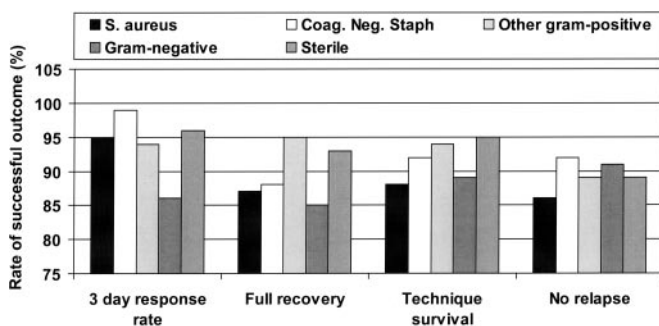


Figure 2. Outcome of peritonitis by organism.

in a variety of adverse outcomes, including the need for hospitalization, PD failure, and even death.² The high incidence of peritonitis in children and the need to preserve membrane function in these patients who face a lifetime of ESRD care mandates an effective approach to therapy. The ISPD pediatric guidelines were designed for that reason, although they are largely opinion based as a result of the limited evidence on the topic that exists in the pediatric nephrology and infectious disease literature. The IPPR, the first large-scale, international clinical project in the field of pediatric nephrology since the International Study of Kidney Disease in Children (ISKDC) in the early 1970s, was in turn established to collect information pertaining to the presentation and treatment of peritonitis in children who receive PD on a global basis. Although a number of publications have described the microbiology of peritonitis in adult patients,^{9–16} this prospective collection of 491 episodes of nonfungal peritonitis is the largest number assembled to date with this level of detail in the pediatric literature.

The diagnostic features documented at presentation were noteworthy because a small percentage of patients presented with clear dialysis effluent despite the fact that 56% of the associated cultures were positive. This finding, which has previously been reported in the adult literature,³ emphasizes the importance of considering the diagnosis of peritonitis in all PD patients with abdominal pain, even if cloudy effluent is initially absent.

The bacteriologic profile of the peritonitis episodes was predominated by staphylococcal organisms, nearly evenly divided into *S. aureus* and coagulase-negative *Staphylococcus*. This result is somewhat different from that recently obtained by Mujais¹⁷ in a survey of >4000 episodes of peritonitis in adult pa-

tients from the United States and Canada. In that study, coagulase-negative *Staphylococcus* was three times more common than *S. aureus* as a cause of peritonitis. Most concerning in our data was the finding of a high rate of culture-negative peritonitis. It is generally agreed that by following recommended culture techniques, culture-negative peritonitis should not account for >20% of peritonitis episodes.^{3,17,18} Evaluation of those sites with frequent culture-negative episodes is now being undertaken. Finally, although a higher incidence of Gram-negative infections in infants (“diaper peritonitis”) has repeatedly been suggested in clinical reviews, we confirm for the first time a statistical association of young age and Gram-negative infection. Additional age-independent circumstances that favor Gram-negative peritonitis were the use of spiking connection systems and the presence of a gastrostomy.

Current pediatric recommendations for empiric antibiotic therapy include the combination of ceftazidime with either a first-generation cephalosporin or a glycopeptide, with the selection based on an opinion-based risk stratification scheme that takes into consideration age, clinical presentation, and history of infection.⁷ The choice of a first-generation cephalosporin *versus* a glycopeptide is often made to minimize the use of a glycopeptide because of an inherent concern regarding the promotion of drug resistance.^{16,19–21} Previous clinical trials in adults have investigated whether there is a clinical advantage associated with the use of a glycopeptides *versus* a cephalosporin in PD-associated peritonitis, and the studies have yielded mixed results, with no difference noted overall between the two antimicrobial agents.²²

Although the combination of ceftazidime with either a first-generation cephalosporin or a glycopeptide was used in all peritonitis episodes, the assignment of empiric therapy to the risk profile given in the guidelines was adhered to in only two thirds of the cases. In part, this may have been related to the participating physician’s prerogative to alter the recommended treatment regimen on the basis of the patient’s clinical status using factors other than those delineated in the risk stratification scheme. Fortunately, this gave us the opportunity to assess independently the relative efficacy of the empiric treatment and the predictive role of the risk factors for an adverse course of peritonitis, as delineated in the guidelines. In the global data analysis, neither the presence of any of the assumed risk factors nor the actual choice of empiric antibiotic therapy

significantly predicted either the early treatment response or the final functional outcome, and there was no significant interaction between the two factors. Hence, the opinion-based assignment of young infants as well as children with severe clinical presentation, previous or ongoing exit-site infection, or methicillin-resistant *S. aureus* history preferentially to glycopeptide treatment with the intention of resulting in a superior outcome does not seem to be supported by clinical evidence.

