Encapsulating Peritoneal Sclerosis in Incident PD Patients in Scotland

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1. Introduction

1.1 Background
Encapsulating peritoneal sclerosis (EPS) is a devastating and potentially life threatening complication of peritoneal dialysis (PD). EPS was first described in 1980 and is characterised by progressive peritoneal fibrosis and thickening with encasement of bowel loops (Ghandi et al 1980). EPS results from chronic intra-abdominal inflammation and fibrosis but the trigger for this is unknown. The aetiology is thought to be multi-factorial. Early clinical studies identified acetate dialysate and chlorhexidine as causes (Slingeneyer 1987, Oules et al 1983). However, despite the removal of these causal factors from clinical practice, EPS continues to occur. The duration of exposure to PD therapy represents the most consistent “risk factor” identified in studies to date (Kawanishi et al 2001, Kawanishi et al 2004, Rigby et al 1998, Brown MC et al 2009).

1.2 Diagnosis of EPS
The clinical features of EPS have been described in previous clinical studies (Kawanishi et al 2001, Kawanishi et al 2004, Rigby et al 1998, Nomoto et al 1996, Summers et al 2005, Brown MC et al 2009). The progressive peritoneal fibrosis compromises bowel motility and absorption, ultimately causing bowel obstruction (often sub-acute) and severe malnutrition. Typically EPS is also associated with progressive loss of ultrafiltration, causing fluid accumulation. Ascites may also develop (Perks et al 2004).

The clinical, radiological and pathological criteria for the diagnosis of EPS have been defined by the International Society for Peritoneal Dialysis (ISPD) in 2000 (Kawaguchi et al 2000) and these criteria should be met by all patients included in clinical and epidemiological studies in the post millennium. EPS may be diagnosed while the patient is on PD but many cases become apparent after stopping PD including after renal transplantation (Fieren et al 2007, Korte et al 2007, de Freitas DG et al 2007) Brown MC et al 2009).

1.3 “Incidence” of EPS
EPS is an infrequent complication in patients after more prolonged exposure to PD but the exact incidence is unknown. Most previous studies are from Japan/Northeast Asia, where the duration of PD therapy tends to be longer. Multi-centre studies from Japan report “incidence”
rates of 0.8-2.5% of PD patients (Kawanishi et al 2001, Kawanishi et al 2004, Nomoto et al). Whether the findings from these studies can be extrapolated to Western populations and practice is uncertain. A recent case series from the UK identified 27 cases of EPS, representing an “incidence” of 3.3% in their PD population over 7 years (Summers et al 2005). An earlier Australian case series identified 54 cases over 14 years, representing an “incidence” of 0.7% (Rigby et al 1998). The data from these studies is summarised in Table 1 below.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year of publication</th>
<th>Number of EPS Cases*</th>
<th>Dates of Study</th>
<th>Denominator Population (prevalent + incident patients)</th>
<th>Overall “Incidence”</th>
<th>Mean PD Exposure (yrs)</th>
<th>Mortality (over study period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nomoto et al</td>
<td>Japan</td>
<td>1996</td>
<td>62</td>
<td>1980 - 1994</td>
<td>6923</td>
<td>0.9%</td>
<td>5.1</td>
<td>43.5 %</td>
</tr>
<tr>
<td>Rigby et al</td>
<td>Australia</td>
<td>1998</td>
<td>54 (46)</td>
<td>1980 - 1994</td>
<td>7374</td>
<td>0.7%</td>
<td>4.3</td>
<td>56 %</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Korea</td>
<td>2003</td>
<td>31</td>
<td>1981 - 2002</td>
<td>3888</td>
<td>0.8%</td>
<td>5.8</td>
<td>25.8 %</td>
</tr>
<tr>
<td>Kawanishi et al</td>
<td>Japan</td>
<td>2001</td>
<td>17</td>
<td>1999 - 2001</td>
<td>2216</td>
<td>0.8%</td>
<td>10</td>
<td>35 %</td>
</tr>
<tr>
<td>Kawanishi et al</td>
<td>Japan</td>
<td>2004</td>
<td>48</td>
<td>1999 - 2003</td>
<td>1958</td>
<td>2.5%</td>
<td>4.3</td>
<td>37.5 %</td>
</tr>
<tr>
<td>Summers et al</td>
<td>UK</td>
<td>2005</td>
<td>27 (23)</td>
<td>1998 – 2003</td>
<td>810</td>
<td>3.3%</td>
<td>6.1</td>
<td>29.6 %</td>
</tr>
<tr>
<td>Brown MC et al.</td>
<td>UK</td>
<td>2009</td>
<td>46</td>
<td>2000-2007</td>
<td>1638</td>
<td>2.8%</td>
<td>5.4</td>
<td>56.5%</td>
</tr>
</tbody>
</table>

