

## SHORT REPORTS

### Sclerosing Encapsulating Peritonitis: A Case Successfully Treated with Immunosuppression

Sclerosing encapsulating peritonitis (SEP) associated with peritoneal dialysis (PD) has been reported frequently since its initial description by Gandhi in 1980 (1). The etiology remains elusive: peritonitis might be the most important risk factor, but acetate-based dialysis solutions, chlorhexidine as a disinfectant, and  $\beta$ -blocking drugs have also been implicated as causative agents.

Sclerosing encapsulating peritonitis, a particular presentation of sclerosing peritonitis (SP) should be distinguished from simple peritoneal sclerosis (SS). The latter is almost always present, in variable degrees, in PD patients for more than a few months and leads to a deterioration of membrane permeability. Bioincompatibility of solutions and time on PD are its presumed etiological factors. Usually, SEP presents as small bowel obstruction, malnutrition, sometimes with blood-stained dialysate, and is characterized by cocooning of the small bowel by a very thick fibrous sheath, often with sparse calcified plates lining the peritoneum.

The mean SP incidence in recently published studies ranged between 3.5 (2) and 4.2/1000 patients/year (3). Sclerosing encapsulating peritonitis is a severe complication, although rare, with a mortality rate exceeding 60%, due to sepsis and malnutrition. The treatment is still debated: surgical management is difficult and frequently leads to fatal bowel perforation. Immunosuppressive agents have been associated with some success, supporting the hypothesis that SEP could be immunologically mediated.

We report a clinical case of a continuous ambulatory peritoneal dialysis (CAPD) patient, with clinical and radiological signs of SEP, successfully treated with prednisone and azathioprine, parenteral nutrition, and transfer to hemodialysis (HD). She recovered from the intestinal obstruction and remains asymptomatic 18 months later.

#### CLINICAL REPORT

The patient is a female Caucasian, born in November of 1975, with juvenile nephronophthisis. She began

HD in May 1984. In March 1985 she had her first cadaveric kidney transplant (CKT), with immediate function but it failed 4 months later because of non-compliance. A definitive vascular access was not possible and she was transferred to CAPD with a lactate-based solution. She had two peritonitis episodes by unknown agents before her second CKT in October 1986. This graft had excellent function, but was complicated with ureteral necrosis, which was surgically resolved, and one corticosteroid sensitive acute rejection. She recovered and her Tenckhoff catheter was removed 5 months later. In June 1993 a late rejection, again due to noncompliance, subsided. A second Tenckhoff catheter was introduced and she returned to CAPD, with some residual renal function, in November 1994 using four bags per day of a lactate-based solution, glucose 1.36%, calcium 1.25 mmol/L Baxter system.

In February 1995 she had a new *Staphylococcus epidermidis* uncomplicated peritonitis. She had a third CKT in May 1995, complicated by immediate vascular thrombosis and graft infarction; she remained on CAPD. In July 1995, she had another uncomplicated *S. epidermidis* peritonitis. Following this incident, she needed one 3.86% glucose dialysis per day to maintain adequate ultrafiltration (UF). She became hypersensitized, with a panel-reactive antigen of 84%. In January 1996, a peritoneal equilibration test (Twardowski method) showed a low-average transport with a 4-hour dialysate-to-plasma ratio (D/P) creatinine of 0.54, similar to that of 1 year before (0.58).

During 1996, there were three new peritonitis episodes (one *Streptococcus viridans* and two *S. epidermidis*) which promptly resolved. In December 1996, acute rejection episodes on stopping steroids led to transplantectomy (second graft). Hemoperitoneum without peritonitis persisted for 3 days. Since then, she has needed one 2.27% and one 3.86% bag per day. On 6 February 1997, she was admitted with a new peritonitis episode, which was treated with vancomycin and ceftazidime. A methicillin-sensitive *S. epidermidis* was identified and treatment was changed to cefazolin. Severe abdominal pain and fever persisted, and the peritoneal catheter was substituted 6 days later. On 18 February 1997, with persisting fever and abdominal complaints, *Candida parapsilosis* was detected in the culture of the catheter tip and in a new sample of peritoneal effluent. Abdomi-

nal ultrasonography (US) showed no collections and was interpreted as normal. The patient was treated with intraperitoneal fluconazole for 2 days, then changed to intravenous amphotericin B. She was transferred to HD, with intradialytic nutritional supplementation. The Tenckhoff catheter stayed in place for 5 more days, maintaining peritoneal washings. Her fever disappeared but her abdominal pain increased severely, relieved only by opioids, and obstructive symptoms, nausea, vomiting, and malnutrition with an 8-kg weight loss developed. A new US was interpreted as normal.

On 10 March 1997, an abdominal computed tomography (CT) showed intestinal adhesions and the bowel abnormally restricted to the central part of the abdomen, peritoneal thickening, and loculation of the abdominal cavity (Figure 1). The typical cocoon image emerged and allowed the diagnosis of SEP. Total parenteral nutrition, epidural analgesia, and immunosuppression with azathioprine 50 mg/day plus prednisone 100 mg/day were prescribed. Surgical management was discussed but not done owing to the unsatisfactory results previously reported. Three days later complaints diminished, epidural analgesia could be stopped and 10 days later she started progressive oral nutrition with intradialytic parenteral supplementation for 1 month more. A follow-up CT scan performed on 18 March 1997 showed some improvement. Azathioprine was stopped at 2.5 months of treatment and steroids were continued for 2 months more with progressive tapering without relapse of pain or occlusion. She remains on HD using a central catheter. The patient recovered her lost weight and had a serum albumin of 3.7 g/dL. A last CT performed in August 1997 showed normal distribution of the bowel; the "cocoon" had disappeared (Figure 2).

#### DISCUSSION

With the increasing number of PD patients and the increasing survival on PD, SP becomes an important problem. An Australian study (3) showed a near exponential increase in SP incidence with time on PD: from 1.9% for patients on dialysis less than 2 years, to 6.4%, 10.8%, and 19.4% for more than 5, 6, and 8 years, respectively, suggesting the duration of the exposure of the peritoneum to PD to be a major risk factor. However, some cases occur early in the course of PD.

