Single-center experience of encapsulating peritoneal sclerosis in patients on peritoneal dialysis for end-stage renal failure

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Background. Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD). It is characterized by a progressive, intra-abdominal, inflammatory process resulting in sheets of fibrous tissue that cover, bind, and constrict the viscera, thereby compromising the motility and function of the bowel. Although recent therapeutic approaches have been reported with variable success, the ability to detect reliably at an early stage patients at risk for EPS would be beneficial and allow treatment standardization. The aim of this study was to evaluate the clinical features of EPS and identify possible risk factors for its development in CAPD and APD patients.

Methods. This was a review of all cases of EPS in a single center over the last 5 years.

Results. There were 810 CAPD and APD patients, managed in our program over this period. We identified 27 cases of EPS, giving an overall of 3.3% in this population. The mean duration of CAPD before diagnosis of EPS was 72.6 ± 39.7 months (range 16–172). Sixteen cases required surgical treatment and were classified as severe; others were treated conservatively (mild to moderate group). Ten patients received tamoxifen treatment with apparent benefit. The overall mortality rate was 29.6%. Eight patients from the severe group and the entire moderate group survived on hemodialysis or transplantation at 48.71 and 27.63 months follow-up, respectively. Peritonitis rates were not different between the 2 groups and peritoneal history was unremarkable compared to overall peritonitis rates in the unit. Data on small solute transport were not available in all patients in this retrospective analysis.

Conclusion. EPS is a serious, life-threatening complication of CAPD. Most cases had PD duration of more than 4 years. Careful monitoring by CT scans of the peritoneal membrane in patients beyond 5 years, and early catheter removal in patients with peritoneal thickening should be considered for long-term CAPD patients. Treatment with tamoxifen may be of benefit in these patients.

Encapsulating peritoneal sclerosis (EPS), first described by Gandhi [1], is a rare but serious complication of peritoneal dialysis (PD), and is life threatening in these patients. The optimum definition of EPS is still debated and the diagnostic criteria used to produce epidemiologic data are by no means uniform [2]. Due to its rarity and the relatively long duration of dialysis prior to its development, there is no satisfactory estimate of the incidence of dialysis-related EPS. Prevalence estimates range from 0.54 to 7.3% [2], while the Japanese experience suggests an overall incidence of 0.9% between 1980 and 1996 [3], and 2.5% from a prospective multicenter study in the late 1990s [4].

EPS is an extremely serious condition with a reported mortality of up to 93%–60% of patients die within 4 months in severe cases with complete intestinal obstruction. Originally known as sclerosing encapsulating peritonitis (SEP), an International Society of Peritoneal Dialysis subcommittee recommended the use of EPS because the old terminology implied infection as a major cause [2]. The early diagnosis and treatment prior to development of symptoms is difficult. Although it is very important to detect the patients at increased risk of developing EPS, there are no known clinical predictors [2, 5]. In patients on peritoneal dialysis, early signs include loss of ultrafiltration and development of high transporter status, probably due to increased peritoneal membrane permeability, which may in itself be a risk factor [6]. One factor linked with the development of the syndrome is duration of therapy. In Australia, an incidence of nearly 20% after 8 years of dialysis has been described [7]. Peritonitis [2, 3, 8] and prolonged use of unphysiologic solutions have also been implicated [9–11].
The hallmark of the condition is peritoneal fibrosis and thickening. A recent analysis from an International Peritoneal Biopsy registry shows that thickening of the membrane usually occurs after 4 or 5 years of PD and is associated with increasing severity of vasculopathy; these findings are not invariably found with long duration of therapy [12]. It is likely that this process continues to eventually produce EPS, although there is no evidence for this.

There are classic clinical, radiologic, macroscopic, and pathologic appearances in advanced cases, represented at laparotomy by intestinal cocooning. In such cases symptoms result from impairment of gut motility due to binding of the intestinal loops to each other, other viscera, and the internal surface of the abdominal wall by an aggressive fibrotic process. This produces partial or total obstruction, giving colicky pain, vomiting, bloating, diarrhea (caused when the partial obstruction spontaneously resolves), and weight loss with malnutrition [2]. If obstruction of the intestine does not resolve, intestinal dilatation and mural ischemia may develop, resulting in bacterial translocation, systemic inflammatory response syndrome (SIRS), sepsis, or even frank peritonitis [8]. This progression is frequently fatal without surgical treatment and, unfortunately, many patients reach this stage before the diagnosis is confirmed [13, 14].