* The number of EPS cases who did not meet the ISPD 2000 criteria for EPS is shown in brackets in the second row of Table 1.

Table 1. “Incidence” of EPS reported from previous studies

**1.4 Incidence of EPS**

The true incidence of EPS has been difficult to establish because:
- EPS is uncommon,
- EPS is associated with poor survival rates,
- misdiagnosis or delayed diagnosis of EPS may occur, especially if the patient develops symptoms after PD has been discontinued,
- most epidemiological studies describing the “incidence” of EPS have been retrospective.

In addition most previous studies have included both incident and prevalent patients on PD on the start date of follow up which does not allow an accurate calculation of incidence (Kawanishi et al 2001, Kawanishi et al 2004, Rigby et al 1998, Nomoto et al 1996, Summers et al 2005). To calculate a true incidence of EPS a cohort of patients must be followed from the
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start of PD to identify all cases diagnosed thereafter. To address this we reported the incidence of EPS in all patients starting PD in Scotland in the time period 01 January 2000 - 31 December 2007 (Brown MC et al 2009). The rate of EPS in this study was 1.5% (19 EPS cases observed in 1238 incident PD patients) or an incidence of 4.9 per 1000 person years. This study showed that the incidence of EPS was 0% in first year of PD, rising progressively to 8.1% (CI 3.6-17.6) at >4-5 years; 8.8% (CI 3.2-23.1) at >5-6 years and 5.0% (CI 1.2-23.8) at >6 years PD exposure (Table 2). It is possible that greater awareness of EPS may have led to increased diagnosis of milder cases but the mortality rate was similar to rates reported in previous studies (Table 1) and was 42% at 1 year after diagnosis.

<table>
<thead>
<tr>
<th>Cumulative PD Exposure</th>
<th>PD Cohort (n=1238)</th>
<th>EPS Cases (n=19)</th>
<th>Incidence (%)</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>480</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-2 years</td>
<td>326</td>
<td>2</td>
<td>0.6</td>
<td>0.2 - 2.1</td>
</tr>
<tr>
<td>2-3 years</td>
<td>202</td>
<td>4</td>
<td>2.0</td>
<td>0.8 - 5.0</td>
</tr>
<tr>
<td>3-4 years</td>
<td>114</td>
<td>4</td>
<td>3.5</td>
<td>1.4 - 8.7</td>
</tr>
<tr>
<td>4-5 years</td>
<td>62</td>
<td>5</td>
<td>8.1</td>
<td>3.6 - 17.6</td>
</tr>
<tr>
<td>5-6 years</td>
<td>34</td>
<td>3</td>
<td>8.8</td>
<td>3.2 - 23.1</td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td>20</td>
<td>1</td>
<td>5.0</td>
<td>1.2 - 23.8</td>
</tr>
</tbody>
</table>

Table 2. Incidence rates of EPS related to total duration of PD exposure (not necessarily continuous)

It is noticeable that there is a dramatic increase in the proportion of patients developing EPS after 4 years of PD (1 in 12 patients at risk). Thus analysis of this incident PD patient cohort up to December 2007 showed that the incidence of EPS increased significantly with PD duration but the confidence limits of the observed incidence of EPS were wide as the number of cases of EPS was low and the PD patient follow up was relatively short. However, 806 patients (66%) of the PD cohort had had less than 2 years PD exposure by the end of 2007 so the incidence of EPS in this patient cohort is likely to increase after longer follow up. This could be addressed by reporting the incidence of EPS in this same cohort of PD patients after a longer period of follow up.