Peritoneal sclerosis has two distinct forms: the SS form – thought mainly dependent on the bioincompatibility of the solutions – with a sclerotic submesothelial layer not exceeding 40  $\mu$ , and without significant inflammatory infiltrate (4); and the SP form where there is a dramatic progression of the sclerosis after an inflammatory insult, such as peritonitis. The

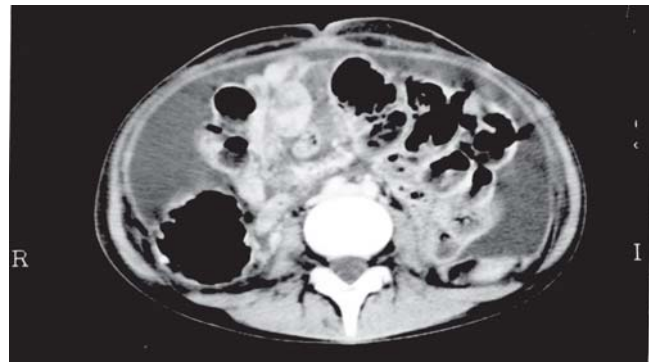


Figure 1 – Abdominal computed tomography image at time of diagnosis of sclerosing encapsulating peritonitis, showing adherent bowel loops, with posterior tethering and luminal narrowing, peritoneal thickening, and loculated fluid.



Figure 2 – Abdominal computed tomography image 5 months after Figure 1, showing normal distribution of the bowel loops, filling of all the cavity, with luminal patency.

thickness of the sclerotic tissue reaches much higher values (1000 – 4000  $\mu$ ) than in SS, and a marked chronic inflammatory infiltrate is invariably present (4). Although bioincompatibility is a risk factor, a definitive etiology for SEP is still unknown. Peritonitis is the most commonly invoked, but not obligatory, pathogenic factor. The underlying process of SP may be immunological. A particular form of SP, SEP (encapsulating form), is characterized by bowel obstruction due to the extensive fibrosis covering and enclosing the gut like a rigid bag. The case we described presented the clinical and radiological features of SEP. The image of a cocoon bowel observed on CT, based on a suggestive clinical presentation, was diagnostic (2,3) and we considered peritoneal biopsy too risky.

This patient was on PD for 42 months and had an incidence of peritonitis of 2.6 episodes/year, much higher than our mean incidence of 0.7 episodes/pt/year. The impact of peritonitis on mesothelial cells, and on their intrinsic fibrinolytic activity are well known. After this damage, the multipotential stem cells of the subserosa may differentiate as mesothelial cells, causing a new epitheliation of the perito-

neum or, to the contrary, leading to fibronogenesis and peritoneal sclerosis. This process of regeneration versus fibrosis is affected not only by the number and duration of peritonitis episodes, but also by their characteristics: persisting peritonitis (2), late peritonitis of a previously damaged peritoneum (2), and the severity of the last peritonitis (2). More aggressive agents such as *S. aureus*, *Pseudomonas*, and fungi are more likely to damage the peritoneum. The increased fibrinous exudate due to increased coagulability and decreased fibrinolysis justifies the decision of some authors, including these authors, to maintain the catheter in place for 48 hours, if possible, to maintain peritoneal washing. The fact that two of three SP cases present after transfer from PD suggests that PD helps to remove fibrin accretion (3).

Peritonitis is only one of many risk factors for SP (3). The peritonitis rate has decreased in the past 10 years and, on the contrary, SP has progressively increased: from 1.5/1000 in the past decade, to 4.2/1000 (3) in the first half of the present decade. In many cases, a previous peritonitis episode could not be documented, which suggests other factors are implicated in SP genesis.

The number of abdominal surgeries, related or not to the catheter, might be another risk factor (2,5). The use of acetate-based PD solution in the early 1980s was undoubtedly related with SP process. Chlorhexidine and  $\beta$ -blocking agents have also been responsible for a considerable number of SP cases. Peritoneal exposure to glucose, hypertonicity, low pH, plasticizers, glucose degradation products (GDP) by heat sterilization, and even trauma from the tip of the catheter (5), have all been implicated as risk factors (2,3). Some antimicrobial agents administered intraperitoneally are likely to negatively affect re-epithelization of the peritoneum. Our patient received fluconazole intraperitoneally for 3 days, as proposed by peritonitis treatment recommendations, although there is little experience with this route of administration. We do not know if it contributed to the SP; however, small bowel obstructive symptoms appeared before its use.

Some authors consider UF failure as an alerting sign for PS, and suggest systematic screening for SP in patients on PD for more than 4 - 5 years who present loss of UF (5). Peritoneal effluent CA125 may also be a sign. Our patient presented UF deterioration.

Imaging of the abdominal cavity became progressively more important during the present decade for the diagnosis of SEP. Abdominal x ray is of low utility (5). Ultrasonography can show peritoneal thickening and a preperitoneal membrane, forming the typical image of trilayer membrane or "sandwich-like" membrane, and a fixed and dilated bowel (5). The CT is the most useful method for this diagnosis (2,3,5). The characteristic image of a cocoon, with the small bowel

restricted to the central part of the abdomen due to the fibrotic sheath covering and closing the loops, and the resulting contracted mesentery, peritoneal thickening, calcifications, and the septa leading to fluid loculation are the features often seen on CT (2,3,5), and were present in our patient. The colonic transit study, although now simplified, takes 2 or 3 days to show an increased colonic transit time (5).

Therapeutic strategy is a difficult decision. One invariable attitude is to stop PD and oral nutrition and transfer the patient to total parenteral nutrition and HD. The cases diagnosed after stopping PD suggest a possible causal relationship between this stop and SP expression, and it may be advisable to maintain the catheter and lavage if infection can be ruled out. Surgical adhesiolysis is invasive and difficult to perform: to find a cleavage plane for the lysis of the adhesions and remove the fibrotic sheath is difficult and sometimes impossible work, especially if fibrosis overpasses the superficial layer. Occasional intestinal perforation may be fatal.

Immunosuppression is another option of therapeutic strategy, as an alternative to surgery or sometimes trying to facilitate the ensuing surgery. The improvement of small bowel obstruction in some SP patients after transplantation encouraged this strategy. Some authors only have SP survivors among those who were treated with immunosuppressive drugs, mostly renal transplanted patients (6). Immunosuppressive regimens were variable between reports, but all of them had prednisone and another drug, usually azathioprine. This supported our decision to use these two drugs, but the ideal prescription is not known; some have advocated intraperitoneal prednisone alone. When we started the immunosuppression, the fungal peritonitis seemed fully treated, with microbiological tests repeatedly negative, but we maintained amphotericin for 14 days.

From the experience acquired with this case, we believe that the therapeutic strategy adopted, which included prednisone and azathioprine, was decisive for the favorable outcome.

