Peritoneal Dialysis International, Vol. 34, pp. 766–774
doi: 10.3747/pdi.2013.00074

0896-8608/14 $3.00 + .00

ENCAPSULATING PERITONEAL SCLEROSIS IN THE ERA OF A MULTI-DISCIPLINARY APPROACH BASED ON BIOCOMPATIBLE SOLUTIONS: THE NEXT-PD STUDY

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♦ ***Introduction:*** **Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD). Over the past decade in Japan, a multidisciplinary approach has been adopted to minimize the incidence and improve outcomes of EPS. This strategy includes planned PD discontinuation for high-risk patients and the introduction of biocompatible solutions. This study examined the current clinical status of EPS in representative PD centers in Japan.**

♦ ***Design, setting, participants and measurements:*** **Patients (*n* = 1,338) from 55 PD centers in Japan who were using neutral-pH solutions from the initiation of therapy (mean age, 62 years; median PD duration, 32 months; concomitant use of icodextrin, 35.2%; PD and hemodialysis combination therapy, 12.2%) were assessed every 6 months to ascertain the reasons for PD discontinuation and the development of EPS development. Outcomes were also recorded. The study period was from November 2008 to March 2012.**

♦ ***Results:*** **There were 727 patients who discontinued PD, including 163 deaths. Among all causes of PD withdrawal except for death, planned PD discontinuation to avoid EPS was utilized in 58 cases (7.1% in total). The strategy was increasingly utilized in proportion to the duration of PD: 0.5% for patients undergoing PD for < 3 years, 0.6% for patients undergoing PD for 5 years, 14.7% for patients undergoing PD for 8 years, and 35.5% for patients undergoing PD for > 8 years. Fourteen patients developed EPS (three cases after PD), which corresponded with an overall incidence of 1.0%. The incidence according to the duration of PD was 0.3% for PD < 3 years, 0.6% for PD = 5 years, 2.3% for PD = 8 years, and 1.2% for PD > 8 years. In terms of therapy, 11 patients were treated with prednisolone (PSL), and surgical enterolysis was utilized in two cases. Complete remission of abdominal symptoms was achieved in twelve patients (85.7%), and three died due to EPS (mortality rate of 21.4%).**

♦ ***Conclusions:*** **Use of the multidisciplinary approach described above reduces the risk of the development of EPS according to PD duration. In cases of *de novo* EPS cases in Japan, this strategy can also attenuate the clinical course of the condition.**

Perit Dial Int **2014; 34(7):766–774 www.PDIConnect.com**
epub ahead of print: 04 Feb 2014 doi:10.3747/pdi.2013.00074

KEY WORDS: Peritoneal dialysis; encapsulating peritoneal sclerosis; neutral solution.

Encapsulating peritoneal sclerosis (EPS) is a serious complication of PD treatment. Its incidence has been reported as 0.3% to 3.3% (1–7), with an associated mortality rate of 25.8 to 56.5% (1–7).

Since EPS was first described in 1980 (8), various studies have been conducted to characterize its pathological background. Among the various clinical factors, long-term PD duration has been consistently demonstrated to be a strong risk factor for the development of EPS (2,3,6,7,9,10). There are progressive pathological changes in peritoneal integrity during the course of PD (11–14), and exposure to the bio-incompatibilities of conventional PD solutions (e.g., low pH, high glucose, lactate buffering, and high glucose degradation products (GDPs)) for extended periods of time might be involved in these changes in peritoneal component cells (15–19), thereby resulting in the progression of peritoneal tissue degeneration and the development of EPS (20,21).

Over the past decade, a multidisciplinary approach has been adopted in Japan to minimize the incidence of

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Received 16 March 2013; accepted 18 August 2013.

EPS and to improve patient outcomes. Indeed, various publications describe the diagnosis and management of EPS (22,23) as well as the introduction of biocompatible solutions (24,25). To note, neutral solutions were introduced between 2000 and 2004 and have since replaced the conventional acid solutions, and these newer solutions are now used in over 95% of all PD patients (26). Further, the PD guidelines published by the Japanese Society Dialysis Therapy (JSDT) in 2009 recommend the planned discontinuation of PD for patients at high risk of developing EPS (27).

Use of a comprehensive multidisciplinary approach for EPS based on the widespread use of innovative solutions may alter the incidence and natural history of the disease in Japan. Therefore, the goal of this NEXT-PD (Neutral solution, Extraneal use, and current PD outcome in Japan) study (28) was to explore the current status of EPS among representative PD centers in Japan.

