PART THREE

Host Defenses and Infection
Racial differences have been reported among various groups with end-stage renal disease maintained on dialysis. In particular, patient survival on dialysis has been reported to be better in African-American patients than in Caucasian patients. Peritonitis rates and dropout from chronic peritoneal dialysis (CPD) have been reported to be higher in African-American patients. We decided to review our experience with peritonitis rates in African-American and Caucasian patients.

From 1994 to 2000, 403 patients were maintained on CPD in the New Haven continuous ambulatory peritoneal dialysis (CAPD) unit. Peritonitis rates were 1 episode in 14 patient-months in Caucasian patients and 1 episode in 13.6 patient-months in African-American patients. Mean ages at the start of dialysis were 52.4 ± 16.2 years in the Caucasian patients and 62.6 ± 14.9 years in the African-American patients.

African-American patients were older. African-American and Caucasian patients had similar peritonitis rates. Time of first episode of peritonitis was not different in the two groups.

Key words
Peritonitis, racial differences

Introduction
Several studies have evaluated the baseline demographics and outcome of peritoneal dialysis patients based on race and urban setting. The 1997 End-Stage Renal Disease (ESRD) Core Indicators Project noted that, for hemodialysis patients, white patients were older than black patients (1). Technique failure and dropout from continuous ambulatory peritoneal dialysis (CAPD) were noted to be higher in African-American patients than in Caucasian patients (2). The primary cause for dropout in that study, done between 1981 and 1989, was a higher peritonitis rate in the African-American patients.

A previous study by our group showed that the percentage of infections caused by gram-positive and gram-negative micro-organisms was not different between Caucasian and African-American patients (3). Survival rate for patients on CPD has been noted to be better for African-American patients than for Caucasian patients (4—6). The cause for the better outcome in African-American patients as compared with Caucasian patients is unclear.

We therefore wondered if the peritonitis rate was different in the African-American and the Caucasian patients in the New Haven CAPD unit.

Methods
We undertook a retrospective review of the peritonitis rates in Caucasian and African-American patients in the New Haven CAPD unit from 1994 to 2000.

The New Haven CAPD unit is located in the central part of New Haven, and our patients come from both the inner city and the surrounding suburbs. We enroll approximately 35% of all incident ESRD patients into the peritoneal dialysis program, thus allowing for a relatively unselected new-patient group. Of patients on chronic peritoneal dialysis (CPD), 90% are maintained on cycler therapy [automated peritoneal dialysis (APD)] and 10% on CAPD.

Data was reviewed to establish the time to first episode of peritonitis and the peritonitis rate for all the patients in the New Haven CAPD unit. The demographic data obtained included age, race, and the presence of diabetes.

Statistical analysis was done using the Student t-test.

Results
Between 1994 and 2000, 403 patients were managed in the New Haven CAPD unit. The peritonitis rate, time to first peritonitis, and number of diabetic pa-
patients were similar in the Caucasian and the African-American patients. African-American patients were older than Caucasian patients at the start of dialysis ($p < 0.01$). Table I presents the data.

**Discussion**

In our urban PD unit, no difference was seen in peritonitis rate or time to first peritonitis between African-American and Caucasian patients. The study by Firanek et al (2) demonstrated higher peritonitis rates in African-American patients. Those authors were uncertain about the causes of the higher peritonitis rates. Of note, most of the patients in the Firanek report were on CAPD, and most of the patients in New Haven are on APD. It would be interesting to speculate that the peritonitis rate in the New Haven African-American patients is similar to that in the Caucasian patients because of the higher use of APD and the improved connection methodology currently available to CPD patients.

The only difference noted between African-American and Caucasian patients in the present study was that the African-American patients were older at the start of dialysis. That finding is the opposite of the finding noted by the 1997 ESRD Core Indicators Project (1). Age does not appear to be a risk factor for the development of peritonitis in our facility (7).