At first glance, the lack of superiority of glycopeptides in controlling peritonitis may seem surprising, particularly in view of the considerable fraction of organisms with *in vitro* resistance to first-generation cephalosporins and the clear overall association between *in vitro* sensitivity and clinical response within 3 d of treatment initiation. However, the majority of cases of empiric treatment failure were observed with Gram-negative organisms, suggesting that the difference in Gram-positive coverage between glycopeptides and first-generation cephalosporins was clinically less relevant than the surprisingly high 20% resistance to ceftazidime. Notably, the combination of first- and third-generation cephalosporins tended to perform better in Gram-negative peritonitis than the combination of ceftazidime with a glycopeptide. This may be explained by the fact that 50% of the Gram-negative bacteria, including some ceftazidime-resistant organisms, showed *in vitro* sensitivity to cefazolin, resulting in a synergistic effect of the cephalosporin combination.

The limited success with ceftazidime for Gram-negative infections highlights the need for therapeutic alternatives. Aminoglycosides have previously been a component of empiric therapy; however, the potential development of ototoxicity, vestibular toxicity, and nephrotoxicity, with the possible accompanying loss of residual renal function, prompted their replacement by a third-generation cephalosporin in empiric treatment guidelines, even when combined with a first-generation cephalosporin.^{23–26} The bacterial resistance patterns collected in this study revealed that 88% of Gram-negative organisms were sensitive to the aminoglycosides as compared with 80% ceftazidime sensitivity; the best overall susceptibility results were evident with testing against either a first-generation cephalosporin or a glycopeptide combined with an aminoglycoside. These findings emphasize the importance of considering modification of current empiric antibiotic therapy recommendations. Aminoglycoside therapy may be acceptable as part of empiric therapy. When used, there should be prompt modification of antibiotic management once susceptibility data reveal that the causative organism is resistant to aminoglycoside antibiotics or that another, less toxic antibiotic displays evidence of equivalent, *in vitro* efficacy. In the case of culture-negative peritonitis, substitution of the aminoglycoside with ceftazidime is likely preferable. Although our results suggest that ciprofloxacin may be an ideal single agent providing broad coverage against both Gram-positive and Gram-negative organisms, the potential for rapid development of bacterial resistance and the use-related risk for poor cartilage

development in young children make this a less desirable choice for initial therapy.²⁷

Finally, the IPPR is the first peritonitis study in pediatrics to provide a systematic assessment of the outcomes of long-term PD-associated peritonitis. While full functional recovery of PD was achieved in 89% of the episodes, 8% resulted in permanent PD technique failure as a result of persistent ultrafiltration problems, abdominal adhesions, persistent infection, secondary development of fungal peritonitis, or, in almost 1% of cases, death from complications of disease management, all of which emphasize the current morbidity associated with peritonitis in children.

CONCLUSION

The IPPR has, for the first time, provided evidence for the capability of evaluating peritonitis, the most important complication of PD, in children around the globe. The information obtained from this analysis will be incorporated into the antibiotic therapy recommendations that will serve as the basis for the upcoming set of ISPD evidence-based treatment guidelines for children. The subsequent formation of the International Pediatric PD Network will provide the opportunity to further the efforts of the IPPR by not only evaluating the rates of peritonitis and the impact of therapy but also by placing equal emphasis on the prevention and treatment of peritonitis in children worldwide.