The Japanese experience has been very helpful in the understanding of the process and its management. Various phases to the disorder are outlined [15]. After the development of EPS is confirmed, the authors advocated initial steroid treatment immediately after onset (inflammatory stage). If steroid therapy was ineffective, the dose was decreased immediately and followed (encapsulating stage) by management with total parenteral nutrition (TPN). If ileus symptoms remained (ileus stage), active laparotomy and total intestinal enterolysis was performed. During surgical treatment of EPS, it is important to perform total enterolysis without damaging the capsule-covered intestine. This is an interesting approach but it is not clear how one clinically defines these stages, unless laparotomy and histologic diagnosis are available.

The purpose of this study was to evaluate the clinical characteristics of EPS patients, and to look for early clinical features that may be associated with EPS in peritoneal dialysis (PD) patients.

METHODS

This study reports all cases of EPS diagnosed at Manchester Royal Infirmary between 1998 and 2003. Clinical records were reviewed in detail and individual data sheets compiled. Information was entered into a standard database program, Microsoft Access (Microsoft, Redmond, WA, USA), and further variables calculated, including total duration of PD and graft survival for those transplanted.

Diagnosis

The patients were arbitrarily divided into 2 categories: severe and mild/moderate. The major diagnostic criteria for the severe group were need for surgery for extensive symptoms and signs of intractable intestinal obstruction, gut ischemia, or gut-related sepsis. These included the presence of significant gastroenterologic symptoms and signs (abdominal pain, vomiting, weight loss, absent bowel sounds, and palpable intestinal mass) with appearances of EPS at laparotomy (Table 1). Radiologic diagnosis entailed a CT scan.

Peritoneal calcification

Computed tomography (CT) findings showed peritoneal thickening and features of significant bowel pathology as exemplified by bowel dilatation, calcification, septation, and nodularity, each of which were classified + to +++ with increasing severity. CT findings were not essential for the diagnosis of EPS but were confirmatory. Several CT scans were done months before the clinical diagnosis (ID S14 and S16 in the severe group whose CT scans show little evidence of severe disease).

Diagnosis of the mild to moderate EPS was made by biopsy at laparotomy (at Tenckoff removal) or by CT scans findings. M4, M9, and M11 had clinical symptoms of vomiting or intermittent abdominal pain that prompted the suspicion that EPS was present; this was subsequently confirmed by CT (Table 2).

Statistics

Group outcome differences were compared with the t test for independent samples, the Mann-Whitney test, and the Fisher exact probability test where appropriate. Multi-regression analysis was not possible because of the small number of patients in the group.

RESULTS

Demographics

Twenty-seven patients were identified from surgical audit records and the renal unit database. Our PD population over this time period comprised 810 patients; this represents 3.3% of PD patients attending for their care at our center over this period.

Of the 27 patients in whom a diagnosis of EPS was made between August 1996 and July 2003, 11 were male
### Table 1. Details of severe EPS patients (S1-S16) entailing diagnostic criteria, time on PD, infections, treatment, and outcome