The present study is important, because it suggests that peritonitis, the leading cause of technique failure in CPD patients, is not more common in African-American patients than in Caucasian patients. Furthermore, the time to first peritonitis episode is not more rapid in African-American patients. The percentage of African-American ESRD patients maintained on CPD is lower than the percentage of Caucasian ESRD patients so maintained (8). The findings of the present study are therefore important for physicians and facilities to keep in mind in terms of educating and advising patients about modality selection for ESRD therapy.

**References**


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Encapsulating peritoneal sclerosis (EPS) is recognized as a serious complication in patients on continuous ambulatory peritoneal dialysis (CAPD). We retrospectively studied the management of CAPD patients who developed EPS in 157 CAPD centers in Japan.

Among 11,549 patients undergoing CAPD between 1980 and 2000 in 157 centers, 256 patients developed EPS. The EPS developed between 10 and 168 months (average: 99.6 months) after the start of CAPD. Of the 256 patients who developed EPS, 104 (40.6%) were using high glucose CAPD solution; however, 135 (52.7%) were not. Only 27 patients who developed EPS (10.5%) were using beta-blockers; many other patients were not. A history of peritonitis was seen in 232 patients (90.6%), but not in 11 other patients (4.3%). The average frequency of peritonitis before development of EPS was 3.3 times higher in patients who developed EPS than in those who did not.

Various therapeutic approaches were tried with 101 of the patients who developed EPS. Steroid therapy, including pulse therapy, was used to treat 84 patients (83.2%), and total parenteral nutrition was used to treat 80 patients (79.2%). Total intestinal enterolysis was performed in 31 patients (30.7%). Immunosuppressive agents were used in only 8 patients (7.9%). After 2 years, 100 patients (39.1%) were known to have died; 143 (55.9%) patients were known to still be alive. The most important problem for the living EPS patients was their mental condition, especially depressive state. However, only 22 of 133 patients (16.5%) were able to consult with a counselor in the hospital. A mental health support system should be provided to EPS patients in Japan.

Encapsulating peritoneal sclerosis (EPS), Japan, incidence

Introduction
Encapsulating peritoneal sclerosis (EPS) is one of the most serious complications in patients on continuous ambulatory peritoneal dialysis (CAPD) and intermittent peritoneal dialysis (IPD). Encapsulating peritoneal sclerosis is characterized by partial or intermittent bowel obstruction, accompanied by marked sclerotic thickening of the peritoneal membrane (1—3). Gandhi et al (1) first reported the complication in 1980, describing the appearance of marked sclerotic thickening of the peritoneal membrane in 5 patients on IPD. Recently, many cases have been reported by many authors (4—6), but little is known about the earliest identifiable abnormalities that might allow the diagnosis to be made before symptoms develop.

A noticeably high number of cases of EPS have been reported in Japan. The Japanese Sclerosing Encapsulating Peritonitis Study Group (3) reported 62 cases of EPS in 6923 patients treated between 1980 and 1994 (0.9%). In a recent re-evaluation of EPS frequency through a survey of 35 centers in Japan (7), 106 cases were identified in 3760 patients (2.8%).

In the present study, we re-evaluated the incidence of EPS in Japan. Furthermore, we retrospectively studied the management of CAPD patients who developed EPS in 300 CAPD centers in Japan.

Patients and methods
At the end of 2000, there were 206,134 end-stage renal disease (ESRD) patients in Japan. Of those ESRD patients, 197,177 (95.7%) were undergoing hemodialysis; 8,650 (4.2%) were undergoing CAPD; 101
(<0.1%) were undergoing home hemodialysis; and 206 patients (<0.1%) were undergoing IPD (7).

Japan has 3220 hemodialysis centers and 1200 CAPD centers. From among the 1200 CAPD centers, we selected 300 by random sampling methods. Our study involved sending a questionnaire about the incidence of EPS during January—March 2001 to the 300 CAPD centers. The study defined EPS as a clinical syndrome followed by encapsulated small bowel with adhesions in patients undergoing peritoneal dialysis. Diagnosis was confirmed by laparotomy or ultrasound findings as described by Holland (8) and Hollman et al (9), and by findings from computed tomography (CT) of the abdomen as described by Korzets et al (10).