CONCISE METHODS

The IPPR is a global consortium of 47 pediatric dialysis centers, composed of 29 European centers, two Asian centers, and 16 centers in the Americas. It was established in October 2001 to address issues of validation of the ISPD pediatric peritonitis treatment guidelines and to evaluate the distribution of causative organisms and their respective resistance patterns (see the acknowledgments for list of participating centers).

Method of Data Collection

Data input was performed exclusively *via* an Internet-based web platform (<http://www.peritonitis.org>). Data pertaining to basic patient and PD modality characteristics, clinical presentation with peritonitis, microbiological results, empiric treatment and its subsequent modifications, clinical treatment response, and final outcomes were submitted sequentially along the course of a peritonitis episode. The data were automatically checked for accuracy and completeness by the need for responses to fall within clinically appropriate ranges and by the requirement for responses to be made to all mandated queries before successful submission. When data that were entered were outside the predetermined range, if mandated responses were not completed, or if calculations (*e.g.*, body mass index) that were based on the data entered seemed to be in error, the system automatically refused final data entry, a message was displayed, and the person who performed the data entry had to correct the data input. In addition,

center-specific demographic data and PD practices were collected by means of an online questionnaire.

Data protection was ensured because the data input was anonymized. The registry protocol was approved by the ethical committees/institutional review boards at each participating center.

Definitions

Peritonitis.

Peritonitis was defined by the presence of (1) cloudy effluent, (2) an effluent cell count of ≥ 100 cells/ μL , and (3) $\geq 50\%$ polymorphonuclear cells in the differential cell count.

Catheter Exit-Site Appearance.

Catheter exit-site appearance was characterized according to a standardized scoring system on the basis of the presence and severity of swelling, crust, redness, pain on pressure, and discharge.²⁸

Treatment of Peritonitis.

Treatment of peritonitis was characterized as being conducted in accordance with the ISPD guidelines when (1) diagnostic criteria for peritonitis were fulfilled and/or an organism was grown on culture, (2) the patient was assessed for the presence of the peritonitis risk factors defined by the ISPD guidelines, and (3) empiric treatment was initiated according to the recommendations of the guidelines (*i.e.*, with either a first-generation cephalosporin and ceftazidime or with a glycopeptide [vancomycin or teicoplanin] and ceftazidime). It was, however, not necessary to initiate treatment according to the recommended risk stratification of therapy described in the guidelines. Antibiotic therapy was intended to be modified in accordance with the results of the dialysate culture and sensitivity testing.

Disease Severity Score (DSS).

The DSS was a quantitative assessment (range 0 to 5) of the clinical status of the patient at presentation that was based on the severity of fever and abdominal pain. The score was calculated as the sum of a maximum score of three points for pain and two for fever.²⁸

Early Treatment Response.

Early treatment response was defined as the clinical response of the patient 72 h after treatment initiation. The response was considered satisfactory when the DSS was ≤ 2 at 72 h after the start of empiric antibiotic therapy and the effluent cloudiness had improved.

Late Treatment Response.

Late treatment response was defined as the clinical outcome of the patient 4 wk after treatment initiation, with consideration of the need for catheter exchange, the occurrence of a relapse, and a composite end point defining full functional recovery. The last was assumed when PD was continued without functional impairment, irrespective of whether a relapse occurred or a catheter exchange was necessary.

Peritonitis Relapse.

Peritonitis relapse was defined as recurrence of peritonitis with the same organism (defined by biochemical differentiation and resisto-

gram or the occurrence of two episodes remaining sterile) within 4 wk after termination of antibiotic treatment. Antibiotic resistograms accompanied most but not all positive cultures. Some resistograms included equivalence assumptions (*e.g.*, Gram-negative organisms regarded as resistant to glycopeptides, clindamycin, and rifampin; enterococci regarded as resistant to cephalosporins).

Statistical Analyses

Differences in group means were assessed by ANOVA followed by Student-Newman-Keuls tests. Differences in proportions were assessed using χ^2 tests. The potential effect of patient characteristics, initial presentation, culture results, and treatment modalities on the relative risk for adverse treatment outcomes (3-d treatment failure, incomplete 4-wk functional recovery, catheter exchange) was assessed by univariate and multivariate logistic regression analysis, calculating OR and 95% CI.