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### Intraperitoneal Fluconazole for Fungal Peritonitis in CAPD: Report of Two Cases

Fungal infection accounts for between 1% and 15% of episodes of peritonitis in patients with end-stage renal disease managed by continuous ambulatory peritoneal dialysis (CAPD) (1,2). Management remains challenging because treatment strategies are controversial. Even if clinical symptoms resolve, many patients cannot resume CAPD secondary to peritoneal fibrosis or adhesion (3). Amphotericin B (AMPH-B) has the greatest activity of all antifungal agents. However, this agent is extremely toxic, it does not diffuse well into peritoneal fluid from the blood (2), and its intraperitoneal (IP) administration is often painful and may increase the risk of peritoneal fibrosis and adhesion (3). Fluconazole (FLCZ) is a relatively nontoxic imidazole with strong activity against yeast, and is well absorbed when given either orally or intravenously (4,5). Some authors have reported that the likelihood of peritoneal adhesions after completion of therapy may be decreased by oral FLCZ (6,7), and it is now widely used as a first-line agent against fungal peritonitis.

However, not all patients given FLCZ have a good outcome. Michel et al. (8) reported that catheter replacement after FLCZ treatment failed because of peritoneal adhesions in one of two cases in which it was attempted. A detailed analysis of 32 patients who received FLCZ treatment demonstrated that only 4 were able to continue CAPD successfully without interruption. Eleven of 26 patients who were managed

with catheter removal were transferred to hemodialysis, and there were four deaths.

Dahl et al. (9) recently investigated the pharmacokinetic characteristics of IP FLCZ in patients undergoing continuous cycling peritoneal dialysis who did not have peritonitis. They concluded that IP administration for fungal peritonitis was the preferred route, since it allowed for outpatient treatment without the need for vascular access, and ensured adequate IP drug concentrations. We report the cases of 2 patients in whom IP FLCZ was successful for fungal peritonitis, and CAPD could be continued.

#### PATIENTS

**Case 1:** The first patient was a 64-year-old woman with glomerulonephritis who began CAPD in February 1986. She had no history of surgery or abdominal disease. In early January 1992, she was diagnosed with acute tonsillitis and was given antibiotics. Nine days later she developed a cloudy peritoneal effluent. Upon examination, her temperature was 37.2°C and she had diffuse abdominal tenderness. Her peripheral white blood cell count was 14 500/mm<sup>3</sup>. No fungi were seen on Gram stain. We initially performed intra-abdominal lavage with cephapirin (250 mg/L) while continuing peritoneal dialysis. Because peritoneal fluid cultures showed *Candida albicans*, treatment with intravenous FLCZ (200 mg start; 100 mg daily) was started on the third hospital day. The effluent cleared within 48 hours. However, 1 day later, the dialysate once again became cloudy. On the sixth hospital day, IP FLCZ (25 mg/L of dialysate) was started instead of intravenous FLCZ. After 2 days the dialysate became clear and no micro-organism was cultured from this fluid. Intraperitoneal FLCZ was continued for 1 week and then oral FLCZ (100 mg daily) was administered for 2 weeks. There has been no relapse of the infection since that time.

**Case 2:** The second patient was a 57-year-old man with chronic glomerulonephritis who had been on hemodialysis for 10 years when he elected to switch to CAPD in January 1996. In March 1987, a cardiac pacemaker was implanted for sick sinus syndrome. Late in October 1996, he was diagnosed with trichophytosis in his fingers. Seven days later he showed a cloudy peritoneal effluent. Intraperitoneal lavage was performed initially, using a temporary catheter as a drainage tube. A few lavages per day were performed using heparinized physiological saline solution. Peritoneal dialysis was continued without antibiotic treatment because the patient showed no other symptoms. Three days later he developed a low-grade fever and anorexia. He came to our hospital on 4 November. His peripheral WBC was 6950/mm<sup>3</sup>, and Gram stains were negative. We performed IP lavage, while continuing

peritoneal dialysis, with IP cefmetazole sodium (250 mg/L of dialysate) on the first day, and intravenous cefmetazole sodium (1 g daily) on the second day. After 6 days of therapy, symptoms and signs remained unchanged and *C. albicans* grew from a dialysate fungal culture. Intravenous FLCZ (200 mg start, 100 mg daily) was begun. Still the dialysate showed no improvement, and on the eighth day of treatment, IP FLCZ (25 mg/L of dialysate) was started.

After 2 days, signs and symptoms remained unchanged. The patient's Tenckhoff catheter was removed and replaced immediately with a temporary peritoneal catheter. The temporary catheter was introduced into the peritoneal cavity through the same wound. A purse-string suture was placed around the catheter. A culture of the first cuff and a second culture of the Tenckhoff catheter yielded *C. albicans*. Hemodialysis was started the next day via a femoral vein catheter. Peritoneal lavage was continued twice daily using a heparinized physiological saline solution (1000 mg/L) with FLCZ (50 mg), which was flushed in at 1 L and immediately drained. This was continued until the dialysate culture was negative.

On day 28 of treatment the temporary catheter was removed. Simultaneous serum and dialysate concentrations of FLCZ measured by HPLC-UV at the time of catheter removal were 7.1 µg/mL and 20.3 µg/mL, respectively. Although the patient complained of thirst throughout the lavage period, there were no changes in his blood pressure, weight, or other clinical characteristics. After removal of the catheter, oral FLCZ (100 mg daily) was continued for 3 weeks. On day 45 of therapy and after serum C-reactive protein was no longer detected, a new indwelling Tenckhoff catheter was placed. Subsequent cultures of the patient's peritoneal fluid have shown no change, and he has successfully resumed CAPD. The peritoneal clearance and ultrafiltration capacity in this patient did not change after treatment.

#### DISCUSSION

Fungal peritonitis is an increasingly frequent serious complication of peritoneal dialysis that usually results in catheter loss. The goals of treatment should include eradication of infection as rapidly and as safely as possible, in a manner that allows the patient to continue dialysis. It is desirable that the infection is treated successfully without withdrawal of peritoneal dialysis as in Case 1. However, in the majority of patients, removal of the IP catheter is required, as in Case 2.

In both cases, we initially administered intravenous FLCZ after *C. albicans* was isolated in the peritoneal dialysate. Even after 2 days, signs and symptoms remained unchanged, and so we changed

to IP FLCZ. We waited 2 days to determine efficacy because, according to published reports in all cases in which peritonitis was cured without catheter removal, the effluent cleared within 48 hours (7,10,11).