In addition, the questionnaire asked for information about the past history of risk factors including peritonitis, high glucose solution, and beta blockers in patients with EPS. We asked about the management in the selected CAPD centers of patients with EPS, including the preventive approach, the therapeutic approach, and the mental support provided to patients with EPS.

Results

Incidence of EPS in Japan
Within the 3-month study period, 157 CAPD centers responded to our questionnaire. The 157 centers reported that 11,549 patients were undergoing CAPD between 1980 and 2000, and that 256 of those CAPD patients (2.2%) developed EPS. The EPS developed between 10 months and 168 months (average: 99.6 months) after the start of CAPD. All 256 CAPD patients with EPS showed typical clinical symptoms, including abdominal pain, nausea, vomiting, an abdominal mass, ascites, severe protein loss leading to malnutrition, and obstruction.

Past history of risk factors in patients with EPS
Figure 1 shows the history of certain risk factors in patients that developed EPS. Of the 256 patients with EPS, 104 (40.6%) had a history of using high glucose CAPD solution; however, 135 (52.7%) had no such history. The history of high glucose solution was unknown for 17 patients [6.6%, Figure 1(A)]. Only 27 patients who developed EPS (10.5%) had a history of using beta-blockers; many other patients did not. The history of beta-blocker use was unknown in 48 patients [18.8%, Figure 1(B)]. A history of peritonitis was seen in 232 patients (90.6%), but not in 11 patients (4.3%). Peritonitis history was unknown for 13 patients [5.1%, Figure 1(C)]. The average frequency of peritonitis before development of EPS was 3.3 times higher in patients who developed EPS than in those who did not.

Therapeutic approach
Various therapeutic approaches were tried with 101 of the patients with EPS. Figure 2 shows the various approaches.

Steroid therapy, including pulse therapy, was used to treat 84 patients (83.2%), and total parenteral nutrition (TPN) was used to treat 80 patients (79.2%). Total intestinal enterolysis was performed in 31 patients (30.7%). Immunosuppressive agents were used in only 8 patients (7.9%). Combination therapy for example, nothing by mouth, TPN, and steroid therapy was performed in many patients with EPS.

In addition, surgical viscerolysis was performed in 53 patients (52.5%).

Of the 256 patients who developed EPS, 100 (39.1%) died of various causes. Two years after diagnosis, 143 (55.9%) patients were known to still be alive. The status of 13 patients was unknown [5.1%, Figure 1(D)]. The most important problem for the living EPS patients was their mental condition, especially depressive state. However, only 22 of 133 patients...
(16.5%) were able to consult a counselor in the hospital.

**Discussion**

In the present study, we re-evaluated the incidence of EPS in Japan. Among 11,549 patients undergoing CAPD between 1980 and 2000 in 157 centers, 256 were reported to have developed EPS. The EPS developed between 10 and 168 months (average: 99.6 months) after the start of CAPD. Of the 256 patients who developed EPS, 104 (40.6%) were using high glucose CAPD solution; however, 135 (52.7%) were not. Only 27 patients who developed EPS (10.5%) were using beta-blockers; many other patients were not. A history of peritonitis was seen in 232 patients (90.6%), but not in 11 other patients (4.3%). The average frequency of peritonitis before development of EPS was 3.3 times higher in patients who developed EPS than in those who did not.

In 1980, Gandhi et al (1) reported first case of EPS. A wide variety of incidences of the condition have been reported from a number of countries (11—13) A study of the registry of the European Dialysis and Transplant Association, conducted in 1985, reported on 214 cases from 112 centers in 19 countries (13). The authors estimated a frequency range from a low of 0.3 per 1000 in Spain to a high of 3.1 per 1000 in Belgium (13). With respect to those previous data, we found that the highest frequencies are observed in Japan; in other countries, such as the United States, Canada, and the countries of Europe, the frequencies are relatively lower.