1.5 Study aims
The primary aims of the current study were:

a. describe all of the cases of encapsulating peritoneal sclerosis (EPS) occurring between 01 January 2000 - 30 June 2009 in the above cohort of patients who had commenced peritoneal dialysis (PD) in Scotland between 01 January 2000 - 31 December 2007
b. calculate the true incidence of EPS in this PD cohort.
2. Methods

2.1 Patients
The cohort of patients aged over 18 years who started peritoneal dialysis (PD) between 01 January 2000 and 31 December 2007 in Scotland (n=1238) was identified from the Scottish Renal Registry. We sent each of the 10 adult renal units in Scotland a list of their patients in this cohort and a note of the diagnostic features of EPS. We asked them to identify known or potential cases diagnosed after 01 January 2000. All units were originally approached in the summer of 2006 and at intervals thereafter.

2.2 Inclusion criteria for EPS diagnosis
Casenotes and electronic patient records for each possible case were examined by one data collector (MC Brown) to ensure all met the ISPD diagnostic criteria (Kawaguchi et al 2000). To confirm the diagnosis of EPS a patient had to have:
clinical features and
either typical radiological and/or
histopathological features.
Clinical features include abdominal pain, nausea, vomiting, abdominal distension, anorexia, weight loss, unexplained/resistant anaemia, unexplained fever, elevated inflammatory markers, loss of ultrafiltration, bowel obstruction and/or unexplained ascites. Typical radiological features include ascites, typically loculated with multiple strands or septations, peritoneal thickening, thickening of bowel wall, calcification, thickened mesentery and/or matted bowel in the central abdomen. Positive pathology included the typical macroscopic appearance at laparotomy or laparoscopy or biopsy consistent with EPS with gross interstitial thickening with loss of mesothelium.

2.3 Exclusion criteria for EPS diagnosis
Exclusion criteria for EPS were met if there was an alternative explanation for the above findings:
previous bowel perforation,
TB,
cirrhosis,
intraperitoneal (IP) malignancy/chemotherapy,
VP shunt or TIPSS,
IP lavage with disinfectant or talc contamination

2.4 Calculation of EPS incidence rates
We have assumed that the individual units had adequate systems locally to identify patients diagnosed with EPS since 2000. In addition we looked for EPS in the European Dialysis and Transplantation Association (EDTA) coded causes of death in the Scottish Renal Registry records to identify any additional cases. To calculate the incidence and rates per time on PD we have only included patients who developed EPS and who were first exposed to PD after 01 January 2000. The rates are given as the incidence with the 95% confidence intervals. All cases have been used to describe the clinical presentation. Cases of EPS in this national cohort of incident patients on PD were used to calculate incidence rates between 01 January 2000 and 30 June 2009. Statistical analyses were performed using SPSS®. The incidence of
EPS was calculated as number of EPS cases divided by number of patients at risk, taking into account the person-time during which events were observed and time elapsed before EPS diagnosis.

2.5 PD-associated peritonitis
Peritonitis was defined as a PD effluent white cell count above 100 per mm³. Peritonitis rates were calculated as the number of patient months on PD divided by number of infections and expressed as number of months between episodes.

3. Results
3.1 Patient demographics
31 of the 1238 patient cohort had developed EPS before 30 June 2009. The median duration of PD before the diagnosis of EPS was 4.0 years (interquartile range 2.9-5.2 years). The mean duration of exposure to PD of the patients who did not develop EPS was 1.8 years. The rate of peritonitis in the patients with EPS was 1 episode every 19.2 months which is very similar to the peritonitis rate in Scotland 2000-2009 (Scottish Renal Registry Report 2009). The clinical details of the 31 patients who developed EPS have been compared with the patients who did not develop EPS in Table 3 below.