PATIENTS AND METHODS

The NEXT-PD study is a nationwide, multicenter, prospective observational study that was launched in 2007. Peritoneal dialysis centers in Japan with more than 20 patients at the time of registration were invited to join the study in May 2007. We announced the project to 170 centers, 71 of which agreed to participate. During the center-registration period (from November 2008 to December 2009), 55 centers were enrolled in the study after obtaining permission from their local ethics committees. The centers' patients met the criterion of being treated with the dual-compartment bag to reduce the use of GDPs (so-called neutral-pH solutions with lactate buffer) beginning at the initiation of PD therapy. This included patients who were treated with concomitant use of icodextrin solution (Extraneal, Baxter Co., Ltd., Japan) and those who were treated with combination therapy consisting of PD and intermittent hemodialysis (HD), e.g., PD for 5 or 6 days and HD once a week (29). The patients' clinical courses were followed until discontinuation of PD, with further follow-up to ascertain their clinical outcomes every 6 months thereafter until the end of March 2012.

Clinical data were confirmed by the attending physicians of the respective PD centers using multiple questionnaires. The causes of PD discontinuation were classified as follows according to whether or not patients were alive at the time of PD discontinuation: (1) PD discontinuation due to death from cardiovascular disorders, stroke, cancer, infectious disorders, cachexia, EPS, bleeding, and other conditions; (2) Alive at the time of PD discontinuation with PD-related complications (e.g., peritonitis, exit-site infection, skin-tunnel infection, catheter malfunction, hernia, diaphragmatic communication), PD-unrelated comorbidities (e.g., major abdominal surgery, dementia, cachexia/malnutrition, cancer), dialysis inadequacy (overhydration, uremia, inadequate ultrafiltration, poor compliance), EPS-related reasons for PD discontinuation (e.g., prevention of EPS, development of EPS), social issues (e.g., socioeconomic problems, care-giver issues), kidney transplantation, and others.

Diagnosis of EPS was made using the definition of the International Society for Peritoneal Dialysis (22) and using recommendations established in Japan in 2005 (23). In patients who developed EPS, the therapeutic regimen and clinical outcome of each case was confirmed.

This study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine (Sendai, Japan) and by the local committees of the respective dialysis centers. Written informed consent was obtained from all study subjects.

Continuous data are expressed as mean ± standard deviation (SD), and categorical data are expressed as numbers and percents.

RESULTS

During the study period, 1,358 patients who provided informed consent were registered; however, 20 were excluded because of lack of information regarding primary data. Thus, a total of 1,338 patients were finally enrolled as study subjects. Patients who had active peritonitis and EPS at the time of registration were excluded from the study. The study subjects' clinical profiles are shown in Table 1. Icodextrin solution (Extraneal) was used in 35.2% of the patients, with none of them having ever received a high-strength solution (4.25% dextrose). None of the patients underwent PD with amino-acid solutions or bicarbonate-buffered solutions, since these are not commercially available in Japan. Combination therapy with PD and HD was used in 12.2% of the study subjects.

As of the end of 2010, there were 9,157 PD patients in Japan, and neutral solution was used for 95% of the patients, with 40% of the patients receiving Extraneal, and an estimated 18% of PD patients treated with a combination of PD and HD therapy (26). The latest profile of the Japanese PD patients was as follows: males, 62.9%; mean age, 61.0 years; PD duration, 40.3 months; comorbid diabetes, 28.9%; no episode of peritonitis, 81.6% (30). Upon reviewing those profiles, the study cohort was representative of current PD patients in the modern Japanese population.

TABLE 1
Clinical Profiles of the Study Subjects

N	1,338
Male	64.7%
Age (years)	62±12
PD duration (months, median)	32 (1–110)
Primary Kidney disease	
Chronic glomerulonephritis	39.4%
Diabetic nephropathy	33.0%
Nephrosclerosis	12.1%
Polycystic kidney disease	2.1%
Others	13.4%
Peritonitis, no episode	72.8%
Presence of RRF	77.4%
Peritoneal Equilibration Test (*n*=924)	
High/High average	13.2%/39.2%
Low average/Low	37.7%/10.0%
APD	32.0%
Use of icodextrin (Extraneal)	35.2%
PD+HD combination therapy	12.2%
PD fluid prescription (daily) (*n*=1,308)	
>10 L	9.7%
>8 to 10 L	21.3%
>6 to 8 L	34.0%
>4.5 to 6 L	19.7%
≤4.5 L	15.3%

PD = peritoneal dialysis; RRF = residual renal function; APD = automated peritoneal dialysis; HD = hemodialysis.