In 1982, the first case of EPS was reported in Japan (3), and with increasing use of CAPD, many more cases were reported (3,14). In a report by the Japanese Sclerosing Encapsulating Peritonitis Study Group, Nomoto et al (3) found 62 cases of EPS (0.9%) in 6923 CAPD patients treated between 1980 and 1994, although the annual incidence in Japan ranged from 0 to 4.3 per 1000 patients on CAPD.

Based on that previous report, the incidence of EPS was lower in Japan. Nomoto et al (3) reported that the possible reasons were that our patients were treated exclusively with lactate-buffered dialysis solution and that povidone iodine was used as an antiseptic. In addition, several other differences for example, in race, duration of dialysis therapy, and diet, among others might play a role in the development of EPS in patients on CAPD.

In a recent (1998) re-evaluation of the incidence of EPS in 35 centers in Japan, 106 cases among 3760 patients (2.8%) were reported (15). Based on that report, the incidence of CAPD in Japan was close to the incidence of previous reports in other countries. In the present survey (January—March 2001), we found the incidence of EPS to be 256 cases in 11,549 CAPD patients (2.2%).

The reason that the incidences of EPS are completely different among the studies remains unclear. One possibility is differences in the background of the patients. In 1990, 16,543 ESRD patients were newly introduced to dialysis, and the main causes of ESRD were chronic nephritis [7,261 cases (43.9%)], diabetes mellitus [4,326 cases (26.2%)], nephrosclerosis [900 (5.4%)], and others [4,056 (24.5%)]. In 2000, 31,925 ESRD patients were newly introduced to dialysis, and the main causes were diabetes mellitus [11,685 cases (36.6%)], chronic nephritis [10,381 cases (32.5%)], nephrosclerosis [2,428 (7.6%)], and others [7,431 (23.3%)]. The causes of introduction to dialysis therapy completely changed during the intervening decade.

Changes in the duration of CAPD treatment might also contribute to the difference in EPS incidence. In the present study, 256 patients developed EPS between
10 months and 168 months (average: 99.6 months) after the start of CAPD. In the report by Nomoto et al (3), 62 patients developed EPS between 10 months and 138 months (average: 65.4 months) after the start of CAPD. The duration of CAPD is a major risk factor for EPS (14), and the difference in CAPD duration would explain the contradictory results between the Nomoto et al data and ours.

The etiology of EPS in CAPD patients is probably multifactorial (14—16). The Japan Registry report by Ota and Kawaguchi (17) published in 1992 reported that the peritonitis incidence was significantly higher in patients who develop EPS than in those who do not (1 episode every 20.0 months for patients with EPS vs. 1 episode every 32.4 months for control patients on CAPD). In the present study, the average frequency of peritonitis before the development of EPS was 3.3 times higher in patients who developed EPS than in those who did not. Of 256 patients with EPS in our study, 232 (90.6%) had a history of peritonitis; on the other hand, 11 patients (4.3%) did not. Bacterial peritonitis seems to be more common in patients who develop EPS. However, no significant difference was seen in the duration of EPS between the 1 episode every 30.2 months for our study patients and the 1 episode every 32.4 months in the data from the Japan Registry report by Ota and Kawaguchi (17). Based on those data, the role that peritonitis may play in the development of EPS remains undetermined.

High glucose solution (tonicity) is an important risk factor for EPS. In the present report, 104 (40.6%) of the patients who developed EPS were using high glucose solution; 135 (52.7%) of the patients had never used high glucose solution. Those data suggest that high glucose solution is not a major factor in the development of EPS.

Given the current data, we could not elucidate a conclusive management strategy for EPS, because treatments and results both varied. Only one common problem emerged for special consideration: mental care for patients with EPS.