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>EPS Cases (n=31)</th>
<th>PD Cohort (n=1207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (IQR)</td>
<td>53.9 (43 - 64) years</td>
<td>55 (45 - 70) years</td>
</tr>
<tr>
<td>Proportion male</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td>Proportion Caucasian</td>
<td>94.8%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Median number of peritonitis episodes (IQR)</td>
<td>2 (1-4)</td>
<td>1 (1-2)</td>
</tr>
</tbody>
</table>

Table 3. Summary of demographics of patients who did and did not develop EPS
The interquartile ranges (IQR) of median values are recorded in brackets.

3.2 Clinical presentation
Most patients had more than one clinical feature attributable to EPS. All patients had at least one of these three symptoms: abdominal pain, vomiting and/or abdominal distension (with ascites or in the context of bowel obstruction).

3.3 Patient outcomes
By the study end on 30th June 2009, 22 patients (71.0%) had died. 13 (60.0%) deaths were attributable to EPS. Median survival from diagnosis was 116 days (range 1-660 days, IQR 20-
297 days). The “survivors” had a median of 1076 days follow-up since diagnosis (range 63-1764 days, IQR 537-1309 days). Overall the mortality rate was 54.8% at one year after diagnosis.

3.4 Incidence of EPS
We identified 31 EPS cases in the patient cohort giving an incidence of EPS of 2.5% in this patient cohort with a minimum follow up of 1.5 years. We searched the SRR database (for International Classification of Disease codes; ICD-9/ICD-10) reported in hospital discharge statistics but no additional cases were found.

The incidence according to the duration of PD exposure is shown in Table 4. The incidence rates of EPS are higher than published previously, particularly for duration of PD exposure <5 years.

<table>
<thead>
<tr>
<th>Cumulative PD Exposure</th>
<th>PD Cohort (n=1238)</th>
<th>EPS Cases (n=31)</th>
<th>Incidence</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>470</td>
<td>1</td>
<td>0.2 %</td>
<td>0.1 - 1.1</td>
</tr>
<tr>
<td>1-2 years</td>
<td>327</td>
<td>3</td>
<td>0.9 %</td>
<td>0.3 - 2.6</td>
</tr>
<tr>
<td>2-3 years</td>
<td>198</td>
<td>5</td>
<td>2.5 %</td>
<td>1.1 - 5.8</td>
</tr>
<tr>
<td>3-4 years</td>
<td>117</td>
<td>6</td>
<td>5.1 %</td>
<td>2.4 - 10.7</td>
</tr>
<tr>
<td>4-5 years</td>
<td>63</td>
<td>6</td>
<td>9.5 %</td>
<td>4.5 - 19.3</td>
</tr>
<tr>
<td>5-6 years</td>
<td>35</td>
<td>6</td>
<td>17.1 %</td>
<td>8.2 - 32.8</td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td>28</td>
<td>4</td>
<td>14.3 %</td>
<td>5.8 - 31.7</td>
</tr>
</tbody>
</table>

Table 4. Incidence of EPS related to duration of PD exposure

3.5 Other possible “risk factors”
14 patients (45.2 %) had used high strength dextrose (3.86% or equivalent) at some point during PD treatment. 29 (93.5 %) patients had used Extraneal (Icodextrin). There was no obvious relationship to any specific brand of PD dialysate fluid. The incidence of peritonitis was similar in the patients who did and did not develop EPS. 3 of the patients who developed EPS had never had peritonitis. The spectrum of organisms causing peritonitis was comparable between the EPS cases and the PD population unaffected by EPS.