OVERALL OUTCOMES

As of the end of March 2012, PD was discontinued in 727 patients due to all-cause deaths in 163 patients. Transfer to another therapeutic modality was utilized for 564 patients, of whom 33 were lost to follow-up due to transfer to other centers before the end of the study and four were excluded due to lack of data of final outcome. Therefore, 527 patients were included in the final analysis. The mean observation period was 39 ± 2 months for patients on PD and 21 ± 12 months for those after PD withdrawal. The number of patients according to PD duration as of the end of March 2012 is shown in Figure 1 (PD duration: < 3 years in 23.0%, 3 to 5 years in 40.3%, and > 5 years in 36.7%). The leading cause of death was cardiovascular disorders (28.0%), followed by cachexia (16.6%), infectious diseases (14.6%), stroke (14.0%), neoplasms (7.0%), EPS (1.2%; two cases), and bleeding (0.6%).

The overall leading cause of PD discontinuation, other than death, was PD treatment-related complications (31.6%), followed by inadequate dialysis (29.8%), PD-unrelated comorbidities (12.5%), social factors (12.1%), EPS-related causes (7.7%; PD discontinued to prevent EPS in 34 cases, and development of EPS in nine cases) and kidney transplantation (5.8%).

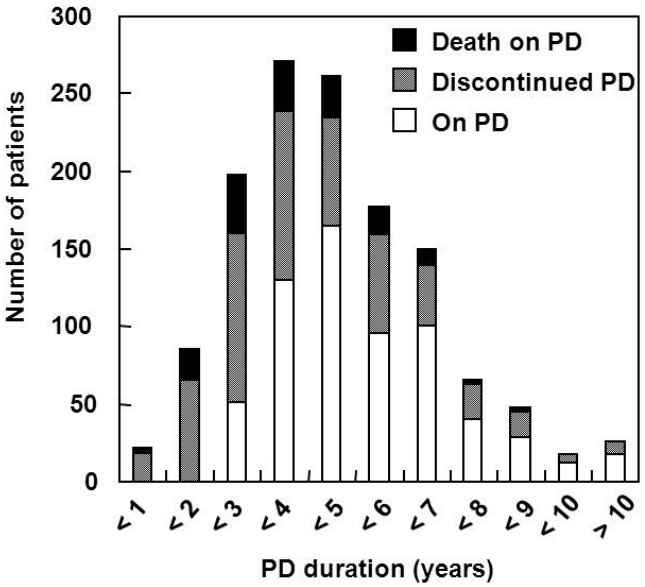

Figure 1 — Distribution of the number of patients according to the duration of PD. PD = peritoneal dialysis.

PD DISCONTINUATION DUE TO EPS-RELATED CAUSES ACCORDING TO PD DURATION

The reasons for PD discontinuation according to PD duration are shown in Figure 2. The incidence of "planned PD discontinuation to avoid EPS" increased in proportion to the duration of PD: 0.5% for PD < 3 years, 0.6% for PD = 5 years, 14.7% for PD = 8 years, and 35.5% for PD > 8 years.

Factors influencing the decision to stop PD are summarized in Table 2. Prevention of EPS was the fifth main reason (7.1%) to stop PD, occurring in 58 patients (PD duration, 75 ± 28 months). Since "reasons for prevention of EPS" were not pre-specified, the exact profiles of EPS prevention were not clearly determined. Clinical backgrounds in those patients included peritonitis in 15.5%, inadequate ultrafiltration in 24.1%, higher transport state (high and high average) in 50.0%, and use of > 3 bags of 2.5% dextrose solution in 20.7%.

PROFILES AND OUTCOMES OF EPS PATIENTS

There were 14 patients who developed EPS during the study period. The distribution of these patients according to the duration of PD is shown in Figure 3. Eleven patients developed clinical symptoms of EPS while on PD, while three patients developed EPS after withdrawal from PD. The mean age of the patients with EPS was 63.9 ± 11.5 years, and their mean PD duration was 67.3 ± 18.8