Reported cases of fungal peritonitis treated with FLCZ are few. Even the route of administration remains controversial. Based on investigations of serum concentrations of FLCZ, oral administration of FLCZ seems to be quite sufficient. Oral treatment produced adequate IP dialysate concentrations. However, the dialysate concentration (20.3 µg/mL) of FLCZ measured in our Patient 2 was fairly high; it was over double the concentration (2.3 - 9 µg/mL) reported by Levine *et al.* (6) who administered the same dose orally. Presuming that this high dialysate concentration was effective in Patient 1, IP administration seems to be a method that should be tried initially.

When the infection cannot be cured with administration of FLCZ, it is generally agreed that the Tenckhoff catheter needs to be removed, because the catheter is colonized with the causative fungi and it exacerbates the infection (12,13). Nagappan *et al.* (14) have reported that, in mild cases, the infection can be eradicated by catheter removal alone. Amici *et al.* (15) have stated that it is important to heighten local antifungal drug concentrations and wash out inflammatory and fungal debris to prevent peritoneal adhesion after catheter removal. Keogh *et al.* (16) reported that insertion of a temporary peritoneal catheter is effective for the continuation of IP lavage and IP drug administration. They repeated peritoneal lavage frequently for 8 - 18 days, until the fluid was microbiologically clear, using 0.5- to 1.0-L exchanges with miconazole and heparin.

In our opinion, if the original catheter is removed, a few lavages per day are enough to avoid formation of massive peritoneal adhesions and are easy enough even for outpatients to comply with. Therefore, we removed the Tenckhoff catheter and inserted a temporary catheter simultaneously through the same wound in Patient 2. Then we commenced peritoneal lavage, using a heparinized physiological saline solution (1000 mg/L) with FLCZ 50 mg, and continued it only twice per day until the dialysate culture was negative. Lavage by physiological saline solution seemed to be effective in removing high dextrose in the peritoneal liquid, since the growth of fungus is frequently related to high concentrations of dextrose. We suggest the following regimen:

1. Commence administration of IP FLCZ.
2. If clinical resolution is not observed after 2 days, remove the Tenckhoff catheter and insert a temporary peritoneal catheter immediately.
3. Commence peritoneal lavage with physiological saline solution and continue administration of IP

FLCZ.

4. After the causative fungi can no longer be isolated, remove the temporary peritoneal catheter.
5. After no inflammation can be found (i.e., serum C-reactive protein is undetectable), implant a new Tenckhoff catheter.

There were no side-effects in our patients due to FLCZ, and no further episodes of fungal peritonitis were observed. The use of IP FLCZ as well as peritoneal lavage with physiological saline solution after removal of the Tenckhoff catheter allowed us to successfully continue CAPD. This is an easy procedure. We will continue to study this approach in the future.

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### Methicillin Resistance Patterns Associated with Peritonitis in a University-Based Peritoneal Dialysis Center<sup>a</sup>

The development of *Streptococcus faecalis* isolates exhibiting vancomycin resistance has recently resulted in the recommendation to avoid vancomycin as initial empiric therapy in many clinical settings, including treatment of peritonitis in patients on chronic peritoneal dialysis (PD) (1-4). Many practitioners have embraced this recommendation, although some remain unconvinced (5,6). Limited clinical data are presently available describing the outcomes in patients with PD-associated peritonitis treated in this manner (6-9).

We describe the antibiotic susceptibility data, specifically regarding methicillin sensitivity, for gram-positive PD peritonitis cases, at a university center, to facilitate additional discussion of this important issue.

<sup>a</sup> Presented as an abstract at the American College of Clinical Pharmacy 1998 Spring Practice and Research Forum, Palm Springs, CA, April 1998.



## METHODS

All cases of peritonitis occurring in a university-based PD program over a 5-year period were retrospectively identified by review of ongoing, unit-maintained, quality assurance documents. Definition of peritonitis in our program was made clinically with laboratory confirmation (white blood cell count  $> 100/\text{mm}^3$  in dialysis effluent, with  $> 50\%$  polymorphonucleocytes) using recommended criteria (1). For the purpose of calculating peritonitis rates, billing records were reviewed to determine the total number of patients at risk for each time interval. Directed chart review of patient medical records was performed to obtain dialysate culture results and antibiotic sensitivity data for each bacterial strain isolated from dialysis effluent. Relapsing peritonitis (same organism, occurring within 30 days of completion of antibiotic treatment) was not counted as a new case or bacterial isolate. Recurrent peritonitis (occurring greater than 30 days after completion of antibiotic course, or infection with a different organism) was counted as a separate case.

Antibiotic sensitivities were determined by a standardized disk-diffusion method performed in the Clinical Microbiology Laboratory of the University of Michigan Medical Center, Ann Arbor, MI, U.S.A. Antibiotic susceptibility data were not available for some *Staphylococcus epidermidis* isolates during a portion of the study period because of laboratory policy, resulting in missing antibiotic susceptibility data in 39 of 123 gram-positive isolates. Results are reported with descriptive statistics only.

## RESULTS

Over the 5-year period reviewed, a total of 202 episodes of peritonitis occurred during 345 patient-years at risk, resulting in a mean peritonitis rate of 0.58 episodes per patient-year at risk (Table 1). Dialysis effluent cultures resulted in no growth in 34 of 202 cases (17%) over the study period. Dialysis culture identified 182 isolates, including 123 gram-positive organisms (68%), 51 gram-negative organisms (28%), and 8 (4%) nonbacterial organisms. *Staph. epidermidis* was the most common bacterium isolated in each year and for the entire study period (58/182 isolates, 32%).

*In vitro* antibiotic sensitivity data were available for 84 of 123 gram-positive bacterial isolates (Table 2). Overall, methicillin resistance was reported in 40% (34/84) of gram-positive isolates over the 5-year study period. Of the 48 *S. epidermidis* isolates tested for *in vitro* antibiotic sensitivity, 50% (24/48) were methicillin resistant, while 26% (8/31) *S. aureus* isolates were reported as methicillin resistant.

## DISCUSSION

Antibiotic sensitivity patterns of gram-positive bacteria isolated from dialysate of patients with acute peritonitis at the University of Michigan Medical Center over a 5-year period demonstrated a significant incidence of methicillin resistance (and presumably resistance to other beta-lactam antibiotics). Of particular concern, approximately one quarter of *S. aureus* isolates demonstrated *in vitro* methicillin resistance. Overall peritonitis rates and distribution of causative organisms were consistent with previous reports from this and other centers.

Several limitations were present in our study, including its retrospective nature, relatively small numbers of peritonitis cases, incomplete antibiotic sensitivity data for *S. epidermidis* isolates, and the lack of clinical outcome results. In an attempt to validate our antibiotic sensitivity results for staphylococcal isolates, we subsequently compared the methicillin resistance rates from peritonitis isolates to general resistance patterns from staphylococcal isolates reported for all isolates from the University of Michigan Microbiology Laboratory and found similar methicillin resistance rates (C. Pierson, personal communication).