Therapeutic options for EPS consist of fasting, intestinal resting under TPN, and obtaining natural relief. A variety of treatments have been reported (15). Considering the sporadic nature and low incidence of EPS, studies of the treatments have been limited to case reports or small series (18). It is well accepted that TPN, sometimes for a prolonged period of time, forms an integral part of the conservative approach and surgical intervention alike, because good results have been reported in patients with mild EPS. However, there is no agreement in the literature on whether the treatment of choice is surgery or conservative therapy, including corticosteroids and immunosuppressive agents, with or without TPN. Although isolated reports of successful outcomes after surgical intervention exist, especially in patients in whom the peritoneal cocoon is related to severe peritonitis, the prognosis after surgery is usually poor (15,19).

Conclusion
In the present study, we re-evaluated the incidence of EPS in Japan. The management of CAPD patients who developed EPS was retrospectively studied. In 157 centers in Japan, 256 patients with EPS were reported from among 11,549 patients undergoing CAPD between 1980 and 2000. The incidence of EPS was 2.2%. The EPS developed between 10 months and 168 months (average: 99.6 months) after the start of CAPD. A variety of treatments were tried. Based on the current survey, a mental health support system should be provided to EPS patients in Japan.

References
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Glucocorticoid Protects Against the Development of Encapsulating Peritoneal Sclerosis on Peritoneal Dialysis

**Key words**
Aquaporin (AQP), encapsulating peritoneal sclerosis (EPS), glucocorticoid

**Introduction**
In patients on continuous ambulatory peritoneal dialysis (CAPD), progressive reduction of peritoneal function based on loss of ultrafiltration capacity remains the major clinical problem with the therapy. Encapsulating peritoneal sclerosis (EPS) is one of the most serious complications in patients on continuous ambulatory peritoneal dialysis (CAPD). The condition is characterized by partial or intermittent bowel obstruction accompanied by marked sclerotic thickening of the peritoneal membrane (1–3). Gandhi et al (1) first reported the complication in 1980. They described the appearance of marked sclerotic thickening of the peritoneal membrane in 5 patients on intermittent peritoneal dialysis (IPD). However, the mechanism of the peritoneal function failure is little known, and no reports discuss the causes and therapy of EPS. No report mentions the participation of transporters, including aquaporins (AQP) and glucose transporters (GLUTs), in EPS.

Previously, we reported that low-pH dialysis solution (DS) induces peritoneal fibrosis (4). We reported that AQP-1 and AQP-4 play an important role in water transport in patients on CAPD. In addition, glucocorticoid might be an effective treatment to prevent the progression of peritoneal sclerosis in patients on CAPD (5).

The present study was designed to investigate whether low-pH dialysis solution induces peritoneal fibrosis or not. Furthermore, we examined the effect of treatment with glucocorticoid (GC) in a new model of EPS in rats undergoing CAPD.

**Materials and methods**
The study was performed in 12-week-old male Wistar—Kyoto rats weighing between 200 g and 250 g.
Peritoneal catheter insertion was carried out according to a previously described method (6). The protocol was carried out in strict accordance with the guidelines from the National Institutes of Health (7) and was approved by the Institutional Animal Care and Use Committee of Saitama Medical School.

The rats were divided into four groups and were infused with various solutions for 40 days as follows: (A) pH 3.5 DS, 10 mL (pH 3.5, containing 1.35% glucose, \( n = 5 \)); (B) pH 3.5 DS, 10 mL + GC (0.1 mg dexamethasone daily, \( n = 5 \)), (C) pH 7.0 DS, 10 mL (pH 7.0, containing 1.35% glucose, \( n = 5 \)); and (D) pH 7.0 DS, 10 mL + GC (\( n = 5 \)). At the end of 40 days, all rats were humanely killed by decapitation after peritoneal equilibration test (PET) measurements had been taken. Expression of mRNA of aquaporins (AQPs), glucose transporters (GLUTs), and transforming growth factor-β1 (TGFβ1) in peritoneum were studied by semi-quantitative reverse-transcriptase polymerase chain reaction (RT-PCR). Ultrafiltration volume (UFV) and peritoneal function were measured by the PET.