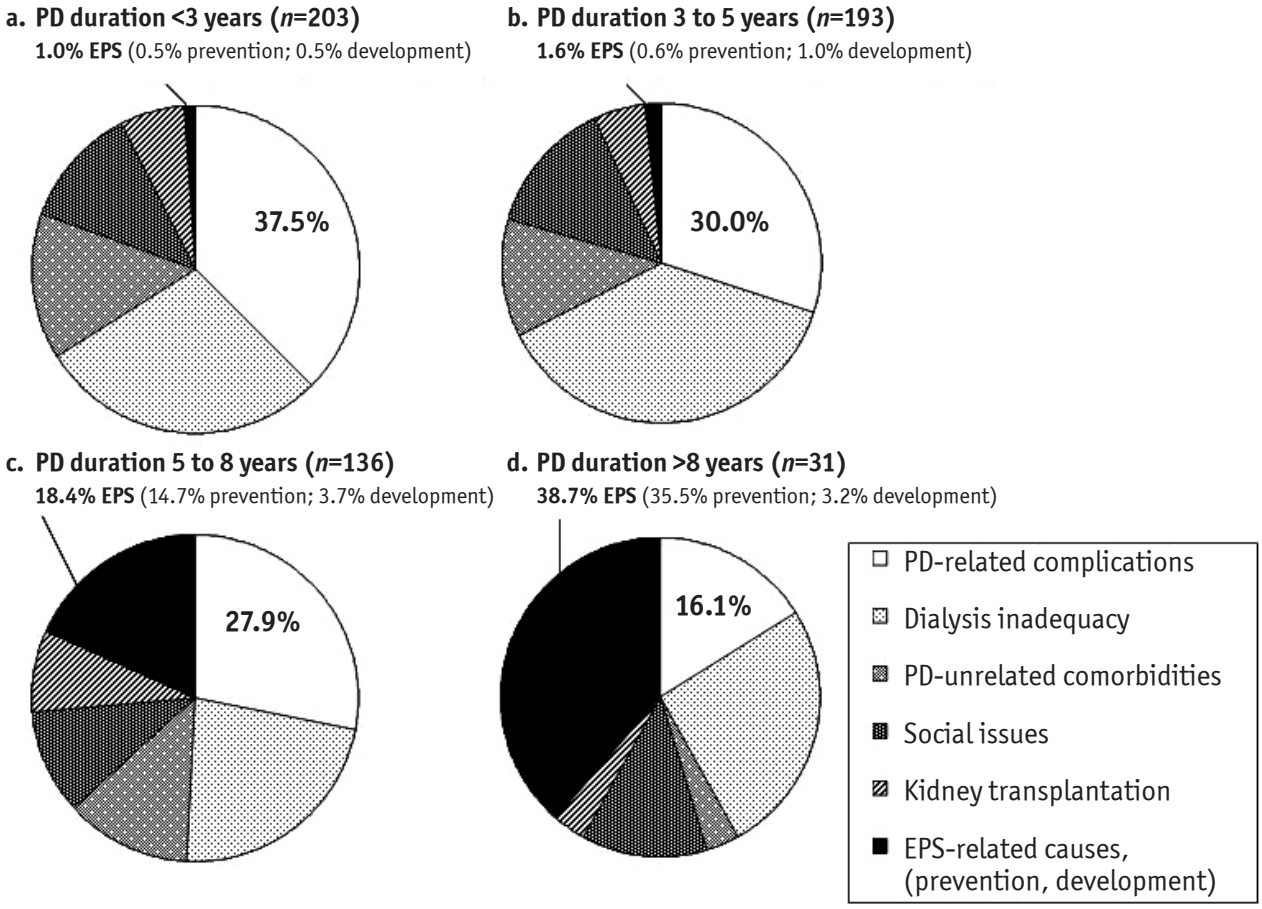

Figure 2 — Reasons for PD discontinuation according to the duration of PD; cases with PD duration <3 years (a), 3 to 5 years (b), 5 to 8 years (c), and >8 years (d). Among patients who discontinued PD due to PD-related complications, catheter-related peritonitis occurred in 88.0% (66 cases) of patients with a PD duration of <3 years, 93.0% (53 cases) of patients with a PD duration of 3 to 5 years, 73.7% (28 cases) of patients with a PD duration of 5 to 8 years, and 80.0% (four cases) of patients with a PD duration of >8 years. PD = peritoneal dialysis; EPS = encapsulating peritoneal sclerosis.

months. Three patients developed EPS after a preceding episode of catheter-related peritonitis, and seven patients had no previous episodes of peritonitis while on PD. The clinical profiles of the EPS patients are shown in Table 3-A. The overall incidence of EPS development was 1.0% (2.3 per 1,000 patient-years).