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age (years)</th>
<th>CAPD months</th>
<th>Time since diagnosis</th>
<th>Peritoneal Infections N</th>
<th>Peritoneal thickening</th>
<th>Peritoneal dilatation</th>
<th>CT Findings</th>
<th>Surgical indication</th>
<th>Procedure</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>F</td>
<td>45</td>
<td>96</td>
<td>51</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Prednisolone, Cya</td>
<td>Alive HD</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>M</td>
<td>20</td>
<td>68</td>
<td>40</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Sepracoat, Tamoxifen</td>
<td>Alive HD</td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td>M</td>
<td>27</td>
<td>93</td>
<td>54</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>AliveTx</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>F</td>
<td>29</td>
<td>40</td>
<td>27</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>AliveTx</td>
<td></td>
</tr>
<tr>
<td>S5</td>
<td>F</td>
<td>34</td>
<td>96</td>
<td>71</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Tamoxifen</td>
<td>Alive HD</td>
<td></td>
</tr>
<tr>
<td>S6</td>
<td>F</td>
<td>27</td>
<td>50</td>
<td>3</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>AliveTx</td>
<td></td>
</tr>
<tr>
<td>S7</td>
<td>F</td>
<td>47</td>
<td>137</td>
<td>39</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Tamoxifen</td>
<td>Alive HD</td>
<td></td>
</tr>
<tr>
<td>S8</td>
<td>F</td>
<td>31</td>
<td>24</td>
<td>59</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Prednisolone</td>
<td>Alive HD</td>
<td></td>
</tr>
<tr>
<td>S9</td>
<td>F</td>
<td>38</td>
<td>158</td>
<td>4</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis abscess</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Tamoxifen, Rapamycin</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S10</td>
<td>M</td>
<td>57</td>
<td>62</td>
<td>0</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Sepsis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Sepracoat</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S11</td>
<td>M</td>
<td>49</td>
<td>78</td>
<td>6</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis abscess</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Tamoxifen, Rapamycin</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S12</td>
<td>F</td>
<td>65</td>
<td>34</td>
<td>2</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Medical Unit For Surgery</td>
<td>Nil</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S13</td>
<td>M</td>
<td>28</td>
<td>77</td>
<td>5</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Sepsis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S14</td>
<td>F</td>
<td>27</td>
<td>172</td>
<td>4</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Small bowel obstruction</td>
<td>Adhesiolysis Peritoneal Toilet</td>
<td>Nil</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S15</td>
<td>M</td>
<td>68</td>
<td>104</td>
<td>5</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>S16</td>
<td>F</td>
<td>45</td>
<td>79</td>
<td>4</td>
<td>++ + + + +</td>
<td>++ + + + + + +</td>
<td>++ + + + + + + +</td>
<td>Peritonitis</td>
<td>Peritonectomy Adhesiolysis</td>
<td>Nil</td>
<td>Died</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Cya, cyclosporine; Sepracoat, see text for details; HD, hemodialysis; Tx, transplantation. The classification and severity of CT findings (+ to ++++) are as in Table 2. Three patients (S7, S13, S16) did not have CT scans; the diagnosis was based entirely on clinical and laparotomy findings.

### Table 2. Mild/moderate EPS patients (M1-M11) with details of diagnostic criteria, number of peritoneal infections, CT findings, treatment, and outcomes

<table>
<thead>
<tr>
<th>ID</th>
<th>Gender</th>
<th>Age (years)</th>
<th>CAPD duration months</th>
<th>Time since diagnosis</th>
<th>Peritoneal Infections N</th>
<th>Peritoneal thickening</th>
<th>Peritoneal dilatation</th>
<th>CT Findings</th>
<th>Diagnostic criteria</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>F</td>
<td>29</td>
<td>41</td>
<td>51</td>
<td>0</td>
<td>Laparotomy</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>Not Identified On CT</td>
<td>Nil</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M2</td>
<td>M</td>
<td>24</td>
<td>78</td>
<td>45</td>
<td>6</td>
<td>Biopsy</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>Nil</td>
<td>Nil</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M3</td>
<td>M</td>
<td>38</td>
<td>39</td>
<td>34</td>
<td>1</td>
<td>Biopsy</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>Biopsy</td>
<td>Nil</td>
<td>Alive Tx</td>
</tr>
<tr>
<td>M4</td>
<td>F</td>
<td>55</td>
<td>42</td>
<td>59</td>
<td>0</td>
<td>CT Scan</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>CT Scan</td>
<td>Nil</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M5</td>
<td>M</td>
<td>40</td>
<td>22</td>
<td>56</td>
<td>0</td>
<td>At Tenckoff removal</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>At Tenckoff removal</td>
<td>Nil</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M6</td>
<td>M</td>
<td>69</td>
<td>94</td>
<td>41</td>
<td>1</td>
<td>Ultrasound</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>Ultrasound</td>
<td>Nil</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M7</td>
<td>F</td>
<td>54</td>
<td>86</td>
<td>39</td>
<td>1</td>
<td>Biopsy</td>
<td>No CT</td>
<td>++ + + + +</td>
<td>Biopsy</td>
<td>Nil</td>
<td>Alive PD</td>
</tr>
<tr>
<td>M8</td>
<td>M</td>
<td>34</td>
<td>36</td>
<td>53</td>
<td>1</td>
<td>At Tenckoff removal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ Tamoxifen</td>
<td>Alive PD</td>
</tr>
<tr>
<td>M9</td>
<td>M</td>
<td>27</td>
<td>77</td>
<td>24</td>
<td>6</td>
<td>CT Scan</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ Tamoxifen</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M10</td>
<td>F</td>
<td>59</td>
<td>81</td>
<td>23</td>
<td>4</td>
<td>Laparotomy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ Tamoxifen</td>
<td>Alive HD</td>
</tr>
<tr>
<td>M11</td>
<td>F</td>
<td>50</td>
<td>16</td>
<td>17</td>
<td>2</td>
<td>CT Scan</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ Tamoxifen</td>
<td>Alive HD</td>
</tr>
</tbody>
</table>