**Peritoneal equilibration test**

The PET in each rat was performed under pentobarbital anesthesia (50 mg/kg). The animal was placed on a heating pad to maintain a temperature of 37°C. An intra-abdominal catheter (PE-50) was placed, and a 20-mL dose of 10% glucose solution was injected into the abdominal cavity of the rat. Two hours later, the solution in the abdominal cavity was measured as for a conventional equilibration test (5).

**Studies of AQP, GLUT, and TGFβ mRNA expression in the peritoneum**

Semiquantitative RT-PCR was carried out to determine which AQP transcriptions were detectable in the peritoneum. Total RNA was isolated from the extracted and homogenized peritoneum using TRIzol reagent (Gibco BRL, Rockville, MD, U.S.A.), chloroform, phenol:chloroform:isoamyl alcohol, isopropyl alcohol, and ethyl alcohol extraction.

In brief, 5 µg of total RNA was mixed with 10’U of Super-Script II reverse-transcriptase (Gibco BRL), 500 mmol/L of oligonucleotide, 2.5 mmol/L of deoxynucleoside triphosphates (dNTPs). The mixture was incubated at 42°C for 60 minutes. The PCR was performed by incubating 1 µL of the RT product with PCR mixture (Takara Co., Tokyo, Japan) containing 2.5 mmol/L of dNTPs and 5’U of recombinant Taq DNA polymerase, and 0.2 mmol/L each of the primers for AQP-1 through AQP-4, GLUT-1 through GLUT-5, and TGFβ1. The initial denaturation step was conducted at 94°C for 5 minutes. The temperature profile of the PCR was 30’cycles at 94°C for 1 minute, 58°C for 2 minutes, and 72°C for 3 minutes, followed by the final extension step at 72°C for 5 minutes. The PCR products were size-fractionated by 1% agarose gel electrophoresis, and stained with ethidium bromide. Visualized bands were optically scanned (GT9600: Epson Co. Ltd., Tokyo, Japan) and quantified by image-analyzing software (MacSCOPE, version 2.56: Mitani Corp., Fukui, Japan). To control for differences in RNA loading and PCR efficiency, PCR using the GAPDH primer set (Clontech, Palo Alto, CA, U.S.A.) were simultaneously carried out. Values of AQP mRNA were normalized to corresponding values of GAPDH mRNA (AQP mRNA/GAPDH and TGFβ1 mRNA/ GAPDH mRNA band density) (4).

The semi-quantitative RT-PCR was performed using these primer sets:

**AQP-1**

- sense primer: CTTCGTCTTTCATCAGCATCG
- anti-sense primer: TGAGCACAACTGATGTGACC

**AQP-2**

- sense primer: AGTGCTGGCTGAGTTCTTGG
- anti-sense primer: CTCGAAGGAAGGAGACATGG

**AQP-3**

- sense primer: ATGCTCCACATCCGCTACCG
- anti-sense primer: TCAGATCTGCTCCTTGTGCT

**AQP-4**

- sense primer: ATGGTGCTTTTCAAAGGCGT
- anti-sense primer: GAAGACAGACCTTGCGATGC

**GLUT-1**

- sense primer: AGCTAACATTGGCCTGGACC
- anti-sense primer: CATCTATAACACAGCGAGCATG

**GLUT-2**

- sense primer: CCTGGATGAGTTATGTGAGCATG
- anti-sense primer: ATGTTAGAAGGCTGAGCATG

**GLUT-3**

- sense primer:
CTGGGATCAATGCTGTGTTCTA
anti-sense primer:
GGCTGCATGCTGTTCAACTCC:
GLUT-4 sense primer:
CCAGCAGCTCAGGCATCAAT
anti-sense primer:
CTGGGTTTCACCTCCTGCTCTA:
GLUT-5 sense primer:
ACTACTACGCTGACCAGATC
anti-sense primer:
GGCCCACGATGAAGTTAGAGA
TGFβ1 sense primer:
TCGATTTTGACGTCACTGGAGTTGT
anti-sense primer:
GGGGTGCCATGAGGAGGAGG

Statistical analysis
Results are expressed as mean ± standard error of the mean (SEM) of the experiments. Comparisons between groups were made using the Student t-test for unpaired data, with \( p < 0.05 \) required for significance.