The clinical outcomes of the 14 patients with EPS are shown in Table 3-B and in Figure 4. The mean observational period was 21 ± 12 months after the development of EPS. Regarding therapeutic interventions for EPS, 11 patients received oral prednisolone (PSL; 10 to 30 mg daily at initial treatment), and two patients underwent surgical enterolysis. Five patients died (three patients died due to EPS-related causes), resulting in an all-cause mortality rate of 35.7% and an EPS-related mortality rate of 21.4%. There was a statistically significant difference between the mean age of the survivors (n = 9) and the patients who died (n = 5) (64 ± 11 years vs 72 ± 7 years, respectively; $p < 0.05$). During the observation period, 12 of the 14 patients with EPS were reported to have recovered sufficiently to achieve normal oral intake with no clinical signs of ileus.

DISCUSSION

The progression of peritoneal damage is likely related to multiple clinical factors, including the duration of treatment, peritonitis, use of concentrated glucose solutions, and the use of bio-incompatible acid solution. There are several relevant clinical factors that could alter EPS development in modern Japanese PD practice. The Japanese Society for Dialysis Therapy (JSDT) PD guidelines (27) recommended planned discontinuation of PD for patients at high risk of developing EPS. Specifically, these guidelines state that PD should be discontinued in patients with signs of increasing peritoneal permeability (as detected via routine peritoneal equilibrium testing) in order to avoid the development of EPS. Solutions with improved biocompatibility (e.g., neutral-pH, non-glucose icodextrin) were introduced at the beginning of this

century in Japan and are now relatively standard solutions in the clinical setting; indeed, neutral-pH solution is used in 95% of patients, and icodextrin is used in 40% of patients at present (26).

This study assessed the status of EPS among patients who had been treated with biocompatible solutions at one of 55 representative PD centers in Japan. During the total observation period (mean of 39 months on PD and mean of 21 months after PD), 14 patients developed EPS. The

TABLE 2
Factors Influential in Stopping PD

Cause	N (%)
Overhydration	156 (19.0)
Peritonitis	145 (17.6)
Underdialysis	98 (11.9)
Poor compliance	89 (10.8)
Prevention of EPS	58 (7.1)
Cognitive impairement	43 (5.2)
Social issues	41 (5.0)
Inability of nursing care	38 (4.6)
Exit-site infection/Skin-tunnel infection	35 (4.3)
Major abdominal surgery	21 (2.6)
Catheter dislocation	11 (1.3)
Cahexia/Malnutrition	9 (1.1)
EPS	9 (1.1)
Hernia	8 (1.0)
Diaphragmatic communication	6 (0.7)
Cancer end-stage	3 (0.4)
(Others)	52

PD = peritoneal dialysis; EPS = encapsulating peritoneal sclerosis.

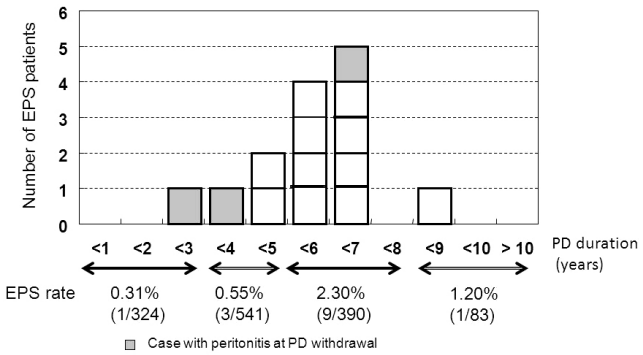

Figure 3 — Number of EPS patients, and incidence of EPS according to the duration of PD. The incidence of EPS according to the duration of PD is as follows: <3 years of PD, 0.31% (95%CI: 0.05 to 1.73); 3 to 5 years of PD, 0.55% (95%CI: 0.19 to 1.62); 5 to 8 years of PD, 2.31% (95%CI: 1.22 to 4.33); >8 years of PD, 1.20% (95%CI: 0.21 to 6.51). EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; CI = confidence interval.

TABLE 3-A
Demographics of the 14 Cases of Encapsulating Peritoneal Sclerosis (EPS)

No	Age (years)	Sex	KD	PD duration (months)	PD modality	Use of Ico	D/P (Cr)	Preceeding peritonitis	Post-PD EPS (months)	Clinical grade
1	74	F	Sec	25	PD	None	HA	+	—	II
2	79	F	NS	44	PD	+	HA	+	<6	I
3	64	M	ND	52	PD	+	HA	None	—	II
4	62	M	CGN	58	PD	+	HA	None	—	II
5	75	M	DN	65	PD	None	ND	None	—	I
6	60	M	NS	67	PD	+	HA	None	—	II
7	67	F	CGN	67	PD	+	LA	None	—	I
8	60	M	DN	68	PD	+	HA	None	—	I
9	58	M	NS	74	PD	+	ND	+	—	I
10	37	F	CGN	77	PD+HD	+	LA	None	<6	I
11	51	M	CGN	79	PD+HD	None	HA	None	—	I
12	59	M	CGN	82	PD+HD	None	L	None	6 to 12	II
13	79	M	NS	82	PD	None	LA	None	—	I
14	70	M	CGN	102	PD+HD	+	ND	None	—	I