HD, hemodialysis; Tx, transplantation. The classification and severity of CT findings (+ to ++++) are as in Table 1. Two cases (M2, M5) had no CT scans and diagnosis was based on peritoneal findings and biopsy of the peritoneum. Three cases (M4, M9, M11) were diagnosed on CT findings alone; it is possible that in these 3 cases the disease represents peritoneal thickening associated with peritoneal dialysis; this aspect is discussed in the text.
and 16 female with a mean age of 42 years (SD 13 years). These patients exhibited wide variety in the causes of their chronic renal failure with no predominant diagnosis.

**Patient groups**

We divided the patients into 2 groups. The first group, termed severe, comprised EPS patients who developed any standard surgical indication for laparotomy (peritonitis, intractable intestinal obstruction, gut ischemia, or gut-related sepsis). The second group, termed mild or moderate, were the remaining patients, where the diagnosis was (1) attributable to clinical and radiologic features but the patients did not require surgery for their gastrointestinal manifestations, or (2) patients who had attributable symptoms and similar macroscopic changes at laparoscopy or laparotomy for other indications (e.g., cholecystectomy, Tenckhoff replacement). Both groups had the same macroscopic pathologic process identified within their peritoneal cavity. CT scans were used to aid diagnosis, but it is apparent that these were not discriminatory enough for a definitive diagnosis based on CT alone; our arbitrary definition of severity of EPS (Tables 1 and 2) showed overlap with severe cases by CT (M3 and M8) appearing in the mild/moderate group, whereas S14 and S16 had very little change on CT. The latter 2 cases had their CT scans done several months before surgery and it is likely that the disease process progressed. In the mild to moderate group there were 3 patients (M4, M9, M11) who were asymptomatic but had significant peritoneal thickening on CT. It is questionable whether these patients had EPS or peritoneal thickening associated with long-term PD treatment. CT scans in these patients were done as part of our routine screening measures, established after the initial cases, in our long term (>5 years on PD). While not representing the full blown clinically based EPS picture, they represent a state where there is potential for development of the EPS picture. As such, the future management was discussed with each patient; this entailed options of remaining on PD therapy, a change in dialysis therapy to hemodialysis, and treatment with tamoxifen. These 3 opted for change to HD and were included in the mild group. Patient M7 was found to have peritoneal sclerosis on laparotomy but opted to stay on PD with tamoxifen treatment. He remains well on PD over 37 months after the diagnosis with no change in his clinical or CT scans over this postdiagnosis period.

Sixteen patients fell into the severe category, including 3 patients who were not offered surgery due to comorbidity and very poor clinical state, but in whom the indications for laparotomy were nevertheless present—these 3 patients died. Eleven patients were defined as having mild to moderate EPS, 1 of whom underwent laparotomy performed with a view to pancreas transplantation; the intra-abdominal features of EPS became evident and the transplant was subsequently performed.