Results
Changes in peritoneal function measured by PET
Figure 1 shows the changes in UFV in the rats. The dialysate drainage volume was 17.8 ± 2.2 mL in the pH 7.0 DS group. The pH 3.5 DS group experienced a significant reduction in dialysate drainage volume (2.6 ± 0.5 mL, \( p < 0.01 \). On the other hand, the pH 3.5 DS+GC group experienced significant increases in dialysate drainage volume (10.2 ± 1.7 mL).

Light-microscope findings in the peritoneum
Figure 2 shows the pathologic changes in the peritoneum. After 40 days of intraperitoneal injections of dialysis solution, subserosal tissue thickening became more significant in parallel with the acidity of the solution. Among the solutions employed, the pH 3.5 DS induced loss of mesothelial layer, resulting in typical peritoneal fibrosis. The subserosal fibrous tissue contained spindle-shaped and round mononuclear cells (for example, fibroblasts and monocytes), as well as dense amorphous substances (for example, collagens and fibronectin). In addition, remarkable vascular sclerosis was observed in the subserosal tissue of the rats injected with pH 3.5 solution. In comparison, the pH 7.0 dialysis solution induced only slight subserosal tissue thickening. Administration of glucocorticoid into peritoneum completely improved the changes to the peritoneum. Glucocorticoid treatment prevented the progression of peritoneal fibrosis and adhesion of peritoneum.

Expression of AQP, GLUT, and TGFβ mRNA in the peritoneum
Figures 3 and 4 show the expression of AQP-1, GLUT-4, and TGFβ1 in the peritoneum. Treatment with pH 7.0 DS induced the expression of AQP-1, AQP-4, GLUT-1, GLUT-4, GLUT-5, and TGFβ mRNA in the peritoneum. Expression of AQP and TGFβ1 mRNA were significantly suppressed in the pH 3.5 DS group, accompanied by loss of UFV. On the other hand, expression of GLUTs was significantly increased in rats treated with pH 3.5 DS. Expression of AQP and TGFβ1 were significantly improved in rats treated with pH 3.5 DS+GC, with a gain of UFV.

Discussion
In the present study, long-term intraperitoneal administration of acidic dialysis solution induced severe peritoneal adhesions. The rats treated with low-pH dialysis solution had a disease process and pathologic conditions partially similar to human EPS, in which there is weight loss as well as peritoneal sclerosis and adhesion, resulting in full-bowel EPS and cocoon formation. The typical appearance was multiple surfaces...
covered with granulation tissue, or fibrosis tissue, or both. A number of adhesions were present. Microscopic examination revealed that low-pH dialysis solution induced peritoneal fibrosis and loss of mesothelium. The mRNA of AQP-1, AQP-4, GLUT-1, GLUT-4, GLUT-5, and TGFβ1 were expressed in peritoneum in these rats undergoing peritoneal dialysis. The expression of AQPs was significantly suppressed in rats treated with pH 3.5 dialysis solution. In rats treated with pH 7.0 dialysis solution, no signs of EPS were seen.