EPS = encapsulating peritoneal sclerosis; KD = underlying kidney disease; PD = peritoneal dialysis; PD modality = peritoneal dialysis modality; Ico = icodextrin; D/P (Cr) = Dialysate to plasma creatinine ratio by peritoneal equilibration test; Post-PD EPS = the time to development of EPS after PD withdrawal; F = female; M = male; Sec = secondary kidney disease; NS = nephrosclerosis; ND = not determined; CGN = chronic glomerulonephritis; DN = diabetic nephropathy; PD+HD = the combination therapy of peritoneal dialysis (PD) and hemodialysis (HD); HA = high average; LA = low average; L = low.
Clinical grade: I = sub-clinical ileus symptoms, such as nausea and vomit, accompanying partial adhesion of intestine; II = intermittent ileus symptoms, accompanying encapsulation of intestine; III = chronic persistent ileus symptoms, with extensive encapsulation of intestine.

TABLE 3-B
Treatment and Final Outcomes of 14 Cases of Encapsulating Peritoneal Sclerosis (EPS)

No	Initial PSL (mg/day)	Surgical Enterolysis	Final outcomes[a]	Clinical status[b]	Cause of death[c]
1	20	NP	Dead	1	malignancy
2	30	NP	Dead	1	EPS
3	Pulse	NP	Alive	1	
4	None	NP	Alive	1	
5	20	NP	Dead	ND	EPS
6	None	Performed	Dead	3	EPS
7	10	NP	Alive	1	
8	30	NP	Alive	1	
9	20	NP	Alive	1	
10	30	NP	Alive	1	
11	None	Performed	Alive	1	
12	10	NP	Alive	1	
13	20	NP	Alive	1	
14	10	NP	Dead	1	malignancy

EPS = encapsulating peritoneal sclerosis; PSL = oral prednisolone; NP = not performed; ND = not determined.
[a] Final outcome at the end of the observation period.
[b] 1 = oral intake fully possible, without abdominal symptoms; 2 = oral intake possible, but with intermittent abdominal symptoms; 3 = oral intake impossible, with the presence of persistent ileus symptoms.
[c] EPS denotes the clinical events directly associated with EPS development and therapy.

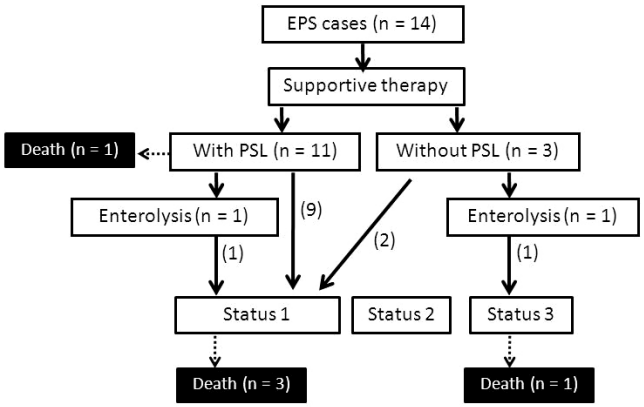

Figure 4 — Clinical outcomes of EPS patients (*n*=14) during the study period. Status 1 = normal oral intake with no presenting abdominal symptom; Status 2 = normal oral intake possible, but with presenting intermittent episodes of ileus signs; Status 3 = oral intake impossible, with presenting ileus signs. EPS = encapsulating peritoneal sclerosis; PSL = oral prednisolone.

incidence of EPS according to the duration of PD was 0.3% for PD < 3 years, 0.6% for PD = 5 years, 2.3% for PD = 8 years, and 1.2% for PD > 8 years (Figure 3). Studies have shown that, among PD patients on conventional acid solutions, the overall incidence of EPS markedly increases along with an increase in the duration of PD: e.g., 10.8 to 19.4% at 6 to 8 years in Australia (2) and 3.5 to 8.1% at 4 to 5 years in a Scottish renal registry (6). However, this phenomenon was not observed in the present cohort that was treated with neutral-pH solution. Recent studies suggest that the use of neutral solutions is associated with improved mesothelial layer integrity, decreased thickening of the submesothelial compact zone, and less vasculopathy when compared with those that occur in response to conventional acid solutions (31–33). These observations suggest that this newer solution might help attenuate the risk of EPS.