**Time on CAPD**

The mean duration of CAPD, overall, was 72.6 months (SD 39.7 months). There was a significantly longer mean duration of PD in the severe group, 84.3 months compared with 55.6 months in the mild to moderate group ($P = 0.040$, Mann Whitney, $P = 0.032$, $t$ test). Patients had an average of 2.62 PD (SD 2.2) catheters in their lifetime on PD. There was no significant difference in patient age or mean number of PD catheters inserted per patient.

**Time since diagnosis (survivors)**

The mean time since diagnosis in the surviving patients originally classified as “severe” was 48.71 months. The mean survival time since diagnosis of patients in the mild to moderate group is 27.63 months.

**Peritonitis**

There were a total of 71 episodes of peritonitis diagnosed during the period of peritoneal dialysis, giving an overall peritonitis rate of 1 episode every 27 patient months of therapy. The organisms responsible for the peritonitis are shown in Table 3, the most common being *Staphylococcus aureus*, followed by *Coagulase negative staphylococci*. There was no significant difference in the peritonitis rates between the 2 groups (severe, 1 episode/28 patient months; mild-moderate, 1 episode/25 patient months). There was a greater mean number of peritonitis episodes in the severe group, 3.1 compared with 2.0 per patient, and this was not statistically significant. The unit’s overall peritonitis rate over this period was roughly 1 episode per 20 to 30 patient months.

**Treatment and outcome**

Once a diagnosis of EPS was made 13 patients underwent laparotomies for acute surgical indications. There were 4 perioperative deaths, giving an overall
surgical mortality of 31%. Two patients also had Sepra-coat®, which is a 0.4% solution of hyaluronic acid in a phosphate-buffered saline infused into the peritoneal cavity through a cannula placed at one end of the laparotomy incision during final closure. It is intended to reduce postoperative formation of de novo adhesions resulting from incidental tissue damage in abdominal/pelvic surgery. Various medical treatments for EPS were prescribed to different patients, including tamoxifen (10), prednisolone (2), cyclosporine (1), and rapamycin (2). In the severe group, 8 patients died, 3 of whom did not have surgical intervention. Two received specific therapy (tamoxifen and rapamycin). Both these patients had extremely severe disease with extensive postoperative complications of intra-abdominal sepsis/fistula and persistent obstruction. The patients with severe EPS who underwent major laparotomy were found to benefit from several weeks of nasogastric aspiration, IV feeding, and daily HD. Of the 9 survivors in this severe group, 6 received specific therapy. All of the survivors were maintained successfully on hemodialysis (5 patients) or transplantation (3 patients) at a mean duration of 27.63 months postdiagnosis, with no further complications. Intergroup comparison of requirement for TPN revealed an increased requirement in the severe group that was significant \( P = 0.005 \), as well as a significantly decreased overall survival \( P = 0.005 \). Of the 27 patients, 13 required total parenteral nutrition, 11 perioperatively and 2 for nutritional support without surgery.

In the mild-moderate group of 11 patients, all were alive for a mean period of 48.71 months since diagnosis. All but 2 were on hemodialysis, 1 with a successful transplant and 1 patient continued on PD and tamoxifen with improved ultrafiltration and adequate dialysis 26 months since diagnosis (made at laparotomy for cholecystectomy; peritoneal biopsy confirmed EPS). It is possible that in this patient there was regression of the fibrotic process and represented a very mild form of the disease. At laparotomy significant fibrosis was evident but the patient wanted to remain on PD; hence, the decision to continue. A recent CT scan showed no evidence of significant peritoneal thickening. Four patients in this group have been on long-term tamoxifen at a dose of 10 mg daily.

In total, 8 of 27 patients died as a result of EPS, giving an overall mortality of 29.6%. All the deaths were in the severe group. Most survivors continued on hemodialysis or had renal transplants with no significant abdominal symptoms.