Continuous ambulatory peritoneal dialysis has been used successfully to treat patients with chronic end-stage renal failure. A large number of patients treated by CAPD have already been reported being as well as those treated by hemodialysis. Encapsulating peritoneal sclerosis is recognized as a serious complication of CAPD patients (1—3). The complication was first reported by Gandhi et al (1) in the United States, who described the appearance of marked sclerotic thickening of the peritoneal membrane in 5 patients on IPD for renal failure. With the increasing use of CAPD, the number of reported cases of EPS rose (8,9). The cause of EPS is unknown, but it is probably multifactorial. Previous contributions to the literature on EPS have implicated a variety of factors, including peritonitis, particulate matter, plasticizers, or other chemicals present in the dialysate, chronic use of certain beta-blocker medication (practolol, atenolol, metoprolol, and propranolol), formaldehyde, antiseptics (chlorhexidine acetate), and acidic dialysate (3). Encapsulating peritoneal sclerosis is a curious condition in which bowel and mesentery are drawn together within a fibrotic cocoon-like sac. The sac is covered
by a layer of attenuated mesothelium. Histologically, the peritoneum shows proliferation of fibroconnective tissue, inflammatory infiltrates, and dilated lymphatics, with no evidence of foreign-body granulomas, giant cells, or birefringent material (10).

Rippe et al (11) reported that water-only cell membrane pores that reject solute transport were predicted by the three-pore model of capillary permeability to play a key role in CAPD. Water transport during PD requires ultrasmall pores in the capillary endothelia of the peritoneum. The molecular identity of the ultrasmall pores has been discovered, and the pores have been found to be present in many epithelia and endothelia (12). The pores have been named aquaporins (AQPs), and the pore type present in most continuous endothelia has been designated AQP-1.

The AQP-1 water channels were reported to be widely expressed in epithelia and capillary endothelia involved in fluid transport. They provide a major route for osmotically driven water transport across the peritoneal barrier in PD (13). Solute and water transport across the peritoneal membrane during PD is best described in the three-pore model by Rippe et al (14). In the present study, we examined the expression of
AQP-1 and AQP-4 in the peritoneum in a rat model of EPS. In rats treated with pH 7.0 DS, expression of AQP-1 and AQP-4 was significantly enhanced, in parallel with an increment in UFV. On the other hand, in rats treated with pH 3.5 DS, the expression of AQP-1 and AQP-4 was significantly suppressed, accompanied by loss of UFV. The use of glucocorticoid completely restored the expression of AQP-1, AQP-4, and TGFβ1, accompanied by an improvement in peritoneal function. The results suggest that glucocorticoid was effective in preventing peritoneal sclerosis during CAPD.

In an attempt to prevent peritoneal fibrosis and EPS, various improvements have been made. Recently, several reports indicated the efficacy of immunosuppressive therapy on the course of EPS (15). Rats treated with acidic DS sustained severe tissue damage. That result might negate the experimental findings; but treatment with glucocorticoid restored the expression of AQP-1 and AQP-4. Expression of AQP-1 protein is induced by corticosteroids in perinatal rat lung, but it is not known whether other hormonal controls exist (16). Recently, Moon et al (17) reported that the dexamethasone induction is abrogated by deletion of two glucocorticoid response elements —0.5 kb from the transcription initiation site. The promoter activities stimulated by the glucocorticoid response element (GRE) may reflect AQP-1 expression patterns in lung and kidney. The GREs lying between position —0.6 kb and —0.45 kb were found to be operative in mouse erythroleukemia (MEL) cells. From those findings in previous experiments, enhanced expression of AQP-1 after prednisolone treatment is probably regulated by glucocorticoid elements of prednisolone.

In the present study, acidic dialysis solution induced increases in the expression of GLUTs. Those changes were compatible with the high peritoneal permeability and loss of ultrafiltration volume seen in long-term CAPD patients. Our results showed that glucocorticoid protects against the overexpression of GLUTs in the peritoneum. We speculate that glucocorticoid plays an important role in protecting the peritoneum from fibrosis and EPS. However, to clarify the mechanism of EPS, further experiments are required.

**Conclusion**

We conclude that low-pH dialysis solution induces the development of EPS. Newly developed neutral dialysis solutions protect against the development of EPS during peritoneal dialysis. In addition, glucocorticoid protects against the development of EPS during peritoneal dialysis.

**References**


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