Our goal in performing this study was not to add to the literature describing clinical outcomes of PD-associated peritonitis, but rather to document the antibiotic resistance patterns of bacterial isolates from a large tertiary-care medical center, with specific emphasis on beta-lactam resistance in gram-positive organisms. Furthermore, during the study period, our peritonitis treatment protocol included initial intraperitoneal vancomycin and tobramycin, with adjustment of antibiotic coverage as indicated by culture and sensitivity results and clinical improvement. Several studies have already been published documenting the efficacy of similar regimens, and our clinical results are similar to the published experience. Our *in vitro* data should be interpreted with caution however, as *in vitro* antibiotic sensitivity does not necessarily predict clinical outcome, particularly in PD-associated peritonitis. In this setting, high concentrations of antibiotic are added directly to the peritoneal cavity and significant changes in peritoneal antibiotic concentration may occur, depending on the administration scheme used (10). Furthermore, peritonitis outcome is related to organism-specific factors in addition to specific antibiotic treatment (11).

Current recommendations for treatment of PD-related peritonitis include initial treatment with a first-generation cephalosporin and aminoglycoside intraperitoneally, with subsequent adjustment of antibiotic regimen based on culture and sensitivity data as well as clinical response to initial therapy (1). We-

TABLE 1  
Peritonitis Data and Dialysate Culture Results

Year	Patients at risk (n)	Peritonitis episodes (n)	Peritonitis rate <sup>a</sup>	Culture-negative peritonitis (n)	Bacterial isolates	
					Bacterial isolates (n)	Gram+ : gram- : other
1993	75	41	0.55	7	36	26:10:0
1994	76	54	0.71	12	44	32:12:0
1995	65	49	0.75	8	43	28:13:2
1996	65	31	0.48	6	30	18:9:3
1997	64	27	0.42	1	29	19:7:3
Total	345	202	0.586 <sup>b</sup>	34	182	123:51:8

<sup>a</sup> Peritonitis episodes per patient-year at risk.

<sup>b</sup> Mean peritonitis rate over study period.

TABLE 2  
*In Vitro* Methicillin Resistance of Gram-Positive Organisms

Year	Coagulase-negative staphylococci (%)	Coagulase-positive staphylococci (%)	Other gram-positive organisms (%)	Annual total (%)
1993	5/10 (50)	1/9 (11)	0/0 (0)	6/19 (32)
1994	5/12 (42)	1/5 (20)	0/0 (0)	6/17 (35)
1995	4/12 (33)	3/8 (38)	1/1 (100)	8/21 (38)
1996	5/6 (83)	1/2 (50)	1/2 (50)	7/10 (70)
1997	5/8 (63)	2/7 (29)	0/2 (0)	7/17 (41)
Total	24/48 (50)	8/31 (26)	2/5 (40)	34/84 (40)

ber *et al.* reported successful treatment of PD-associated peritonitis with a regimen including continuous intraperitoneal cefazolin and gentamicin in the setting of a low-incidence of *in vitro* beta-lactam antibiotic resistance (9).

Concern over the recommendation to use cefazolin instead of vancomycin for empiric initial treatment has been raised, in part because of uncertainty about the effectiveness of such regimens in treating beta-lactam-resistant staphylococcal infections (5,12). Van Biesen and colleagues propose that cefazolin is not the empiric gram-positive agent of choice for all PD centers, despite published recommendations (5). A review of culture and susceptibility data in their center revealed that a widely recommended protocol using cefazolin and gentamicin would cover only 78% of peritonitis episodes, assuming that *in vitro* sensitivity data predict clinical outcome. Based on these data, this group devised a new protocol using vancomycin and gentamicin initially, then oral ciprofloxacin for ambulatory patients. Intraperitoneal ceftazidime and ciprofloxacin are used in patients requiring hospitalization. With this protocol, an *in vitro* coverage rate of 96% is predicted.

Clinical experience with intermittent cefazolin for treatment of peritonitis in situations where increasing beta-lactam resistance is present have been mixed.

Lai *et al.* reported a gram-positive response rate of 95% with a regimen of cefazolin 500 mg/L and gentamicin 20 mg/L, once daily, in 19 peritonitis episodes (7). In a retrospective study of 55 patients, Vas *et al.* compared vancomycin 2 g weekly plus tobramycin 60 mg daily against cefazolin 1.5 g daily plus tobramycin 60 mg daily in the treatment of PD-associated peritonitis. There was no significant difference in overall efficacy between the regimens, with a success rate of 74% and 77%, respectively. However, the cefazolin/tobramycin regimen resolved only 45% of episodes due to methicillin-resistant coagulase-negative staphylococcal infections, while the vancomycin/tobramycin regimen resolved 73% (8). In a retrospective examination of 118 cases of gram-positive peritonitis in 85 patients, Alves and Dantas reported that vancomycin was twice as effective as cefazolin when used as first-line therapy for *S. aureus*, despite high antibiotic sensitivity to cephalosporins (6).

Although micro-organisms are generally considered resistant to cefazolin when the minimum inhibitory concentration (MIC) is > 64 mg/L, the high concentrations used in continuous intraperitoneal (IP) dosing (cefazolin 125 mg/L) may be sufficient to overcome this "apparent resistance." In contrast, an intermittent once-daily cefazolin dose may not achieve sustained peritoneal concentrations high enough to



treat these "apparently resistant" micro-organisms (10). For this reason, the Ad Hoc Advisory Committee for the Management of Peritonitis advises that a first-generation cephalosporin be administered IP, continuously rather than intermittently (1). Unfortunately, to date no studies have been performed to specifically test the effectiveness of continuous IP cefazolin against methicillin-resistant organisms.

Empiric initial treatment of peritonitis is currently the subject of great debate and variable clinical practice. Appropriate concern over the widespread use of vancomycin and the emergence of vancomycin-resistant bacterial strains has been raised. On the other hand, it remains unclear whether replacement of vancomycin by cephalosporins in treatment of PD-associated peritonitis is prudent, especially in centers with a high prevalence of beta-lactam-resistant gram-positive organisms. The question will best be answered by adequately-sized, prospective, randomized clinical trials. Until the results of such studies are available, we remain concerned about the possible consequences to our patients of current recommendations to avoid initial vancomycin use in PD-associated peritonitis.