Factors other than the use of neutral solutions, including the use of planned discontinuation of PD, might also have contributed to a decrease in the incidence of EPS in this patient population. In the present study, "planned PD discontinuation to avoid EPS" was ranked fifth among all causes of PD withdrawal except for death, and the use of this strategy increased in proportion to the duration of PD. Indeed, in patients with PD duration of > 8 years, planned PD discontinuation was the most frequent reason for PD withdrawal (Figure 2). Peritonitis is a critical issue that cannot be underestimated for EPS development. It is possible to speculate that the avoidance of long-term PD due to planned PD discontinuation may have resulted in a reduced number of patients who never had a peritonitis episode, and this could have reduced the number of high-risk patients of EPS (Table 4).

Taking this modern Japanese practice into consideration, we compared the profiles of the patients in the current NEXT-PD study with the profiles of the patients in a previous Japanese study conducted 10 years ago (4). In the previous study, EPS occurred in 48 cases among 1,958

TABLE 4
Comparison Between Previous and Current Surveys

	Kawanishi *et al.* (4)	NEXT-PD
N	1,958	1,338
Study period (years)	1999 to 2004	2008 to 2012
Age (years)	57±14	62±12
PD period (months, mean)	69.7±44.7	25.7±23.0
Number of PD termination	453	727
PD period <5 years	46.3%	63.3%
Observation period of study	Up to 48 months	Up to 40 months (39±2 months)
Observation period after PD stop	Up to 48 months	Up to 40 months (21±12 months)
EPS development		
Number of EPS (rate)	48 (2.5%)	14 (1.0%)
post-PD EPS	68.8%	2.4%
Age (years)	55±9	64±11
PD periods (months, mean)	114.3±44.1	67.3±18.8
No peritonitis episode during PD	21.0%	42.8%
Peritonitis-related EPS	25.0%	21.4%

PD = peritoneal dialysis; EPS = encapsulating peritoneal sclerosis.
Data denotes mean ± SD.

prevalent patients, corresponding to an overall incidence of 2.5%; the EPS incidence was 0%, 0.7%, 2.1%, 5.9%, 5.8%, and 17.2% in patients who had undergone PD for 3, 5, 8, 10, 15, and more than 15 years, respectively. That study enrolled patients from the same representative PD centers as those used in the present study. Comparison of these two studies (Table 4) clearly highlights the trend of the current Japanese PD practice of premature withdrawal from PD when compared with that used a decade ago. The JSDT PD guidelines recommended the planned discontinuation of PD in patients at high risk of developing EPS (27) as follows: "*First, if progression of peritoneal deterioration is confirmed in patients with long-term PD or after peritonitis, discontinuation of PD should be evaluated with a due consideration of the risk of development of EPS. Second, it is recommended to routinely perform the peritoneal equilibrium test (PET) to evaluate peritoneal deterioration*." A national survey conducted by a JSDT committee in 2010 (34) revealed that the above recommendation is widely acknowledged and that 35% of the PD facilities in Japan restrict the duration of PD to less than 7 years, despite the fact that the JSDT PD guidelines did not recommend any "expiry date".

Uniform therapeutic regimens for EPS have yet to be established. However, since the successful use of immunosuppressive therapy described by Junor *et al.* in 1983 (35), PSL therapy has been used for the management of EPS in Japan (36–38). In the present study, PSL was the only therapeutic agent administered to patients with EPS. Patients with EPS in the present study had relatively good outcomes; one third achieved clinical remission, and the EPS-related mortality rate was 21.4% (three died due to EPS-related reasons). We speculate that PSL therapy suppressed the initial inflammatory activation in patients with EPS, thereby preventing the subsequent development of intestinal adhesions. However, the reported data on PSL therapy for EPS is observational in nature, and its exact clinical impact needs to be addressed in future prospective randomized studies.

