Many observational studies have been conducted on the occurrence of encapsulating peritoneal sclerosis (EPS). However, poorly biocompatible acidic glucose-based dialysis solutions were used in all previous studies. Today, dialysis solutions that are more biocompatible have become widely available. We therefore initiated a new prospective observational study on the occurrence of EPS. The study design is based on that of a previous study conducted in Japan that used solutions high in glucose degradation products (GDPs). Patients undergoing dialysis with a low-GDP dialysis solution, which is considered to show excellent biocompatibility, will be followed for 4 years, and the study will evaluate withdrawal from peritoneal dialysis, incidence of EPS, and factors related to EPS occurrence with the new dialysis solution. This study is expected to clarify the effects of biocompatible dialysis solutions.

**Key words**
Encapsulating peritoneal sclerosis, EPS, neutral dialysis solution, icodextrin

**Introduction**
Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD) and has, in the past, discouraged the introduction of PD (1,2). However, recent advances in clinical research have established the pathogenesis, course, and a treatment strategy for EPS (3).

A prospective survey carried out in Japan provided abundant information concerning the occurrence of EPS (4). That survey showed that the risk of EPS and associated mortality increased significantly in patients undergoing PD for 8 or more years. However, those results were obtained using conventional acidic glucose-based dialysis solutions.

Peritoneal deterioration and degeneration associated with prolonged exposure to a poorly biocompatible dialysis solution are suspected to play a central role in causing EPS, and a high-biocompatibility dialysis solution low in glucose degradation products (GDPs) and with a neutral pH has been used as the standard dialysis solution in Japan since 2003. Solutions with icodextrin, a new osmotic material, have also begun to be widely applied. Thus, in Japan, a therapeutic system with attention to the prevention of complications is considered to have been established, but the real clinical situation (incidence of EPS and withdrawal from PD) with the new dialysis solution is currently unknown. Clarification of these points is important to verify the clinical significance of new dialysis solutions.

The present study will prospectively investigate drop-out from PD, the incidence of EPS, and factors related to EPS occurrence in patients undergoing therapy using the new PD solutions (low-GDP neutral-pH solution and icodextrin solution).

**Patients and methods**
The study will enroll patients treated by PD with the new dialysis solutions from the initiation of PD therapy. Patient registration will require prior approval of the study by the ethics review boards of participating facilities and the consent of patients. Registration of 2000 or more patients is expected.

This prospective observational study will register patients from April 2008 to the end of March 2010, and...
the patient observation period will run from April 2008 to the end of March 2014.

These specific points are being investigated (Figure 1):

- Basic characteristics of the patients at registration
- Circumstances of withdrawal from PD, should withdrawal occur
- Whether EPS develops and the status of the patients every 6 months after withdrawal
- Whether EPS develops and the status of the patients at the end of the observation period

**Diagnostic criteria for EPS**

For study purposes, EPS is being defined according to the guidelines (5) of the Ad Hoc Committee of the International Society for Peritoneal Dialysis (ISPD) and is being clinically staged using the method described by Kawanishi et al. (6):

- Stage 1: Increase in non-inflammatory ascites
- Stage 2: Increase in inflammatory ascites (increased leucocytes in ascites), general inflammatory reaction
- Stage 3: Increase in inflammatory ascites and bowel obstruction symptoms
- Stage 4: Continuous or severe bowel obstruction symptoms

Symptoms of bowel obstruction are organized into three classes:

- Class 1: Oral intake of usual meals. No symptoms of bowel obstruction.
- Class 2: Oral intake of usual meals is possible, but symptoms of bowel obstruction occasionally appear.
- Class 3: Oral food intake is impossible. A state of bowel obstruction persists.

**State of registration**

At the end of 2009, 1266 patients (823 men, 443 women) had been registered. The diseases leading to PD in the study group are chronic glomerulonephritis (41%), diabetic nephropathy (34%), nephrosclerosis (12%), polycystic kidney disease (2%), generalized diseases (3%), and urologic diseases (1%). The cause was unclassifiable in 7% of the patients. The mean duration of PD in the group at registration was 31.6 months (range: 0 – 182 months). In 12.4% of the patients, PD and HD are being performed in combination. Automated PD is being used in 33% of the patients, and Extraneal solution (Baxter Healthcare, Tokyo, Japan), in 37%. The mean volume of dialysis solution being used is 8 L daily, and in 77% of the group, the residual urine volume is 100 mL or more daily. At registration, data from a peritoneal equilibration test (PET) showed low transport in 10% of the group, low-average transport in 38%, high-average transport in 39%, and high transport in 13%, a distribution that does not differ from the typical distribution of PET transport categories.