ACKNOWLEDGMENTS

This study was previously published in abstract form (*J Am Soc Nephrol* 16: 709A, 2005).

Participants of the IPPR: N. Aksu, S. Mir, N. Ozkayin, Izmir; A. Sirin, B. Sadikoglu, Istanbul; M. Zimmering, Berlin; F. Schaefer, R. Feneberg, Heidelberg; R. Munoz, Mexico City; E. Sojos, Buenos Aires; O. Donmez, Bursa; K.E. Bonzel, Essen; N. Majkowski, J. Lane, Chicago; S. Testa, G. Ardissino, Milano; L. Sever, Istanbul; D. Drozd, Krakow; S.R. Alexander, Stanford; D.E. Müller-Wiefel, Hamburg; I. Mader, Wroclaw; I. Salusky, Los Angeles; I.S. Ha, Seoul; J. Flynn, New York; K. Rönnholm, Helsinki; A. Zurowska, Gdansk; M. Ekim, N. Besbas, S. Bakkaloglu, Ankara; E. Verrina, Genoa; G. Offner, Hannover; B.A. Warady, Kansas City; K. Arbeiter, Vienna; M. Fischbach, Strasbourg; C.K. Blaszak, Little Rock; E. Simkova, Prague; G. Klaus, Marburg; P. Waber, M. Seikaly, Dallas; M. Sharbono, Birmingham; A.R. Watson, Nottingham; A. Gür Güven, Antalya; J. Symon, Seattle; C. Stefanidis, Athens; A. Al-Uzri, Portland; P. Kingwatanakul, Bangkok; U. John, Jena; L. Stapenhorst, Cologne; K. Haluany, Leipzig; D. Gipson, Chapel Hill.

DISCLOSURES

The IPPR was funded by grants provided by Baxter Health Care and the International Society of Peritoneal Dialysis.

REFERENCES

- Alexander SR, Warady BA: The demographics of dialysis in children. In: *Pediatric Dialysis*, edited by Warady BA, Schaefer FS, Fine RN, Alexander SR, Dordrecht, Kluwer Academic Publishers, 2004, pp 35–46
- Warady BA, Schaefer FS: Peritonitis. In: *Pediatric Dialysis*, edited by Warady BA, Schaefer FS, Fine RN, Alexander SR, Dordrecht, Kluwer Academic Publishers, 2004, pp 393–414
- Piraino B, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, Kuijper EJ, Li PKT, Lye WC, Mujais S, Paterson DL, Fontan MP, Ramos