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## Effect of Erythropoietin Therapy on Serum Apolipoprotein A1 Levels in Patients Undergoing Chronic Peritoneal Dialysis

Recombinant human erythropoietin (EPO) is widely used in the treatment of anemia in patients on peritoneal dialysis (PD) (1,2). Erythropoietin treatment increases food intake and improves tissue oxygenation, protein metabolism, glucose utilization, and insulin resistance. All these factors may influence lipid metabolism in PD patients. In the literature, there are only a few but conflicting reports on the effects of EPO on the lipid profile in hemodialysis (HD) (3-10), and fewer still in PD (4,5,9) patients. The current study assesses the changes in the lipid profile associated with EPO treatment in PD patients.

#### PATIENTS AND METHODS

Nineteen patients (6 women aged 47 - 75 years, 13 men aged 26 - 74 years) undergoing standard PD with EPO therapy from 1 to 38 months were retro-

spectively analyzed. Eight patients were diabetics. None of the patients suffered from nephrotic syndrome, thyroid or liver disease, or iron deficiency or were receiving lipid lowering drugs. In patients studied repeatedly, the factors that may affect hematocrit and lead to changes in EPO therapy, such as an underlying inflammation, changes in iron, nutritional state, and hydration were not found. The clinical characteristics are shown in Table 1 and the results of lipid profile analyzed as previously reported (11) are shown in Table 2.

In order to evaluate the relationship between EPO doses and serum concentrations of lipids and lipoproteins, and to exclude (or diminish) the effect of Hct changes on these parameters, the latter were adjusted

to Hct by the formula (serum concentration of lipid)  $\times$  (1 - Hct) (13).

Data were evaluated by Student's *t*-test, analysis of variance, and linear regression and are presented as mean  $\pm$ SEM. Paired *t*-test was used for paired data. The Mann-Whitney test and Spearman's *r* were used for assessment of lipoprotein (a).

## RESULTS

As expected, patients with diabetes mellitus exhibited significantly higher basal serum concentrations of glucose than did nondiabetic patients (Table 1). The other parameters compared (Table 1), including abnormal serum concentrations of lipids and lipopro-

TABLE 1  
Clinical Characteristics of Studied Patients

Groups	Total	Nondiabetics	Diabetics
Number of patients	19	11	8
Women/men	6/13	5/6	1/7
Age (years)	58.3 $\pm$ 2.6	58.9 $\pm$ 4.1	57.6 $\pm$ 2.7
Lean body mass (%)	60.1 $\pm$ 2.8	60.6 $\pm$ 2.8	59.6 $\pm$ 5.9
Body mass index (kg/m <sup>2</sup> )	23.8 $\pm$ 0.7	23.3 $\pm$ 3.1	24.6 $\pm$ 1.4
Time on dialysis (months)	13.4 $\pm$ 2.6	15.0 $\pm$ 3.5	11.2 $\pm$ 4.1
Residual renal function (mL/min)	2.1 $\pm$ 0.6	1.3 $\pm$ 0.4	3.5 $\pm$ 1.3
Kt/V	2.1 $\pm$ 0.1	2.0 $\pm$ 0.1	2.1 $\pm$ 0.2
Normalized protein catabolic rate (g/kg/24 hr)	1.1 $\pm$ 0.0	1.0 $\pm$ 0.0	1.2 $\pm$ 0.1
Serum $\beta$ 2-microglobulin (mg/L)	24.8 $\pm$ 1.8	27.6 $\pm$ 2.1	21.0 $\pm$ 2.7
Serum glucose (mg/dL)	129.6 $\pm$ 14.2	98.0 $\pm$ 5.0	173.0 $\pm$ 26.7 <sup>a</sup>
Serum albumin (g/L)	38.4 $\pm$ 1.3	39.9 $\pm$ 1.6	36.3 $\pm$ 2.0
Peritoneal $\beta$ 2-microglobulin clearance (mL/min)	1.1 $\pm$ 0.1	0.9 $\pm$ 0.0	1.2 $\pm$ 0.2
Peritoneal albumin clearance (mL/min)	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0
Hemoglobin (g/L) <sup>b</sup>	116.2 $\pm$ 4.3	118.6 $\pm$ 0.6	113.0 $\pm$ 4.3
Erythropoietin (U/kg/wk)	83.5 $\pm$ 14.5	64.8 $\pm$ 18.9	98.7 $\pm$ 22.4

Mean  $\pm$ SE. To convert residual renal function values to mL/s multiply by 0.01667. To convert glucose values to mmol/L multiply by 0.05551.

<sup>a</sup> *p* < 0.05 versus nondiabetics.

<sup>b</sup> Hematocrit (%) = 0.36 + 0.29 hemoglobin (g/L); *r* = 0.959, *p* < 0.0001, *n* = 19.

TABLE 2  
Lipid Profile (No Adjustment to Hematocrit) of Studied Patients

Groups	Reference interval <sup>a</sup>	Total	Nondiabetics	Diabetics
Triglycerides (mg/dL)	<160	225.6 $\pm$ 21.5	225.2 $\pm$ 26.2	226.2 $\pm$ 38.4
Total cholesterol (mg/dL)	<200	246.2 $\pm$ 10.9	241.4 $\pm$ 14.2	252.7 $\pm$ 18.0
LDL cholesterol (mg/dL)	<130	161.2 $\pm$ 8.0	156.1 $\pm$ 11.3	168.1 $\pm$ 11.4
HDL cholesterol (mg/dL)	>35	39.9 $\pm$ 2.7	40.2 $\pm$ 13.6	39.5 $\pm$ 3.7
Lipoprotein(a) (mg/dL)	0-30	70.1 $\pm$ 17.5	52.5 $\pm$ 13.0	94.4 $\pm$ 37.3
Apolipoprotein A1 (mg/dL)	119-240	126.6 $\pm$ 7.3	118.6 $\pm$ 8.5	137.7 $\pm$ 12.3
Apolipoprotein B (mg/dL)	52-163	144.1 $\pm$ 9.8	142.8 $\pm$ 9.6	145.5 $\pm$ 20.2

Mean  $\pm$ SE. To convert triglycerides to mmol/L, multiply by 0.01129. To convert total cholesterol, LDL-, and HDL-cholesterol to mmol/L, multiply by 0.02586. To convert lipoprotein(a), apolipoprotein A1, and apolipoprotein B to g/L, multiply by 0.01.