**DISCUSSION**

Peritoneal fibrosing syndromes include a spectrum of changes present in PD patients ranging from a thickened peritoneum to EPS. EPS is a rare but serious complication with a high mortality rate [2, 7]. In this study we report on 27 cases in which the disease process has produced intestinal compromise and symptoms. In dividing the cases into those with indications for urgent surgery (severe) and those in whom the diagnosis was made radiologically or by laparotomy for other indications (mild to moderate group), we highlight that there is a spectrum of severity in this condition. The severe cases indeed represent the more advanced stages, and the high mortality reflects the extensive fibrotic process and the various pathologic sequelae. The large numbers of severe cases identified at our unit has led to an increased awareness and index of suspicion regarding this condition. This has, in turn, led to more aggressive investigation of PD patients with suspicious symptoms, usually by CT, allowing us to identify a number of cases of EPS of mild to moderate severity. While there is no proof that early intervention (discontinuation of PD and use of tamoxifen) in this group led to the resolution of the problem, we believe that as a precautionary measure, stopping PD and early tamoxifen may well have helped. The experiment was limited as it was not possible to randomize patients to various options. None of the cases in the mild-moderate group have so far developed intestinal problems requiring surgery, and all remain well after a mean period of 35 months' postdiagnosis.

EPS has also been linked with the nature of dialysis solution used. Peritoneal dialysis solutions are unphysiologic in having low pH and high osmolality. The peritoneum undergoes thickening of the peritoneal interstitium and basement membrane reduplication in the mesothelium, as well as in the capillaries. Such changes have been judged to occur secondarily to the unphysiologic composition of the dialysis solutions, and also the direct action of glucose [16] and glucose degradation products, which bring about advanced glycosylation end product (AGE) related changes in the peritoneal membrane [10]. Some of the changes are diabetiform in nature, with alterations of peritoneal microvessels and neovascularization [9]. Glucose degradation products (GDP) are generated during the sterilization process [17]. All of these factors are potentially harmful to the peritoneal membrane.

In keeping with previous reports, the majority of symptoms reported were those resulting from partial or total occlusion of the intestinal lumen [14], namely pain (usually colic), vomiting, abdominal distension, or weight loss. In the severe cases, necessity for surgical treatment was caused by complete intestinal obstruction, secondary peritonitis, gut-related sepsis, or gut ischemia. Invariably, these patients underwent a trial of conservative treatment that failed to resolve their acute symptoms and signs. Despite some similarity in acute presentation, these patients had a progressive, intra-abdominal fibrosing pathology that is distinct from the more common peritoneal
adhesions. The risk of progression to the sequelae listed above is seemingly higher.

Our study confirms the link between duration of PD and likelihood of manifesting EPS, originally suggested by the study of Rigby and Hawley [7], which showed an incidence of 1.9%, 6.4%, 10.8%, and 19.4% after 2, 5, 6, and 8 years of PD, respectively. In our series, patients had a significantly higher mean duration of PD in the severe group compared with the mild to moderate. This evidence makes a strong case for the condition being caused, or driven by, the effects of PD, rather than some non-PD related factor. In addition to the link with PD duration, studies have shown a link between frequency of peritonitis and probability of developing EPS [2, 3, 8]. Our data do not support this hypothesis as the peritonitis rates were not particularly high in these patients, nor were the rates significantly different between the severe and the mild-moderate group. It is feasible that the episodes of infection may have varied widely in severity and/or duration from the severe and the mild-moderate group. It is clear that EPS represents a range of pathologic states, and no 1 diagnostic criterion is going to suffice. Keen clinical suspicion and awareness of the problem in patients at risk is as important as the various investigations. It is apparent that CT scan alone cannot be the sole criteria for the diagnosis of EPS—it needs a clinical component. The finding of thickening of the peritoneum on CT scans does highlight the potential risk of progression to the full-blown EPS picture, and there is a need to address this with patients and form the basis of any ‘informed’ changes to therapy and greater vigilance. CT was the major imaging modality, but ultrasound, plain, and contrast radiography were also used to identify peritoneal thickening, fluid collections, and complete or partial intestinal obstruction.