This study possesses several limitations. First, we could not arrive at a definitive conclusion regarding the effect of neutral solution on the incidence and natural history of EPS, as this study was not designed to compare neutral solutions to acid conventional solution (acid conventional solutions are no longer used in Japan). Second, some of the clinical definitions, such as the timing of PD discontinuation and the application for combination therapy or use of icodextrin, differed between centers, which may have introduced some bias. Third, the use of combination therapy with PD and HD in some patients may have eliminated the need for concentrated glucose solutions and may have decreased the levels of interleukin-6 in the PD effluent (39), thereby decreasing the risk of developing EPS. Fourth, the incidence of EPS in this study did not necessarily reflect national data, since only leading PD centers were registered in this study. Finally, because of the relatively small number of EPS occurrences in this study, multivariate analysis to identify contributing factors could not be performed. Thus, the exact effect of neutral solution and

planned PD discontinuation for EPS should be addressed in future studies.

Despite the above issues, we believe that the present data show that adoption of a multidisciplinary approach in Japan can reduce the incidence of EPS among patients undergoing PD. Nevertheless, since this disorder can also develop in both non-uremic and HD patients (22), a better understanding of the precise mechanisms of EPS is an issue of vital importance in order to prevent EPS.

ACKNOWLEDGMENTS

The study was conducted with the assistance of funding from the Japan Kidney Foundation (2007 to 2012).

The study members would like to express special thanks to Dr. Kawaguchi (Jikei University School of Medicine) and Dr. Tranaeus (formerly of Baxter Co., Ltd.) for reviewing this manuscript and offering their valuable comments. Collaborators: Katsuo Suzuki (Goryokaku Nephroclinic); Mari Ishida (Kitasaito Hospital); Masahiko Ogihara (Ogihara Urinary Organs and Eyes Clinic); Hirofumi Nakano (Kashima Hospital); Tomoyoshi Kimura (Sendai Shakai Hoken Hospital); Minoru Ito (Yabuki Hospital); Yoshitaka Maeda (JA Toride Medical Center); Hiromichi Suzuki (Saitama Medical University Hospital); Akihiko Matsuda (Saitama Medical Center); Takahiro Mochizuki (Kameda Medical Center); Satoru Kuriyama (Tokyo Saiseikai Central Hospital); Noriyuki Katoh (Showa University); Jiro Inuma, Chieko Hamada, Keiichi Wakabayashi (Juntendo University); Takayasu Otake (Shonankamakura General Hospital); Yasushi Ohashi (Toho University); Keitaro Yokoyama (Jikei UniversityHospital); Hironori Tayama (Showa University Fujigaoka Hospital; Makoto Nishina (Tokai University Hachioji Hospital); Shinya Kaname (Kyorin University Hospital); Hideaki Iwasawa (Tokyo Medical University Hospital); Chieko Higuchi (Tokyo Women's Medical University Medical Center East); Hidetomo Nakamoto (Musashiranzan Hospital, Tokorosawa Jin Clinic); Tsutomu Sakurada (St. Marianna University School of Medicine); Hiroyuki Terawaki (Fukushima Medical University); Kenji Kasai (Fuji City General Hospital); Yasuhiko Ito (Nagoya University Hospital); Masato Yamakawa (Minato Medical Coop-Kyoritsu General Hospital); Hiroaki Asada (Okazaki City Hospital); Hiroki Maruyama (Niigata University); Mizuya Fukasawa (University of Yamanashi Medicine, Iida Hospital); Junji Koyama (Aichi Medical University Hospital); Noriyuki Iwamoto (Tojinkai Hospital); Harumi Kitamura (Osaka University Hospital); Yoko Adachi (Shakaihoken Kobe Central Hospital); Yasuhiro Akai (Nara Medical University Hospital); Sukenari Koyabu (Owase General Hospital); Mithuru Yoshimoto (Ohno Memorial Hospital); Satomi Yonemoto (Kitano Hospital); Noriko Takahara (Ako City Hospital); Makoto Hiramatsu (Okayama Saiseikai General Hospital); Tamaki Sasaki (Kawasaki Medical School Hospital); Misaki Moriishi (Tsuchiya General Hospital); Hitoshi Sugiyama (Okayama University Hospital); Yasuyuki Yoshino (Yoshino Miyake Station Clinic); Akihisa Nakaoka (Sanin Rosai Hospital); Seikon Kin (Shimane Prefectural Central Hospital); Akihiro Sakata (Tokushima Red Cross Hospital); Yusuke Kuroki (Fukuoka Red Cross Hospital); Yoko Obata (Nagasaki University Hospital); Masahiro Tominaga (Nijigaoka Hospital); Takashi Harada (Nagasaki Jin Hospital); Masahito Tamura (University of Occupational and Environmental Health); Kazuhiko Tsuruya, Hisako Yoshida (Kyushu University Hospital).

DISCLOSURES

None of the authors of this study have any conflicts of interest to declare.

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