<sup>a</sup> From Ref. 12.

teins (Table 2) did not differ significantly between the two subgroups (diabetics and nondiabetics). Therefore, we analyzed the results of both subgroups together. As shown in Figure 1(a), a significant positive correlation was observed between weekly subcutaneous EPO doses and serum concentrations of apolipoprotein A1 (ApoA1). When serum concentrations of ApoA1 were corrected for Hct, the correlation coefficient improved [Figure 1(b)]. Since the EPO effect could obviously be mediated via its effect on hemoglobin, we compared ApoA1 levels with hemoglobin and Hct [Figures 1(c), 1(d)]. It can be seen that these parameters were not significantly correlated. In addition, ApoA1 levels were positively correlated with high-density lipoprotein (HDL)-cholesterol, residual renal function, and Kt/V ( $0.05 > p < 0.09$ ). Moreover, the multivariate stepwise analyses (not shown) showed that the dose of EPO was a stronger independent determinant of serum ApoA1 concentrations than any other factor examined (see Table 1 and Table 2). No effect of EPO treatment on other lipids or lipoproteins was found (results not shown). Serum concentrations of glucose correlated significantly with

total cholesterol (TC), triglycerides (TG), and apolipoprotein B (ApoB) (not shown).

In some patients studied repeatedly ( $n = 6$ ), we found that increases in the dose of EPO were associated with increases in serum concentrations of ApoA1 (Figure 2), and decreases in the dose of EPO ( $n = 3$ ) were associated with decreases in serum concentrations of ApoA1 (not shown).

DISCUSSION

The present study demonstrates that long-term EPO treatment (up to 38 months) significantly improves ApoA1 levels in PD patients. This beneficial effect of EPO treatment on serum ApoA1 levels in PD patients has not been previously reported. Viron *et al.* (4) assessed 5 PD and 7 HD patients receiving EPO for 6 months. They found no changes in the lipid pattern in PD patients. Pollock *et al.* (5) also found no changes in lipid profile, including ApoA1, in 31 patients on PD treated with EPO for 3 to 18 months. However, these authors demonstrated a significant fall in TC, TG, low-density lipoprotein-cholesterol (LDL-C), and

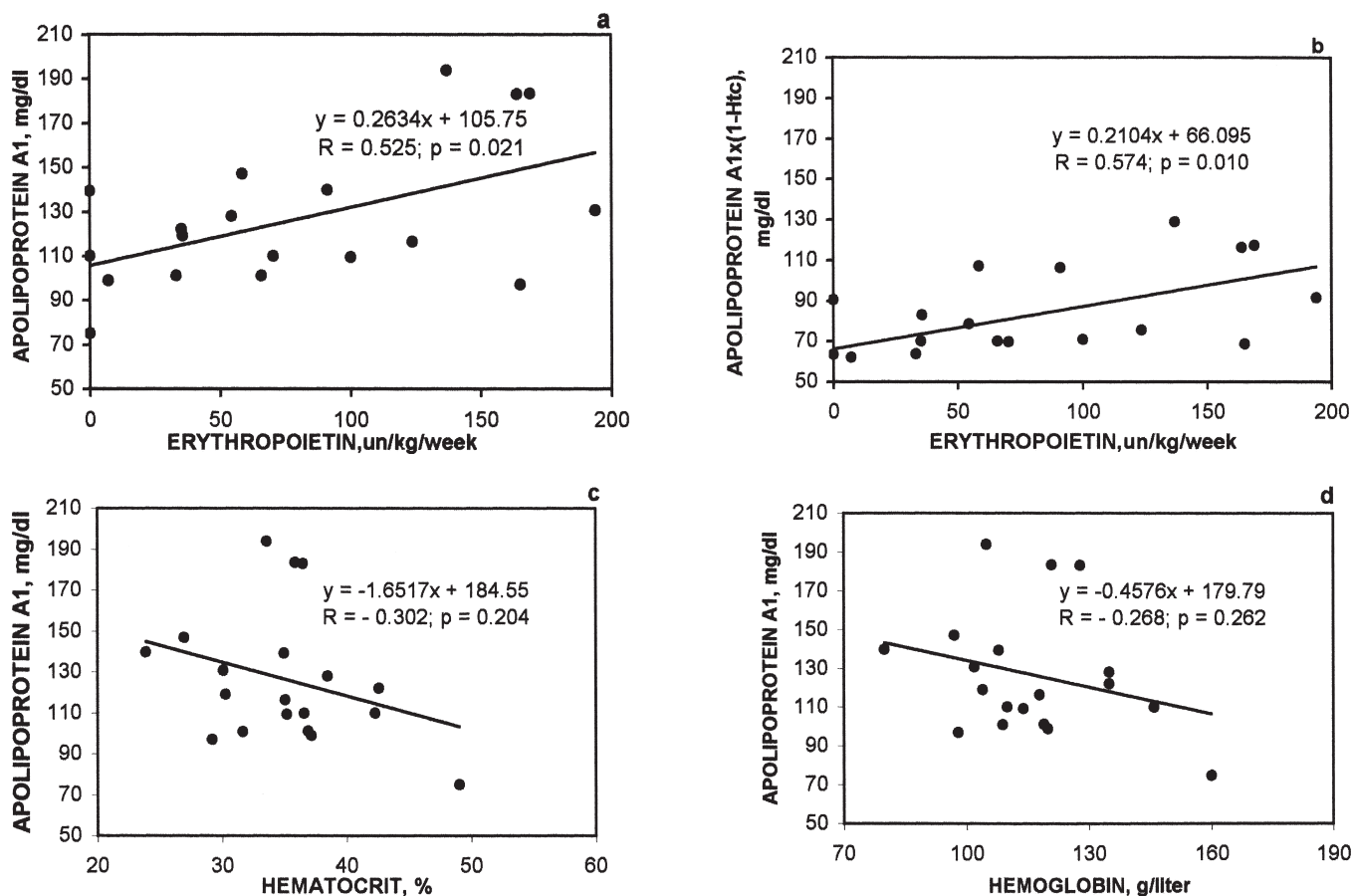


Figure 1 – Relationship between serum apolipoprotein A1 levels and weekly subcutaneous doses of erythropoietin (a,b), blood values of hematocrit (c), and hemoglobin (d) in 19 patients on peritoneal dialysis, serum apolipoprotein A1 levels adjusted to hematocrit (b) (13).