An alternative approach to disease definition and early identification is analysis of the relationship between decrease in effectiveness of dialysis, as measured by development of a hyperpermeable membrane and loss of ultrafiltration [21]. Complete data on ultrafiltration measurements prior to diagnosis of EPS were not obtainable for this sample, but in our study PD was stopped in all patients at or prior to diagnosis except 1 who continues on PD and tamoxifen. Continuation of PD even following extensive surgery for EPS has been successful [22]. It is proposed that given the association shown by our study between severity and total duration of PD and the previous successful case reports of treatment by peritoneal rest [7, 8, 13, 23–28] that wherever possible, patients should be switched to hemodialysis or transplanted at diagnosis. However, even removing the putative driving force for the disease process by withdrawing PD is not always successful [29].

Evaluation of medical treatments for EPS is difficult. Virtually the entire literature is based on anecdotal case reports and any kind of structured study is rare. Candidate treatments have included immunosuppression with steroids, azathioprine and cyclosporine, enteric rest with TPN and, most recently, tamoxifen. Immunosuppression has produced clinical improvement in isolated cases and small series [7, 23, 24, 28, 30] as well as being associated with increased survival [31, 32], while tamoxifen has been successfully used [33].

Tamoxifen’s effect on transforming growth factor beta (TGF-β) in the ovary [34] and in vitro [35] must be borne in mind alongside its anecdotal successes. It has, however, been widely reported as successful in the treatment of retroperitoneal fibrosis [36–38], but how well this translates to EPS is unclear. A recent report of its ‘prophylactic’ use in 9 cases of peritoneal sclerosis showed that none developed EPS, while in the control group of 14 patients with sclerosis 4 developed the syndrome and 3 died [39]. In our study, the use of tamoxifen may provide some benefit, especially in...
the mild-moderate group, but this cannot be stated categorically until further CT scans and long-term follow-up data are available. Prospective data will continue to be collected on these patients.

Many other therapies have been proposed with variable results. In anecdotal reports or limited series, TPN and surgery (alone or in combination) have been associated with improved survival. Bhandari et al [40] recommended immunosuppression before surgery. TPN alone has no benefit [6], but needs to be used in combination with surgery, usually prior to it. Our experience would concur with this.

Given that the pathologic lesions characterizing the disease result from the deposition of largely acellular material (mainly extracellular matrix proteins like fibrin and collagen), it is perhaps questionable to use agents that are demonstrably profibrotic, such as cyclosporine [41]. Newer immunosuppressives such as mycophenolate-mofetil and rapamycin are believed to have less profibrotic profiles [42] and would certainly be candidate therapies. There is currently a wide variety of experimental antifibrotic agents, such as antibodies to the profibrotic cytokine, TGF-β [43] or peptides which inhibit its activation [44], under investigation. It is hoped that such agents may provide future therapeutic options.

From our experience and that in the literature we would suggest that the optimum management of this condition entails great awareness and high index of suspicion to identify a subclinical disease process. This can be approached by investigation of the population at risk—long term (>5 years on PD) with high transporter status and loss of ultrafiltration. Appropriate investigations include imaging (CT scan for fibrosis, thickening, and calcification) and perhaps regular peritoneal equilibration tests. This study does not provide evidence for this. EPS has been associated with high transporter status, which occurs with long-term PD, and may be a further marker, and this, however, is questionable as there have been some reports of patients with low solute transport developing EPS. The optimum medical treatment is at present unclear, but our experience, though anecdotal, supports the use of tamoxifen. Potentially profibrotic effects of concomitant medications should be considered. Change of dialysis method to hemodialysis or transplantation should be instigated at diagnosis, if possible, to reduce disease progression. In cases of EPS with obstruction, aggressive nutritional support must be given to any at risk patient. Most patients having a trial of conservative management for obstructive symptoms should receive TPN. At surgery, meticulous surgical technique to avoid enterotomies is vital. These are the main source of operative morbidity and mortality through the production of fistulas and sepsis.

**REFERENCES**

10. **GILEROT G, DEVUYST O:** Molecular mechanisms modifying the peritoneal membrane exposed to peritoneal dialysis. *Clin Nephrol* 60:1–6, 2003