**Discussion**

Several studies in Japan have reported incidences of EPS ranging between 0.8% and 2.8% (1). Reported incidences in other countries vary widely. Rigby et al. reported EPS in 54 of 7374 patients (0.7%) in Australia (2).

Given that all previous surveys had been retrospective in nature, Kawanishi et al. started a prospective survey in 1999 in Japan, aiming to investigate the incidence of EPS and its relationship to withdrawal from PD (4). A total of 1958 patients treated with PD at 57 facilities were observed during a 4-year period. Of those 1958 patients, 48 developed EPS, for an incidence of 2.5% (3.18 episodes per 1000 patient–years). In 33 of the 48 cases (68.8%), EPS developed after withdrawal from PD. The mean duration on PD in those patients was 114.3 months (range: 36 – 201.4 months). The EPS incidence increased and the prognosis worsened with PD duration. The EPS incidences (and mortality rates) were 0%, 0.7% (0%), 2.1% (8.3%), 5.9% (28.6%), 5.8% (61.5%), and 17.2% (100%) in patients that had undergone PD for 3, 5, 8, 10, 15, and more than 15 years respectively. The risk of EPS was high in patients on PD for 8 years or longer (Figure 2). Conversely, a PD duration of less than 8 years using the glucose-based dialysis solutions available at the time was found to be safe.
Based on that study, the Japanese Society for Peritoneal Dialysis recommended the use of an algorithm for continuing or terminating PD with regard to EPS. The algorithm described how a consideration of PD withdrawal should take into account peritoneal transport status, measurements of markers of inflammation, and the patient’s acceptance of the risk of EPS (3).

Recently, the Scottish Renal Registry study showed that the risk of EPS increases after 3 years on PD, but decreases after 6 years (7). However, the mortality rates for EPS and non-EPS cases in that study were not different from ours. Moreover, the findings of a peritonitis rate of 1 episode in 17 patient-months and of a high use of 3.86% dextrose solution indicate that the quality of patient management was suboptimal, which likely led to a decline in the number of long-term patients.

On the basis of those research results, the advisability of deliberate discontinuation of PD for the prevention of EPS is being discussed. According to the ISPD statement, the evidence for setting a maximum PD duration for the prevention of EPS is insufficient, and continuation or discontinuation of PD should be determined by considering the condition of the individual patient (8). Similarly, Garosi and Oreopoulos questioned the setting of an “expiry date” to prevent EPS (9).

The data from all studies to date have been obtained using acidic glucose-based dialysis solutions (high-GDP solutions), which are considered to be poorly biocompatible. Low-GDP solutions have been shown in a number of animal experiments to be effective at preventing peritoneal damage (10–12) and in clinical studies to improve life expectancy (13,14). The use of a low-GDP solution from the initiation of PD may decelerate peritoneal degeneration and prevent EPS.

The biocompatibility of PD solutions that use icodextrin, a newly developed osmotic material, is a controversial subject. In Europe, contamination with heat-resistant acidic bacteria (*Alicyclobacillus acidocaldarius*) and peptidoglycans occurred during the manufacturing process at the beginning of the product’s use. In current products, the levels of peptidoglycan contamination fall below the measurable limit, but increases in inflammation products have been reported (15). Recently, case reports strongly suggesting the involvement of icodextrin solutions in the development of EPS have emerged (16). However, in a large 2-year clinical study, icodextrin solution had no more effect on peritoneal function than did a glucose solution high in GDPs (17).

**Conclusions**

We initiated a new prospective observational study on the occurrence of EPS. Since 2003, only low-GDP solutions have been used for PD in our centers. Patients in whom PD was initiated from then onwards were therefore selected as the study subjects. An evaluation of the effects of icodextrin solution is also included in the study. The study design is based on an earlier study when high-GDP solutions were in use. A comparison of the results is expected to clarify the effects of biocompatible dialysis solutions.

**References**


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