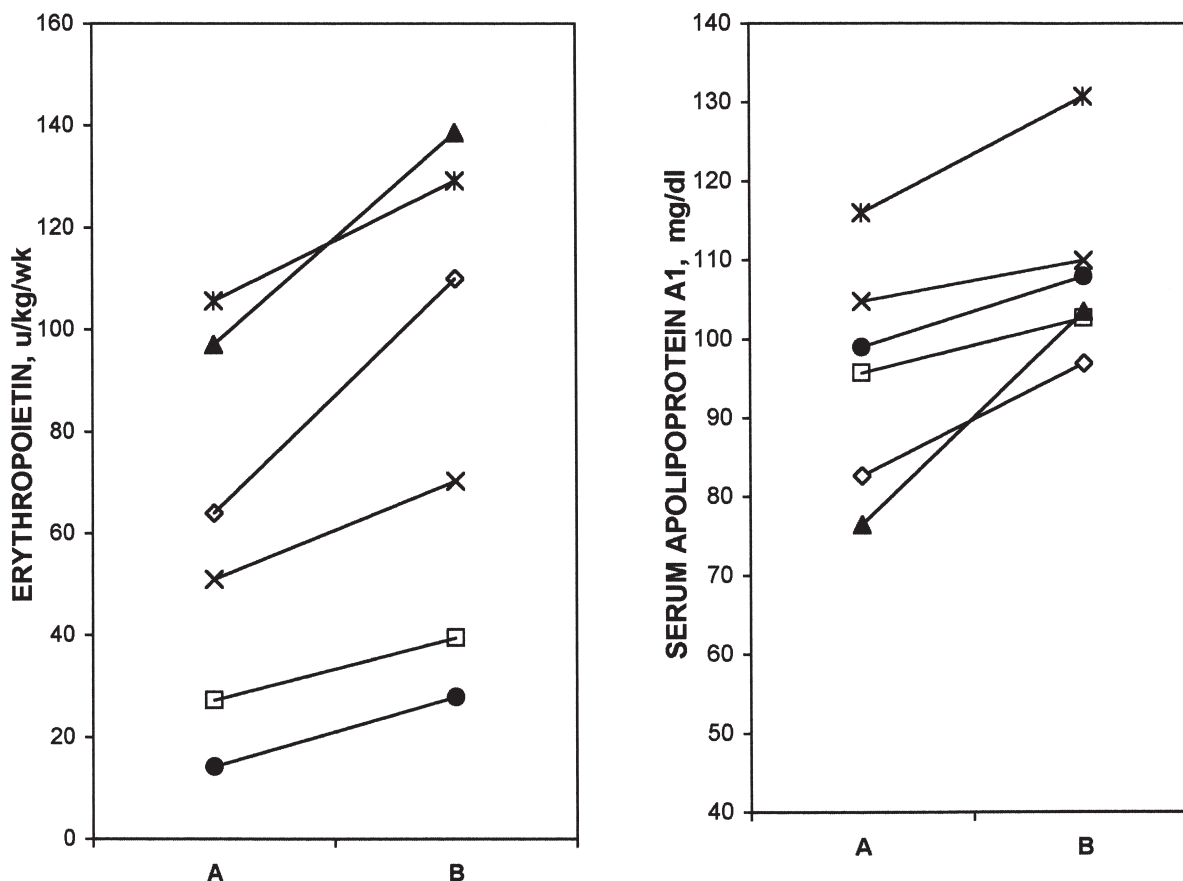


Figure 2 – Individual changes in weekly subcutaneous erythropoietin doses and serum concentrations of apolipoprotein A1 (no adjustment to Hct) in patients on peritoneal dialysis: A and B are time intervals (months; mean  $\pm$ SE) such that A =  $9.3 \pm 2.7$  versus B =  $26.6 \pm 3.4$ ,  $p < 0.05$  by paired  $t$ -test. Subcutaneous erythropoietin doses (U/kg/week; mean  $\pm$ SE): A =  $59.8 \pm 14.9$  versus B =  $85.9 \pm 19.1$ ,  $p < 0.05$  by paired  $t$ -test. Serum apolipoprotein A1 concentrations (mg/dL; mean  $\pm$ SE): A =  $95.7 \pm 5.8$  versus B =  $108.6 \pm 4.7$ ,  $p < 0.05$  by paired  $t$ -test.

ApoB when the results of lipid and lipoprotein changes in PD and HD patients were assessed together. Mak (9) documented normalization of plasma concentrations of TG, TC, and LDL-C in 12 adolescents (6 patients on continuous cycling PD and 6 patients on regular HD) after correction of their anemia by EPO, at a mean interval of 6 months. This improvement in lipid profile was associated with reversed insulin resistance (9). These results corroborate the findings of Borissova *et al.* (14) and Allegra *et al.* (6) that also show an improvement in insulin sensitivity in HD patients after EPO treatment. Insulin resistance is a well-known complication of uremia (15) and may, in part, contribute to the abnormal lipid profile in dialysis patients. In the present study, serum concentrations of glucose correlated significantly with TC, TG, and ApoB as further evidence of insulin resistance. However, no effect of EPO treatment on lipids and lipoproteins, other than ApoA1, was found.

Hematocrit is a strong confounding variable of lipoprotein measurement, especially in plasma (13), and is strongly affected by EPO. In the present study the

improvement in the ApoA1 profile related to EPO treatment could not be explained by the changes in Hct. First, there was no significant correlation between Hct and ApoA1 levels. Second, both measured and Hct-adjusted ApoA1 levels were significantly correlated to EPO (Figure 1). Moreover, the multivariate stepwise analyses selected EPO as a stronger independent determinant of serum ApoA1 concentrations. An increase in Hct due to EPO treatment could potentially influence peritoneal transport of small solutes and macromolecules, including peritoneal loss of ApoA1. In the present study, in agreement with the results of Burkart *et al.* (16), we found no changes in peritoneal transport characteristics in relation to EPO dose changes. Therefore, the increase in the serum concentrations of ApoA1 could not be explained by the differences in peritoneal transport of solutes and water induced by EPO. Alternatively, the decrease in insulin resistance and, probably, increase in hepatic synthesis of ApoA1 associated with EPO treatment may account for the elevated ApoA1 levels in PD patients.

Several studies in the HD population have showed a significant increase in serum ApoA1 concentrations during long-term EPO treatment (4,6,8,10), suggesting that EPO treatment is responsible for this improvement. We have extended this observation to patients undergoing PD, in whom serum ApoA1 concentrations were positively correlated with subcutaneous weekly EPO doses.

In summary, long-term EPO therapy seems to increase the serum concentrations of ApoA1 in PD patients. ApoA1, a major apolipoprotein of HDL, is generally accepted as a protective factor for coronary artery disease (CAD): ApoA1 is associated with severity of coronary damage (17). However, a possible relationship between degree of CAD and increasing ApoA1 levels after EPO treatment in PD patients remains to be studied in a larger population of PD patients.

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