4. Discussion
4.1 Incidence of EPS
The main aim of this study was to calculate an accurate incidence of EPS and so establish the risk of EPS for patients starting PD in Scotland. This report provides a more definitive
evaluation of the incidence of EPS since all of the patients in this PD cohort have a minimum of 1.5 years follow up. Our study was retrospective until June 2006 and prospective from 01 July 2006 - 30 June 2009. From previous studies it is apparent that EPS occurs very rarely if PD duration is under 18 months, and the average duration of PD exposure before the onset of EPS is 4-6 years (Kawanishi et al 2004, Rigby et al 1998, Nomoto et al 1996, Summers et al 2005, Brown MC et al 2009). Although the initial period of this study was retrospective we would expect that most cases would be reported after 2004 which is 2-3 years before we first contacted the units. In fact the first patients diagnosed from this PD cohort were in mid 2004. If any cases before 2004 were missed this would mean that the rates we report are an underestimate. We performed secondary checks of the SRR database for relevant diagnostic codes (EDTA cause of death and ICD-9 and ICD-10 codes) to identify any cases that may have been missed. However, we did not identify any other cases.

It is known from previous data that EPS often develops after stopping PD. This means that more cases from our cohort may still develop EPS and the incidence we have reported should be regarded as the minimum risk of developing EPS after PD. For this reason we are continuing to follow up the 2000-2007 PD cohort prospectively.

As our understanding of the aetiology of EPS remains poor large, prospective, multi-centred studies are required to address the clinical problems created by an apparently rising incidence of EPS. As clinicians we should be able to inform our patients of the significant risks associated with the treatments we administer. Our study allows quantification of the minimum risk of developing EPS in patients starting PD in the modern era.

4.2 Duration of PD as a risk factor for EPS

The figures reported in this study show a higher incidence of EPS after more than 3 years of PD therapy than in the earlier report after shorter follow up. This is at least in part due to the significantly more patients at risk with more than 3 years exposure to PD. The latest data suggest that after 4 years of PD therapy almost 1 in 10 patients will develop EPS. Previous studies have reported rates at 4 years PD exposure of 5% in Australia and <1% in Japan (Rigby et al 1998, Nomoto et al 1996). It is difficult to determine whether the higher rates found in this study represent an increase in the true incidence and/or increased clinical awareness of EPS or whether it reflects differences in our study design compared to previous studies. When we utilise the same method of calculating the incidence of EPS (number of cases/incident and prevalent PD patients in time period) as in previous studies, the results shown in Table 1 indicate an apparently increasing rate of EPS in the more recent studies. The rates in this report are comparable to a previous study from Manchester in the UK and to the overall incidence in the more recent studies from Japan (Kawanishi et al 2004, Summers et al 2005).

The risk of developing EPS is inversely related to the technique failure rate. A large proportion of the patients in this study with a minimum follow up period of 1.5 years were only on PD for less than 1 year so would be at low risk of developing EPS. In contrast the small portion of patients who were maintained on PD for at least 4 years has a relatively high incidence of EPS (16 of the 126 at risk patients) (Table 4).

4.3 Other risk factors for EPS

The peritonitis rates in the previous report on this incident PD cohort also showed comparable peritonitis rates between those patients who developed EPS and those patients...
who did not (Brown MC et al 2009). Similar peritonitis rates in patients who do and who do not develop EPS have also been shown in other studies (Hendriks et al 1997). A study of 111 patients who developed EPS showed 12 patients had no previous peritonitis episodes, 28 had one previous episode, 30 had two previous episodes and 33 had three or more previous episodes (Balasubramaniam G et al 2009). Peritonitis per se is therefore not a risk factor for the PD population although it has been reported that some patients develop an acute onset of EPS shortly after an episode of severe peritonitis (Summers et al 2005, Brown MC et al 2009).