- A, Schaefer F, Uttley L: Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 25: 107–131, 2005
4. Keane WF, Everett ED, Golper TA, Gokal R, Halstenson C, Kawaguchi Y, Riella M, Vas S, Verbrugh HA: Peritoneal dialysis-related peritonitis treatment recommendations. 1993 Update. The Ad Hoc Advisory Committee on Peritonitis Management. International Society for Peritoneal Dialysis. *Perit Dial Int* 13: 14–28, 1993
 5. Keane WF, Alexander SR, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, Huang CC, Kawaguchi Y, Piraino B, Riella M, Schaefer F, Vas S: Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. *Perit Dial Int* 16: 557–573, 1996
 6. Keane WF, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, Kawaguchi Y, Piraino B, Riella M, Vas S: Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit Dial Int* 20: 828–829, 2000
 7. Warady BA, Schaefer F, Holloway M, Alexander S, Kandert M, Piraino B, Salusky I, Tranaeus A, Divino J, Honda M, Mujais S, Verrina E; for the International Society for Peritoneal Dialysis (ISPD) Advisory Committee on Peritonitis Management in Pediatric Patients: Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. *Perit Dial Int* 20: 610–624, 2000
 8. Feneberg R, Warady BA, Alexander SR, Schaefer F; Members of the International Pediatric Peritonitis Registry: The International Pediatric Peritonitis Registry: A global internet-based initiative in pediatric dialysis. *Perit Dial Int* 24[Suppl 3]: S130–S134, 2004
 9. Kavanagh D, Prescott GJ, Mactier RA: Peritoneal dialysis-associated peritonitis in Scotland (1999–2002). *Nephrol Dial Transplant* 19: 2584–2591, 2004
 10. Perez Fontan M, Rodriguez-Carmona A, Garcia-Naveiro R, Rosales M, Villaverde P, Valdes F: Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. *Perit Dial Int* 25: 274–284, 2005
 11. Chow KM, Szeto CC, Leung CB, Kwan BC, Law MC, Li PK: A risk analysis of continuous ambulatory peritoneal dialysis-related peritonitis. *Perit Dial Int* 25: 374–379, 2005
 12. Szeto CC, Leung CB, Chow KM, Kwan BC, Law MC, Wang AY, Lui SF, Li PK: Change in bacterial aetiology of peritoneal dialysis-related peritonitis over 10 years: Experience from a centre in South-East Asia. *Clin Microbiol Infect* 11: 837–839, 2005
 13. Kim DK, Yoo TH, Ryu DR, Xu ZG, Kim HJ, Choi KH, Lee HY, Han DS, Kang SW: Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: A single center's experience over one decade. *Perit Dial Int* 24: 424–432, 2004
 14. Zelenitsky S, Barns L, Findlay I, Alfa M, Ariano R, Fine A, Harding G: Analysis of microbiological trends in peritoneal dialysis-related peritonitis from 1991 to 1998. *Am J Kidney Dis* 36: 1009–1013, 2000
 15. Krishnan M, Thodis E, Ikonopoulou D, Vidgen E, Chu M, Bargman JM, Vas SI, Oreopoulos DG: Predictors of outcome following bacterial peritonitis in peritoneal dialysis. *Perit Dial Int* 22: 573–581, 2002
 16. Kan GW, Thomas MA, Heath CH: A 12-month review of peritoneal dialysis-related peritonitis in Western Australia: Is empiric vancomycin still indicated for some patients? *Perit Dial Int* 23: 465–468, 2003
 17. Mujais S: Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl* 70: S55–S62, 2006
 18. Tranaeus A: Peritonitis in paediatric continuous peritoneal dialysis. In: *CAPD/CCPD in Children*, 2nd Ed., edited by Fine RN, Alexander SR, Warady BA, Boston, Kluwer Academic Publishers, 2000, pp 301–347
 19. Lye WC: Empirical treatment of CAPD peritonitis: To each his own? *Perit Dial Int* 24: 416–418, 2004
 20. Teitelbaum I: Vancomycin for the initial therapy of peritonitis: Don't throw out the baby with the bathwater. *Perit Dial Int* 21: 235–238, 2001
 21. Flanagan MJ, Lim VS: Initial treatment of dialysis associated peritonitis: A controlled trial of vancomycin versus cefazolin. *Perit Dial Int* 11: 31–37, 1991
 22. Khairullah Q, Provenzano R, Tayeb J, Ahmad A, Balakrishnan R, Morrison L: Comparison of vancomycin versus cefazolin as initial therapy for peritonitis in peritoneal dialysis patients. *Perit Dial Int* 22: 339–344, 2002
 23. McCracken GH: Aminoglycoside toxicity in infants and children. *Am J Med* 80: 172–181, 1986
 24. Warady BA, Reed L, Murphy G, Kastetter S, Karlsen E, Alon U, Hellerstein S: Aminoglycoside ototoxicity in pediatric patients receiving long-term peritoneal dialysis. *Pediatr Nephrol* 17: 178–181, 1993
 25. Shemin D, Maaz D, St. Pierre D, Kahn SI, Chazan JA: Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. *Am J Kidney Dis* 31: 14–20, 1999
 26. Baker RJ, Senior H, Clemenger M, Brown EA: Empirical aminoglycosides for peritonitis do not affect residual renal function. *Am J Kidney Dis* 41: 670–675, 2003
 27. Grady R: Safety profile of quinolone antibiotics in the pediatric population. *Pediatr Infect Dis J* 22: 1128–1132, 2003
 28. Schaefer F, Klaus G, Mueller-Wiefel DE, Mehls O; Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS): Intermittent versus continuous intraperitoneal glycopeptide/cefazidime treatment in children with peritoneal dialysis-associated peritonitis. *J Am Soc Nephrol* 10: 136–145, 1999