All except two cases in our series had used Extraneal dialysate. It is very difficult to untangle whether this reflects ultrafiltration failure in the early stages of EPS or whether the use of such fluids somehow promotes the development of EPS. Only around half of the EPS patients had used high strength dextrose. Patients who develop EPS have been shown to have higher peritoneal transport rates and lower net ultrafiltration compared with matched control patients (Hendriks et al 1997) but peritoneal transport characteristics were not available in this study. It has been reported that patients with ultrafiltration failure, defined as net ultrafiltration less than 400ml after a 4 hour dwell time using 3.86% dialysis fluid, are at high risk of developing EPS if PD is continued (Sampimon et al 2011). In this recent study half of the patients with ultrafiltration failure who remained on PD for more than 3 years developed EPS (Sampimon et al 2011).

4.4 Screening for EPS
EPS may have been under-recognised in PD patients in the past and a high index of suspicion is needed in long term PD patients with symptoms due to subacute obstruction or ascites. However, it is important to avoid misdiagnosis of EPS and therefore all cases must fulfill well defined criteria in reaching a diagnosis of EPS as in this study.

At present radiological techniques are unable to establish a diagnosis of “early” EPS. CT scans which were performed coincidentally in PD patients prior to development of EPS did not show features indicating developing EPS (Tarzi et al 2008). Thus there is no evidence that regular screening of long-term PD patients by radiological techniques would be able to detect pre-symptomatic EPS or beneficially alter PD management.

Previous studies have suggested that 5 years should be the time-point for screening for EPS or discontinuing PD because of the risk of EPS (Nomoto et al 1996, Summers et al 2005, Kawaguchi et al. 2005). By 5 years 21 of the 31 cases in our case series already had developed EPS indicating that screening for EPS (if a reliable screening test was available) would already have missed two thirds of the cases and two thirds of cases would have occurred before switching dialysis modality. The data in this study lend further support to the UK EPS and ISPD guidelines on EPS which state that the optimal approach to patients on long duration PD is currently unclear but routine pre-emptive switching to haemodialysis or screening for EPS after a specified time on PD are not recommended (Woodrow et al 2009, Brown E et al 2010). Indeed many of the cases of EPS in this study and other studies (Fieren et al 2007, Korte et al 2007, de Freitas DG et al 2007, Brown M et al 2009) occurred after stopping PD. Thus pre-emptive switching to haemodialysis could potentially be associated with development of EPS rather than being preventive of EPS and at present there is no data showing any benefit from such a policy. Furthermore modality switch from PD could have significant detrimental implications for some PD patients who have social or medical reasons for not commencing haemodialysis.
5. Conclusions

Abdominal pain, vomiting, abdominal distension and weight loss are the most common symptoms at the time of diagnosis and the majority of patients in this series were diagnosed after stopping PD. Total time on PD was the main risk factor associated with EPS. Follow up of the PD patient cohort from 2000-2007 with a minimum patient follow up of 1.5 years has shown that symptomatic EPS developed in more than 1 in 10 of patients who received PD for at least 4 years.

The incidence rates reported in this study are higher than previously reported and have implications for patient education during renal replacement planning. This data may be used to inform patients of the minimum risk of developing EPS after starting PD.

6. Acknowledgements

6.1 Assistance from colleagues

The authors wish to express their thanks to the nurses, doctors and administrative staff of all the individual renal units for their assistance in identifying the cases of EPS and providing their clinical records. The authors also wish to thank the Scottish Renal Registry staff.

6.2 Disclosure of conflicts of interest

Dr. Robert Mactier wishes to declare the following potential conflicts of interest:

Study investigator for multicentre research studies conducted by Roche, Amgen and Baxter, Member of the clinical advisory board for Baxter in 2005 and 2010

Sponsorship to attend scientific meetings from Leo, Roche and Baxter

To his knowledge, he has had no other direct support from the renal technology industry.

Dr Michaela Brown does not have any conflicts of interest to declare.

7. References


Progress in Peritoneal Dialysis is based on judgement of a number of abstracts, submitted by interested people involved in various aspects of peritoneal dialysis. The book has a wide scope, ranging from in-vitro experiments, mathematical modelling, and clinical studies. The interested reader will find state of the art essays on various aspects of peritoneal dialysis relevant to expand their knowledge on this underused modality of renal replacement therapy.

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